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REVIEW

How histone modifications influence cellular radiosensitivity: Pharmaceutically targeting epigenetic regulators as a promising avenue to overcome radioresistance



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Abstract Cancer remains the leading cause of mortality worldwide. Radiotherapy (RT), a cornerstone of oncological treatment for over a century, has achieved great success in various cancers. However, radioresistance remains the primary factor leading to the failure of radiotherapy. Histone modifications in cancer cells are known to play a pivotal role in regulating radiosensitivity by modulating chromatin structure, either by loosening or tightening it. Here, we provide a comprehensive summary of the link between aberrant histone modifications and radiation resistance across various cancer and normal tissue cells. Furthermore, we discuss the regulatory mechanisms of histone modifications and the enzymes on the recruitment of proteins that recognize histone modifications. Consequently, these processes substantially affect the radiosensitivity of tumors. In addition to cancer cells, we highlight the intricate interplay between histone modification and radiosensitivity, both within and beyond the cancer cells. Meanwhile,

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various drugs targeting histone modifications emerge as a promising therapeutic strategy to overcome radioresistance of tumors as well as radioprotection. The combination of histone modification inhibitors with radiotherapy presents a novel approach to enhance cancer treatment outcomes in clinical practice. Nevertheless, the underlying mechanisms through which histone modifications influence cancer radiosensitivity require further elucidation to identify novel targets for radiotherapeutic intervention.

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1. Introduction

Cancer remains the leading global cause of death. In 2020, it resulted in the deaths of nearly 10 million individuals[1−3]. In China, the latest data for 2022 indicates a rise of over 4.8 million cancer cases for the entire year[4,5]. It is predicted that cancer cases could increase by 60% over the next 20 years. Although progress has been made in prevention, screening, early diagnosis, and treatment, resulting in a slight decrease in the cancer death rate, efforts to reduce cancer mortality are necessary according to data from global cancer statistics[3]. Various treatment modalities such as surgery, radiotherapy, chemotherapy, immunotherapy, targeted therapy and stem-cell transplantation are employed in the management of cancers. Particularly, radiotherapy is a prominent therapeutic approach for malignant tumors[6]. Over half of cancer patients undergo radiotherapy either as a standalone treatment or in conjunction with other modalities. It remains the most-effective cytotoxic therapy for localized solid cancers[7]. Currently, radiotherapy offers substantial benefit to more than 50% of cancer patients worldwide[8].

Since Dr. E. Gruber first used X-ray treatment for tumors in 1896, radiotherapy technology has developed over 100 years. Radiation-induced damage to tumor cells involves both direct and indirect mechanisms. The direct damage mechanism involves radiation rays directly acting on the DNA of tumor cells, causing DNA strand breaks such as DNA single-strand breaks (SSBs), DNA double-strand breaks (DSBs) and others[9]. Radiation causes indirect damage by ionizing intracellular water, leading to the production of reactive oxygen species (ROS) that can cause indirect DNA damage. Significantly, DSBs are the most lethal lesions induced by ionizing radiation and could trigger a series of cellular DNA damage responses. However, radiotherapy is a double-edged sword that causes inevitable normal tissues damage. Radiotherapy targets tumor cells but can also harm normal tissues, affecting treatment. This damage often impacts the skin, lungs, intestines, and brain[10,11]. The complex molecular mechanisms involve oxidative stress, inflammation, cell depletion, aging, and the release of proinflammatory and profibrotic cytokines. In recent years, there has been rapid development in radiotherapy to alleviate or avoid normal tissue damage, leading to the emergence of various new radiotherapy technologies and advanced radiotherapy equipment, such as intensity-modulated radiotherapy (IMRT), three-dimensional radiotherapy (3D-CRT) and image-guided radiotherapy (IGRT)[12−17]. Unfortunately, radiotherapy frequently encounters limitations due to radioresistance, particularly in malignancies such as lung, breast, cervical, pancreatic, and prostate cancers[18,19]. Radiation-induced damage to normal tissues significantly impacts radiotherapy outcomes. Developing biomarkers and cellular assays to predict delayed tissue injury post-treatment is crucial for optimizing personalized radiotherapy plans.

Radioresistance in cancer cells leads to cancer relapse, poor treatment response, poor prognosis, decreased quality of life, and increased disease treatment burden. Furthermore, radioresistance induces damage to cancer-adjacent normal tissues, disrupting the physiological and biochemical functions of normal tissue. The radioresistance of cancer cells is still a major limitation for radiotherapy applications. Efforts are continuously ongoing to explore targets for radiosensitization and develop radiosensitizers for improving the outcomes of radiotherapy. Malignant tumors acquire radioresistance through various mechanisms, including enhanced DNA damage repair capacity, enhanced ability to scavenge ROS, reprogramming of metabolism, promoting epithelial−mesenchymal transition, formation of tumor microenvironment, cancer stem cell activation and abnormal regulation of programmed cell death[20−23]. Histone modifications are substantially involved in the above events, thus influencing cancer radioresistance[24−26].

Several studies conducted on clinical tumor tissues and tumor cell lines have consistently demonstrated that histone-dominated epigenetic alterations play a significant role in the initiation, progression, unfavorable prognosis, as well as the development of radioresistance in malignant tumors. One of the hallmarks of malignancies is the covalent modification of histones and the unregulated expression and activity of histone-modifying enzymes[27−32]. Dysregulation of the histone modification enzyme usually leads to alterations in the chromosomal structure of tumor cells[33]. Many factors lead to radioresistance, such as activation of oncogenes or inactivation of tumor suppressor genes[34] and dysregulated signaling pathways[35], which impact the choice of DSB damage repair pathways and the repair efficiency[36], and eventually manifest as radioresistance. In addition, changes in histone modifications have been observed in cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), T cells and other cells that make up the tumor microenvironment (TME) and are involved in driving the formation of tumor resistance phenotypes[37,38]. Histones participate in epigenetic regulation of radiotherapy through a variety of manners, including post-translational modification of histone tails, regulation of the expression and activity of histone modification enzymes[39], substitutions between normal histones and histone variants, patterns of post-translational modification of histone variants[40], regulation of chromatin and nucleosomes by chromatin remodeling/remodeling complexes[41]. Moreover, the other two major pathways of epigenetic regulation, non-coding RNA and DNA methylation, could also regulate radioresistance through histone modification or regulators[42,43], indicating the dominant role of histones in regulation of radiosensitivity. Therefore, targeting histone modifications may be an

effective measure to overcome the radiotolerance of tumor cells and repair radiation-induced normal tissue injury. In this review, we focus on the role of histone modifications in tumor radiosensitivity and abnormal histone modifications in radiation-induced injuries. Recent evidence indicates drugs targeting histone modifications emerge as a promising strategy to overcome radioresistance and the combination of histone modification enzyme inhibitors and radiotherapy is likely to be a promising avenue to enhance the efficacy of radiotherapy.

2. Histones regulate DNA damage induced by radiotherapy

During radiotherapy, ionizing radiation could destroy the integrity of macromolecules, either directly and indirectly[44]. High linear energy transfer (LET) ionizing radiation such as heavy ions, neutrons and α particles induces DNA damage primarily *via* direct ionization, rather than indirect damage. On the other hand, indirect damage is predominant in low-LET radiation including X-rays and γ-rays. Low-LET radiation acts on non-DNA molecules such as water, producing ROS, resulting in genomic DNA damage[45]. Apart from DNA damage, radiation effects also include cancer cell cycle arrest, senescence, autophagy, necrosis and pyroptosis[46]. Significantly, DNA is the predominant target molecule for the action of ionizing radiation[47]. When cells are exposed to ionizing radiation, the high-energy electromagnetic waves or/and particles destroy DNA and also ionize intracellular water to produce ROS causing indirect DNA damage. Moreover, DNA damage induced by ionizing radiation includes SSBs, DSBs and clustered DNA lesions[48]. Complex DSBs, either formed directly by irradiation or by the processing of non-DSB clustered lesions, are repaired in slow kinetics or left unrepaired and cause cell death or pass mitosis. In surviving cells, large deletions, translocations, and chromosomal aberrations are observed post-radiation. Thus, radiation-induced clustered DNA lesions are slowly and inefficiently repaired, leading to genome instability and mutagenesis[49].

Cells could quickly initiate a complex network of DNA damage response (DDR) pathways in response to genomic DNA damage, particularly DSBs. This DDR process is triggered within minutes of detecting damaged DNA[50]. SSB could be repaired using the intact complementary strand as a template, and damaged bases are repaired by both the base and nucleotide excision repair pathways[51]. Thus, the death of a cell with an intact genome is rarely caused by base damage and SSB. In contrast, DSBs are challenging to repair and are considered "lethal damage" that can cause tumor cell apoptosis. Despite this, tumor cells can also have increased DSB repair activity, leading to resistance to radiotherapy[48]. Taking X-ray irradiation as an example, although the number of DSBs caused by 1−2 Gy X-rays is only 4% of that of SSB, it is the main cause of cell death[52]. Presently, DSBs are primarily repaired through the mechanisms of homologous recombination (HR) and non-homologous end joining (NHEJ). HR is contingent upon the appropriate cell cycle and exhibits a low repair efficiency, yet it is characterized by error-free repair. Conversely, NHEJ can transpire during any phase of the cell cycle, boasting a high repair efficiency, albeit with a propensity for error correction[53−55]. The occurrence of DSB indicates possible chromosomal breakage. Based on DSBs repair, chromosomal aberrations or deletions can be detected in the subsequent mitosis[56]. The fate of cells is determined by the proper response and effective repair of DSBs. This process begins with the initial relaxation of the chromatin structure and processing of DNA ends, which creates space for DNA damage repair. Subsequently, repair proteins of DNA damage are recruited, including high molecular weight protein kinases such as DNA-PKcs, ATM, ATR and DNA damage repair complexes are formed. Once DNA damage repair is completed, chromatin undergoes reshaping and returns to its normal state[27].

As a branch of genetics, epigenetics refers to the heritable gene expression changes caused by external modification without changing the DNA sequence. The main mechanisms involved in epigenetics are well documented[57]. Key epigenetic mechanisms include DNA methylation, non-coding RNA, histone post-translational modifications (PTMs), and chromatin remodeling complexes[58]. In the context of cancer treatment, ionizing radiation administered during radiotherapy mainly targets nuclear DNA and histones within tumor cells. The direct interaction of ionizing radiation with nuclear DNA leads to abnormal modifications that significantly impact radiosensitivity of tumor[59-61]. Epigenetic reprogramming may regulate the function of pathways associated with complex disorders and contribute to response in the progression of the whole tumor in cancer treatment[62,63].

In recent years, increasing evidence has shown that the dynamic changes of chromatin structure mediated by histone PTMs have great influences on the efficiency with which ROS diffuse within chromatin and approach DNA during the indirect damage caused by low-LET ionizing radiation, which affects the outcome of radiotherap[64,65]. Histones, along with DNA, form the fundamental unit of chromosomes and play a major role in their structure[52].

Histone PTMs edit genetic information that regulates both gene expression and chromosome structure, similar to how DNA base sequences code[66]. Histones, which can be classified into five types as H1, H2A, H2B, H3 and H4, are notably rich in basic amino acids like arginine and lysine. These positively charged amino acids play a crucial role in interacting with the negatively charged phosphate groups within DNA, facilitating the compaction and coiling of DNA to give rise to the chromatin structure[67]. Among the histone types, H1 serves as the linking component of the nucleosome, while H2A, H2B, H3 and H4 are recognized as the core elements of the nucleosome[68]. Notably, histones H3 and H4 feature extended tails emanating from the nucleosome, rendering them more susceptible to undergoing various covalent modifications at distinct sites[69]. These post-translational alterations, such as methylation, acetylation and phosphorylation, exert significant influences on the functionality and interactions of histones[70]. With the development of high sensitivity mass spectrometry technology, various novel histone acylation markers such as malonylation, crotonylation, propionylation and butyrylation have been identified in recent decades[71]. Since most PTMs are reversible, the function of the proteome can be regulated in a cell type-specific manner to diversify gene expression. The diversified modification of the histone amino-terminal expands the genetic code, so it is called the "histone code"[72].

Histone PTMs are reported to be associated closely with radiotherapy[73]. Although radiotherapy has detrimental effects on the structure and function of diverse organelles, biofilms, and biomolecules[74−77], extensive and compelling evidence substantiates the notion that genome DNA is the paramount damage target of ionizing radiation and the DDR is crucial for cell survival[78]. In the short term, DNA damage leads to extensive changes in abnormal gene transcription and protein modification during and after translation, particularly in the modification of DNA damage repair-related proteins[79,80]. In cancer treatment, it triggers tumor cell apoptosis and exerts prolonged effects on cancer cell

migration, invasion, and proliferation. The genome DNA of eukaryotic cells is enveloped by histones and localized within the nucleus to be a part of assembly nucleosome[81]. Additionally, histone H1 acts as a linker histone contributing to the stability of DNA between nucleosomes, although it is not a component of nucleosomes[82]. Nucleosomes concatenate to form beaded filaments of chromatin, which could be further condensed/compressed chromosomes during mitosis[83]. As the carrier of DNA, the spatial structure of chromatin/chromosome has a highly controllable regularity and regulates DNA-related biological processes. PTMs occurring on histone tails have the potential to induce substantial alterations in chromatin structure. These modifications influence the efficacy of interactions between physical or chemical agents that cause DNA damage, as well as regulate the recruitment or inhibition of chromatin-associated proteins, such as transcription factors, enzymes, and DNA damage repair proteins. Moreover, PTMs impact the formation, distribution and repair of DNA damage resulting from exposure to ionizing radiation[84].

Histone PTMs studies have undergone a complex journey of discovery and development over the past century. The initial discovery of histones within acidic extracts of red blood cells in 1884 marked the first step in this process. However, progress in understanding histone-modifying enzymes remained stagnant for nearly eight decades. It was not until 1964 that Phillips successfully demonstrated the presence of acetyl groups in histones isolated from calf thymus, proving their existence (Fig. 1)[85]. Subsequently, in 1974, R. Schekman accurately predicted the structure of the nucleosome, the fundamental unit of chromatin, elucidating the assembly of DNA and histones in the initial stage (Fig. 1)[86]. The year 1979 heralded the discovery that H1, a histone variant, undergoes phosphorylation[87]. Moving forward, in 1984, Mond provided a resolution of 7 nm for the nucleosome structure, laying the groundwork for understanding the functional roles of histones (Fig. 1). The study on *Saccharomyces cerevisiae* revealed the involvement of the N-terminal tail of histone proteins in gene expression regulation and the formation of heterochromatin in 1988[88]. The significance of histone modifications in gene activation was highlighted when histone deacetylases were discovered in 1996, demonstrating the reversible nature of histone PTMs (Fig. 1). Succeeding this, C. D. Alis discovery in the same year that histone acyltransferase A (HATA) from Tetrahymena shares homology with the transcription activator Gcn5 in yeast emphasized the enzymes histone transferase activity, directly linking histone PTMs to gene activation for the first time (Fig. 1). In 2001, T. Jenuwein and C. D. Alis proposed the concept of the "histone code" suggesting that an array of histone modifications constitutes an inheritable regulatory mechanism, extending the regulatory capacity of the DNA genetic code (Fig. 1)[89]. Furthermore, HADCi was first used in the study of radiosensitivity of human colon carcinoma in 2001, marking a significant milestone in the exploration of histone modifications (Fig. 1)[90]. FDA approved the HDAC inhibitor vorinostat for the treatment of advanced primary cutaneous T cell lymphoma[91]. We summarized the major milestone breakthroughs in histone PTMs over time (Fig. 1). Histone function after PTMs as part of the chromatin toolbox comprising chromatin modifying enzymes, chromatin remodelers, and histone PTM reader, which through their concerted action function to assist in numerous biological processes[92].

3. Histone PTMs and their modification enzymes

Histone modification enzymes consist of numerous families. More than eight types of histone modifications have been identified, including acetylation, methylation, phosphorylation, ubiquitination, SUMOylation, biotinylation, ADP-ribosylation, citrullination, proline isomerization and lactylation[93–100]. The most well-studied modifications are acetylation, methylation, phosphorylation, and ubiquitination, which can be reversed by specific families of histone modification enzymes[101]. Aberrant expression of histone-modifying enzymes plays an important role in cancer. Furthermore, diverse histone modification sites exert distinct regulatory roles in cancer progression. A comprehensive characterization of structurally and functionally diverse histone modification sites was described in Fig. 2.

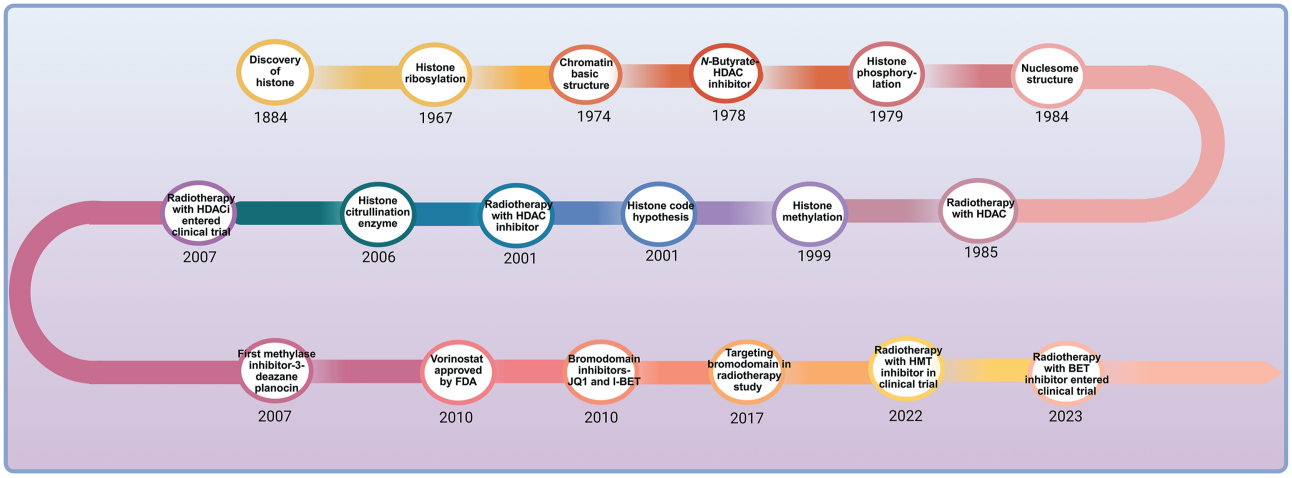


Figure 1 Evolution of combination of targeting histone modification and radiotherapy and remaining challenges. This comprehensive timeline encapsulates the seminal advancements that have propelled the pursuit of histone modification as a strategic frontier in anticancer therapeutics. It delineates the historical milestones in the combination of epigenetic regulation with radiotherapy, signifying a paradigm shift in cancer treatment. HDAC, histone deacetylase; BET, bromodomain and extra terminal domain; PTM, posttranslational modification; HMT, histone methyltransferase.

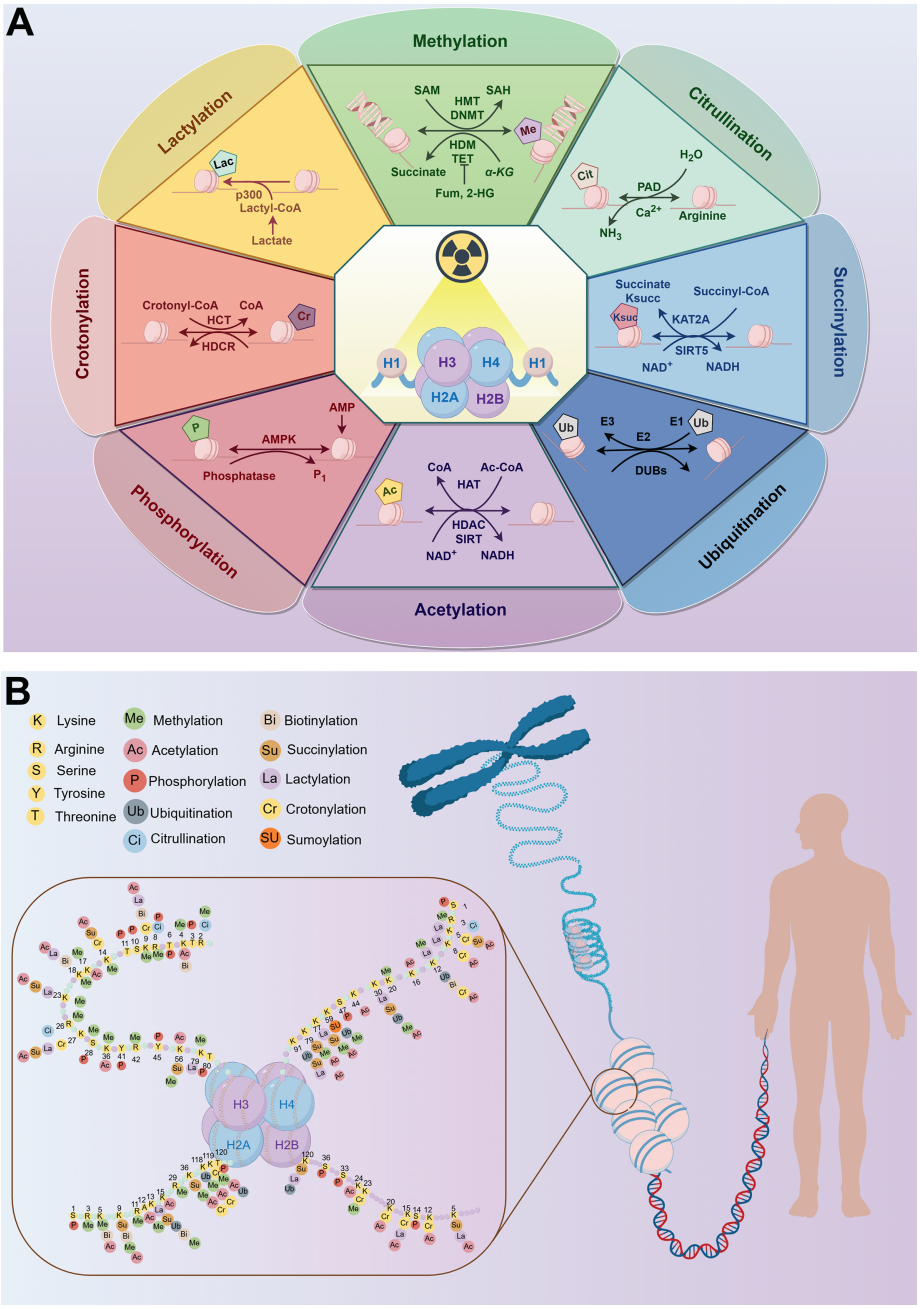


Figure 2 Overview of histone modifications and modification sites. (A) Major histone modification types: This panel illustrates the eight most common types of histone modifications that play a pivotal role in regulating chromatin structure and gene expression. The figure highlights the diversity of post-translational modifications that can occur on histones, influencing various cellular processes including DNA repair and response to radiation. (B) Common histone modification sites: This schematic represents the primary sites on histone proteins where modifications are known to occur. The diagram details the specific amino acid residues on the histone tails that are subject to post-translational modifications, emphasizing the importance of these sites in mediating the cellular response to radiation, as they can alter chromatin accessibility and the recruitment of DNA repair machinery.

3.1. Acetylation and deacetylation

The main type of histone PTMs involved in regulating transcriptional activity, chromatin structure, and DNA damage repair is the N-terminal acetylation of histone lysine residues[102]. Acetylation of the lysine residue adds an acetyl group ($-COCH_3$) to create a negatively charged site on the histone. The resulting negative charges repel the negatively charged DNA, causing chromatin structure to loosen and form an open chromatin conformation that is highly accessible[103]. Histone acetylation has various functions

and is regulated by two competing enzyme families: histone lysine acetyltransferases (KATs), which add acetyl groups, and histone deacetylases (HDACs), which remove them[104].

The KATs family is divided into two main types, types A and B. Type A KATs are primarily located in the nucleus and can be further subdivided into three major families: the GCN5-related *N*-acetyltransferases family (GNAT) superfamily, the MYST family, and the CBP/p300 family. On the other hand, Type B KATs are mainly present in the cytoplasm and modify free histones[105]. Numerous KATs are part of large transcriptional activation complexes and are recruited to specific DNA regions when activators or transcription factors interact with *cis*-acting elements. These KATs modify histones through acetylation, resulting in a locally open chromatin conformation that activates the expression of specific genes. A host of KATs are found to be associated with tumorigenic transformation[106]. KATs are also transcriptional cofactors of several tumor suppressor genes, such as KAT3A/B (CBP/p300), which regulate the acetylation of p53[107].

The HDACs family comprises 18 enzymes that remove acetyl groups from lysine and restore the positive charge of histone side chains. Overexpression of HDACs is observed in multiple tumor types, which results in a significant reduction in histone acetylation levels and silencing of tumor suppressor gene expression. The HDAC family can be divided into four main classes[108], based on sequence homology to yeast. Class I Rpd3-like enzymes are comprised of HDAC1, 2, 3 and 8. Class IIHda1-like enzymes are further divided into two subclasses: IIa (HDAC4, 5, 6, 7 and 9) and IIb (HDAC6 and 10). Class III Sir2-like enzymes consist of seven sirtuins, which are NAD-dependent protein deacetylases and/or ADP ribosylase[109]. Class IV contains only HDAC11, which shares sequence similarity to both class I and II proteins[110]. Aberrant expression of HDACs is associated with various malignant tumors, including solid and hematological malignancies. In most cases, high levels of HDAC are correlated with advanced disease and poor outcomes for patients. For instance, high expression of HDAC1, 2 and 3 is associated with poor prognosis in gastric and ovarian cancers. Furthermore, overexpression of HDAC8 is correlated with late-stage diseases and a low survival rate in neuroblastomas. Widespread dysregulation of HDAC has also been observed in multiple myeloma. Overexpression of Class I HDACs, particularly HDAC1, is specifically linked to a worse prognosis[111]. Dysregulation of HDACs may suppress tumor-suppressor genes and promote tumorigenesis. Therefore, HDAC inhibitors are being studied as potential drugs to inhibit *in vivo* tumor growth[112]. Recent studies have shown that HDAC inhibitors are closely related to tumor radiosensitivity. Inhibiting HDAC may increase cancer cells' radiosensitivity by suppressing DNA repair. MS-275 and its effect on the radiosensitivity of prostate cancer have been revealed and the addition of the HDAC inhibitor MS-275 before or after irradiation did not lead to an increase in mitotic phase cells or apoptosis. This suggests that MS-275 enhances the radiosensitivity of prostate cancer by affecting DNA damage repair[113]. Furthermore, the HDAC inhibitor trichostatin A (TSA) has also been shown to enhance the radiosensitivity of prostate cancer by affecting DSB repair[114].

3.2. *Methylation and demethylation*

Histone methylation primarily occurs on the arginine (Arg/R) and lysine (Lys/K) residues of H3 and H4. This process is catalyzed by histone methyltransferases, which transfer a methyl group from *S*-adenosylmethionine (SAM) to histones[115]. These arginine and lysine residues could be mono-methylated, with lysine residues also capable of trimethylation. To date, six lysine residues in histone H3 and H4, namely H3K4, K9, K27, K36, K79 and H4K20 (Fig. 2) have been found to be methylated[116]. The physiological and pathological functions of histone methylation at lysine or arginine residues have been extensively studied and documented[117]. In humans, more than 60 members of histone methyltransferases (HMTs) have been identified. These HMTs primarily consist of histone lysine methyltransferases (HKMTs) and protein/histone arginine methyltransferases (PRMTs)[118]. Correspondingly, there are also histone demethylases being identified, such as lysine-specific histone demethylase 1A (KDM1A), lysine-specific demethylase 1 (LSD1), lysine demethylase 2A (KDM2A), jumonji histone demethylase 1A (JHDM1A), and F-box and leucine-rich repeat protein 11 (FBXL11). Histone methylation is mainly regulated by these two types of counterpart enzymes[35].

The HKMT family members include enhancer of zeste homolog 2 (EZH2), euchromatin histone−lysine *N*-methyltransferase 2 (G9a), histone−lysine DOT1-like (DOT1L) and set domain containing 2 (SETD2) and are involved in tumorigenesis and tumor progression[117]. In cancer cells, there is an overall change in histone methylation, and one of the main explanations is that changes in metabolic enzymes lead to the production of cancer metabolites and impair the function of iron-dependent dioxygenases that regulate histone demethylation[118]. Representative changes associated with histone methylation include widespread abnormal increases and losses of H3K27me3. Abnormal changes in histone methylation also result in changes in the expression of some important genes. For example, EZH2 mediates the silencing of anti-metastasis genes (including tissue inhibitors of metalloproteinase and E-cadherin), which promote cell diffusion and anchoring-independent growth[119]. In addition, EZH2 enhances tumor angiogenesis, and its inhibition has been shown to suppress the differentiation of cancer stem cells into endothelial cells. The overexpression of EZH2 in endothelial cells has been shown to depend on paracrine VEGF stimulation and promote angiogenesis by promoting H3K27 trimethylation on the promoter of the vasohibin 1 (*VASH1*) gene. siRNA-mediated EZH2 silencing leads only to mild tumor suppression. In contrast, targeting of mouse EZH2 to the tumor vascular system rather than tumor cells has a stronger inhibitory effect on tumor growth[120]. G9a is a histone methyltransferase that could methylate lysine residues at positions 9 and 27 of histone H3, leading to transcriptional repression. The role of G9a in cancer has been well established. It is upregulated in response to hypoxia and acts as a promoter of tumorigenesis by silencing tumor suppressor genes. Recent studies have shown that G9a is essential for maintaining cancer cell proliferation and survival[121]. Knockdown of *G9a* in liver cancer cells leads to reduced cell growth and sphere formation. In addition, there is increasing evidence suggesting that G9a may also be necessary for driving tumor angiogenesis[122,123]. Histone demethylase JHDM1D is a member of the jumonji histone demethylase family (also known as KDM7A), and its function is comparable to that of HMT EZH2. Interventions targeting either of the enzymes lead to H3K9/H3K27 demethylation and activation of anti-angiogenic gene transcription. JHDM1D specifically demethylates the inhibitory marks of mono-methylation of histone H3K9 and H3K27, countering the epigenetic gene regulation of HMTs. Overexpression of JHDM1D in nutrient-deprived tumor cells displays anti-tumor effects by regulating angiogenesis. Overexpression of JHDM1D in tumor cell xenografts leads to a decrease in pro-

angiogenic factors (including VEGF-B and vasohibin), thereby inhibiting tumor growth[124].

Histone methylation, regulated by radiation-sensitive histone methyltransferases (HMTs) and histone demethylases (HDMs), affects DNA damage repair by recruiting DNA repair-associated proteins, regulating the expression of DNA repair genes, and mediating dynamic chromatin changes[125] (Fig. 2). Some studies have shown that H3K4 demethylation occurs during NHEJ and HR repair processes[126]. KDM5B is a member of the histone demethylase family that can recruit Ku70 and BRCA1 to promote NHEJ and HR repair. Some small molecule inhibitors of KDM5B can increase the accumulation of γH2AX after radiotherapy, thereby increasing the radiosensitivity of breast cancer cells[127]. In addition, in lung cancer cells, inhibition of KDM5B by JIB-04 inhibits DNA damage repair, making lung cancer cells more sensitive to radiation[128].

3.3. *Phosphorylation and dephosphorylation*

Histone phosphorylation could occur at serine, threonine, and tyrosine residues, mediated by protein kinases. In comparison to the relatively stable methylation modification, phosphorylation is a transient, inducible, or pathway-specific modification[129]. Therefore, it is closely associated with many dynamic processes such as DNA damage response and chromosome segregation. The phosphorylation of histones is mainly mediated by protein kinases. There are five major classes of protein kinases responsible for histone phosphorylation, including the AGC group, CaMK group, CMGC group, classical PTK group and other groups such as receptor-like protein kinases (RLKs) and ethylene signaling transduction elements (CTRL)[130]. The primary sites of histone phosphorylation include H3T3, H3T6, H3S10, H3T11 and H3S28[131] (Fig. 2). Histone phosphorylation at H3S10 (H3S10ph) is closely linked to cancer progression. An increase in H3S10ph expression has been observed in various types of cancer, such as invasive breast cancer, oral[35], squamous cell carcinoma[132], gastric carcinoma[133,134], spongioblastoma[135], melanoma[133], and nasopharyngeal cancer. Increased abundance of H3S10ph has been observed in several types of cancer, and it is associated with poorer prognosis as the abundance of H3S10ph increases. Many H3S10 kinases, including MSK1/2, PIM1, CDK8 and AURORA kinase, have long been regarded as targets for cancer therapy[136]. These kinases regulate signal pathways and transcription factor activity to influence gene expression. Aberrant kinase activity can cause significant changes in chromatin structure[137].

As an important factor for radiosensitivity, DNA damage repair is regulated by histone phosphorylation. Histone H2AX phosphorylation is a marker for DNA damage. Checkpoint kinase 1 (CHK1) is a kinase responsible for phosphorylation of H3S57, and overexpression or inhibition of H3S57 phosphorylation shows opposite effects on replication stress recovery rate, the binding of 53BP1 to chromatin, and dependence on RAD52[138]. These findings suggest that dynamic phosphorylation of H3S57 is necessary for DNA repair and recovery from replication stress[139]. Therefore, phosphorylation of H3S57 may be a potential target for modulating radiosensitivity.

3.4. *Ubiquitination and SUMOlylation*

As mentioned before, methylation, acetylation and phosphorylation modifications add small chemical groups to histones. In contrast, ubiquitination covalently attaches a larger 76-amino acid ubiquitin molecule to histone[140]. The process of ubiquitination begins with the activation of ubiquitin by ubiquitin-activating enzymes (E1s), which transfer the activated ubiquitin to ubiquitin-conjugating enzymes (E2s). Finally, ubiquitin is transferred from E2 to the substrate by ubiquitin ligases (E3s)[35]. As for the functional side, Ubiquitination alters the interaction between histones and DNA, thereby changing the chromatin structure from an open (euchromatin) to a closed (heterochromatin) state[141]. This modification plays a critical role in gene expression regulation by modulating the affinity of transcription factors for structural gene promoters[142]. Ubiquitination is classified into monoubiquitination (mono-ubiquitination) and poly-ubiquitination (ubiquitin chain) based on the number of ubiquitin molecules attached to a lysine residue in a protein[143]. Poly-ubiquitination could further be classified into different types depending on the lysine linkage between ubiquitin molecules, including K6, K11, K27, K29, K33, K48, K63 and K119 linkages[144]. The most common ubiquitination site is K119 in H2A[144] (Fig. 2). The level of H2AK119ub1 is generally decreased in prostate cancer patients, while the level of H2BK120ub1 is frequently reduced in tissues of breast cancer, lung cancer, and colorectal cancer compared to normal tissues[145,146]. In addition, DNA and RNA sequencing data have shown that genes encoding for E3 ubiquitin ligases and DUBs are frequently altered in cancer cells[147].

Ubiquitination plays a critical role in the radiosensitivity of tumors. Exposure to ionizing radiation induces a significant upregulation of H2BK120ub1, highlighting its functional role in mediating DSB repair[148]. In addition, H2AK119ub1 is involved in DNA damage repair, as it is monoubiquitinated at K119 by BMI1 in response to DSBs[149]. When DNA damage occurs, RING finger protein 168 (RNF168), an E3 ligase, will be recruited to the damaged chromatin site. Meanwhile, the UDR motif of 53BP1 directly interacts with RNF168-catalyzed mono-ubiquitination of H2AK15, thereby facilitating the protein's accumulation at DSB sites[7]. RNF168-catalyzed mono-ubiquitination of H2A(X) at K13/K15 residues enhances NHEJ activity while inhibiting HR efficiency, likely by targeting 53BP1 to DSBs to suppress DNA end resection processes[150]. At the same time, USP44 inhibits RNF8/RNF168-mediated histone ubiquitination at DSBs and targets these lesions in an RNF168-dependent manner. Overexpression of USP44 suppresses 53BP1 recruitment to damaged chromatin, suggesting its role in modulating the DNA damage response pathway[151]. Deubiquitination of H2BK120ub1 by USP22 is critical for efficient DSB repair *via* both the NHEJ and HR pathways[152]. These findings suggest that dynamic regulation of histone ubiquitination is critical for efficient DSB repair.

The small ubiquitin-like modifier (SUMO) represents an evolutionarily conserved post-translational modification system universally present in eukaryotes. Five SUMO isoforms (SUMO-1, -2, -3, -4, and 5) are expressed in humans, each exhibiting distinct expression patterns and functional specificities[153]. Primary SUMOylation of human histone H4, as well as weak SUMOylation signals from H2A, H2B, and H3, were first observed in 2003, and subsequent studies identified SUMOylation at K12 of H4 (13) and K18 of H3[154] (Fig. 2). The SUMOylation pathway proceeds through three enzymatic steps. Initially, the C-terminal region of SUMO is activated by the heterodimeric E1 enzyme complex (SAE1/SAE2 in humans, corresponding to Aos1/Uba2 in *Saccharomyces cerevisiae*). Subsequently, the activated SUMO is transferred to the catalytic cysteine residue of the E2 conjugating enzyme Ubc9. Finally, SUMO E3 ligases facilitate the transfer of SUMO from Ubc9 to lysine residues on substrate

proteins, determining both the efficiency and specificity of SUMO conjugation[155].

In vitro reconstitution of nucleosomes using SUMO-modified H4 revealed diminished structural stability and an inability to form dinucleosomes, implicating H4K12 SUMOylation in disrupting inter-nucleosomal interactions and thereby impeding chromatin condensation. Furthermore, the ATP-dependent chromatin remodeler RSC complex exhibits enhanced binding affinity toward SUMOylated histones, as demonstrated by studies[156], underscoring SUMOylation's role in modulating nucleosome positioning and chromatin architecture. Notably, during DSB repair, SUMOylation of H2A.Z at persistent DSB sites is critical for tethering damaged chromatin to the nuclear periphery. This process involves Rad52, a known SUMO substrate, which likely facilitates homologous recombination by coordinating with SUMOylated chromatin components. Collectively, these findings highlight histone SUMOylation as a pivotal regulatory mechanism governing chromatin dynamics and radiosensitivity[157].

3.5. Other histone modifications and modifying enzymes

The peptidyl−arginine deiminase (PAD) family, consisting of five isoenzymes (PAD1−4 and PAD6), is primarily responsible for the catalysis of citrullination. This process involves the conversion of arginine residues in the protein peptide chain to citrulline residues through the action of protein arginine deiminase[158]. Under physiological conditions, the activity of PAD enzymes is typically low. However, under pathological conditions, PAD enzymes can become more active, leading to the citrullination of various structural proteins, including histones such as H1, H2A, H3 and H4. Specifically, PAD4-mediated citrullination has been observed to significantly impact chromatin structure by promoting chromatin decondensation and DNA fragmentation. This process is closely regulated, as the removal of the positive charge through citrullination of histone tails is known to be associated with the decondensation of chromatin[159]. Citrulline is considered a marker in radiation-induced intestinal injury, and its inhibition may be associated with specific genes. The interaction between PAD4 and p53, in conjunction with HDAC1-mediated histone deacetylation of estrogen-regulated genes, was recently reported. In the context of apoptosis, the total cellular localization indicates the involvement of PAD4−p53 complexes, and the apoptosis resistance observed in PAD4 knockout mice suggests their significant impact on radiosensitivity[160]. Furthermore, a PAD4 inhibitor promotes radiosensitivity of nasopharyngeal carcinoma cells[161]. A recent study in lymphatic hematopoietic tissue revealed the role of all-trans retinoic acid (ATRA) in inducing the leukemia cell differentiation process of HL-60, with a specific focus on PAD4 expression. The findings highlighted the pivotal role of PAD4 in promoting the differentiation of HL-60 cells into granulocytes by stimulating the expression of hematopoietic transcription factors, such as Sox4 and purine rich box-1 (PU.1), through histone citrullination to affect the progression of leukemia[162]. The impact of PAD inhibitors on cancer radiosensitivity remains to be fully elucidated[163,164].

ADP-ribosylation is a reversible post-translational protein modification that transfers one ADP-ribose moiety from NAD^+ to specific amino acid residues of substrate proteins by releasing nicotinamide[165]. All core histones and the linker histone H1 can be ADP-ribosylated. Poly ADP-ribose polymerase (PARP) is an enzyme known for its involvement in responding to environmental stress-induced DNA damage[166]. Upon activation, PARP1 catalyzes the attachment of ADP-ribose moieties to histone proteins' amino terminal tails, particularly at H2AK13, H2BK30, H3K27, H3K37 and H4K16 (Fig. 2). PTMs are anticipated to induce chromatin condensation and facilitate the recruitment of DNA repair mechanisms to the damaged sites[167]. The observed histone ADP-ribosylation and detection of PARP1 during DNA repair have prompted the utilization of PARP1 inhibitors in the management of breast and ovarian cancers. Cancer cells develop a dependence on PARP1-dependent DNA repair pathways, which makes them vulnerable to the effects of PARP1 inhibitors[168]. Consequently, the use of PARP1 inhibitors in BRCA mutant cancers leads to tumor cell death and enhances radiosensitivity. In cervical cancer, PARP1 levels are significantly associated with a radioresistant phenotype[169].

4. Histone PTMs and cancer radiosensitivity

Cancer pathogenesis is closely linked to abnormal reprogramming of histone modifications, which contributes to malignant progression[170,171]. Abnormal reprogramming of histone modifications plays a crucial role in the pathogenesis of cancer, particularly in its malignant progression (Table 1[132,172-203]). Various factors, such as chromatin accessibility, key gene expression, DNA damage repair-related protein recruitment, and complex maintenance, have a substantial impact on the resistance of tumors to radiotherapy and chemotherapy[204]. These factors are regulated by the expression and activity of abnormal histone modification enzymes, as well as abnormal histone post-translational modification. It is noteworthy that human cancers often exhibit commonalities in the abnormalities of histone modification enzyme expression and activity, highlighting the significance of these aberrations in cancer development[205], which is the theoretical basis for targeting histone modification to overcome radiotherapy resistance[206]. Low levels or absence of histone H4K16ac and H4K20me3 were evident in leukemia, breast cancer, lung cancer, and colon cancer cell lines. This finding was validated through comparisons of normal and primary tumor tissues during cancer progression. Therefore, the absence of H4K16ac and H4K20me3 is considered a common hallmark of human cancer[207], which was further validated in subsequent studies of breast and liver cancers[208,209]. The upregulation of the histone lysine-specific demethylase (LSD1) is a common occurrence in many human tumor cells, including acute myeloid leukemia[210], breast cancer[211,212], lung cancer[213], colon cancer[214], prostate cancer[215] and oral squamous cell cancer[216]. Besides, it is considered to be related to dryness, hypoxia, epithelial-mesenchymal transition, and radiotolerance[217,218]. A member of the histone lysine demethylase KDM4 family (KDM4A-D) is also believed to be a driver of cancer and is highly expressed in a variety of tumor cells[219−222]. Furthermore, high expression of KDM4 family members in classical Hodgkin lymphoma and primary liver cancer is associated with radioresistant phenotypes[223,224].

More often, epigenetic modifications, including histone modifications, are highly heterogeneous in tumor tissues and cells. The heterogeneity may be different according to cancer types, patients, diseased regions, and even classified by a single cell of the cancer tissue. The phenomena are defined as inter-patient, intra-tumor, inter-metastatic, and intra-metastatic heterogeneities[27,225]. HDAC1 is

Table 1 Histone modification landscape in cancers.

Cancer	Histone PTMs alteration	Mechanism	Ref.
Colorectal cancer	HDAC2↑	Upregulated the levels of c-Fos and c-Jun.	172
	KDM4A↑		173
	KDM4B↑		174
	USP4↑	Reduce the expression of p53 and promote DDR	175
	LSD1↑	Downregulating DKK1 and Wnt/β-catenin pathway	176
	KDM6B↑	Regulate Wnt signalling, interacts with p53 during neural stem cell differentiation and stabilizes p53	177
Melanoma	JMJD3↓	Upregulate the epithelial-to-mesenchymal transition	178
	KDM2A		173
Lung cancer	HDAC4↑	Leading to sensitization to apoptosis	179
	MLL2↓	Highly enriched in DNA damage repair, NF-κB pathway, JAK/STAT signaling and chromatin modification	180
	G9a↑	Reduce cell proliferation	181
	EZH2↑	Progression and metastasis of lung cancer.	182
	SMYD2↑	Represses p53 function	183
	SETD8/PRSET7↑	Deregulate PCNA expression	184
	PRMTs↑	Promote EMT	185
	USP7↑	Stabilizes CHK1 and β-catenin through its DUB activity and promotes DDR	186−188
	KDM2A↑		
	LSD1↑	Chromatin remodeling	189
Cervical cancer	HDAC10↑	Regulates DNA mismatch repair	190
	RNF8↑	Promote the accumulation of p53-binding protein 1 (53BP1) and breast cancer type 1 susceptibility protein (BRCA1) at dsbs	191
Breast cancer	LSD1 ↓	Regulate several TGFβ1 signaling pathway that are critically involved in cell proliferation, survival, and epithelial-to-mesenchymal transition	192
	USP51↑	Interact with and stabilize digeorge syndrome critical region 8 and promote the recruitment of DGCR8 and its partner RNF168 at dsbs	193
	MLL1	Promote proliferation	194
	MLL2	Upregulate c-Myc	195
	G9a	Repress FBP1 to promote cancer stem cell	196
	EZH2	Repress CDKN1B to promote proliferation	197
Prostate cancer	LSD1↑	Activate AR-mediated growth signals	198
bladder carcinomas	EZH2↑	Inhibit cell proliferation	199
neuroblastoma	LSD1↑	Chromatin remodeling	189
	LSD1↑	Promote AR-dependent transcription	200
	USP1↑	Deubiquitinating and stabilizing inhibitor of DNA binding 1 (ID1) and CHK1 to promote DDR	201
	KDM3c↓		173
	USP3↑	Activating the ATR−CHK1 signaling pathways and leading to the enhancement of DDR	202
	Jak2↑	DNA repair structure, transcription and chromatin compaction	132
Acute myeloid leukemia	KDM2b↑	Promote Hoxa9/Meis1-induced.leukeinic·transformation	203

reported to be expressed in a significant proportion of cancers such as gastric cancer, prostate cancer, lung cancer, breast cancer, and colon cancer. However, colorectal cancer, gastric cancer, and cervical cancer are predominantly associated with HDAC2[114,226]. Furthermore, colon and breast cancers exhibit high levels of HDAC3 expression, while neuroblastoma cells are characterized by the abundant presence of HDAC8[227]. High expression of EZH2 is a characteristic feature of several solid cancers, including prostate cancer, melanoma, endometrial cancer, breast cancer, esophageal cancer, gastric cancer, anaplastic thyroid cancer, and nasopharyngeal cancer[228,229]. Mutations of amino acid residues in histones may lead to abnormal gene regulation of cells and transformation into cancer cells, in addition to altered expression levels of histone modification enzymes and abnormal histone modification[228]. Specifically, mutations in H3K27, G34 and K36 residues, located at or near histone modification sites, have been well studied and are associated with the development and progression of brain tumors, chondroblastoma, and squamous cell carcinomas of the head and neck[230−233]. During clinical examination, such as needle biopsy, analyzing the expression of histone modification enzymes and the histone modification landscape in patient tumor tissue forms the basis for the targeted use of epigenetic drugs.

4.1. Breast cancer

Radiotherapy stands as a cornerstone treatment for breast cancer, and histone PTMs dysregulation plays a core role in the radioresistance of breast cancer. Yet the attainment of intrinsic or adaptive radiotolerance by certain molecular subtypes of breast cancer cells, or its gradual acquisition during treatment, poses a

substantial barrier towards the realization of optimal efficacy and prognosis of the therapy. Hence, there exists a critical need to comprehend the underlying causes of radioresistance in breast cancer, and institute appropriate measures to bolster the effect of radiotherapy while concurrently thwarting cancer recurrence and metastasis[234]. Numerous studies have demonstrated that abnormal histone modification plays a crucial role in the development of breast cancer, its aggressive behavior, resistance to radiotherapy and chemotherapy, and poor prognosis[32,34,235,236,237,238,239,240,241,242,243]. It has been suggested that breast cancer cells develop radiotolerance due to imbalanced expression of KATs and HDACs. The high expression of HDACs and low expression of KATs result in global histone deacetylation (H3K9ac, H3K9AC and KATS), leading to histone hypoacetylation and an overall condensed chromatin state. Furthermore, the study assessed HDAC activity in 38 tumor samples, indicating that breast cancer tumors generally exhibited higher levels of HDACs compared to normal breast tissue. Interestingly, this study revealed that tumors of the same histopathological type exhibited variable HDAC activity, emphasizing the heterogeneous nature of breast cancer tissues even within a relatively small sample size[32]. Additionally, low levels or absence of H3K9ac may indicate a shift in histone modification of H3K9 from acetylation to methylation, leading to radioresistance. Studies have demonstrated significantly increased levels of H3K9me2 and H3K9me3 in MCF-7 cells compared to HeLa cells after 2 and 5 Gy γ-ray irradiation, reflecting the high resistance of MCF-7 cells to radiation[244]. Immunohistochemical tests were conducted on histone modifications in tumor tissues obtained from 880 patients with diverse forms of breast cancer. In their examination of 606 invasive breast cancer samples, a low or absent expression of H4K16ac was observed in 78.9 percent of cases. The study found a positive correlation between low levels of H4K16ac and the presence of positive vascular invasion as well as larger tumor size[242]. The study revealed that high expression of H4K20me3 was present in 69.8% of more invasive breast cancers. Conversely, low H4K20me3 expression is associated with a poor prognosis and increased aggressiveness of breast cancer, consistent with previous results[207]. In addition, an upregulation of lysine acetyltransferase 7 (KAT7) was observed in multiple breast cancer cell lines. This up-regulation was found to enhance the PI3K/AKT signaling pathway and confer radiotolerance by activating the transcription of PIK3CA. Furthermore, the acetyltransferase activity of KAT7 was found to play a pivotal role in the radioresistance of breast cancer[239].

It has been shown that in invasive ductal carcinoma, the upregulation of long non-coding RNA (lncRNA) HOTAIR promotes the expression of DNA damage repair factors KU70, KU80, DNA-PKS and ATM, thereby inducing radiation resistance. Additionally, they found that HOTAIR triggers the synthesis of lysine methyltransferase 6 (KMT6) and recruits the promoter of KMT6 to the cancer driver gene Myc, potentially through a non-catalytic dependent pathway, thus playing a pivotal role in the induction of radiation resistance[126]. This process involves histone modifications and histone modification enzymes, with long non-coding RNAs (lncRNA) and KMT6 being identified as key players in the development of radiological resistance in breast cancer[245]. The regulatory relationship between HOTAIR and KMT6 has been shown in tumors, including GBM[246,247]. lncRNA *DUXAP8* expression was found to be up-regulated in radioresistant breast cancer tissues, and its high expression predicts poor clinical outcomes in breast cancer patients. lncRNA *DUXAP8* promotes the binding of KMT6 to the promoter region of *E-cadherin* and *RHOB*, resulting in the silencing of the target genes and inducing the radioresistant phenotype of breast cancer cells[248].

4.2. Brain tumors

Radioresistance is an intrinsic feature of brain tumors, particularly for glioma stem cells (GSCs). Recent studies have highlighted the significant role of abnormal histone modifications in this context[249,250]. Due to the complexity of brain structure, the existence of the blood−brain barrier, and the invasion of tumors, it is difficult to achieve the ideal curative effect by surgery and chemotherapy. Therefore, developed radiotherapy techniques such as stereotactic radiotherapy, image-guided radiotherapy, and intensity-modulated radiotherapy are now regarded as important options for the treatment of brain tumors, and radiotherapy is often combined with chemotherapy to prevent tumor recurrence after surgical resection[251]. However, the radiation resistance of tumor cells driven by abnormal histone PTMs and mutation of histone amino acid residues remains an important cause of treatment failure and recurrence of brain tumors[252−256]. A subgroup of pediatric high-grade gliomas (pHGG) is characterized by lysine to methionine mutation at position 27 of histone H3 (H3K27M mutation), which drives the global loss of histone H3K27me2 and H3K27me and was defined as Histone 3 K27M-mutated diffuse midline gliomas (DMGs) by WHO[249]. The DMGs account for about 80% of the diffuse pontine glioma[257]. Amended in 2021, the WHO named it diffuse midline glioma H3K2-altered because concurrent mutations always occur when H3K27M mutates. Mutations in genes such as *TP53* and *PIK3CA* are present in (diffuse intrinsic pontine glioma) DIPG with lysine at position 27 of histone variant H3.3 mutated to methionine (H3.3-K27M)[250]. Besides, gliomas with the variant are prone to being radioresistant[253,258]. Several studies reported that TP53 mutation induced radiation resistance in DIPG of H3.3-K27M[259]. H3K27M mutations of glioma can produce violent reactions to radiotherapy, but in the end, they show a high propensity for leptomeningeal and subependymal spread[260].

In glioblastoma (GBM), another common high-grade glioma, the increased expression of KMT6 has been confirmed to be closely related to the malignant degree and invasive potential of the tumor[261,262]. Unlike the overall loss of H3K27me3 in DMGs or DIPGs, high KMT may indicate high levels of H3K27me3 in GBM. S.H. Kim found that KMT6 is regulated by the upstream MELK/FOXM1 pathways, to protect GSCs from radiation-induced cell death[263]. Similar to the situation described above in breast cancer, high expression of KMT6 may induce overexpression of oncogenes such as *Myc*, resulting in the enhancement of GBM radiotolerance[245,264]. HDACs, such as HDAC4[265,266] and HDAC6[267,268], have been proven to be essential in the development, progression, and redioresistance of GBM. Data from the public TCGA database indicate that HDAC 1, 2, 3 and 7 expression is increased in GBM and positively correlated with their malignant degree[269]. Studies showed that the high expression rate of HDAC4 and HDAC6 was 70.9% in 31 patients with primary GBM receiving temozolomide combined with radiotherapy. Consequently, the high expression of HDAC4 and HDAC6 was positively correlated with the poor prognosis of patients. The results of cell culture experiments indicated that

depletion of HDAC4 or HDAC6 inhibited the radiation tolerance or stemness potential, but had no significant effect on the radiosensitivity of normal neurons[270].

4.3. Lung cancer

Radiotherapy, as a primary treatment for lung cancer, is essential in the management of the disease. The radiotolerance exhibited by lung cancer has been associated with abnormal histone modifications[271]. Specifically, the role of RNF2 (also known as RING1B and RING2), a member of the Ring finger protein family, is noteworthy as it functions as an E3 ubiquitin ligase responsible for the mono-ubiquitination of histone H2A lysine 119 (H2AK119ub). The PRC1 complex, in which RNF2 is present, is associated with various complexes that partake in transcriptional repression. Previous research has demonstrated that the PRC1 complex can be mobilized to the promoter of silenced genes by the PRC2 complex-induced H3K27me3. This recruitment results in the establishment of H2Aub, leading to transcriptional repression. Furthermore, the synergistic action of the PRC1 and PRC2 complexes effectively silences the expression of specific genes[272].

4.4. Liver cancer

Radiotherapy of liver cancer is a kind of important local treatment. The expression of histone lysine demethylase KDM4C (also known as GASC1) was significantly up-regulated in hepatocellular carcinoma cell lines such as HL-7702, HepG2, Hep3B and Huh7, in comparison with normal liver parenchymal cell lines. Moreover, it was found that KDM4C plays a role in promoting cell growth, proliferation and radiotolerance by inhibiting CXCL[224].

4.5. Other cancers

In ovarian cancer, the expression of class I HDACs has been positively correlated with the malignancy of the tumor[273]. In ovarian cancer cells, the expression of HDAC1 and HDAC2 is significantly positively correlated with the expression of Ki-67, which is essential for the proliferation of ovarian cancer cells. The expression of HDAC3 is negatively correlated with the expression of E-cadherin, which can affect the invasion and migration of ovarian cancer cells. As for histone methylation, EZH2 upregulation has been widely established in ovarian cancer. EZH2 expression promotes cell proliferation and invasion, inhibits apoptosis and enhances angiogenesis in epithelial ovarian cancers (EOCs). Knockdown of EZH2 inhibits the growth of EOCs and induces apoptosis and suppresses the invasion of EOC cells[274]. EZH2 inhibits TIMP2 expression *via* H3K27me3, thereby inducing chromatin compaction and transcriptional silencing, which enhances the radiosensitivity of EOCs[275]. The decrease of H3K27me3 globally was inversely associated with the aggressiveness of prostate cancer[276]. The histone deacetylase inhibitor LBH589 is used to modify chromatin structure, making cells more susceptible to radiation damage. Combining LBH589 with radiotherapy is an effective treatment for prostate cancer[277]. Histone deacetylase inhibitors valproic acid and depsipeptide sensitize retinoblastoma cells to radiotherapy by increasing H2AX phosphorylation and p53 acetylation−phosphorylation[278]. HADCis are reported to exert a therapeutic effect on sarcoma cells. Using HADCis to treat sarcomas not only directly induces apoptosis through the extrinsic death receptor pathway and intrinsic mitochondrial pathway, but also enhances the susceptibility of sarcoma cells to apoptosis[279]. HADC induces cell cycle arrest in sarcomas. HDAC1 and 2 directly bind to the promoters of the cell cycle-associated *p21* and negatively regulate its expression[280]. A study has shown that histone deacetylase inhibitor TSA induces G1 cell cycle arrest in osteosarcoma cells *via* the p53-independent activation of *p21* through the specific Sp1 sites in its promoter[281]. In cervical cancer, overexpression of HDAC1 suppresses the radiosensitivity *via* regulating the HIF-1α/VEGF signaling pathway, suggesting that HDAC1 may act as a crucial participant in regulating cervical cancer radiosensitivity[282].

5. Histone PTMs regulate chromatin function

The regulation of chromatin function by histone PTMs occurs primarily in two ways. Firstly, PTMs can alter the charge carried by histones, affecting the interaction between histones and the DNA phosphate backbone, which in turn influences the higher-order structure of chromatin. The primary PTM mediating this process is acetylation modification[283]. Moreover, studies suggest that histone methylation may not change the number of charges carried by lysine. Instead, it impacts chromatin structure[284], with its role dependent on the location and characteristics of the methylation. For example, methylation at H3K4, H3K36, and H3K79 typically associates with high transcriptional euchromatin states[285−287]. whereas methylation at H3K9, H3K27, and H4K20 generally leads to transcriptional repression of heterochromatin[28,288,289]. Secondly, PTMs can block or recruit reader proteins. For instance, acetylation modification can attract proteins containing bromodomains[290,291] while methylation modifications recruit chromodomain proteins[292]. Conversely, phosphorylation of H3S10 can prevent the binding of HP1 to H3K9me3[293], H3K79me, and H4K16ac, repress the interaction between Sir2 protein and nucleosomes[294]. Thus, histone PTMs play a crucial role in gene expression and other cellular processes by regulating the recruitment of various proteins to chromatin.

Beyond the mechanisms previously noted, histones contribute to epigenetic regulation through additional means, including histone variants, ATP-dependent chromatin remodeling complexes, non-coding RNA and DNA methylation. Histone variants are a diverse group of proteins that differ from conventional histones in their amino acid sequence and function. Eukaryotes contain various histone variants, which serve as binding sites for specific modifying enzymes. These enzymes significantly alter chromatin structure and function and play crucial roles in genomic processes such as development, differentiation, transcription and DNA damage repair[295,296].

ATP-dependent chromatin remodeling complexes also contribute to histone-mediated epigenetic regulation. These complexes possess domains capable of identifying PTMs of specific histones. They may be recruited to chromatin to facilitate changes in chromatin structure by sliding nucleosomes, altering the configuration of histone octamers, or replacing H2A−H2B polymers[297−299].

Non-coding RNA and DNA methylation could also contribute to the regulation of epigenetics *via* histone PTMs or HMTs. Non-coding RNAs interact with histones and recruit histone-modifying enzymes to specified genomic regions. DNA methylation inhibits the binding of transcription factors and

hinders histone acetylation, ultimately leading to reduced gene expression[106].

5.1. Histone PTMs regulate chromatin structure

Chromatin state is strongly linked to histone PTMs[66,300,301]. The chromatin of eukaryotic cells is a complex of cellular genomic DNA, histones, non-histones, and a small amount of RNA. Chromatin can be divided into two types, euchromatin and heterochromatin, based on its structure, morphological features, and transcriptional activity state. Euchromatin has a low degree of folding/compaction and is in a stretched state, characterized by high acetylation of histone tails, with high chromatin accessibility and transcriptional activity. Heterochromatin is in a condensed state with a high degree of folding and compression, and its histone tail is characterized by deacetylation, H3K9me3 and H3K27me3 modification, which have lower chromatin accessibility and transcriptional activity[126,302,303,304]. This is only a simple classification to be convenient for statements. The structure of chromatin is far more than "loose" or "condensed". In particular, some scholars have identified many liquid-like domains, other than loose or condensed, and it is believed that condensed chromatin seems to be the default chromatin state in higher eukaryotic cells. But "condensed" liquid-like domains relieve the physical constraints imposed by long strings of interacting nucleosomes, which reflects the complexity of the chromosome structure[305].

To date, a large number of enzymes and protein complexes are involved with changes in chromosomal structure, and are classified into two groups. Firstly, ATP-dependent chromatin remodeling complexes, switch/sucrose non-fermentable (SWI/SNF), imitation of switch (ISWI), chromodomain helicase-DNA binding (CHD) are included which can use the energy generated by ATP hydrolysis to cause chromatin configuration changes or nucleosome sliding. Thereby, DNA biological activity including transcription, replication, repair, and recombination will be altered[298]. One of the essential features of chromatin remodeling complexes is that they contain domains (such as bromodomains) that recognize PTMs of specific histones and are recruited to chromatin using the energy of ATP hydrolysis to alter the structure of chromatin or catalyze histone variant replacement[306]. Secondly, histone PTMs are mediated by histone PTM enzymes[39]. The dynamic regulation of histone lysine acetylation, a common modification, is primarily conducted by KATs and HDACs[307,308]. The interrelationship between the process of histone lysine acetylation and deacetylation, mediated by Kats and HDACs, respectively, holds a significant influence over the structural state of chromatin (Fig. 3C). In the instance of Kats-mediated acetylation, the positive charge carried by histone lysine is removed. This action subsequently weakens the interaction between the histone tail and the phosphate backbone of the negatively charged DNA, leading to a loosening of chromatin. On the other hand, HDACs instigate histone lysine deacetylation, which effectively restores the positive charge level of lysines. The consequence of this process is a restored compact state of chromatin. It is important to recognize that the state of chromatin, either loosened or compacted, is ultimately dictated by these two opposing complexes[309] (Fig. 3C). Specifically, the precise condition of chromatin necessary for efficient DNA damage repair is typically modulated by these processes[35].

Histone ubiquitination plays an important role in chromatin remodeling. Ubiquitin-specific peptidase 11 (USP11) acts as a histone deubiquitinase to catalyze H2AK119 and H2BK120 deubiquitination. USP11 is physically associated with the chromatin remodeling NuRD complex involved in chromatin condensation[310]. In addition, Ub conjugation at this H2B site on the nucleosome was shown to interfere with the compaction of chromatin *in vitro*[311]. H2BK120ub1 induces chromatin opening and serves as a platform for both the NHEJ and HR proteins, promoting optimal DSB repair through both pathways. The CUE domain of chromatin remodeling enzyme SMARCAD interacts with H2A-ubiquitinated nucleosomes, thereby facilitating ubiquitination-mediated chromatin remodeling. This regulatory mechanism demonstrates that histone ubiquitination plays a pivotal role in promoting chromatin structure opening through coordinated molecular recognition and enzymatic activity[312].

5.2. The relationship between DNA damage and chromatin structure

An abundance of evidence suggests a pivotal role of chromatin structure in modulating the generation and dispersion of radiation-induced DNA damage[66,313,314]. Notably, cells in the metaphase are more vulnerable to radiation-induced DNA damage, especially during G2/M phase. This heightened sensitivity is primarily attributed to the highly condensed state of chromosomes during this phase[315]. Previous research has demonstrated an apparent lack of disparity in DSB sites in G2/M phase cells post-exposure to ionizing radiation. The possible explanation posited for this phenomenon draws on the limited sensitivity of heterochromatin to DNA damage. This is purportedly as a result of its DNA being enshrouded and safeguarded by related chromatin proteins. Notably, examples of these protective chromatin-related proteins include heterochromatin protein 1α and β (HP1α and β). The presence of these proteins potentially provides an effective shield, contributing to the observed immunity towards DNA damage within heterochromatin[316]. Subsequent research demonstrates that after ionizing radiation, the incidence of DSB generation is less frequent in dense chromatin compared to loose chromatin[317–319] (Fig. 3D). In tumor cells repeatedly exposed to X-rays, leading to acquired radioresistance to both X-rays and carbon ion beams, there is a significant increase in heterochromatin domains[320]. The potential for clinical fractionation irradiation gradually augments the proportion of heterochromatin in tumor cells. It has been shown that tumor cells grown in a three-dimensional culture had a significantly higher proportion of heterochromatin as opposed to those cultured in two dimensions. This increase in heterochromatin, as they further instantiated, hinges on the chromatin condensation activated by HDAC1, HDAC2 and HDAC4 enzymes. It is this exact chromatin condensation and subsequent upsurge in heterochromatin that empowers the tumor cells radiotolerance. Thus, the organization of the cell culture setting and presence of specific enzymes significantly steer the relationship between heterochromatin production and radiation resistance in tumor cells[321]. The observed phenomenon suggests that solid tumors could develop radiotolerance due to a high heterochromatin ratio. Indeed, numerous tumor cell types exhibit distinct heterochromatin characteristics[322]. In the examination of ovarian cancer tissue sections, an increase in the heterogeneity and contrast of nuclear chromatin was observed upon the induction of DNA damage by ionizing radiation. This observation suggests a transition from euchromatin to heterochromatin. Concurrently, there was a notable decrease in chromatin homogeneity, further indicating substantial chromatin alterations. The chromatin

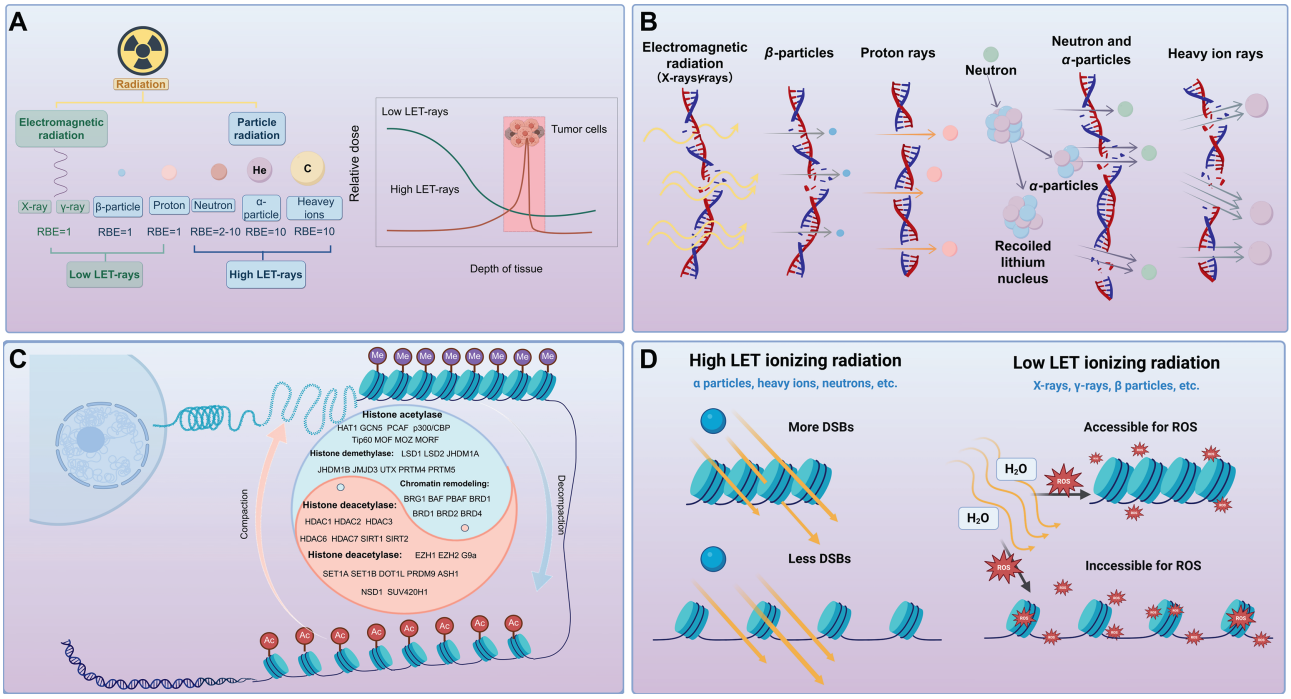


Figure 3 Histone modifications influence the efficiency of DNA damage by ionizing radiation through the regulation of chromatin structure. (A) Classification of ionizing radiation and linear energy transfer (LET): This panel provides an overview of the different types of ionizing radiation and introduces the concept of LET, which quantifies the amount of energy deposited per unit length of the radiation's path. (B) DNA damage induced by different types of ionizing radiation: This figure illustrates the distinct patterns of DNA damage caused by various types of ionizing radiation. High-LET radiation, such as alpha particles and neutrons, is shown to induce complex, clustered damage, while low-LET radiation, such as X-rays and gamma rays, typically causes more isolated, single-strand breaks. (C) Chromatin compaction and relaxation through histone modifications: This schematic represents how histone modifications can lead to either the compaction or relaxation of chromatin structure, depicting the histone tails with various modifications that can influence the degree of chromatin condensation. (D) Response of compact and relaxed chromatin to High-LET and Low-LET radiation: This panel contrasts the response of tightly packed and loosely organized chromatin to high-LET and low-LET radiation. High LET radiation primarily causes direct damage to biomolecules, inflicting more severe harm on tightly packed chromatin; whereas low LET radiation causes damage that relies on the diffusion of ROS, leading to more severe damage to loosely packed chromatin.

remodeling process, as implied by these changes, appears to be mediated by HDAC2[323]. Investigations have consistently demonstrated a more uniform and stronger heterochromatin protein 1 (HP1) expression in radioresistant MCF-7 cells throughout the entire nucleus, relative to their wild-type counterparts. This observation implies that radiotolerance in MCF-7 cells is, in part, due to an enhanced compactness of chromatin structure. It is thus hypothesized that these characteristics stem from elevated HDAC activity and repressed KAT activity[32].

Histone PTMs are linked to chromatin condensation and gene silencing, such as in the cases of H3K9me2/3 and H3K27me3[284,324]. Current report reveals that the methylation of H3K9 and H3K27 is integral to the construction and spatial arrangement of heterochromatin, managed by an active redistribution mechanism[126,325]. The previously mentioned HP1 enhances chromatin compaction at a higher order by binding to H3K9me3[326,327]. Additionally, HP1α may foster heterochromatin domain formation *via* phase separation, a process possibly reliant on its interaction with H3K9me2/3[328–331]. The results from a study aimed to ascertain the impact of irradiation on human embryonic stem cells (hESCs), normal human fibroblasts (IMR90), and fibrosarcoma cells showed that the same dose of ionizing radiation produced many more DSBs in hESCs than in IMR90 and HT1080 cells. Exposure to ionizing radiation resulted in a significant increase in the heterochromatin marker H3K9me3 in HT1080 cells and to a lesser extent in IMR90 cells, but no change in hESC. This observation suggests that histone methylation modification is abnormal in HT1080 tumor cells, which is closely related to heterochromatin formation and protects cells from DSB caused by ionizing radiation[332]. Recent studies have uncovered the critical role of histone lysine methyltransferase KMT1A (SUV39H1) in the formation of H3K9me3 within heterochromatin, a process instrumental in setting up and sustaining the structure of heterochromatin. DNA damage induces heterochromatin loosening and the change of heterochromatin structure is associated with KMT7 (SET7/9)-mediated KMT1A methylation and decreased KMT1 activity[333].

H3K27me3 contributes to local chromatin condensation and transcriptional silencing, potentially influencing the expression of tumor suppressor genes and DSB repair[334–336]. Consequently, tumor cells exhibit resistance to both radiotherapy and chemotherapy[337]. The creation and preservation of H3K27me3 primarily rely on KMT6 (EZH2), the key methyltransferase of the PRC2 complex[338,339]. It is recruited to the sites of DSBs instigated by ionizing radiation[335,340]. Investigations conducted on U2OS cells demonstrated an enhancement in radiosensitivity following the

depletion of KMT6[335]. Furthermore, extensive *in vivo* and *in vitro* experiments collectively illustrate the efficacy of siRNA-EZH2 treatment in concert with radiotherapy, acting to notably ameliorate the radiosensitivity of lung cancer[341]. It appears, in some cases, that maintaining a balanced expression level of KMT6 (EZH2) and H3K27me3 is essential, given that their low expression or absence may trigger the formation of radioresistant tumor phenotypes. The loss of H3K27me3 creates an epigenetic shift towards H3K27ac, which, in turn, modifies the transcriptional behavior of medulloblastoma cells. This modification consequently culminates in the overstimulation of the AKT signaling pathway, and ultimately engenders a radioresistant phenotype[342]. The phenomenon of PTMs crosstalk, which is intrinsically tied to the onset and maturation of tumors[343] is no rare occurrence. Previous report reveals that following irradiation, a pronounced reduction in H3K27me3 levels in three tumor cell types (MDA-MB-231, A549 and U251) is detected[344−346]. This decrease in H3K27me3 levels has been primarily attributed to the H3K27 demethylase KDM6A (UTX), which intriguingly tends to be present in higher quantities within tumor cells as compared to normal cells. It thus acts to safeguard the survival of these tumor cells following the irradiation process. Notably, a contrasting observation is made with MRC5 and MRC9 cells, wherein no such drop in H3K27me3 levels has been detected post-irradiation[347]. This suggests that tumor cells may acquire an ability to resist radiation through dynamic epigenetic regulation. On an interesting note, pre-irradiation treatment of tumor cells with the KDM6A (UTX) inhibitory agent GSKJ4[348,349] effectively hindered the ionizing radiation-induced reduction in H3K27me3. This, in turn, obstructed the repair of DSBs instigated by ionizing radiation and thereby accentuated their radiosensitivity[350].

On the other hand, the ubiquitination of histones H2A and H2B exhibits high site-specificity and serves as a critical PTM regulating DDR. Among these modifications, RNF168-mediated H2A ubiquitination plays a pivotal role in modulating HR and NHEJ pathways, as demonstrated in studies[351]. Furthermore, following DNA damage, the ATM kinase phosphorylates specific residues—Ser172 and Ser553 in RNF20, and Ser114 in RNF40—thereby facilitating the recruitment of the RNF20/RNF40 heterodimer to DSBs. This recruitment drives the catalysis of H2B monoubiquitination (H2Bub1), a modification that does not participate in the early accumulation of sensor proteins such as 53BP1 and MDC1. However, H2Bub1 is indispensable for the timely recruitment of downstream DDR factors, including NHEJ components (*e.g.*, XRCC4, KU80) and HR mediators (*e.g.*, RPA, RAD51, BRCA1), as well as the E3 ligase complex RAP80. These coordinated events underscore the distinct roles of H2A and H2B ubiquitination in DDR signaling, bridging early sensor activation and late repair pathway selection[352,353]. Moreover, numerous deubiquitinating enzymes (DUBs) are involved in the removal of H2AK13/15ub from damaged chromatin to terminate the DDR signaling[354]. In cells, USP51 is recruited to chromatin after DNA damage and modulates the dynamic assembly and disassembly of 53BP1 and BRCA1 foci[354].

5.3. The efficiency of the DNA damage response is influenced by chromatin structure

The compactness of chromatin structure impacts the ability to recruit DNA damage repair proteins[355,356]. DNA damage induced by ionizing radiation triggers a cascade of cellular responses that are collectively known as the DDR. This pivotal process, involving DNA damage recognition and repair, significantly determines the course of cells post-irradiation. A multitude of studies have revealed an intriguing interplay between chromatin dynamics around DSB sites and the effectiveness of DDR, rendering the ability of cells to effectively execute DDR[357−360]. However, the recruitment of repair factors is slower in dense heterochromatin than in euchromatin, and the DNA repair process is less efficient in heterochromatin[359,361,362]. The repair of various types of DNA damage in heterochromatin may require complementary mechanisms[304]. Several studies showed that after the induction of DSBs, chromatin undergoes a transient loosening (about 1.5 min), followed by a wider range of chromatin compression. Although chromatin compaction is beneficial for upstream/early signaling pathway transduction of DDR, it is detrimental for downstream/subsequent damage repair and recovery, and its overall effect on DNA damage repair is negative[363].

The dynamic regulation of histone acetylation by KATs and HDACs has the most striking effect on chromatin structure. For example, the ability of histone H4K16ac to promote chromatin loosening and reduce nucleosome packing, thus allowing access to transcription factors and recruitment of repair proteins, is highly apparent. Even acetylation on a single residue (H4K16) can alter the compaction level of a nucleosome array[358,364]. As mentioned in Section 2.1, although histone methylation cannot change the number of charges carried by lysine, it can still affect the structure of chromatin. The specific effect depends on the location and modification characteristics of methylation. For example, methylation modification at sites such as H3K4, H3K36 and H3K79 is usually related to the formation of an euchromatin state with high transcriptional activity. Studies have shown that histone methylation modification at H3K36me2, H3K79me2 and H4K20me2 alleles plays an important role in DSB repair, which can recruit damage repair proteins such as 53BP1 and Crb2 to promote DSB repair[285,365,366,367,368]. The efficient recruitment of damage repair proteins by methylation sites requires an unfolded chromatin environment. Under certain conditions, the unfolded chromatin is shaped by histone methyltransferases and corresponding methylation modifications. The histone lysine methyltransferase SETMAR induces high levels of H3K36me2 and global euchromatinization[369]. More often, the unfolded chromatin environment is co-shaped by other histone modifications. For example, in the absence of DNA damage, the compact chromatin structure does not allow 53BP1 to bind to the key site H4K20me2, and H4K16ac passively unwinds chromatin when DSBS occurs. Thus, the formation of 53BP1 foci was promoted[370].

In some cancer cell lines, high levels of histone acetylation lead to higher chromatin accessibility and more efficient DNA damage repair, thereby acquiring radiotolerance. STORM super-resolution microscopy was used to observe that after 1 Gy X-ray irradiation. HeLa cells have about 30 DSB sites per cell on average, and obvious chromatin loosening and remodeling occur. Chromatin organization is lost from a 200 to 400 nm thick irregular frame and reshaped to a dispersed sub-100 nm structure. At the same time, the structure of the residual to the residual sub-100 nm structure creates space for the signaling of the DDR and recruitment of related proteins such as γ-H2AX, MDC1 and 53BP1[371]. By inhibiting the function of HDAC1/2 in cervical cancer to elevate H3K56ac level, GAGE (G antigen 1) enhances the chromatin release and accessibility, and improves the efficiency of DNA damage repair, thereby contributing to the radioresistant phenotype of cervical cancer. The increase in GAGE level was significantly positively correlated with cancer

radioresistance[372]. Studies showed that the microenvironment of tumor cells can also affect DSB damage repair by affecting the state of chromatin modification. With increased cell density and increased levels of metabolites such as lactate, tumor cells have increased H3K56ac, which promotes chromatin release and DDR initial signaling[373]. In addition to acetylation, other forms of histone PTMs also have the effect of loosening chromatin. For example, H4K12sumo inhibits magnesium-dependent chromatin compaction and nucleosomal interactions, albeit with a poorer regulatory effect than H4K16ac[313,374,375]. It has been found that histone PARylation factor 1 (HPF1) -dependent histone ADP ribosylation triggers rapid chromatin unfolding in U2OS cells. Thus, it promotes the recruitment of DNA damage repair factors CHD4 and CHD7 (two chromatin remodeling complexes) to DNA damage sites and promotes NHEJ and HR[360].

In addition, histone modifications and the chromatin structure they control have an impact on the choice of DSB repair pathways. Recent studies have found that in the process of DSB repair, the loose chromatin structure with high transcriptional activity is more conducive to HRR, while the dense chromatin structure (heterochromatin) formed by histone deacetylation is more conducive to NHEJ[36,376,377]. For example, H4K16ac supports preferential recruitment of BRCA1 over 53BP1 to DSB sites, thus tilting the balance toward HRR[364]. In human osteosarcoma cells (U2OS) and human cervical cancer cells (HeLa), HDAC1 and HDAC2 were observed to aid in promoting hypoacetylation of H3K56 and H4K16[378,379]. This act, as found, helps facilitate NHEJ by their recruitment to DNA damage sites[377].

5.4. Loosen or tighten chromatin structure is regulated by histone PTMs?

The role of histone modification-mediated dynamic chromatin changes in response to ionizing radiation-induced DNA damage is intricate and significant. These alterations in chromatin structure, notably, have opposing effects on DNA damage and repair processes depending on the chromatin structure involved. Compact chromatin, or heterochromatin, exhibits fewer DNA damage sites upon exposure to ionizing radiation, hence safeguarding the genomic DNA's integrity. Conversely, a more relaxed chromatin structure, also referred to as euchromatin, is crucial during the DNA damage repair process. Euchromatin enables the formation of a highly active chromatin environment, facilitating the recruitment of DNA damage repair proteins and maintaining complexes. This dichotomy in chromatin structures presents a challenge for the clinical application of drugs targeting histone modification enzymes in combination with radiotherapy, especially regarding improving radiosensitivity. The central query becomes whether to tighten or loosen the chromatin structure to mitigate the radiation resistance of tumor cells. Abundant cellular experiments and clinical trials have demonstrated that histone deacetylase inhibitors (HDACi) primarily function by loosening chromatin structures, subsequently enhancing radiation sensitivity amongst tumor cells[380]. The influence of HDACi dosage and duration on tumor cell radiosensitivity varies greatly[381]. It has been shown that exposure to a low dose (25 nmol/L) TSA (a classical HDACi) increases *HO-1*, *SOD* and *CAT* expression by triggering the *Akt/Nrf2* antioxidant signaling pathway. Consequently, this led to decreased radiosensitivity in HeLa and HepG2 cells[382]. Nevertheless, this phenomenon was restricted to low-dose (1−2 Gy) X-ray exposure. Paradoxically, when the irradiation dosage escalated to 4−6 Gy, 25 nmol/L TSA treatment continued to enhance the radiosensitivity of these cell lines. This suggests that low HDACi dosages may boost radioresistant gene or signaling pathway expression by relaxing chromatin and thereby enhancing cellular radiation resistance under low irradiation doses. However, during high irradiation doses, the increased accessibility of relaxed chromatin permits extensive attacks on genomic DNA by free radicals and ROS, leading nonetheless to augmented radiosensitivity. Further analysis has been conducted on the impact of high-dose TSA on cellular radiosensitivity, indicating that 24 h of exposure to TSA can significantly escalate cellular radiosensitivity. However, shorter drug exposure times (*e.g.*, 6 h) were found to decrease cellular radiosensitivity. These studies emphasize the complexity of how epigenetic modification impacts radiosensitivity and underscore the importance of carefully gauging the dosage and timing of related drugs in line with specific radiotherapy dose fractionation plans in practical applications. This is crucial to avoid not only undermining the radiosensitivity enhancement effect but also potentially inducing radiotolerance

In addition, most of our current understanding of the effect of histone modification on radiosensitivity is based on the experimental results of low-LET radiation or photon radiation (X-rays and γ-rays). The mechanism of DNA damage by histone modification is mainly an indirect effect, which depends on the generation and diffusion of ROS and other free radicals at the microscopic scale to get close to the DNA molecule and cause damage (Fig. 3A and B). Uniformly, sparsely distributed DNA damage is usually caused in the nucleus[383]. Dense chromatin sterically prevents free radicals and ROS from accessing DNA molecules and proteins covered in heterochromatin also protects genomic DNA from damage. Inversely, in the case of loose chromatin, free radicals and ROS produced by the interaction of ionizing radiation with other molecules are readily accessible to DNA molecules due to their high accessibility (Fig. 3D). However, in the case of high LET radiation (heavy ions, α particles, neutrons, etc.), the damage is mainly a direct effect, and the DNA damage caused in the nucleus is usually densely distributed along the incident track of the particles (Fig. 3D)[383]. Whether highly compressed heterochromatin is still effective in protecting genomic DNA remains to be determined. Exposing mouse squamous cell carcinoma NR-S1 cells to a cumulative dose of 60 Gy, several studies have demonstrated that NR-S1 cells exhibit resistance to both X-ray and carbon ion beams. It is believed that the resistance to radiation is attributed to the increase in the number of heterochromatin domains[320].

However, several studies draw the opposite conclusion. For example, in one study, nontumorous lung Beas-2B cells and lung cancer A549 cells were irradiated with 8 Gy of γ-rays or 1 Gy of α-particles, respectively. Daughter cells (DCs) were collected in 2−3 weeks. DCs from γ-irradiated cells (DCs-γ) were radioresistant. However, the daughter cells derived from α-particle-irradiated cells (DCs-α) did not show any changes in colony formation rate and cell proliferation activity after further α-particle-irradiation. Further analysis showed that the radioresistance of DCs-γ was due to the increase of heterochromatin and HDACi could attenuate the radioresistance of DCs-γ by loosening chromatin[384]. Other studies show distinct results that following carbon ion microbeam irradiation, highly condensed chromatin would exhibit complex and aggregated DSBs, referred to as cluster damage. This was accompanied by a notably slow or sometimes

non-existent repair process. They further observed an augmentation in DNA damage accumulation correlating with an increase in the number of carbon ions in the microbundles. Notably, although the phenomenon was observed across both euchromatin and heterochromatin, the effect was significantly pronounced in the latter[385]. In addition to biological experiments, software was used to simulate and analyze the damage of particle beams to the nucleus[386,387]. The DNA fabric software was used to build nuclear models of DNA molecules with different compressed forms and the Monte Carlo toolkit Geant4-DNA was used to simulate and analyze the differences in the formation and complexity of DSBs caused by proton beams on heterochromatin and euchromatin[386]. The results showed that heterochromatin had more direct damage and less indirect damage than euchromatin.

In the above studies, contradictory conclusions regarding the protective role of heterochromatin under high-LET radiation were drawn. The conflicting results may stem from differences in cell lines used across studies, variations in quality/physical parameters of ionizing radiation, distinct time points for measurement, and chromatin marker variability. For instance, theoretically, if the fluence of particle radiation like carbon ions or alpha particles is high enough to uniformly and densely cover the entire cell nucleus, the genomic DNA would be severely damaged regardless of chromatin being relaxed or compact[388].

Based on existing evidence, we speculate that loose chromatin is detrimental for cells to cope with low-LET radiation but beneficial for dealing with high-LET radiation. It also facilitates the recruitment of proteins and enzymes needed for the DNA damage response and repair. Conversely, compact chromatin is advantageous for cells to handle low-LET radiation but not high-LET radiation, and it hinders the recruitment of the aforementioned key proteins and enzymes. Throughout this process, the quality or physical parameters of radiation also play a role. Understanding this phenomenon helps us modulate tumor cell radiosensitivity by using histone-modifying drugs to adjust chromatin tightness. It can also guide the adjustment and optimization of radiotherapy parameters (Fig. 3A and B).

6. Histone PTMs affect tumor cell radiosensitivity by histone modification readers

In 2001, the theory of "the histone code" was initially proposed[389]. This groundbreaking hypothesis maintains that "histone codes" serve as vital mechanisms for controlling chromatin structures and functions. The concepts related to the histone code hypothesis include "writers/writers", "scavengers/erasers", and "readers/effectors"[390]. PTM writers and erasers mainly refer to the enzymes responsible for establishing or removing histone modifications, as briefly described in the previous sections. Readers mainly refer to proteins and molecules that recognize and bind specific histone modifications to translate histone codes into biological functions[391]. According to the hypothesis of histone codes, posttranslational modifications of histones can block or recruit certain proteins called readers to bind to chromatin or histones, where the function of recruitment is more common. Readers contain one or more effector modules and recognize covalent modifications of proteins and DNA, and different histone PTMs recruit readers with corresponding effector modules[392,393]. Methylation modification draws proteins with chromo and tudor-domain[292,367,394]. While phosphorylation modification attracts w14-3-3 proteins[7,391,395,396].

Numerous proteins, possessing reader domains and demonstrating the capacity to execute complex biological operations, are closely connected to cancer. To date, the bromodomain is the most comprehensively studied reader, bound to histone acetylation modification and capable of specific recognition of the *ε-n*-lysine acetyl motif[397]. The bromodomain is an evolutionarily conserved structure consisting of four α helices separated by variable ring regions that form a hydrophobic pocket that recognizes acetylated lysine[398]. The human genome encodes 61 bromine domains, which are present in 46 different proteins and can be divided into eight families based on structural or sequence similarity[399]. Proteins containing bromodomains can be further classified by their structure into bromodomain and extra-terminal (BET) or non-BET families of bromodomain proteins. The BET family includes bromodomain containing proteins (BRD) such as BRD2, BRD3, BRD4, and BRDT, which typically contain two N-terminal bromodomain domains (BD1 and BD2) and an additional ET. Among them, BD1 and BD2 are responsible for binding to acetylated lysine of histones, thus participating in regulating gene transcription and chromatin remodeling, and ET provides the structural basis for binding to transcription factors, such as E2F[400]. The non-BET family of bromodomain proteins does not contain the BD1 and BD2 domains. For example, BRD1, BRD5 and BRD7 contain only one bromine domain, so they are called "semi-BET proteins". The difference between the BET and non-BET family mainly lies in the number and function of their domains. At present, a large number of studies have shown that bromodomain proteins play an important role in regulating DNA damage repair. The difference between the BET and non-BET family mainly lies in the number and function of their domains. At present, a large number of studies have shown that bromodomain proteins play an important role in regulating DNA damage repair[401].

6.1. Effects of bromodomain proteins on chromatin remodeling and DNA damage repair

DNA damage occurs during DNA replication or under harmful stimuli. To ensure the accurate transmission of genetic information, DNA must undergo timely and correct repair. This crucial repair process could be carried out through homologous HR and NHEJ, complemented by the deployment of appropriate cell cycle checkpoints. Thus, maintaining the integrity of these repair mechanisms is imperative for preventing tumorigenesis[402]. Cancer cells are commonly eradicated through radiotherapy and chemotherapy, two treatments that provoke genetic instability and DNA damage. As such, focusing on investigating the integral pathways and regulatory factors involved in DNA repair in these cancer cells might pave the way to enhance the efficacy of these treatments. By interrupting and wrecking the DNA repair mechanisms inherent to cancer cells, it could potentiate the effects of both radiotherapy and chemotherapy against cancer. This hypothesis, of augmented therapeutic effects stemming from the disruption of DNA repair in cancer cells, has been corroborated by clinical evidences[128,403]. Currently, five mechanisms exist for modifying various types of DNA damage: base excision repair (BER), mismatch repair (MMR), nucleotide excision repair (NER), and DSB-further subdivided into HR and NHEJ[404]. Bromodomain proteins have a crucial regulatory function in the DNA damage repair pathways[401], thereby influencing tumor radiosensitivity[405,406]. BRD4, BRM, BRG1 and BAF180 (PBMR1) are brominated structural proteins that act as histone acetylation readers and can facilitate DNA damage repair (Fig. 4).

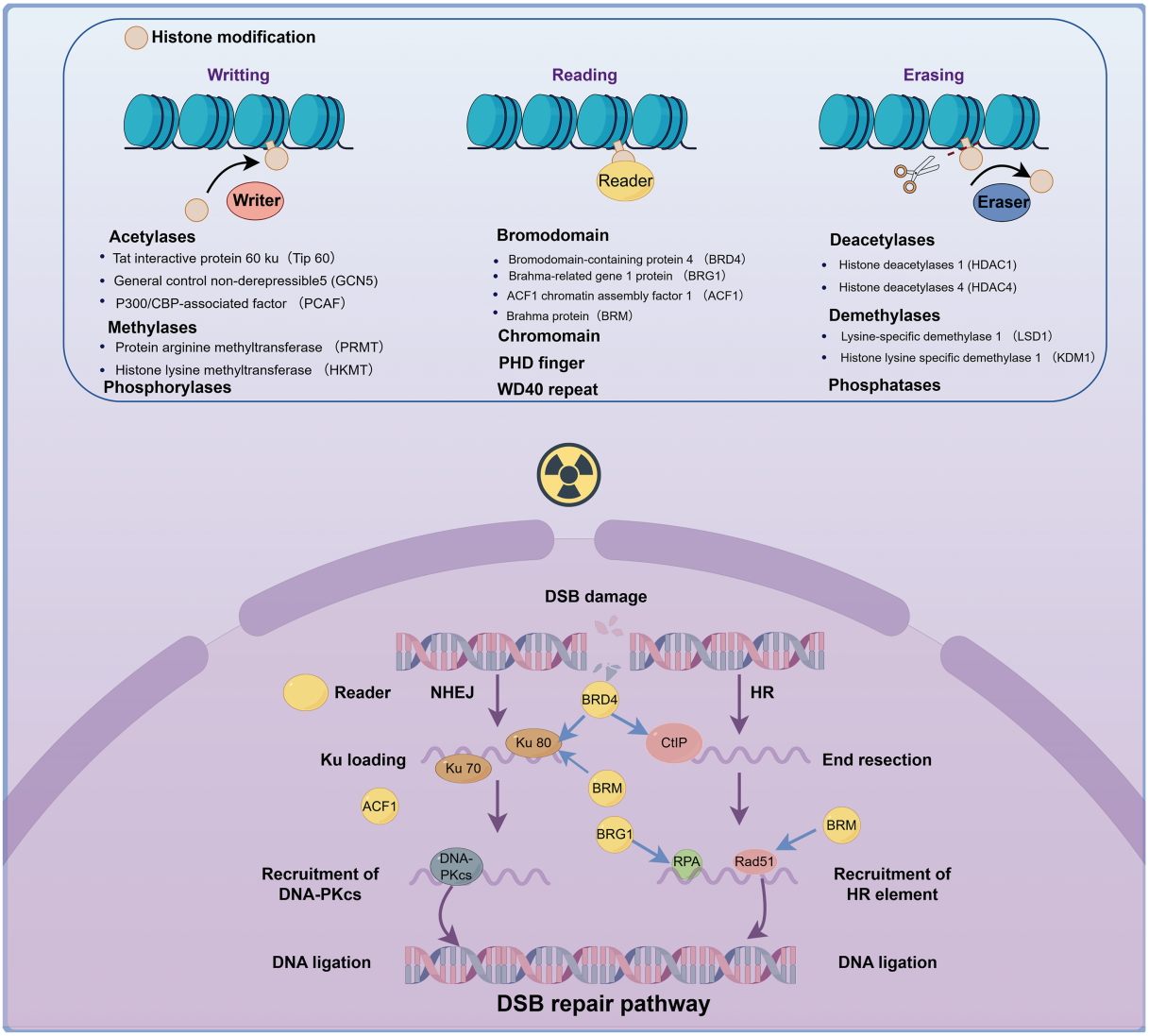


Figure 4 Histone modification readers regulate the DNA damage repair pathway. Histone modification readers regulate the NHEJ and HR DNA damage repair pathways. As outlined, BRD proteins regulate Ku loading by binding Ku 70 and Ku 80, end resection by interaction with CtIP, and recruitment of HR elements through interplay with Rad51 and RPA. BRD protein, bromodomain protein; CtIP, c-terminal binding protein; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; NHEJ, non-homologous end joining; HRR, homologous recombination repair.

6.1.1. BRD4

Bromodomain-containing protein 4 (BRD4), a member of the BET family, is integral to both DNA damage signaling and repair. Furthermore, it also functions as a significant regulator of transcription and plays a critical role in transcriptional regulation[407]. In the homologous repair process, a complex formed by BRCA1 and RAD51 binds to impaired DNA, thus facilitating DNA repair by unwinding the DSBs. However, the inhibition or absence of the BET protein compromises the transcription of BRCA1 and RAD51[408]. The concept of BRD4 regulating DNA homologous repair *via* regulating chromosome remodeling processes and the investigation in this study established a methodical depiction of how BRD4 coordinates the HR repair pathways. This series of coordinated events encompasses the recruitment of SWI/SNF chromatin remodeling complexes, the expulsion of histones from the DSB due to BRG1 recruitment, and the execution of DNA terminal excision to expedite RAD51 loading and HR. BRD4 provides an open window to the potential of other BET proteins, establishing a collaborative effort with BRD4. A noteworthy interaction occurs with BRD4 by the promoters and enhancers of CtIP (C-terminal binding protein), wherein BRD4 modulates its transcript. Interestingly, when BRD4 is silenced, it leads to an obstruction of DNA terminal excision, generation of ssDNA, and the following HR processes. The unwinding function of the CtIP/MRN complex is requisite for RAD51 loading (Fig. 4), thereby suggesting that the influence of BRD4 extends to the functions of RAD51[409]. Additionally, several studies have shown that suppressing BRD4 impacts the transcriptional activity of BRCA1 and RAD51 in ARID2-deficient liver cancer[410]. During cervical cancer radiotherapy, BRD4 inhibition can decrease BRCA1 and RAD51 transcriptional expression, thus impairing DNA damage homologous repair. Consequently, targeting BRD4 is a proven strategy to enhance the radiosensitivity of cervical cancer[411].

The integral part that BRD4 undertakes in DNA repair particularly highlights its significance within the realm of cancer[412]. Remarking on this function of BRD4, an observed disruption in non-HR repair emanates from the inhibition of BRD4 by siRNA. This manifestation hints towards an internal disturbance within the DNA damage repair pathways that are essentially involved in NHEJ. Further, this obstruction of BRD4 has been found to precipitate a notable decline in the recruitment of key DNA repair proteins, such as 53BP1, Artemis and Ku80, to the damaged chromatin (Fig. 4). The silencing of BRD4 resulted in the exacerbation of radiation-induced DNA damage. As such, these observations collectively underpin the pivotal role that BRD4 holds in the operation of the DNA repair mechanism[413]. Moreover, it was also observed in senescent cells that BRD4 inhibits the transcription of 53BP1, which impaired NHEJ repair and increased autophagy in senescent cells, and inhibited the transformation of senescent cells into cancer cells[414]. In non-small cell lung cancer (NSCLC), BRD4 inhibition heightens the radiosensitivity of cancer cells[406].

The pivotal role of BRD4 in DNA repair is evidenced by its involvement in the repair of physiological DSBs, particularly in the process of class switch recombination (CSR)[415]. This process is further facilitated by the capacity of BRD4 to recruit key repair factors such as 53BP1 and uracil DNA glycosylase, underscoring its significance in the CSR process. Additionally, the bromo domains of BRD4 are essential for identifying γ-H2AX phosphorylation. Cumulatively, these mechanisms considerably highlight the importance of BRD4 in the DNA repair pathway[416]. DNA damage repair is a pivotal factor to affects tumor radiosensitivity, and BRD4 can regulate DNA repair to affect the tumor radiosensitivity through the common DNA repair pathway.

6.1.2. ACF1

ATP-utilizing chromatin assembly and remodeling factor 1 (ACF1) regulates the NHEJ pathway, functioning as an auxiliary subunit of the ISWI chromatin remodeling complexes. Through direct interactions with Ku and the ATPase SNF2H (SMARCA5), ACF1 coordinates their damage localization and instigates the NHEJ process[417]. The lack of ACF1 could disrupt the NHEJ pathway and inhibit Ku binding to DSBs. ACF1-facilitated chromatin modification could enhance Ku's detection and rectification of chromatin DSBs. The synergy between SNF2H and ACF1 enhances the nucleosome remodeling efficiency[417]. This suggests that ACF1, a significant protein, is potentially linked with SNF2H at the DNA injury site, promoting chromatin remodeling. Primarily, ACF1 contributes to the DNA damage repair process by specifically focusing on the recognition of DNA damage and the precise location identification of NHEJ factors (Fig. 4). The protein functions extend to affecting the HR process. Empirical evidence illustrates that the inhibition of ACF1 substantially impedes the HR process. However, it must be noted that the exact influence ACF1 exerts on HR repair remains ambiguous and warrants further investigation[418].

6.1.3. BRG1/BRM

Brahma related gene 1 (BRG1)/Brahma homologue (BRM) controls the NHEJ pathway. These proteins, with closely matching amino acid sequences, are both ATPases in the BAF chromatin remodeling complex. They exhibit structural and functional similarities, as well as associations with tumors[419]. Numerous studies have demonstrated that, within the NHEJ pathway, DNA damage triggers the recruitment of BRG1 and BGM to the impaired sites[420–422]. BRG1 promotes the formation of γ-H2ax, a process achieved by its BRD domain recognition of GCN5-mediated H3 acetylation[422]. Conversely, BRM enhances NHEJ progression by facilitating Ku recruitment. This process involves BRM clearing chromatin barriers at the DSBs' end, thereby aiding Ku binding[421] (Fig. 4). In the context of HR, cells deficient in BRG1 display significant abnormalities[423,424]. Researches revolve around the role of BRG1 in the late stage of HR, after DNA terminal excision. This has been inferred from the observations that BRG1 deficiency results in the persistence of RPA-bound single-strand DNA. This, in turn, decreases the occurrence of RAD51 binding sites. Moreover, the interaction discovered between BRG1 and RAD52 has demonstrated the involvement of the process of RAD51 binding to single-strand DNA (Fig. 4). These established correlations, thus, underscore the significance of BRG1 in the course of HR, post DNA terminal excision[424]. Certainly, BRG1 significantly contributes to the initial stage of HR. A lack of BRG1 results in reduced expression of chromosomal binding RPA, subsequently impeding DNA binding to RAD51, and thus halting the onset of HR repair[424]. Moreover, ATM swiftly mediates the dose-dependent phosphorylation of BRG1, facilitating its binding to γ-H2AX nucleosomes to create repair foci[425]. Several studies have shown that the HR process is more significantly affected by the downregulation of BRG1 than by BRM, indicating a minimal impact from BRM. To clarify, BRG1 inactivation resulted in impaired DNA terminal excision, leading to a reduced nucleosome density at DSB[426]. Research on the PARP1−BRG1−SIRT1 pathway reveals that BRG1 suppresses transcription by clustering chromatids around promoters, yet in DNA repair scenarios, BRG1 relaxes chromatids to facilitate HR at DSB sites[427].

BRG1 is pivotal in governing tumor radiosensitivity, as evidenced in HT29 colon cancer. The mechanism begins with the interaction between BRG1 and γ-H2AX-containing nucleosomes, an event facilitated through the BRG1 bromodomain (BRD). The BRD is a protein module with proficiency in recognizing the H3 acetylated lysine component, which fosters the ATM-mediated formation of γ-H2AX through its nucleosome remodeling activity. This process leads to the recruitment of GCN5 histone acetyltransferase, catalyzing an increase in H3 acetylation. The elevated acetylation, in turn instigates a further recruitment of γ-H2AX nucleosomes by BRG1. This synergistic relationship between BRG1, γ-H2AX, and acetylated H3 culminates in an efficient pathway for the accumulation of γ-H2AX and acetylated H3 at the DSB site. Furthermore, in xenograft mouse models, it has been observed that BRG1-BRD escalates the radiosensitivity of HT29 tumors. This heightened sensitivity originates from the inflicted damage on γ-H2ax and its downstream 53BP1 pathway by BRG1-BRD, which subsequently leads to inefficient DNA repair. Thus, the role of BRG1 extends to the regulation of DSB and DNA repair processes, affecting radiosensitivity[428]. In NSCLC cells with *BRG1* mutations, concurrent *BRM* knock-down leads to the formation of Rad51-foci. Notably, there was a significant enhancement in radiosensitivity within the mutant group[429]. These findings suggest that BRG1 can affect the radiosensitivity of tumor cells through both non-homologous and homologous repair pathways. In addition, BRM may act synergistically with BRG1, and BRG1 is a potential molecular target for sensitizing radiation of tumor cells.

6.1.4. BAF180

BRG1-associated factor 180 (BAF180), a subunit of the SWI/SNF complex, regulates tumor cell radiosensitivity *via* both homologous and non-homologous repair pathways. The BRD of BAF180 restricts the PBAF complex to DNA breaks, thereby regulating the

chromatin state required for c-NHEJ, a process that is carried out in concert with BRG1[420]. Thus, BAF180 might cooperate with BRG1, as BRG1 expression offers a potential viable marker for tumor cell radiosensitivity[420].

6.2. Effects of chromodomain proteins on chromatin remodeling and DNA damage repair

This structural module specifically recognizes di-/tri-methylated lysine residues at histone H3 positions K9 and K27, constituting a critical component of the "histone code" decoding system. Proteins harboring chromo domains encompass notable examples such as chromodomain helicase DNA-binding protein (CHD), the transcriptional repressor HP1, polycomb protein (Pc), and the human retinoblastoma protein (RB1)[430].

6.2.1. CHD proteins

Within the CHD enzyme family, CHD1, CHD2, CHD3.1, and CHD4 play distinct roles in DNA damage repair pathways[431]. *CHD1* deficiency stabilizes 53BP1, enhances NHEJ activity, and suppresses error-free homology-directed repair of DSBs[432]. CHD2 facilitates chromatin expansion and H3.3 deposition at DNA breaks, thereby promoting the assembly of NHEJ repair complexes at these sites[433]. In addition, CHD3 contributes to heterochromatic DSB repair by regulating chromatin accessibility in silenced genomic regions[434]. Additionally, CHD4 coordinates signaling and repair processes post-DNA damage. Specifically, CHD4 depletion disrupts the chromatin response of RNF168 E3 ubiquitin ligase at DSBs, impairing local ubiquitination and BRCA1 recruitment, which are critical for efficient repair[435].

6.2.2. HP1

Heterochromatin protein 1 (HP1) represents a family of evolutionarily conserved nuclear proteins ubiquitously present in eukaryotic organisms. These chromatin-associated regulators are primarily involved in chromatin architecture modulation and transcriptional silencing through epigenetic mechanisms[430]. Three distinct subtypes have been characterized: HP1α, HP1β, and HP1γ. Currently, a series of recent research has established a connection between HP1 proteins and the DNA damage response[436]. A reduction in the levels of HP1 proteins can lead to the loosening of heterochromatin, thus circumventing the necessity for ATM signaling[437]. A recent observation noted an enhanced mobility of HP1β at damaged regions within heterochromatin. As a consequence, it is reasonable to anticipate that the depletion of *HP1* is advantageous for the repair process in heterochromatin[438]. This evidence demonstrated that chromodomain proteins play a significant role in DNA damage and radiosensitivity.

6.3. Effects of ubiquitin-binding domains on chromatin remodeling and DNA damage repair

6.3.1. BRCA1

Histone ubiquitination exerts a critical influence on cellular radiosensitivity. Mono-ubiquitination of H2AK15 by RNF168 is required for recruitment of the tumor protein 53BP1 to DSBs[439], while poly-ubiquitination of H2AK15 by RNF168 (K63 linkage) recruits the BRCA1-A complex[440]. Both 53BP1 and the BRCA1-A complex regulate DNA end resection. The BRCA1 (breast cancer susceptibility gene 1) protein plays a pivotal role in maintaining genomic stability through HR[441]. BRCA1 interacts with key proteins such as RAD51 to form complexes, and its E3 ubiquitin ligase activity enhances HR efficiency by regulating DNA end resection and protecting repair intermediates. By counteracting strand-cleavage barriers imposed by the 53BP1 and its effector proteins, BRCA1 facilitates a critical step in DNA strand cleavage. Additionally, BRCA1/BARD1-mediated H2A ubiquitination promotes HR[442] (Fig. 4), while RAD18 is recruited to DSBs in an RNF8-dependent manner, directly binding to the recombinase RAD51C to further stimulate HR. Therapeutically viable vulnerability of BRCA1-deficient mouse mammary cells confirmed the radiosensitivity regulated by BRCA1[443]. Moreover, the above-mentioned important roles of BRCA1 have suggested them as attractive, valuable, and sensitive diagnostic biomarkers in the prediction of radiotherapy outcomes[444].

6.3.2. 53BP1

53BP1 (p53-binding protein 1) regulates DNA repair pathway selection by promoting NHEJ and suppressing HR. Recent studies reveal that 53BP1 not only specifically recognizes H2AK15 monoubiquitination but also detects diubiquitinated H2A[445,446] (Fig. 4). Histone ubiquitination recruits 53BP1 to DNA damage sites, inhibiting HR by blocking DNA end resection and shifting the repair balance toward NHEJ, exerting a critical influence on cellular radiosensitivity[447].

7. Histone variants and chromatin remodeling complexes induce chromatin alteration

Substitution of canonical histones with variants affects nucleosome structure, accessibility to histone tails, and the introduction of a variety of new sequence motifs[40].

7.1. H2AX phosphorylation: γ-H2AX

H2AX is an important histone H2A variant, accounting for 2% to 25% of the mammalian H2A variant pool, a proportion that is dependent on cell and tissue type[448]. The amino acid sequence of H2AX was first determined in 1989[449]. "The histone folding motif in H2AX and H2A is largely similar, with the main distinction being the SQE motif in the C-terminal of H2AX, where X denotes any hydrophobic amino acid[449,450]. PI3K-related kinases in DNA damage response, ATM[451], ATR[452,453] and DNA-PK[454], all of which can phosphorylate the Ser in this sequence. The most typical phosphorylated site among them is S139 in mammals within H2AX, called γ-H2AX[455–457]. Initially, γ-H2AX forms at the site of DSBs within a few seconds of exposure to ionizing radiation; it quickly peaks at half of its maximum level and reaches the maximum level within 9 to 30 min[448]. Modified chromatin domains containing γ-H2AX could reach megabase sizes and their spread across chromatin is influenced by topologically associated domains (TADs). They also serve as an anchor platform for other proteins involved in the DDR[458]. Studies show that after DNA damage, γ-H2AX clusters around the damage site and repairs euchromatin preferentially before repairing heterochromatin. This process involves decondensing heterochromatin while preserving histone modifications[459]. In addition, methylation of lysine 134 of H2AX is also critical for the formation of γ-H2AX[460]. After the formation of γ-H2AX, protein molecules such as BRCA1, Nbs1/Mre11/Rad50, 53BP1, MDC1 and Rad51 can be recruited to modify the broken double-stranded DNA in two ways: NHEJ and HR[355]. In conclusion, γ-H2AX is involved in the

recruitment and maintenance of DNA damage repair proteins, histone modification enzymes, and chromosomal remodeling complexes, as well as mediating chromatin remodeling and silencing[35]. γ-H2AX foci are widely used as markers to detect DNA double-strand damage due to their sensitivity[356,461]. The formation of γ-H2AX could also indicate the DNA damage repair capacity of cells[462]. In addition, 53BP1 and BRCA1 are also important markers of DNA damage repair capacity. They will accumulate at DSB sites and participate in the regulation of the repair process. By examining the localization and aggregation of these proteins in the nucleus, the activity and efficiency of DSB repair could be assessed[463].

7.2. *Chromatin remodeling complex*

The structural alteration of chromatin, known as chromatin remodeling, involves the utilization of remodeling enzymes to relocate, eliminate, or reassemble nucleosomes by harnessing energy from ATP hydrolysis[464]. By controlling the architecture of chromatin, remodeling enzymes and other chromatin-binding proteins modulate the binding affinity of DNA regulatory sequences to other factors, thereby significantly impacting diverse DNA processes such as transcription, replication, repair and recombination[465]. Chromatin remodeling complexes are primarily categorized into four families: switch/sucrose non-fermentable (SWI/SNF), imitation of switch (ISWI), chromodomain helicase-DNA binding (CHD) and inositol requiring enzyme 80 (INO80)[466]. Bromodomain-containing proteins are essential constituents of chromatin remodeling complexes, recognizing histone acetylation modifications, contributing to genome positioning, and are closely related to radiosensitivity, as discussed earlier[467]. Furthermore, the ISWI family comprises the prolyl hydroxylase domain protein (PHD), which can recognize histone methylation[468]. Recent research indicates that PHD plays a significant role in hypoxia regulation, a pivotal factor in affecting radiosensitivity[466,467]. Notably, PHD domain proteins are involved in regulating the response to hypoxia by interacting with hypoxia-inducible factor (HIF)[464]. Specifically, under hypoxic conditions, PHD domain proteins facilitate the degradation of HIF, thus governing the cellular response to hypoxia[465]. In addition, PHD domain proteins can also regulate the hypoxic response by interacting with other proteins. In fully oxidized cells, HIF-α subunits are hydroxylated at proline residues by the oxygen-dependent PHD enzyme[466,469]. Hydroxylation of proline allows it to bind the von Hippel-Lindau protein (pVHL). This is an E3 ubiquitin-ligase that targets HIF-α for proteasomal degradation[470]. In addition, HIF-α is inhibited by the factor asparaginyl hydroxylation of HIF-1 (FIH) in the absence of hypoxia, thereby preventing HIF-α from binding to the co-activator protein p300/CBP[471]. Given the critical role of PHD in cancer hypoxia regulation[472], the involvement of PHD proteins in radiosensitivity of tumor cells merits exploring.

The chromatin remodeling complex plays a significant role in DNA damage repair. This complex can organize the chromatin structure, leading to the exposure of damaged DNA regions, thus enabling repair enzymes to access and mend the affected sites. Moreover, the activities of chromatin remodeling complexes influence DNA replication and transcription processes through their impact on DNA supercoiling, consequently affecting DNA repair mechanisms. Abnormal function of the chromatin remodeling complex can result in reduced efficiency or increased errors in DNA damage repair, thereby elevating the risk of gene mutations and disease development. Nearly 25% of cancer cases are associated with SWI/SNF gene mutations. Furthermore, abnormal expression of SWI/SNF subunits has been closely linked to the initiation and progression of tumors, highlighting its significance in oncology. SMARCA4 is silenced in 15% to 50% of human NSCLC tissues, with a high mutation rate observed in 35% of NSCLC cell lines[473,474]. The ISWI family members are highly linked to cancer progression, and increased levels of SMARCA1 are associated with worse overall survival in NSCLC[475]. SMARCA5, a core ATPase subunit, is frequently overexpressed in various tumors[476], including breast cancer[477], gastric cancer[478], acute myeloid leukemia[479] and pancreatic ductal adenocarcinoma[480]. The literature has documented an oncogenic function of SMARCA1, resulting in the suppression of cellular survival and cell cycle advancement through abnormal methylation[476]. This aberrant methylation of SMARCA1 contributes to the tumorigenesis process. The NuRD complex, a representative member of the CHD family, is closely associated with cancer progression as a transcriptional repressor that plays a critical role in DNA damage response[480]. Moreover, the INO80 complex is frequently highly expressed in cancer cell lines and tumor tissues, including lung cancer, colon cancer, and melanoma[481,482]. Genetic profiles of INO80 family loci have been identified in cancer, indicating their potential significance in carcinogenesis[483–485]. However, further investigation is required to elucidate the underlying mechanisms associated with these observations.

8. Histone PTMs regulate cancer radiosensitivity *via* the tumor microenvironment

The tumor is composed of cancer cells and tumor stroma. Tumor stroma consists of distinct cancer-associated vasculature and a variety of cellular components. It contains but not limited to activated CAFs, mesenchymal stromal cells (MSCs) as well as pericytes[486–488]. The tumor stroma, consisting of abundant stromal components, creates a dynamic environment that plays a crucial role in supporting cancer progression. As such, it is considered to be a potential source of cancer biomarkers and therapeutic targets. Interestingly, a low tumor-stroma ratio (TSR) has demonstrated a significant association with poor survival outcomes, therefore serving as a vital predictor for evaluating the prognosis and treatment efficacy of cancer patients. Furthermore, the intricate nature of these stromal components exerts a notable influence on tumor establishment, progression, and treatment resistance. It is important to note that tumor stroma is characterized by both cancer-promoting and cancer-inhibiting effects[489–491]. In advanced cancers, activated stroma promotes epigenetic changes in cancer cells[492], driving cancer progression[493]. The stroma has been found to help cancer cells develop stem-like properties, creating a conducive environment for primary cancer cell growth and metastatic cancer cell colonization[494]. In non-malignant tissues, stroma typically restricts the proliferation, migration, and invasion of differentiated epithelial cells in the extracellular matrix to maintain organ size and structure[495]. In this part of the review, we focus on the mechanisms of CAFs, ECM, stromal vasculature and tumor-associated endothelial cells in regulating tumor radiosensitivity through epigenetic modifications.

8.1. *Cancer-associated fibroblasts: Turning foes to friends*

Histone modifications modulate cancer radioresistance by regulating the secretion factors of CAFs[496–498]. CAFs are one of the

most important and abundant stromal cell components within the tumor microenvironment. CAFs are permanently activated fibroblasts and exert significant tumor regulatory activity[499]. CAFs are typically derived from fibroblasts, which are activated by TGF-β and platelet-derived growth factors (PDGFs) in the liver and pancreas. Their regulation of cancer cell activity predominantly occurs through contact-based interactions and secretion of regulatory factors. TGF-β, EGF, fibroblast growth factor type 2 (FGF2) and PDGF are considered to be key regulators of CAF recruitment and activation[500]. These actions ultimately influence DNA damage repair, migration, invasion, apoptosis, and metabolic reprogramming of tumor cells, consequently directly impacting tumor radiosensitivity[501]. Studies have shown that CAFs play a significant role in tumor chemotherapy and radiotherapy resistance[502]. Histone PTMs modification can lead to the aberrant activation of CAFs. CAFs foster the radioresistance of cancer cells by secreting cytokines and chemokines[503]. In the context of liver fibrosis, transforming growth factor-β (TGF-β) serves as a predominant regulator and the key secretory factor of CAFs. The interaction between CAFs and cancer cells is primarily mediated by TGF-β. Inhibiting TGF-β signaling through various pathways has been found to effectively suppress tumor growth and metastasis. Additionally, CAFs have been identified to enhance cancer cell growth and migration by inducing epithelial-mesenchymal transition (EMT) through interleukin-6 (IL-6) induction[504]. The heightened IL-6 levels from CAFs can trigger the activation of the JAK/STAT3 signaling pathway, which subsequently stimulates cyclin D1 expression to accelerate tumor cell proliferation[37,505,506,507,508].

Histone modifications have an impact on CAF activation. A common histone mark of active transcription, H3K27ac, has been shown to be important for CAF activation in several studies. Overexpression of the H3K36 demethylase, KDM2A immortalized normal human breast fibroblasts and promoted an inflammatory CAFs (iCAFs) phenotype with enhanced secretion of cytokines, including IL-6, IL-8 and CXCL1[509]. The HDAC 1/3/8 inhibitor Scriptaid inhibits the expression of transcription factor Smad, a TGF-β signal transduction gene, to prevent the TGF-β-induced maturation of endothelial cells into myofibroblast-like CAFs (myoCAFs)[510]. TGF-β also regulates histone methylation during CAF maturation (Fig. 5). In immortalized mouse embryonic fibroblasts, TGF-β increased protein arginine methyltransferase 1 and 4 (PRMT1 and PRMT4) expression in a Snail1-mediated manner, leading to H3 and H4 methylation[511].

The regulation of CAFs by histone modifications affects cancer development. Loss of H3K27me3 increased the expression of Insulin-Like Growth Factor (IGF2) and WNT ligand WNT5A to promote gastric cancer cell migration and invasion[508]. Expression of KDM2A is increased in breast cancer and correlates with lower patient survival rates. Knocking down KDM2A in breast cancer cells decreased the expression of NOTCH signaling molecules such as Jagged1, NOTCH1 and HEY1, leading to a reduction in cancer stemness and angiogenesis[509] (Fig. 5). H3K27 and H3K4 trimethylation loss upregulates cartilage oligomeric matrix protein (COMP), an extracellular matrix protein, to promote breast cancer cell invasion ability[512]. Higher levels of H3K27ac promote the expression of serum amyloid A1 (SAA1), which encodes an acute

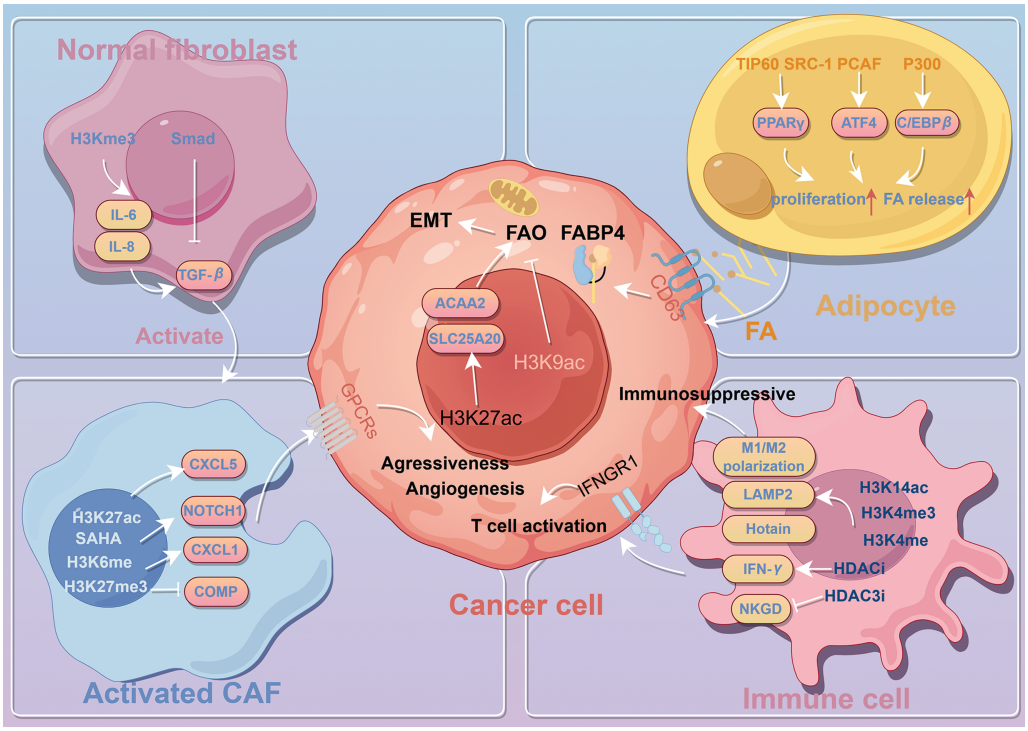


Figure 5 Histone modification beyond cancer cells. Tumor environment cell components such as CAF, cancer associated adipocyte and immune cell release chemokines (TGF-β, CXCL5, CXCL1, IFN-γ) to regulate cancer aggressiveness and angiogenesis which are partially regulated by histone modification. In addition, chromatin recombination complexes TIP60 and PCAF in CAA impact the FA absorption of cancer cells, regulating the energy supply. NKG2D, the natural killer group 2 member D; CAF, cancer associated fibroblast; CAA, cancer associated adipocyte; FAO, fatty acid oxidation; ATF4, activating transcription factor 4; C/EBPβ, CCAAT/enhancer binding protein beta; FABP4, fatty acid-binding protein 4.

phase secreted protein to increase the migration of gastric cancer cells[513]. Cancer cell-derived exosomal HSPC111 promotes CXCL5 secretion by HSCs due to increased H3K27ac marks at the *Cxcl5* promoter (Fig. 5). The HDAC inhibitor TSA significantly enhanced HSPC111-induced CXCL5 expression, and TSA alone increased H3K27ac in the Cxcl5 promoter. CXCL5 overexpression leads to colon cancer liver metastasis[513]. The HDAC inhibitor SAHA (vorinostat) enhances the aggressiveness of cancer cells *via* promoting CAF secretion of tumor-supportive, proinflammatory cytokines, including CXCL1 and IL-8[514].

8.1.1. Therapeutic intervention targeting epigenetics in CAFs

Epigenetic therapeutic intervention targeting CAFs is currently undergoing clinical trials for cancer treatment[515–517]. Emerging research has emphasized investigating the epigenetic regulation of CAFs to transform them into homeostatic fibroblasts (HFS) and reconfigure their role from adversaries to allies[518]. By targeting specific signaling pathways and factors originating from tumors, it is possible to harness the plasticity of CAFs and transition them from tumor-promoting subtypes to a dormant state. For instance, the administration of all-trans retinoic acid (ATRA), calcipotriol and minnilide to activated CAFs has been shown to induce their reversion to a quiescent state, leading to enhanced therapeutic efficacy in pancreatic ductal adenocarcinoma (PDAC)[519].

Treatment against nicotinamide *N*-methyltransferase (NNMT) resulted in reversal of the CAF phenotype, suggesting that stromal methyltransferase activity can be targeted to normalize the metastatic stroma[508]. Furthermore, it has been observed that HDAC inhibitors can activate the cancer-promoting phenotype of CAFs in prostate cancer. This activation was found to enhance the invasiveness of cancer cells by promoting the secretion of tumor-supportive proinflammatory cytokines CXCL1 and IL-8 from CAFs. Specifically, the HDAC inhibitor SAHA (vorinostat) was shown to have this effect. On the other hand, inhibiting histone acetyltransferases (HAT) with drugs like c646 and A-485 may hold promise as potential therapeutic interventions[37].

Clinical trials have been initiated for drugs targeting miRNA due to its significant regulation of CAFs. One approach involves the use of miRNA mimics to counteract the overexpression of specific miRNAs in CAFs. Notably, in clinical experiments, the use of miR-211 has demonstrated efficacy in inhibiting the growth and migration of clinically derived BCAF[520]. On the other hand, although miRNAs have shown great potential in the treatment of BCAF, there is still no miRNA-based therapeutic being approved by the FDA targeting BCAF. This is likely due to the complexity of miRNA regulation and the fact that CAFs have numerous subtypes. Further investigation is required on this specific topic[521,522].

Another approach is to focus on paracrine signaling factors, such as TGF-β and CXCL12 secreted by CAFs, as well as cancer cell-derived PDGF-α/β, b-FGF, and IL-6[507,523]. The TGF-β signaling pathway plays a crucial role in influencing histone modification and DNA methylation in CAFs. It exerts its regulatory effect on epigenetic changes through the SMAD protein family, as well as through the involvement of epigenetic regulators such as c-SKI and SnoN proteins. Notably, inhibitors specifically targeting the TGF-β pathway in BCAFs, including esolimumab, galunisertib and tasisulam, are currently undergoing evaluation in clinical trials[524,525].

In conclusion, targeted therapy for CAFs through epigenetic regulation is becoming increasingly feasible. Advances in epigenetic research technology will lead to a more thorough and precise understanding of the epigenetic characteristics of CAFs, thereby advancing this novel approach to cancer treatment[524].

8.2. Immune cells

Immune escape is a remarkable feature of tumors, resulting in complex reactions within the tumor microenvironment, and making immune cells potential targets for radiotherapy and adjuvant radiosensitivity. Following radiotherapy, the activation of cell survival pathways and stimulation of the innate immune system lead to the occurrence of inflammatory signals. The inflammatory cytokine signaling (IL-1 and TNF-α) and immune cell recruitment are triggered by both direct and indirect radiation effects[526]. It is believed that the co-administration of radiotherapy and immunomodulatory therapy has the capacity to surmount adaptive immunosuppression[527].

Several studies have demonstrated that the accumulation of myeloid-derived immunosuppressive cells can result in a notable decrease in the radiosensitivity of cancer cells. Myeloid-derived suppressor cells (MDSCs) are crucial components of the immune microenvironment that contribute significantly to the progression of cancer[528]. Characterized by their potent immune-suppressive capabilities, MDSCs play a pivotal role in dampening immune responses[529]. In humans, two distinct types of MDSCs exist: polymorphonuclear cell MDSCs (PMN-MDSCs) and monocyte MDSCs (M-MDSCs), both of which exhibit robust immunosuppressive activities, thereby hindering the function of key immune cells, including T cells[530]. Furthermore, PMN-MDSCs and M-MDSCs are known to facilitate the development of tumor blood vessels and promote metastasis within the tumor microenvironment[531].

Despite the tumor-promoting effect of immunosuppression, immune cells in the tumor microenvironment also have a tumor-suppressing function by killing tumors. NK cells and T cells are the primary cells responsible for killing tumors[494,532,533,534]. Histone PTMs modification regulates the functions of various immune cells in the tumor microenvironment, such as the immunosuppressive function of MDSCs. Histone modification marks, including H3K9me3, H3K27me3, H3K4me3, H3K9ac and H3K56ac, play a crucial role in macrophage activation, M1/M2 polarization, and MDSC formation. In MDSCs treated with IL-33, H3K18ac and H3K14ac levels increased significantly, while H3K4me3 level decreased significantly[535,536]. These changes in histone modifications suggest transcriptional activation. Inhibiting the MLL1 complex disrupts lysosomal-associated membrane protein 2 (LAMP2) expression by reducing H3K4me3 at its promoter (Fig. 5), which maintains the immature state and immunosuppressive function of PMN-MDSC[537]. Increased H3K4me3 levels in the promoter region of *Arg1*, nitric oxide synthase 2 (*NOS2*), NADPH oxidase 2 (*NOX2*) and cyclooxygenase-2 (*COX2*) resulted in the activation of their transcription and strengthened MDSC immunosuppression[538]. The binding of DM6A removes H3K27me3, a modification deposited by EZH2. This removal of H3K27me3 activates the transcription of Hotairm1. Subsequently, increased levels of Hotairm1 interact with the S100A9 protein, facilitating its translocation from the cytosol to the nucleus of MDSCs. Consequently, this process triggers the production of MDSCs and augments their immunosuppressive effects[539,540]. Inhibiting CBP/EP300-BRD decreases H3K27ac levels of key genes essential for MDSC development and function, leading to transcriptional inactivation of these genes.

This ultimately results in reduced MDSC accumulation and impaired function[541].

Histone PTMs exert tumor suppressor effects by regulating T cells and NK cells. HDAC3 inhibitors could enhance the differentiation of $CD8^+$ T cells into cytotoxic effector cells[541]. SAHA HDACi enhances checkpoint blockade efficacy by rendering bladder cancer cells visible for T cell-mediated destruction[542]. Entinostat augments NK cell functions *via* epigenetic upregulation of the IFIT1−STING−STAT4 pathway[543]. Entinostat boosts the antitumor effectiveness of NK cells by increasing the NKG2D receptor and its ligands on both NK cells and tumor cells[544] (Fig. 5). Histone PTMs boost T cells' anti-cancer effect by modulating their self-activation process and cancer cell recognition, and boost NK cell anti-tumor activity by controlling NK cell activation and IFN-γ secretion (Fig. 5).

Histone modifications in $CD8^+$ T cells regulate differentiation and memory maintenance. The epigenetic control of gene expression plays a critical role in both the acquisition and maintenance of effector functions in $CD8^+$ T cells, as well as the establishment of antigen-specific memory populations. Recent studies have identified HDAC3 as a key epigenetic regulator governing effector differentiation and cytotoxic potential in $CD8^+$ T cells. While HDAC3 suppresses early cytotoxic activity during initial T cell activation[545], its sustained expression becomes critical for maintaining the persistence of activated $CD8^+$ T cells following resolution of acute infections[546].

Concomitantly, the histone demethylase KDM5 has been shown to suppress immune responses through STING pathway inhibition in $CD8^+$ T cells[547]. Notably, STING activation—resulting from loss-of-function mutations or epigenetic silencing of *STING/cGAS* promoter regions—enhances antigen presentation by upregulating MHC I molecules. This mechanism facilitates $CD8^+$ T cell activation and significantly improves cytotoxic T lymphocyte (CTL) recognition and killing efficiency[548].

8.2.1. Adipocytes

Histone acetylation regulates the effect of cancer-associated adipocytes (CAA) on cancer cells through both lipogenesis and fat metabolism in cancer cells. In the presence of cancer cells, adipose tissue undergoes various changes that contribute to the growth and metastasis of epithelial tumors. Adipocytes are cells that store long-chain fatty acids like triglycerides and cholesteryl esters in lipid droplets[549]. Tumor cells utilize the energy stored in these lipids and fatty acids from adipocytes. Fatty acids can enter the tumor *via* circulation or by interacting with adipocytes in the TME. Once taken up, fatty acids are stored as lipid droplets in tumor cells and subsequently undergo fatty acid oxidation for release[550]. Thus, fatty acid oxidation (FAO) is essential for cancer cells[551−554]. From the standpoint of altered lipolysis, FAO boosts tumor cell growth in conditions of nutrient deprivation, including hypoxia and metastasis, by supplying energy, combating oxidative stress, enhancing drug resistance, and sustaining tumor stemness[555−557]. Adipocytes control cancer cell lipid metabolism by releasing adipokines like adiponectin, leptin, IL-6, IL-8 and MCP1 (Fig. 5), which influence cancer cell growth and spread[558]. Similarly, adipocyte-mediated radiotolerance is one of the mechanisms through which adipokines such as TNFα, IGF-1 and HGF, as well as the activation of NF-κB, regulate the therapeutic response of tumor cells[553,559,560]. Adipocytes stimulate AMPK phosphorylation in cancer cells, leading to increased protein expression of carnitine palmitoyltransferase 1 (CPT1) and acyl-CoA oxidase 1 (Fig. 5), the first enzyme in the β-oxidation pathway. This process regulates how cancer cells induce adipocyte lipolysis[561]. As adipocytes proliferate and mature, stored lipids are transported outward and taken up by cancer cells. There are four major classes of fatty acid receptors, among which the CD36 transporter is associated with multiple pro-tumorigenic phenotypes in cancer cells. The uptake of free FA (such as oleate and palmitate) *via* CD36 activates the Wnt and TGF-β signaling pathways in liver cancer cells, thereby promoting EMT[562].

Histone PTMs modification plays an important role in adipogenesis in CAA. Adipogenesis is a complex process strictly regulated by a well-established cascade of sequence-specific transcription factors. Enhancer binding protein-α (C/EBPα) and peroxisome proliferator-activated receptor-γ (PPARγ) are described as two key transcription factors. HAT family members, such as p300/CBP, Tip60, SRC-1 and PCAF (Fig. 5), are important for adipogenesis[563]. PCAF activates *ATF4*, a pivotal gene in the proliferation of adipocytes[564]. Tip60 regulates the expression of PPARγ, a major regulator of adipocyte differentiation[565]. Co-expression of SRC-1 with PPARγ enhances the transcriptional activity of adipogenesis[566]. During early adipogenesis, p300/CBP acts as a co-regulator of the glucocorticoid receptor C/EBPβ, playing a role in cell proliferation, development and differentiation[567] (Fig. 5).

Histone acetylation plays an important role in the regulation of fatty acid metabolism in cancer cells. Following translocation to the inner side of the cell membrane, the FA binds to fatty acid-binding proteins (FABPs), is escorted to cellular organelles, and is subsequently metabolized[568] (Fig. 5). In colon cancer, elevated acetylation of H3 leads to abnormal expression of FAO-related genes and fosters tumorigenesis[569]. Increased acetylation of H3K27 in pancreatic β-cells upregulates acetyl-CoA acyltransferase 2 (ACAA2) and SLC25A20 expression and promotes FAO[570,571] (Fig. 5). In addition, the changes in lipid metabolism within the tumor microenvironment play a crucial role during tumor treatment. One of the most prominent metabolic alterations in cancer is the dysregulation of lipid metabolism[572]. This dysregulation plays a critical role in meeting the diverse needs of cancer cells, providing them with essential energy, biofilm components, and signaling molecules necessary for a range of processes including proliferation, survival, invasion, metastasis and response to the effects of cancer therapies and changes in the tumor microenvironment. Recent reports indicate that targeting FATP2 ablates the uptake of lipids and renders melanoma cells in an aged microenvironment sensitive to targeted therapy[573]. Targeting fatty acid receptor CD36 impairs oral cancer metastasis[574]. In melanoma cells, adipocyte-derived lipids are taken up by FATP family proteins. Inhibition of FATPs decreases melanoma lipid uptake, invasion and growth[575]. Hence, the action of FATPs presents a potential mechanism for how stromal adipocytes drive tumor progression and targeting FATPs offers a novel microenvironmental therapeutic strategy[576]. In response to glucose limitation, the levels of acetyl-CoA are decreased, subsequently leading to reduced acetylation of H3 histones. This reduction in histone acetylation is accompanied by changes in the acetylation sites. Specifically, the acetylation of sites associated with the promotion of gluconeogenesis and fatty acid oxidation is observed to increase as a result of the activity of the histone acetyltransferase Gcn5[488].

9. Combination of histone PTMs regulating drugs with radiotherapy

We have discussed that post-translational modifications of histones can reshape the radioresponsiveness of tumor cells through

multiple mechanisms[548]. Therefore, the development of therapeutic drugs that overcome tumor radioresistance by targeting histone modification has emerged as a significant advancement in this field[577]. The primary targets of radioresistance inhibitors encompass histone modifying enzymes, notably histone deacetylase[578], histone methylase[579,580], histone citrullinase[98], as well as proteins recruited by histone modification like BET protein[581,582].

HDACi are small molecule compounds, either natural or synthetic, that function to inhibit the enzyme activity of histone deacetylases, thus preventing the deacetylation of histones (Fig. 6). These inhibitors can be categorized into several types, which include fatty acids, hydroxamic acids, cyclic peptides, and benzamides. Fatty acids like butyrate, phenyl butyrate, and valproic acid, hydroxamic acids such as TSA and SAHA (vorinosta), cyclic peptides that include FK-228, apicidin and epoxide hydroxamic acid, as well as benzamides such as MS-275 and MGCD0103, are among the various subtypes of HDACi (Fig. 6). HDACi have demonstrated the ability to boost radiosensitivity in various types of cancer, as indicated by preclinical investigations, which include head and neck squamous cell carcinoma[583], NSCLC[584], colorectal cancer[585], prostate cancer[586], ovarian cancer[587], melanoma[587] and metastatic breast cancer[588]. HDACi has been shown to provoke G2/M cell cycle arrest[589], induce cancer cell apoptosis[590], and hinder DNA damage repair in cancer cells[591]. Moreover, HDACi interacts with DNA damage response proteins, such as 53BP1, contributing to radiosensitization. Combined treatment with HDACi and radiotherapy leads to alterations in chromatin condensation arrangement, ultimately resulting in amplified tumor cell death. The collective treatment with DNA-damaging agents and radiotherapy has been found to significantly augment tumor DNA damage while reducing repair kinetics[592]. In addition, the interaction between HDACi and ionizing radiation has been observed to impact a range of critical DNA repair components and cell cycle mechanisms, ultimately modifying their function and increasing tumor cell death[593]. The HDAC inhibitor Panobinostat when combined with other radiation modes in addition to X-ray, showed a better radiosensitization effect. Panobinostat heightened G2/M phase arrest and intracellular ROS production, as well as amplified DNA damage caused by proton irradiation. Additionally, proton irradiation further intensified the impact of Panobinostat[594]. The combined treatment of heavy ion radiotherapy and the HDACi SAHA significantly delayed tumor growth by increasing apoptosis, upregulating *p53* and *p21* (Waf1/Cip1) expression, and inhibiting proliferation and angiogenesis[595]. Valproic acid (VPA), when combined with proton and photon irradiation, has demonstrated effectiveness in treating hepatocellular carcinoma (HCC) cells. VPA prolonged proton-induced DNA damage and enhanced proton-induced apoptosis[594]. Furthermore, the HDACi SAHA enhances the sensitivity of pediatric sarcoma cell lines to conventional photon radiotherapy (XRT)[596]. SAHA led to heightened sensitivity to heavy ions, elevated DSBs and increased apoptosis in both sarcoma cell lines. Carbon ion combining with HDACi treatments significantly decreased the survival rate of glioblastoma compared to X-ray treatment[597] (Table 2[598–611]).

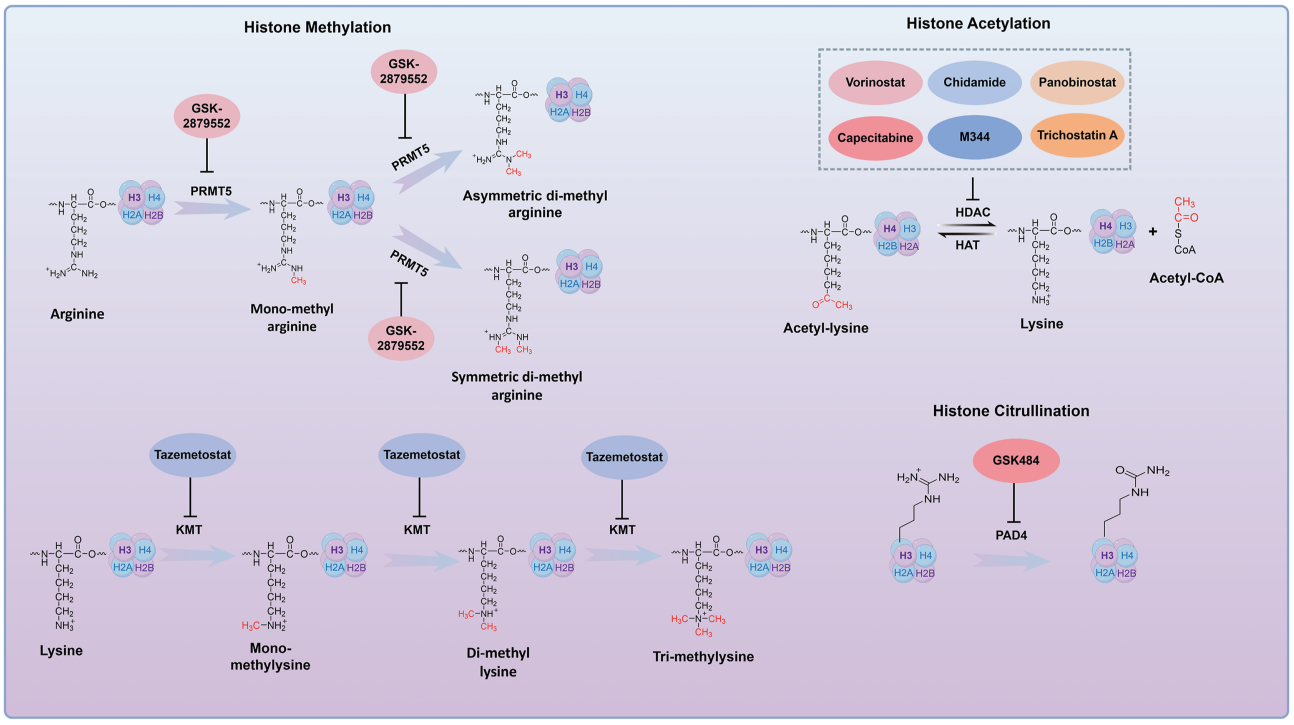
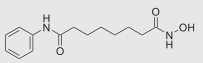
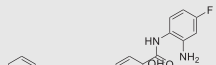
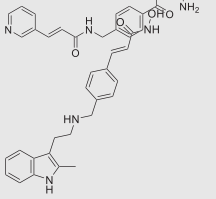
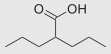
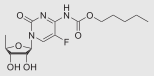
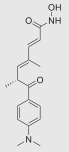
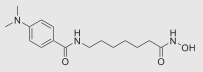


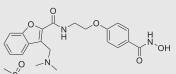
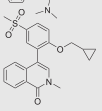
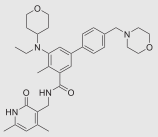
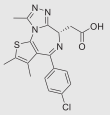
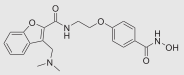
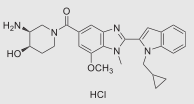
Figure 6 Histone modification enzymes targeting inhibitors. Histone methylation encompasses arginine methylation and lysine methylation. Arginine methylation occurs as mono- or dimethylation, the latter potentially being asymmetric. On the other hand, lysine methylation may involve single, double, or triple methylation. GSK-2879552 is an inhibitor targeting arginase PRMT4, while Tazemetosta inhibits lysine methylase KDM EZH2, thereby modulating histone lysine methylation status. As for histone acetylation, all six inhibitors in the frame act on HDACs, and HDACs have pan-inhibitors, while other histone modification enzymes do not. Additionally, PAD4, a histone citrullination, is the sole histone citrullination that has developed an inhibitor. GSK484 is a small molecular inhibitor targeting PAD4 to effectively regulate histone citrulline levels. PRMT4, protein arginine methyltransferase 4; KMT, lysine methyltransferase.

Table 2 Clinical trials and basic research targeting histone modification in cancer therapy, sourced from the ClinicalTrials.gov database (https://clinicaltrials.gov/ct2/home).

Target	Drug name	Chemical structure	Phase	Cancer	Combination therapy	Mechanism	Ref./NCT number
HADC	Vorinostat		I	Spongioblastoma	Pembrolizumab with radiotherapy		NCT03426891
			II	HPV-related squamous cell carcinoma	Radiotherapy		NCT05608369
			II/III	ETP-ALL	Radiotherapy		NCT3553238
			I	Non-small cell lung cancer	Radiotherapy		NCT00821951
			I	Pelvic cancer	Standard palliative radiotherapy		NCT00455351
			I	Non-hodgkin lymphoma	Nicotinamide, etoposide combination with radiotherapy		NCT00691210
			I/II	Pancreatic cancer	Radiotherapy		NCT00831493
			Preclinical research	Prostate cancer		Cell survival and sensitivity pathway	598
			Preclinical research	Colorectal carcinoma		Decreased modulation of thymidylate synthase; decreased p53 expression	599
			Preclinical research	Colorectal carcinoma		S-phase cells was reduced by OXO3A	600
	Chidamide		II/III	Adult ETP-ALL	Radiotherapy		NCT03553238
	Panobinostat (LBH589)		I	Brain tumors	Stereotactic radiation therapy 10 fractions each of 3.5Gy		NCT01324635
			I	Prostate cancer	External beam radiotherapy		NCT00670553
			I/II	Newly-diagnosed diffuse intrinsic pontine glioma	MTX110 and radiotherapy		NCT03566199
			Preclinical research	Non-small cell lung cancer		Increases duration of gamma-H2AX foci	601
			Preclinical research	Bladder cancer		Mitigates CXCL1 signalling	602
	Valproic acid		II	Brain tumors	With temozolomide and radiotherapy		NCT00302159
	Capecitabine		I	Nonmetastatic pancreatic cancer	Vorinostat and radiotherapy		NCT00983268
	TSA		Preclinical research	Prostatic cancer			277
			Preclinical research	Squamous carcinoma cell line SQ-20B and SCC-35			603
	M344		Preclinical research	Pancreatic cance		Increasing the susceptibility of pancreatic cancer cells to T cell lysis	604

(*continued on next page*)

Table 2 (*continued*)

Target	Drug name	Chemical structure	Phase	Cancer	Combination therapy	Mechanism	Ref./NCT number
	PCI-24781		Preclinical research	Pediatric glioblastoma		Inhibit the expression of the Rad51 protein	605
BET	Trotabresib		I	HER2$^+$ breast cancer	Radiotherapy		NCT06137651
			I/II				
			I	Glioblastoma	Radiotherapy		NCT04047303
EZH2	Tazemetostat			Melanoma	Radiotherapy		NCT04557956
				Pediatric brain tumors			606
PRMT5	GSK3326595		II	Breast cancer			NCT04676516
BRD4	JQ1		Preclinical research	Cervical cancer		Inhibition of RAD51AP1 to enhance DNA damage	411
			Preclinical research	Testicular germ cell		Growth arrest and apoptosis	607
	OTX015		Preclinical research	Prostate cancer		Preventing reversal of stalled replication forks by downregulating RAD51 expression	405
PAD4	GSK484		Preclinical research	Colorectal cancer			609
			Preclinical research	Nasopharyngeal carcinoma		Inhibits neutrophil extracellular traps	610
			Preclinical research	Triple-negative breast cancer			611

EZH2, a histone lysine methyltransferase, is an appealing target for brain tumors. It is the catalytic subunit of Polycomb repressive complex 2, a protein complex that catalyzes the trimethylation of histone 3 at lysine 27 (H3K27)[611]. Tazemetostat, an orally available EZH2 inhibitor (Fig. 6), has entered clinical trials for melanoma. It has recently been approved by the FDA for patients with epithelioid sarcoma and relapsed/refractory follicular lymphoma[612]. Additionally, tazemetostat would enhance animal survival times in PDOX models with fractionated radiation for pediatric brain tumors[606] (Table 2).

Recent progress in cancer therapy has focused on histone citrullination, the inhibitory effect of which has been confirmed in various cancer types, including lung[158], gastric[613], liver[614], bladder and prostate cancer[614]. Particularly, the investigation of protein arginine deiminase (PAD) inhibitors has garnered significant attention, with PAD4 inhibitors being of particular interest[615–617]. In previous studies, PAD4 inhibitors such as Taxol, benzoyl-*Nω*, *Nω*-dimethylarginine (Bz-ADMA), streptomycin, minocycline, and tetracycline were identified[618–622]. However, these inhibitors exhibited poor selectivity and catalytic activity, which were effective only at high micromolar to millimolar concentrations, limiting their application prospects as PAD inhibitors. Fortunately, GSK121 was identified as a lead compound for inhibiting PAD4 (Fig. 6). Subsequent lead compound optimization led to the development of more efficient and reversible PAD4-specific inhibitors, namely GSK199 and GSK484[610]. Among these, the radiosensitizing effect of GSK484 has been verified in colorectal cancer, nasopharyngeal carcinoma and triple-negative breast cancer[608,609,623]. The latest advancements in clinical trials have combined PAD inhibitors with radiotherapy in the treatment of various cancers (Table 2).

The BET protein family, previously discussed in detail, exerts a significant impact on radiosensitivity. It represents a promising target for cancer therapy by modulating homologous repair and non-homologous repair following DNA double-strand break repair, thereby influencing radiosensitivity[428] (Fig. 4). With numerous family members, an array of inhibitors has been produced[624], including JQ1 and its analogues[625], I-BET762, BET-PROTAC, OTX015[626] and trotabresib[627]. Currently, there are different types of BET inhibitors based on their principle of action, including non-selective BET inhibitors, selective BD1 inhibitors, selective BD2 inhibitors, and BET degraders. These inhibitors have been tested in the clinical treatment of NUT midline cancer and various solid tumors. Notably, most of these inhibitors are still in the early stages of clinical development (stages I and II)[628]. Specific inhibitors, such as ABBV-744, AZD5153, dBET57 and MZ1, selectively target the BD1 or BD2 domains of the BET protein family[629]. These inhibitors hold potential for effectively modulating the functions of BET proteins in the context of cancer therapy[630]. A breakthrough has been achieved in combining BET inhibitors with radiotherapy. Trotabresib, a BET inhibitor, has progressed to the phase I clinical trial for HER2 positive breast cancer in combination with radiotherapy in December 2023 (NCT06137651) and the same combination therapy radiotherapy combined trial has also entered the phase I clinical trial for glioblastoma in January 2020. The clinical research revealed consistent

dosing of trotabresib (30 mg/day) in both monotherapy and combination therapy with radiotherapy[631,632]. Notably, one patient achieved a complete response and no serious adverse events, indicating favorable tolerability of the combined therapy in GBM (NCT04324840). JQ1, an inhibitor of the BET protein family member BRD4, enhanced radiosensitivity in several cancer models[406]. In NSCLC, JQ1 upregulates p21 to inhibit DNA repair and induce G2/M cell cycle arrest and apoptosis[406]. In testicular germ cell tumors, the BRD4 inhibitor OTX015 enhances the radiosensitivity by downregulating RAD51 expression, preventing the reversal of stalled replication forks in prostate cancer[405] (Table 2).

Although the combined application of histone modifying drugs and radiotherapy for the treatment of malignant tumors has become a promising therapeutic strategy, the clinical translation still faces many challenges. Histone modifying drugs lack targeting ability, for the relevant modifying enzymes or protein families are expressed in both tumor cells and normal cells. The enrichment of histone modifying drugs in tumors depends on the differences in the levels and activities of histone modifying enzymes between tumor cells and normal tissue cells. Thus, histone modifying drugs often result in systemic toxicity. Vorinostat demonstrated notable adverse effects in Phase II trials, including fatigue, nausea, diarrhea, anorexia, dysgeusia, thrombocytopenia, and thrombosis[633−635]. Similarly, panobinostat trials reported high incidences of fatigue (62.9%), nausea (51.4%), and thrombocytopenia (45.7%)[636]. In contrast, chidamide—a class I HDAC-selective inhibitor—showed reduced toxicity, with primary adverse events limited to thrombocytopenia, leukopenia, and neutropenia, likely due to its target specificity[637]. Moreover, HDAC inhibitors (HDACis) exhibit limited efficacy in solid tumors, failing to demonstrate clinical benefits in breast, renal, and prostate cancers[638]. This is partly attributed to acquired resistance mechanisms. For instance, feedback activation of leukemia inhibitory factor receptor (LIFR). Novel combination therapies aim to address resistance. A hybrid inhibitor targeting JAK1−STAT3−BCL2 signaling pathways has shown promise in enhancing apoptosis induction and overcoming drug resistance[639]. These approaches highlight the potential of multi-targeted strategies to improve therapeutic outcomes in solid malignancies. Signaling in breast cancer diminishes HDAC inhibition efficacy[640].

Overall, both preclinical and clinical studies have demonstrated the potential of combining drugs that target histone modifications with radiotherapy. However, it is essential to consider the potential toxicities that may be induced by the drugs and radiation during clinical trials and actual clinical application.

10. Histone PTMs in radiation-induced injuries of normal tissues

During radiotherapy, ionizing radiation often causes damage to normal tissues. In the typical pathogenesis of radiation-induced tissue damage, direct damage caused by radiation, as well as indirect damage resulting from ROS, occurs within several seconds following radiation exposure, leading to the destruction of subcellular structure, DNA, lipid and proteins. This process results in aberrant DNA damage repair mechanisms and triggers cell death[35]. In the above statement, we have elucidated the alterations in histone modification levels within cancer cells and their implications for DNA damage repair and apoptosis[641,642]. Notably, radiation exposure also alters histone modification levels in normal tissues[643]. Recent studies have highlighted the significant role of histone modifications in mediating radiation-induced injuries[644,645].

10.1. Radiation-induced lung injury

Radiotherapy is an important treatment regimen for lung cancer worldwide. However, the application of high-intensity radiotherapy is frequently constrained by the potential for lung tissue damage, with radiation pneumonitis occurring in approximately 30% of patients receiving thoracic radiation[646]. Radiation pneumonitis (RP) arises from an initial inflammatory response induced by damage to the lung parenchyma, epithelial cells, vascular endothelial cells, and stroma[647]. The clinical manifestations of radiation pneumonitis are cough, dyspnea, chest pain and chest tightness[648]. Acute radiation pneumonitis typically develops within 2−4 months after radiation treatment, while after 6 months following treatment chronic fibrosis tends to present. Furthermore, radiation-induced pneumonitis and fibrosis are the treatment-limiting toxicities among patients who have undergone radiotherapy[649,650]. Unfortunately, the mechanisms of radiation-induced lung injury remain incompletely understood and the strategies for its prevention and treatment need to be explored.

Recent studies have shown that histones are closely related to the occurrence and development of radiation-induced lung injury. In lung parenchyma, pneumocytes show dose-dependent H2A.J expression in response to radiation-induced DNA damage, therefore contributing to pro-inflammatory tissue reactions and promoting radiosensitivity[651]. In radiation pulmonary fibrosis, through the process of EMT, pulmonary epithelial cells acquire a mesenchymal phenotype, ultimately contributing to fibrosis. The downregulation of E-cadherin serves as a biomarker for EMT[652]. Interestingly, in irradiated lung tissue, there was an observed enrichment of H3K9me3 on the E-cadherin promoter, indicating that H3K9me3 may be a potential target for irradiation-induced pneumonitis[653]. Consequently, targeting H3K9me3 at the E-cadherin promoter may represent an effective strategy for the prevention of radiation-induced pulmonary fibrosis.

10.2. Radiation-induced intestinal injury

In abdominal radiotherapy, over 75% of patients are likely to experience acute radiation-induced intestinal injury, which presents as post-radiation bleeding, pain, or fecal incontinence[654,655]. Radiation-induced intestinal injury is associated with significant morbidity and mortality that impairs cancer patients' and survivors' quality of life[647]. High-dose radiation induces intestinal epithelial barrier, vascular endothelial damage and intestinal stem cells damage, which aggravates the inflammatory response of the intestinal tract and results in sepsis and death[656]. In addition, abdominal radiotherapy usually induces gut immune imbalance. Recent preclinical research has shown that decreased numbers of neutrophils, macrophages, and B and T lymphocytes after in the distal colonic mucosa after fractionated radiation[657]. Unfortunately, specific treatment strategies for radiation-induced intestinal injury are lacking[658].

Recent studies have shown that histone modification plays an important role in radiation-induced intestinal injury. The abnormal expression of Sirt1 is often accompanied by radiation injury in normal tissues[659]. In the context of radiation-induced intestinal injury, resveratrol mitigates damage to IEC-6 cells by inhibiting apoptosis and enhancing autophagy through the activation of SIRT1[660]. Propionic acid, a short-chain fatty acid produced by microbial activity, facilitates the radioprotective effect by binding to G-protein coupled

receptor 43 (GPR43) on the surface of intestinal epithelial cells. This interaction results in increased histone acetylation, thereby upregulating the expression of tight junction proteins, such as Occludin and ZO-1, and augmenting mucin levels. Consequently, these molecular events enhance the integrity of the intestinal epithelial barrier and mitigate radiation-induced intestinal damage[661].

Radiation is recognized as being particularly detrimental to proliferating cells, and the response of normal stem cells to radiation exposure is of paramount importance due to their central role in tissue repair and regeneration[662]. In addition to intestinal mature cells, radiation could expedite the senescence process in stem cells, characterized by cell cycle arrest, activation of the DNA damage response, and alterations in senescence-associated secretory phenotypes[663]. This senescent state may result in a loss of regenerative capacity in stem cells. Furthermore, radiation is more prone to induce DNA damage in stem cells, thereby increasing apoptosis in these cells. Protecting stem cell radioresistance is more effective than normal cell protection, and targeting histone modifications offers a potential stem cell therapy[664,665]. High-dose radiation exposure induces gastrointestinal (GI) stem cell death, resulting in denudation of the intestinal mucosa and lethality from GI syndrome. Sirtuin1 (SIRT1) inhibition significantly improved mouse and human intestinal organoid survival after irradiation by stabilizing P53[666]. In addition, HDAC inhibitor protects intestinal LGR5^{+} stem cells against radiation *via* NOTCH signaling[665]. Polycomb-repressive complex 2 (PRC2) impedes the regeneration of intestinal stem cells following irradiation by repressing Cdkn2a expression *via* H3K27 trimethylation[667]. Furthermore, numerous studies have demonstrated that histone modifications significantly influence DNA damage repair mechanisms in stem cells. Acetylation and methylation at various residues of the H3 histone have been demonstrated to significantly influence the radiosensitivity of stem cells. Specifically, a localized downregulation of H3K9ac has been observed in embryonic stem (ES) cells, which is associated with the recruitment of the transcription factor OCT4 to sites of DNA damage[668]. Notably, H3K9 trimethylation plays a critical role in regulating ATM activation following DSBs[669]. Deacetylation and trimethylation of H3K9 have been shown to increase stem cell radiation resistance, reduce radiation-induced apoptotic responses, and induce DDR activation[670,671]. Moreover, persistently elevated levels of H3K56 acetylation in stem cells lead to the formation of a repressive chromatin environment, which hinders the activation of the DDR and enhances radiosensitivity[672,673]. The recruitment of histone deacetylases and the subsequent deacetylation of H3K56ac are essential for the complete activation of DDR in stem cells DDR[674]. Knockdown of H3K56 acetyltransferase p300 reduced H3K56ac and significantly decreased radiosensitivity, restored DDR function, and increased stem cell survival[675].

10.3. Radiation-induced skin injury

During tumor radiotherapy, the skin is particularly susceptible to damage, with approximately 85%−95% of cancer patients experiencing varying degrees of radiation-induced skin damage as a consequence of the treatment[676]. The clinical manifestations of radiation-induced skin injury encompass a spectrum from mild erythema to more severe conditions such as wet desquamation, ulceration, skin necrosis, fibrosis, and telangiectasia. Exposure to high doses of radiation can result in exfoliation of the affected epidermis, accompanied by persistent edema and fibrin exudation[677−679]. Such severe dermatological reactions frequently necessitate the premature cessation of radiotherapy, thereby adversely affecting patient quality of life[680,681]. Thus, further research is required to enhance protective measures against radiation skin injury[679].

After radiation, histone variant H2A.J is increased in epidermal keratinocyte[682]. Histone variant H2A.J is a biomarker for premature senescence after ionizing radiation, which promotes an inflammation response in response to DNA damage[683,684]. In a recent study, shRNA-mediated H2A.J depletion could ablate SASP, without affecting the senescence-associated growth arrest to increase radioresistance of skin[685]. Apart from X-ray, ultraviolet radiation-induced gene expression changes and alterations to histone methylation in primary human dermal fibroblasts. Besides, in human skin exposed to UV irradiation, there is an observed increase in acetylated histone H3 levels, while the activity of HDACs and the expression of HDAC4, HDAC11, and SIRT4 are significantly reduced[686]. In recent studies, alteration of histone modification by UVR may contribute to the upregulation of matrix metalloproteinase (MMPs), matrix remodeling, thus promoting radioresistance of skin[687]. In addition, ultraviolet radiation could influence both histone acetyltransferase and HDAC activities causing decreased histone acetylation[688]. In conclusion, targeting histone modifications might be a potential strategy for radiation-induced skin injury treatment.

10.4. Targeting histone modification against radiation-induced injuries

Despite decades of research into suitable radiation countermeasures, there is still an absence of safe and effective radioprotective pharmaceuticals for the prevention, mitigation, or treatment of radiation-induced injuries. Symptomatic and supportive management plays a crucial role in the treatment and prognosis of patients suffering from radiation injury. Currently, the pharmacological interventions employed in clinical practice predominantly consist of conventional medications, such as moisturizers, nutritional supplements, glucocorticoids, non-steroidal anti-inflammatory drugs, antibiotics, and analgesics[689]. Currently, considering the significant impact of histone PTMs on radiation-induced injury, we provide a comprehensive summary of pharmacological agents targeting histone PTMs for the treatment of injuries.

In radiation-induced skin damage, histone deacetylases inhibit radiation-induced acute and late skin damage[690]. HDAC inhibitors facilitate the healing of wounds induced by radiation and mitigate the development of late-stage skin fibrosis[691]. In radiation-induced lung injury, polydatin induced a huge increase of *Sirt3*, thus promoting the expression of *Nrf2* and *PGC1α* in lung tissues. Studies showed that PD attenuated radiation-induced lung injury by inhibiting epithelial−mesenchymal transition and increasing the expression of Sirt3[692]. Besides, in an animal model of radiation-induced oral mucositis, the administration of the HDAC inhibitor phenyl butyrate was observed to enhance DNA repair and promote the survival of normal cells following radiotherapy, primarily through modulating *Rad51* expression and decreasing oxidative stress[693]. In addition to mature cells, targeting histone PTMs is also a potential therapeutic approach to treat radiation-induced stem cell damage. The safeguarding of stem cells expressing LGR5, a recognized marker of intestinal epithelial stem cells, constitutes a crucial strategy for mitigating radiation-induced damage[694]. Treatment with VPA in irradiated intestinal organoids has been shown to enhance both the population of LGR5-positive stem cells and the subsequent regeneration of organoids post-irradiation. VPA confers a significant protective effect on LGR5-positive stem cells *via* the activation of NOTCH signaling pathways[665]. Following irradiation, the administration of TSA led to an

increase in intestinal total antioxidant and glutathione levels by modulating the expression of antioxidant proteins, such as GCLC, GPX4, and TXNRD1[695]. In conclusion, the study of histone modification represents a promising avenue for advancing therapeutic interventions in the treatment of radiation-induced injuries.

11. Perspectives and challenges

With the continuous advancement of cancer treatment technologies, radiotherapy has been playing an increasingly significant role in cancer treatment. However, radioresistance in tumor cells remains a pressing clinical issue that needs to be addressed. In recent years, epigenetic modifications, particularly histone modifications, have garnered widespread attention as a key regulatory target for overcoming radioresistance[127]. Histone modification primarily impacts the degree of DNA−histone interaction by altering the charge carried by histone proteins. Moreover, the type and location of histone modifications significantly influence the chromatin structure and recruitment of readers, subsequently affecting the susceptibility of cancer cell DNA to ionizing radiation damage and modulating the efficiency of the DNA damage repair pathways[58,69,92]. However, the complex relationship between the histone PTMs landscape of tumors and tumor radioresistance has not been fully revealed. In the context of tumor heterogeneity, further research is needed on the combined application of histone modified drugs and radiation therapy. In this section, we will delve into several critical areas.

(1) **Histone PTMs within cancer cells.** Tumors comprise a heterogeneous collection of cells with distinct genetic and phenotypic properties that can differentially promote progression, metastasis and drug resistance. Tumor heterogeneity, particularly epigenetic heterogeneity characterized by DNA methylation and histone modification, is a critical determinant of radiation resistance. While its role in conferring therapeutic resistance has been increasingly recognized, the underlying mechanisms and targeted strategies remain under-explored and warrant further investigation[696,697]. The progress of omics technologies, including multiplexed-scAEBS, scBS-seq, and single-cell ATAC-seq, has opened up novel prospects for delineating the epigenetic profile of tumors and pinpointing factors associated with resistance[698]. These cutting-edge technologies offer a more holistic perspective of the epigenome. This perspective extends beyond histone modifications to encompass DNA methylation, RNA methylation, and non-coding RNA, while emphasizing the intricate interplay among diverse epigenetic regulators.

(2) **Tumor microenvironment (Histone PTMs beyond cancer cells).** Apart from cancer cells, histone modifications occur in cellular components of the tumor microenvironment, such as CAFs, CAA and immune cells, to influence cancer radiosensitivity[499,514]. Histone modifications regulate the energy supply of CAA to cancer cells by influencing early cell maturation and adipocyte proliferation[567]. Furthermore, aside from fat metabolism, various metabolites and amino acids are exchanged between adipocytes and cancer cells[699]. It is worth investigating whether histone modification in CAA plays a regulatory role in this process, potentially offering a strategy to impede the supply of CAA to tumor cells[35]. Interestingly, the HDAC inhibitor SAHA enhanced the aggressiveness of cancer cells *via* promoting CAF secretion of CXCL1 and IL-8[514]. In addition to impacting tumor aggressiveness, CAFs influence various cellular processes in cancer cells, including epithelial−mesenchymal transition, proliferation, and extracellular matrix remodeling[700]. Furthermore, the genes involved in these processes are subject to regulation by histone modifications. It is plausible that histone modifications in CAFs may have broader implications in cancer progression beyond solely affecting tumor aggressiveness[701]. At present, there is increasing evidence that histone modifications in cellular components of the tumor microenvironment play an important role in the regulation of cancer radiosensitivity. The effect of histone modifications on the cellular components of the tumor microenvironment requires further study. For instance, the potential impact of histone modifications on nerve cells within the tumor microenvironment in influencing the malignancy warrants further investigation. Crucially, the complex architecture of the tumor microenvironment incorporates diverse stromal and immune cell populations not examined in the present study, which highlights critical research avenues for elucidating the epigenetic regulation mediated by histone modifications in malignant progression[702].

(3) **Epigenetic regulation crosstalk in tumor microenvironment.** Beyond their cell-autonomous effects on tumorigenesis through direct effect, histone PTMs alterations epigenetically orchestrate TME remodeling by interactions with other epigenetic regulators[38]. The complex interactions of histone modification, non-coding RNA, and DNA methylation in CAFs may impact the radioresistance of cancer cells. N-methyltransferase (NNMT) has been found to exert its influence on histone methylation levels by modulating the trimethylation of H3K4 and H3K27 in CAFs[339]. LncRNA DNM3OS interacts with KDM6B to regulate H3K27me3. It is reported that inhibiting lncRNA DNM3OS significantly enhances the radiosensitivity of esophageal cancer cells[497]. Furthermore, lncRNA DNM3OS is overexpressed in CAFs[497,561,621]. In conclusion, crosstalk between lncRNA DNM3OS and histone methylation may be correlated with radiotolerance. Therefore, epigenetic crosstalk in CAFs has a broad prospect for regulating cancer radioresistance. The intercellular epigenetic crosstalk among non-malignant cellular constituents within the tumor microenvironment and their potential contribution to radiotherapy resistance remain to be systematically elucidated.

(4) **Histone modifications regulate the radioprotection of normal tissues.** In radiation-induced intestinal damage, expression of histone H3 methylation is increased[703]. And in radiation-induced damage of human dermal fibroblasts, histone PTMs regulate BRCA2 to repair DSB[704]. VPA was identified as a potent radioprotector *via* the inhibition of NOTCH signaling in an intestinal organoid culture system[665]. In the skin damage model system caused by UV, inhibiting EZH2 is a potential anti-aging strategy for preventing UV-induced skin aging[705]. Moreover, UV treatment decreases the expression of HDAC4 to regulate the expression of MMP-1 and type I procollagen[706]. The SIRT1 inhibitors improve the survival of intestinal stem cells, reducing radiation-induced GI syndrome[666]. These findings indicate that targeting histone PTMs could be a viable treatment for radiation-induced normal tissue injury. It

seems likely that histone modification inhibitors can be utilized as a skin medication or skin adjuvant for the prevention or treatment of radiation-induced skin damage.

(5) **Adjuvant radiotherapy.** In addition to mechanistic studies, significant advances have been achieved in the therapeutic effects of histone drugs on tumor radiosensitivity. In recent years, the combination of HADCi bromodomain protein inhibitors and EZH2 inhibitors with radiotherapy has been proven to be effective in clinical and basic research. Despite these advancements, the exploration of histone modifications' impact on cancer radiosensitivity encounters various challenges[105]. More effort is needed to fully characterize the connection between histone modifications and cancer radiosensitivity. For example, the methylation reader chromo domain and Tudor domain proteins and the phosphorylation reader FHA and WD40 domain proteins, remain poorly examined in terms of their connections with radiosensitivity. These proteins are intricately involved in the DNA damage repair pathways and could potentially serve as targets for enhancing radiosensitivity[707]. Notably, there is a lack of research on inhibitors of certain histone modifications, such as histone lactylation, histone sumoylation, and histone crotonylation. Given their important roles in cancer, the development of new inhibitors of these histone modifications holds great promise in overcoming radioresistance.

In recent years, various novel radiotherapy techniques have emerged, with different types of ionizing radiation being utilized for cancer treatment[7]. These include not only photons, electrons, protons, and heavy ions but also different dose-rate regimens such as conventional radiotherapy and FLASH radiotherapy. As discussed earlier, chromatin structure may play distinct roles under different LET (linear energy transfer) conditions. Beyond LET, other physical parameters, such as dose rate, can also influence the interaction between ionizing radiation and chromatin at the molecular and atomic levels. Therefore, the combination of histone modification drugs with radiotherapy presents many complex issues that need to be addressed. Moreover, as an innovative radiotherapy technique, FLASH radiotherapy (dose rate >40 Gy/s) demonstrates a substantial protective effect on mitochondria in comparison to conventional radiotherapy. Mitochondria play a crucial regulatory role in the metabolism of lactate and NO within cancer cells. Consequently, FLASH may have a potential regulatory impact on histone modifications, particularly histone lactylation in cancer[708]. Furthermore, the alterations in histone modifications within the histone landscape under FLASH radiotherapy have not been thoroughly investigated, representing a prospective avenue for future research in FLASH-based cancer therapy. Furthermore, FLASH irradiation does not significantly impair tumor vasculature and preserves the capacity for drug delivery[709]. Consequently, this facilitates the enhanced delivery of histone modification drugs to solid tumors, thereby contributing to the mitigation of radiotherapy resistance associated with these drugs.

In addition, there have been major breakthroughs in the research of histone modification drugs as adjuvant radiotherapy. It is worth noting that the HADCi-related iorinostat and chidamide, currently in phase III clinical trials, may potentially be incorporated into the list of clinical drugs in the future[710]. This development underscores the potential efficacy of combining histone modification drugs with radiotherapy. As we have highlighted earlier, different types of cancer exhibit distinct histone modification abnormalities[501,538]. Therefore, it is essential to consider utilizing cancer type-specific histone modification inhibitors in conjunction with radiotherapy for optimal treatment outcomes.

12. Conclusions

In this comprehensive review, we have explored the intricate landscape of histone PTMs and their pivotal roles in modulating the radiosensitivity of tumors. The aberrant histone modification profiles frequently observed in cancers significantly influence the chromatin structure and function, thereby affecting the efficiency of the DNA damage response and contributing to radioresistance. We have detailed the mechanisms by which histone modifications, including acetylation, methylation, phosphorylation, and others, regulate chromatin dynamics and impact tumor cell radiosensitivity. Additionally, we have highlighted the emerging roles of histone modification readers and the tumor microenvironment in shaping the response to radiation therapy.

Looking ahead, the integration of histone modifying drugs with radiotherapy holds substantial promise for enhancing treatment efficacy and overcoming radioresistance. However, this promising approach is not without challenges. Critical issues such as off-target effects, toxicity, and the need for biomarkers to identify patients who will benefit most from such combinations must be addressed. In addition, with the rapid development of radiotherapy technology, various ionizing radiations with different physical parameters are used for the radiation therapy of tumors. How to adjust the histone modified landscape and chromatin state to make tumor cells most sensitive to ionizing radiation of specific physical parameters is a very complex issue. Furthermore, Future research should focus on elucidating the complex interplay between histone modifications and other cellular pathways or epigenetic modifications, developing more selective and effective histone-modifying agents, and conducting robust clinical trials to validate these therapeutic strategies.

In summary, this review underscores the multifaceted roles of histone PTMs in cancer radiosensitivity and highlights the potential of histone modification-targeting therapies to improve outcomes for patients undergoing radiotherapy. As we continue to unravel the intricate mechanisms underlying histone modifications, we anticipate significant advancements in the development of more effective and personalized cancer treatments.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to polish the grammar and words of our manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Author contributions

Jiawei Song, Hao Bai and Lu Ye wrote the main manuscript text. Jiawei Song, Huaijin Qiao and Junlong Dai prepared Figs. 1−5. Shuyu Zhang and Hao Bai prepared the figures planning. Shuyu Zhang, Weiqun Ding and Hao Bai planned and revised the text. All authors reviewed the manuscript.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Figures were created with biorender.com and figdraw.com.

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