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REVIEW

Obesity−cancer axis crosstalk: Molecular insights and therapeutic approaches

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Abstract Now recognized as a global health crisis, obesity has been linked to an increased risk of many types of cancer, including those of the breast, colon, rectum, uterus, gallbladder, and ovary. Obesity and cancer share several characteristics at the cellular, molecular, and epigenetic levels. Obesity is characterized by chronic inflammation of the adipose tissue (AT), resulting in genotoxic stress that further induces metabolic complications and contributes to the initiation and progression of cancer. The excessive accumulation of AT provides adipokines and lipids to engage tumor cells with stromal and immune cells to infiltrate carcinomas and secrete a plethora of cytokines, chemokines, and growth factors within the tumor microenvironment (TME) that contribute to carcinogenesis. Obesity also alters the metabolic reprogramming of immune cells, including macrophages, neutrophils, and T cells, thereby providing a suitable environment for the growth and progression of cancer. Obesity-associated metabolic dysregulation also perturbs the gut microbiome, which produces metabolites that can further increase the risk of cancer progression. This review will discuss links between obesity and cancer progression, including several crucial pathways that bridge the crosstalk between obesity-associated changes in AT inflammation, immune cells, adipokines, chemokines, and tumor cells to support cancer progression. We will also discuss our insights into the mechanisms by which obesity-driven factors influence metabolic reprogramming and touch base on how obesity mediates microbiome dysbiosis to alter metabolite and affect cancer progression. Altogether, this review highlights the crossroads of the obesity−cancer axis, describes its salient features, and presents possible therapeutic approaches for obesity-related cancers.

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1. Introduction

The World Health Organization (WHO) has declared the worldwide prevalence of obesity to be a global pandemic. In the human body, adipose tissue (AT) functions primarily as a fat depot but it also possesses endocrine functions that regulate normal physiology by producing and secreting adipokines. AT maintains its metabolic homeostasis and fat-storing functions during obesity[1,2], where it supports low-grade chronic inflammation. AT also exacerbates obesity, which is a predisposing factor for several abnormal conditions, including metabolic, autoimmune, cardiovascular, and neurological disorders[3]. Importantly, the inflammatory and endocrine effects of AT during obesity are a major risk for type 2 diabetes mellitus (T2DM), which has been proposed as a crucial factor that links obesity with cancer[4]. The US Centers for Disease Control and Prevention (CDC) documents the linkage between obesity and 13 types of cancers, including colorectal, breast, liver, and pancreatic cancers. Obesity worsens cancer conditions, ultimately leading to death[5], while weight reduction decreases the incidence of colorectal and breast cancer[6]. Therefore, the use of animal models to explore treatment options that affect the obesity—cancer axis provides a clear understanding of the mechanisms by which fat deposition fuels several cancers and cancer-related symptoms. However, the link between obesity and the initiation of cancer, and the underlying mechanisms remain to be explored for a prudent conclusion as to whether and how obesity influences the progression of cancer.

Based on its origin, location, and function, the AT is classified as white AT (WAT), brown AT (BAT), and beige AT. WAT has been traditionally attributed a role in the storage of energy as triglycerides (TG) and releasing fuel when the expenditure of energy exceeds its intake. More recently, WAT has emerged as an important metabolic and endocrine organ that is a key mediator of AT-related inflammation[7]. The pathological expansion of the WAT, known as ectopic fat deposition, may cause immunological and metabolic alterations that affect DNA repair and the resultant mutagenesis and epigenetic disruption of genes, leading to altered gene function and progression toward malignant cellular transformation[8,9]. These epigenetic alterations, changes in adipocyte phenotypes, genetic mutations, and altered functions are key initiation factors for the development of several cancers.

The low-grade chronic inflammation associated with obesity further creates a cancer-promoting microenvironment[10]. Obesity-associated inflammation is marked by the infiltration of immune cells that produce pro-inflammatory cytokines, including interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β[11]. These immune cells, including macrophages, neutrophils, and T cells, also release cytokines and chemokines in the obese AT, leading to gradual DNA damage, thereby promoting the cancer cell proliferation and survival that are essential for tumorigenesis[12]. Obesity also negatively affects the abilities of immune cells to detect and protect against malignant cells in the body[13]. Obesity and AT-secreted adipokines contribute to cell proliferation, metabolic diseases, and angiogenesis, which also promote tumorigenesis[6]. Additionally, obese AT supports metastatic cancer cells and allows tumors to migrate to different peripheral organs[14]. Furthermore, obesity is strongly associated with the enteric presence of the bacterium *Bacteroides fragilis*, which is also abundant in cancer[15]. Thus, there is ample evidence to suggest that obesity promotes cancer, but the underlying mechanisms remain unknown.

The goal of this review is to discuss recent advances toward discovering the mechanisms by which crosstalk and interactions between adipocytes and the AT immune—cancer microenvironment during obesity promote cancer progression. We will discuss the common mechanisms and metabolic pathways shared by obese AT and cancer and shed light on the role of the obesity-induced gut microbiome in cancer progression. Further, we will also discuss several potential therapeutic strategies to ameliorate and/or suppress obesity-related cancers.

2. Sex-based differences in obesity-related cancer progression

Obesity generally occurs in individuals with a body mass index (BMI) of more than 30 kg/m^2, a condition currently shared by approximately 40% of the US population, who are at a greater risk of developing several forms of cancer[16]. Approximately 24% of cancers in men and 55% of cancers in women are attributed to obesity and related disorders, which highlights the increased vulnerability of women to obesity-related cancer, relative to the incidence in men[17]. The rising incidence of obesity underscores the crucial need to understand sex-specific differences and to determine their role in the initiation of cancer.

Obesity is responsible for approximately 31% of endometrial cancers[18], while the development of uterine cancer exhibits a significant association with an increased BMI, with a 5-unit increase in BMI being associated with 45% of uterine cancer[16]. Overweight individuals with an increased BMI account for 7% of postmenopausal breast cancers[19]. Sex-based differences were also evident in the risk of colon cancer, which is approximately 70% in obese men[20]. Weight gain between early and mid-adulthood is significantly associated with a higher risk of colorectal cancer in both men and women, although the male population exhibits the strongest correlation with the development of colorectal cancer[21]. Obesity also poses a significant threat to the development of gastrointestinal cancer in light of its association with intestinal inflammatory diseases[22]. In association with hormonal regulation, other factors contribute to the development of pro-inflammatory and tumor-promoting environments, including altered insulin levels, insulin-like growth factor 1 (IGF-1) signaling, and dysregulated adipokine levels, leading to cancer progression during obesity.

3. AT as an endocrine organ

As a dynamic organ, the primary function of the AT is to store and mobilize energy for the body's needs. This energy balance is regulated by the central nervous system, which receives neural and chemical input from the peripheral organs to maintain homeostasis[23]. Since several such signals are generated by AT-derived adipokines to regulate appetite and insulin sensitization, AT also serves as an endocrine organ to control metabolic processes such as fatty acid oxidation, insulin signaling, *de novo* lipogenesis, and gluconeogenesis[24,25]. Thus, AT can respond based on both metabolic demand and the availability of nutrients in the body, thereby influencing both local and systemic outcomes. By secreting adipokines into the systemic circulation, AT communicates with distant organs, including the liver, skeletal muscles, and heart, and regulates complex metabolic processes to maintain homeostasis.

The WAT secretes many of the AT adipokines, including TNF-α, IL-6, adiponectin, leptin, fatty acid binding protein 4 (FABP4), and plasminogen activator inhibitor-1[26,27]. In addition to its role in maintaining thermogenesis, the BAT regulates energy homeostasis by secreting adipokines (also called batokines), including fibroblast growth factor 21, neuregulin, retinol-binding protein 4, and angiopoietin-like protein 8[27]. Adipokines produced by the WAT and the BAT communicate with other body organs in a complex manner to regulate homeostasis. The adipokine signaling cascades and the recruitment of immune cells through adipokine−cytokine crosstalk play pivotal roles in cancer progression. Adipokines also facilitate a pro-tumorigenic environment by modulating metabolic and inflammatory signaling in the tumor microenvironment (TME).

4. Obesity and cancer development: Uncovering the link

4.1. Role of obesity mediators in cancer progression

One of the most important adipokines secreted by WAT adipocytes is leptin, which serves as a crucial signaling molecule in the neuronal and immune systems that links energy storage and nutritional status[23]. Leptin has pleiotropic effects on physiological processes, including hematopoiesis, glucose uptake, gastric emptying, and kidney function. The cognate leptin receptor expressed on the surface of the AT adipocytes as well as cells in the kidneys, brain, and muscles binds to biologically active leptin that is circulating freely in the blood[28]. As a key player in adipocyte hyperplasia, leptin can exert either an autocrine or a paracrine effect on the differentiation of adipocytes[29]. Under conditions of obesity, leptin resistance leads to the accumulation of excessive leptin (hyperleptinemia) and excess adiposity[30,31]. Mice lacking leptin or leptin receptors lack a satiety response feedback mechanism, leading to excessive adiposity and T2DM[26], yet at higher concentrations, leptin inhibits preadipocyte proliferation[32]. The intricate mechanisms by which leptin regulates obesogenic factors is a key potential research field in which to ascertain the relationships between obesity and cancer.

Leptin signals *via* several signaling cascades, including the well-established Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. After binding to the leptin receptor, leptin eventually activates signaling through JAK2 and its downstream transcription regulators, including STAT3, which further regulates the expression of several other genes[33] (Fig. 1). Leptin also induces the increased activation of the mammalian target of rapamycin (mTOR) and its signaling cascade[34,35]. Since leptin is expressed by tissues with high angiogenic activity, it is not surprising that leptin-related signaling pathways are involved in angiogenesis, tumorigenesis, and metastasis[36]. In breast cancer cells, leptin induces expression of the leptin receptor, which modulates multiple signaling pathways, including the JAK/STAT3 and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways, to promote increased levels of IL-1 signaling[37]. A study with mutant leptin receptors demonstrated that deficiency in the STAT3 binding site is important in stimulating the catabolic pathways by leptin signaling[38]. In addition, STAT3 possesses binding sites in the promoter region of programmed cell death 1 (PD-1) and is associated with increased PD-1 expression in human and murine cancers[39,40]. Further, knockdown of STAT3 by short hairpin RNA (shRNA) transduction inhibited the tyrosine phosphorylation of the STAT3 upstream regulator c-Src as well as downstream regulator c-Myc in breast tumors in the immunocompetent mice[41]. Leptin is also co-expressed with the potent angiogenic factor vascular endothelial growth factor (VEGF), which promotes the expression of VEGF and its associated receptor, VEGF receptor 2 (VEGFR2), *via* the JAK/STAT signaling cascade (Fig. 1)[42]. The association between VEGF and STAT3 was shown in a study in a cohort of 45 breast tumor specimens[43]. The clinicopathological characteristics from the specimens showed the correlation of STAT3 with axillary lymph node metastasis and overexpression of STAT3 was linked with elevated expression of VEGF-D, VEGF-C, and VEGFR3.

Another WAT-derived adipokine is adiponectin, which is abundant in circulating blood under normal physiological conditions but during AT inflammation or other metabolic syndrome, its levels decrease[44]. Adiponectin activates two specific adipokine receptors, AdipoR1 and AdipoR2, which interact with adaptor proteins such as sirtuin 1 (SIRT1), sphingosine-1-phosphate (S1P), or those containing the pleckstrin homology domains 1 (APPL1) and 2 (APPL2) to activate downstream signaling pathways[45,46]. Adiponectin overexpression induces the activation of peroxisome proliferator-activated receptor alpha (PPARα), which increases lipid cell metabolism and eventually leads to the generation of pancreatic β cells[47]. APPL1 crosstalk links the adiponectin pathway with those of other downstream targets for insulin signaling, namely the AMP-activated protein kinase (AMPK), phosphatidylinositol 3-kinase (PI3K), and protein kinase B (Akt) pathways[48,49]. These pathways may also be crucial for enhancing or promoting cancer, yet the mechanisms by which adiponectin shapes the TME remain unclear.

Adiponectin appears to play a dual role in the regulation of growth and proliferation in various cancers. Adiponectin suppresses the proliferation of breast cancer, colon cancer, and pancreatic cancer cells *in vitro*[50-52], primarily facilitated by AMPK signaling. Adiponectin upregulates SIRT1, which deacetylates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), activating expression of mitochondrial genes to reprogram the metabolic pathway in cancer cells[53]. In an orthotopic breast cancer model of nude BALB/c mice, it has been shown that adiponectin administration upregulates SIRT1 expression and decreases the expression level of phosphorylated mTOR[54]. Conversely, adiponectin also facilitates angiogenesis in the process of ischemia[55], perhaps *via* its interactions with PI3K signaling, leading to the synthesis of angiogenic growth factors. Activation of adiponectin is dependent on angiogenic factors, including VEGF and the matrix metalloproteinases (MMPs), including MMP-2 and MMP-9[56]. In humans, adiponectin might be associated with the progression of obesity-related papillary thyroid cancer[57]. In a xenograft tumor-induced angiogenesis model, it has been demonstrated that knockdown of adiponectin reduced tumor-induced angiogenesis, supporting that adiponectin is associated with promoting angiogenesis and tumor growth in murine models[58]. Taken together, these data suggest that adiponectin possesses angiogenic properties and might induce cancer progression.

4.2. Immune interactions with tumor microenvironment during obesity

Obesity-related AT inflammation is caused by elevated secretion of adipokines, chemotactic factors, and pro-inflammatory cytokines to further exacerbate several metabolic and autoimmune diseases[59-61]. The pro-inflammatory environment in obese AT is mediated by adipokines that further increase the expression of pro-inflammatory molecules, thereby contributing to AT hypertrophy and hyperplasia[62,63]. The shift to expression of pro-inflammatory

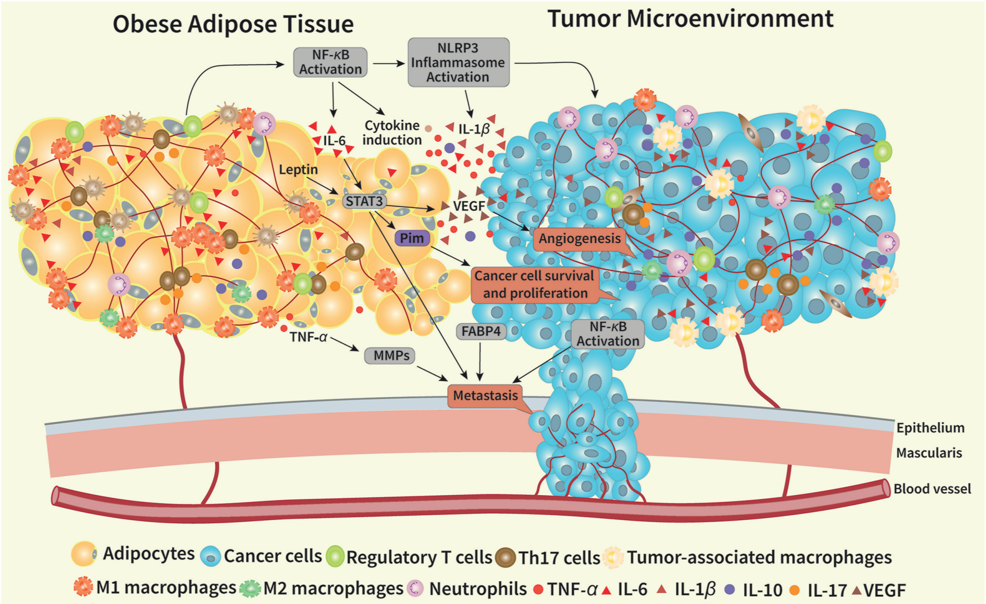

Figure 1 The obese adipose tissue (AT) microenvironment interacts with tumor cells during cancer progression. During obesity, immune cells including M1 macrophages, neutrophils, dendritic cells, and T cells infiltrate the obese AT, leading to chronic low-grade inflammation. Obese AT and cancer cells communicate *via* the cytokine-chemokine network, angiogenic factors, and adipokines to create a pro-inflammatory, tumor-promoting microenvironment to support cancer growth. The key adipokine leptin activates the STAT3 signaling pathway. Obese AT triggers inflammatory signaling pathways such as NF-κB, leading to increased production of IL-6, and further activation of STAT3 signaling. STAT3 also triggers the Pim signaling pathways that promote cancer cell survival and proliferation. IL-6/STAT3 signaling also promotes angiogenesis by inducing expression of VEGF, which drives cellular proliferation and migration to support tumor growth and metastasis. TNF-α produced by M1 macrophages induces production of matrix metalloproteinases (MMPs), which further associate with cancer cell metastasis. NF-κB activation in the cancer cells also lead to the metastatic cascade. Tumor-associated macrophages also produce cytokines that promote angiogenesis and obese adipocytes, and cancer cells express FABP4 at their interfaces that support metastasis by promoting immune invasion.

cytokines and chemokines attracts infiltration of immune cells into the obese AT, which further elevates the expression of chemoattractant molecules, including monocyte chemoattractant protein-1 (MCP-1)[64]. Under obese conditions, AT inflammation leads to the differentiation of monocytes in the WAT, generating macrophages that are predominantly of the M1 phenotype[65]. During chronic obesity-related inflammation, T cell subsets including CD4 and CD8 increase, the number of regulatory T cells (Tregs) decreases[66,67], and neutrophils infiltrate the obese AT[68]. This complex interplay of AT-derived adipokines and crosstalk among different immune cells leads to chronic AT inflammation, which might initiate excessive cellular proliferation and angiogenesis, initiating or contributing to some cancers. In a cohort of 251 melanoma patients from the Cancer Genome Atlas (TCGA), obese individuals having tumors showed an elevated expression of PD-1 compared to non-obese patients, while the aged obese individuals are more prone to the expression of PD-1 and other associated markers, including T cell immunoglobulin and mucin domain-containing protein 3 (TIM3)[69]. Cancer cells and immune cells are in proximity in the TME and the internal networking between these two cell types is governed by secretory factors, including chemokines and cytokines. This internal complex network mutually regulates the migration of regulatory factors into the TME, where they significantly influence tumor initiation and progression[70]. During cancer progression, immune cells such as macrophages, myeloid-derived suppressor cells (MDSCs), and Tregs support tumor growth and dampen host immune responses[71]. Thus tumor-infiltrating immune cells may provide potential biomarkers for identifying the TME.

Interactions between the TME and the immune system are critical for cancer development and progression[72-75]. One of the key cytokines that mediate obesity-related chronic inflammation and TME is IL-6, the effects of which are mainly triggered by the IL-6 signal transducer (IL6ST or glycoprotein 130) and signaling *via* the STAT3 pathway[76,77] (Fig. 1). IL-6 regulates chronic inflammation by increasing accumulation of macrophages in the AT during obesity[78]. Additionally, IL-6/STAT3 signaling has a potential effect on the tumor-infiltrating immune cells. The hyperactivation of STAT3 signaling during tumorigenesis activated immune cell infiltration in the TME, which increases the risk of tumor progression[79]. In a colorectal cancer mouse model, IL-6 is required for cancer occurrences, and activation of STAT3 signaling by IL-6 is required for the survival of intestinal epithelial cells and their progression through the cell cycle[80]. Additionally, it has been reported that knockout of STAT3 as well as inhibition of JAK2 reduced the formation of colon cancer spheroid[81]. In addition, in the murine model of colorectal cancer, knockout of either IL-6 or STAT3 inhibited the occurrence of colorectal cancer[76]. STAT3 targets two proto-oncogene serine/threonine-protein (Pim) kinases, Pim-1 and Pim-2, which are associated with cell survival and proliferation[82]. In conjunction with the IL-6/STAT3 axis, Pim-1 plays a role in cell growth during the progression of several cancers, including pancreatic cancer[83]. IL-6/STAT3 also induces expression of angiogenic factors VEGF and hypoxia-inducible factor-1α (HIF-1α) to promote angiogenesis[84,85] (Fig. 1).

Nuclear factor-kappa B (NF-κB) is a master regulator of inflammatory disorders that plays a key role in the development of obesity and cancer. Activation of NF-κB signaling increases the infiltration of proinflammatory cytokines, such as IL-6, TNF-α, and IL-1β in the obese AT and TME, further worsening obesity and supporting the proliferation of the cancer cells[86]. In both obesity and cancer, NF-κB-mediated inflammation and immune cell infiltration are regulated by different adaptor molecules[87]. To this end, macrophages play a crucial role in the progression of obesity-associated AT inflammation and constitute a vast part of the immunological contribution to tumor initiation, progression, and metastasis[88,89]. The frequency of tumor-associated macrophages (TAMs) is strongly correlated with many tumors, such as those involved in breast, pancreatic, colorectal, and ovarian cancer[90]. The stimulation of TAMs by cytokines including IL-10, IL-6, and angiogenic factors such as VEGF released by tumor cells suppress the immune response, thus promoting tumor angiogenesis[91,92]. After activation, TAMs can produce proinflammatory cytokines, including IL-6, IL-17, and IL-23, and induce cancer progression through the NF-κB signaling or other inflammatory pathways, such as STAT3[93] (Fig. 1).

An important source of inflammation under conditions of obesity is the activation of inflammasomes in AT macrophages, which in turn results in the activation and secretion of pro-inflammatory cytokines IL-1β and IL-18 by caspase-1-dependent mechanisms[94]. In response to different stimuli, the inflammatory sensor NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) recruits and activates the NLRP3 inflammasome, which has been widely studied in the fields of obesity and cancer (Fig. 1). NLRP3 inflammasome activation and excessive IL-1β secretion are involved in obesity-related AT inflammation and other metabolic diseases, including T2DM[95,96]. While some studies report an anti-tumorigenic effect of the NLRP3 inflammasome, for example in colorectal cancer, this cellular complex serves as a key player in tumor development that regulates both the TME and host immune responses, thus promoting cell metastasis and proliferation in the growing tumor[97,98]. In a mouse model of colitis-associated colorectal cancer, high-fat diet (HFD)-induces NLRP3 inflammasomes to increase the tumor burden as well as inflammatory response[99]. During the development of cancer, MDSCs produce anti-inflammatory cytokines and exert immunosuppressive effects[100]. In mouse models, NLRP3 inflammasome activation promotes tumorigenesis by activating MDSCs and Tregs to dampen the activation of T cells and natural killer (NK) cells[98]. The function of IL-1 signaling in MDSCs recruitment during cancer progression is supported by a murine study, which examined that transgenic mice that overexpress human IL-1β in the stomach are associated with the development of gastric cancer[101]. Moreover, NLRP3 inflammasome activation induces signaling pathways such as the Toll-like receptor (TLR)-caspase signaling pathway involving TLR4/caspase-1 or TLR4/caspase-11 to promote the production of proinflammatory IL-1β, which triggers several forms of cancer[102]. In a mouse study, downregulation of NLRP3 by the administration of thymoquinone therapy decreased the secretion of IL-1β and IL-18, reducing the risk of metastatic melanoma[103]. Clearly, further experimental evidence will be needed to provide mechanistic details of the role of NLPR3 inflammasome in cancer, particularly its correlation with obesity-induced tumorigenesis.

4.3. Insulin signaling and metabolic dysregulation are crucial for obesity-mediated cancer

The peptide hormone insulin, synthesized in and secreted by pancreatic β cells, regulates blood sugar under normal physiological conditions. However, conditions such as HFD-induced obesity trigger dysregulation of insulin signaling, leading to insulin resistance that is often associated with T2DM and other metabolic abnormalities[104]. It is therefore not surprising that insulin dysregulation and insulin resistance are also correlated with certain cancers[105], since the mechanisms of cancer progression and insulin signaling overlap[106]. For example, more than 80% of patients diagnosed with pancreatic cancer have insulin resistance[107]. In obesity and cancer, dysregulation of multiple factors, including IGF, pro-inflammatory cytokines, adipokines, and insulin, paves the way for a complex environment that serves as a dominant contributor to cancer progression[108].

PI3K/Akt signaling pathway serves as a bridge between adiposity and insulin action. This pathway is activated by signals from various receptors, including insulin receptors in AT macrophages, resulting in direct upregulation of two transcriptional factors that regulate adipogenesis, namely CCAAT/enhancer-binding protein alpha (C/EBPα) and peroxisome proliferator-activated receptor gamma (PPARγ)[109,110]. The production of adipokines such as adiponectin and visfatin involves signaling through the PI3K/AKT pathway[109]. Thus, in addition to its role in obesity-induced insulin resistance, PI3K/AKT signaling cascade plays a role in cell survival and proliferation during cancer progression. For example, PI3K/AKT signaling directly regulates the growth of proliferating tumor cells through the cell cycle inhibitor p27[111], epidermal growth factor receptors (EGFRs), and IGF2[112,113]. Further, crosstalk between the EGFR/PI3K/Akt and NF-κB axes plays a role in regulating several types of cancer. To this end, it has been demonstrated that inhibiting insulin receptor substrate (IRS) by NT157 decreased cell proliferation in a human pancreatic adenocarcinoma cell line[114]. Moreover, in NP-29 pancreatic cells, IRS1 undergoes phosphorylation at multiple tyrosine sites and combined blocking of both IGF receptors and EGFR has shown potential synergistic effects in eliminating pancreatic cancer stem cells[115]. Signaling transduction *via* the type I and type 2 IGF receptors (IGF-IR and IGF-IIR, respectively) induces tyrosine kinases that promote tumor growth and metastasis. Tumors that have been depleted of cells by ionizing radiotherapy can repopulate by inducing angiogenesis, as follows: dying cells provide a signal to cleave and activate caspase-3, initiating a caspase-3/PKCδ/Akt/VEGF signaling cascade that ultimately releases VEGF to signal proliferation of the surviving cells[116]. In breast cancer cells, IGF promotes mitochondrial biogenesis by inducing factors like PGC-1β, and Bcl-2 interacting protein 3, thereby further promoting tumor growth[117,118].

In addition to its roles in obesity and cancer, insulin is also a key player in lipid metabolism. Insulin inhibits lipid biosynthesis, which helps to reduce the proliferation of cancer cells. Lipid metabolism and biosynthesis are highly relevant to cancer, since several cancers exhibit highly abundant expression of fatty acid synthase (FASN), perhaps due to the aberrant activation of the *de novo* fatty acid synthesis pathway. In colorectal cancer, upregulation of FASN increases expression of the angiogenesis marker VEGF, thereby upregulating angiogenesis, and is associated with metastasis[119]. FASN expression also significantly decreases the overall survival of patients with pancreatic cancer[120]. The sphingolipid S1P serves as a crucial modulator of cancer growth and progression: the balance between the levels of S1P and ceramide plays a prominent role in cell survival and proliferation[121]. Finally, cancer-related stem cells utilize lipid metabolism for their functions in the TME. Thus, metabolic dysfunction primarily related to insulin and lipid metabolism provides a fundamental link between obesity-related metabolic dysregulation and cancer-associated etiologies.

5. Metabolism of immune cells in the AT correlates with cancer progression

The intricate interplay between adipokines and insulin signaling underscores the metabolic disturbances caused by obesity-related inflammation and its effect on the development of cancer. Beyond these metabolic drivers, the immune system also plays a crucial role in immune cell metabolism during obesity-related cancer progression. Specifically, metabolic dysregulation in AT macrophages and T cells and the resultant shift in cellular metabolism further accelerate the cancer risk fostered by obesity. Macrophages and monocytes undergo substantial metabolic and epigenetic reprogramming to shift toward phenotypes that facilitate cellular proliferation and the production of effector molecules[122,123]. There are two major subsets or phenotypes of macrophages, the M1 classically activated macrophages (proinflammatory) and the M2 alternatively activated macrophages (anti-inflammatory). The metabolism of M1 macrophages exhibits increased glycolysis and reduced Krebs cycle-related oxidative phosphorylation (OXPHOS[124]), while that of M2 macrophages exhibits increased OXPHOS[125]. T cells are also metabolically reprogrammed to proliferate and achieve effector functions[126]. Binding of an antigen by a T cell initiates the expression of signaling molecules and activates pathways that regulate metabolic reprogramming. The metabolic reprogramming pathways shared by macrophages and T cells reinforce the systemic nature of the intricate interplay within the obesity−cancer axis.

These shared metabolic reprogramming pathways are regulated by the HIF-1, whose α subunit is stabilized post-translationally in conditions of low oxygen availability (hypoxia), such as those found in the AT during obesity. AT macrophages and T cells maintain hypoxic conditions in the AT by inducing the production of interferon gamma (IFNγ) and NF-κB to further increase synthesis and stabilization of HIF-1α[127-129]. HIF-1α also regulates the expression of genes involved in angiogenesis and energy metabolism and is critical for metabolic adaptation in macrophages and T cells[130]. In macrophages, signaling *via* the TLR and AKT pathways activates NF-κB, resulting in upregulation of HIF-1α transcription[131], as shown in Fig. 2. In M1 macrophages, stimulation by lipopolysaccharide and IFNγ results in a metabolic switch from OXPHOS to glycolysis *via* multiple transcription factors, including NF-κB and HIF-1α (Fig. 2), while blocking the glycolytic pathway in these cells decreases IFNγ-induced expression of HIF-1α[132]. In hypoxic T cells, the HIF-1α−glycolytic axis regulates metabolic reprogramming by upregulating IFNγ production and synthesizing several effector cytokines, including granzyme B[133]. HIF-1α expression is also correlated with the activation of inflammatory T helper 17 (Th17) cells and its promotion of proinflammatory conditions can lead to T cell exhaustion[134-136] (Fig. 2).

TME is also hypoxic, which favors the rapid growth of tumor cells that have also undergone metabolic changes that allow them to use glycolysis and OXPHOS for energy production[137]. In both activated T cells and tumor cells, expression of HIF-1α induces that of angiogenic genes such as VEGF and activates the PI3K/Akt and MAPK pathways to increase expression of HIF-1α [138] (Fig. 2). During the progression of breast cancer, upregulation of HIF-1α is associated with higher expression of VEGFA[139]. Although HIF-1α expression is also a potential risk for renal cell carcinomas and neuroblastoma, xenograft studies depicted that overexpression of HIF-1α retards tumor growth in renal cell carcinomas; however, the mechanism is not well understood[140]. HIF-1α also recruits growth factors, including IGF2 and transforming growth factor (TGF), to receptors on cancer cells to induce their proliferation[141] (Fig. 2). Thus, it is not surprising to learn that overexpression of HIF-1α in cancer cells is associated with the failure of cancer treatments, thereby increasing the rate of mortality.

6. The impact of obesity-associated inflammation in cancer metastasis

While genetic alterations in tumor cells play a role in the progression of cancer, such progression also depends on a complex systemic process that includes the interaction with tumor cells in TME. Particularly, the interaction between the tumor cells and the associated stroma is a powerful association that impacts the initiation, progression, and metastasis of cancer[142]. The association of stromal cells with TME plays a critical role in the development of tumors. Mechanistic insights into stromal cell recruitment and TME reveal a unique connection between tumor biology and cancer progression that might also be directed by the body's responses to malignancy in several organs that are distant from the site of the primary tumor[143]. Obesity is associated with hypertrophic and hyperplasic adipocytes, which secrete adipokines to recruit immune cells into the AT and induce the production of proinflammatory cytokines, leading to insulin resistance and cancer. Further, since tumor metastasis contributes to cancer mortality, the surprising discovery of a possible link between metastatic tumor cells and the dysfunctional AT during obesity will lead to the discovery of novel therapeutics that target inflammation/obesity-induced cancers.

Cancer cell metastasis starts with the invasion of tumor cells into surrounding tissues. The chromosomal instability of cancer cells affects the segregation of chromosomes during the mitotic phase of the cell cycle[144]. These processes activate pathways such as DNA sensing and NF-κB signaling, leading to the dissemination of tumor cells (Fig. 1). Subsequently, epithelial−mesenchymal transition (EMT) enables tumor cells to maintain a migratory phenotype, which is caused by several factors, such as hypoxia and metabolic stress[145]. Obesity-related chronic inflammation not only increases the EMT but also increases interactions among tumor cells to mimic normal physiological processes, facilitating metastatic progression. Further, obesity exacerbates the pro-inflammatory microenvironment and metabolic stress, which plays a crucial role in cancer metastasis.

The metastatic cascade of tumor cells links with the obese AT *via* several mechanisms. In intra-abdominal cancers and gastric and ovarian cancers, adipokines are secreted by adipocytes, which metastasize into the omentum, thereby further contributing to the migration and invasion of tumor cells by interacting with leptin and adiponectin[146]. Tumor cells that are metabolically adapted to high lipid environments utilize fatty acids as a source of energy, mainly by FABP4. In acute myeloid leukemia (AML), increased expression of FABP4 under obesity increases tumor aggressiveness by promoting immune invasion. FABP4 is highly expressed at the adipocyte−cancer cell interface and blocking FABP4 significantly decreases lipid accumulation and omental metastasis (Fig. 1)[14]. In breast cancer, adipocyte-induced MMP-11

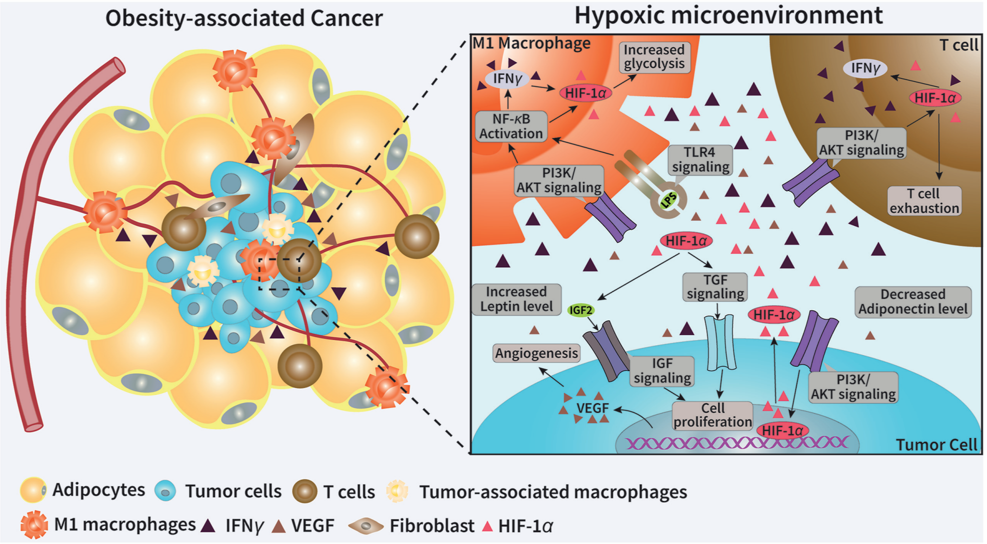

Figure 2 Immune cell metabolism and hypoxia drive cancer progression. During obesity, adipocytes and resident immune cells in the obesogenic microenvironment become deprived of oxygen (hypoxic), as do macrophages, T-cells, and tumor cells in the tumor microenvironment, leading to hypoxia-driven metabolic reprogramming. For tumor cells, these metabolic changes contribute to tumor progression. Under hypoxic conditions in the AT, IFN-γ activates the PI3K/AKT/NF-κB signaling pathway to induce expression of hypoxia inducible factor 1α (HIF-1α), which promotes metabolic reprogramming in M1 macrophages and activated T cells. This process contributes to T-cell exhaustion and inflammation, thereby affecting immune cell function. In tumor cells, HIF-1α secreted by these immune cells activates PI3K/AKT pathways to increase HIF-1α levels and triggers expression of angiogenic genes like VEGF. HIF-1α also recruits growth factors (*e.g.*, IGF2) to tumor cells, increasing their proliferation. HIF-1 is also associated with decreased adiponectin and elevated leptin expression.

causes the dedifferentiation of adipocytes into fibroblast-like cells, corroborating the evasion of cancer cells[147]. Additionally, obesity-associated low-grade inflammation exacerbates the metastatic potential by disrupting the differentiation of adipocytes, further leading to hypoxia and increased expression of HIF-1[148]. The increased level of HIF-1 decreases the expression of adiponectin expression and elevates that of leptin (Fig. 2), a shift that is related to the increased cancer risk, particularly in triple-negative breast cancer (TNBC)[149]. Leptin also increases tumor cell migration and invasion *via* JAK/STAT signaling, promoting the cancer stem cells (CSCs) phenotype that leads to metastasis (Fig. 1)[150,151].

In the context of obesity-related cancer, obese adipocytes dedifferentiate into preadipocytes and are reprogrammed into cancer-associated adipocytes (CAAs) that play a critical role in tumor progression[152]. Compared to normal adipocytes, CAAs produce higher levels of proinflammatory mediators, such as MCP-1, RANTES, IL-6, and TNF-α, and they exhibit increased promotion of cancer invasion and metastasis[153]. In addition, obesity is associated with the recruitment of M1 macrophages in AT, which consistently maintain a proinflammatory microenvironment conducive to tumor progression. In cancer cells, MCP-1 induces NOTCH1 signaling, which further induces the activity of CSCs and the formation of new blood vessels[154]. RANTES expression in the adipocytes fosters increased motility and invasiveness of cancer cells and correlates with lymph node and other metastasis during TNBC, reducing patient rates of survival[155]. IL-6 that is secreted by hypertrophic obese adipocytes or CAAs serves as a major regulator for obesity-associated hepatocellular carcinoma (HCC) by increasing angiogenesis and metastasis (Fig. 1)[156]. M1 macrophages and adipocytes consistently produce a higher level of TNF-α as obesity progresses and an increase in TNF-α induces the production of MMPs in epithelial tumors, facilitating EMT to promote invasion and metastasis of tumor cells (Fig. 1)[157]. In addition, proinflammatory cytokines in the obese AT stimulate the function of CSCs and elevate the expression of CSC-related genes, further increasing tumorigenesis and migration of cancer cells[14].

7. Obesity-modulated microbiome and cancer interaction

In the field of obesity and metabolism, the role of the microbiome in the regulation of these key processes is an emerging research area. Several intertwined mechanisms by which the microbiome is reprogrammed during obesity may also serve to accelerate the progression of cancer. For example, bacterial species that comprise the human microbiome are associated with various forms of cancer, with eleven entire microbiomes being directly carcinogenic to humans[158]. Proper maintenance of the gut microbiota is critical to regulate nutrients and energy usage and to promote the health and well-being of the host, while failure to do so correlates with disease conditions including autoimmune diseases and cancer. Any alteration or disruption in the gut microbial population potentially affects the host metabolism, meaning that the microbiota are critical players in the development of obesity and associated metabolic disturbances. These changes can initiate inflammatory and metabolic processes, cell differentiation, and abnormal multiplication, any of which might facilitate cancer progression.

The main function of the intestinal microbial flora is the extraction of energy from food ingredients such as polysaccharides and complex carbohydrates that are not digested by the host due to the absence of the appropriate enzymes. In contrast, bacterial species in the gut microbiome that express these enzymes can metabolize these substances to produce metabolites, including propionate and butyrate[159]. Interestingly, the differences in metabolite levels observed in obese vs lean mice can further exacerbate the conditions of obesity[160], while germ-free mice that lack microbiota are protected from developing obesity on the consumption of HFD[161]. Thus, characterizing the intestinal microbiota, defining their relationships with obesity-associated inflammation, and subsequently identifying specific microbial targets may result in the development of potential therapeutic options for the treatment of obesity and related disorders.

Microbiota from obese individuals exhibit greater utilization of carbohydrates and more production of pro-inflammatory mediators than those from lean individuals[162]. For example, microbial glutamate levels are differentially affected in obese individuals relative to lean controls. In some cases, an altered microbiome can be detrimental, while in other cases, it can be helpful for gut and overall health. A decrease in microbiota-related metabolites including trimethylamine *N*-oxide (TMAO) and its precursors choline and carnitine is associated with significant weight loss[163]. Conversely, the administration of *Akkermansia muciniphila* reverses HFD-induced obesity and T2DM[164], while *B. uniformis* ameliorates HFD-induced obesity in mice[165]. Our unpublished findings reveal that *Bacteroides* species are significantly downregulated in mice with HFD-induced obesity (Fig. 3), supporting the notion that these bacterial species may have potential as modulators of obesity-related metabolic disorders. Altogether, these studies suggested that interactions with the gut microbiome are critical in the regulation of obesity, but that these complex interactions depend on the intestinal environment, which may affect the incidence of obesity-associated cancer.

The association of at least 20% of cancers with various infectious agents may be related in part to the significant correlation between the gut microbiota and the progression of cancers such as those of the breast, lung, and skin[166,167]. In humans, obesity-driven microbial dysbiosis (modulation of microbial content) is linked with abnormal metabolism and carcinogenesis[167,168], while in animal models, alteration of gut microbiota significantly increased the risk of colorectal cancer[169,170]. However, the mechanisms by which the gut microbiota influence the disruption of host immune responses during the progression of cancer or the association of cancer cells with the host microbiome in the context of tumorigenesis remain unclear.

Nevertheless, inflammation and dysregulation of the immune system contribute to microbiome-related carcinogenesis, further paving the way for the development of cancer. The process of inflammation is a critical regulator of the regulation and biosynthesis of microbial metabolites, primarily by modulating the TME. During tumor progression, tumor cells adopt multiple strategies to alter various signaling pathways to maintain a suitable milieu to support their growth. The role in this process of microbial metabolites is becoming clearer. For example, levels of short-chain fatty acids (SCFAs) are elevated in hepatocellular carcinomas, where they promote tumor progression in nonalcoholic fatty liver disease[171], and butyrate increases Treg expression and promotes the effector function of T cells[171]. Given these roles, the notion that microbial metabolites may prove to be useful additions to effective anti-tumor therapies is well supported. The development of such therapies for obesity-mediated cancers will require a more thorough understanding of the microbiome and the function of its metabolites.

8. Divergent perspectives on metabolic reprogramming and immune interactions in obesity-related cancer

The TME is a complex microenvironment composed of fibroblasts, infiltrating immune cells, tumor cells, and stromal cells. It has been well established that metabolic strategies employed by cancer cells are distinctly different compared to normal cells. Cancer cells produce a variety of mediators that alter the metabolic environment to sustain their growth, thereby facilitating the progression of tumor and metastasis. The peripheral immune system and TME play crucial roles in both the progression and the prevention of cancer. The metabolic heterogeneity in the immune cell population provided by natural killer cells or cytotoxic T cells can shape immune responses and suppress tumor growth, whereas TAMs, Tregs, and MDSCs can render immunosuppressive action for the tumor's evasion of the immune system[172]. Within these intricate pathways of metabolism, the accumulation of lactic acid

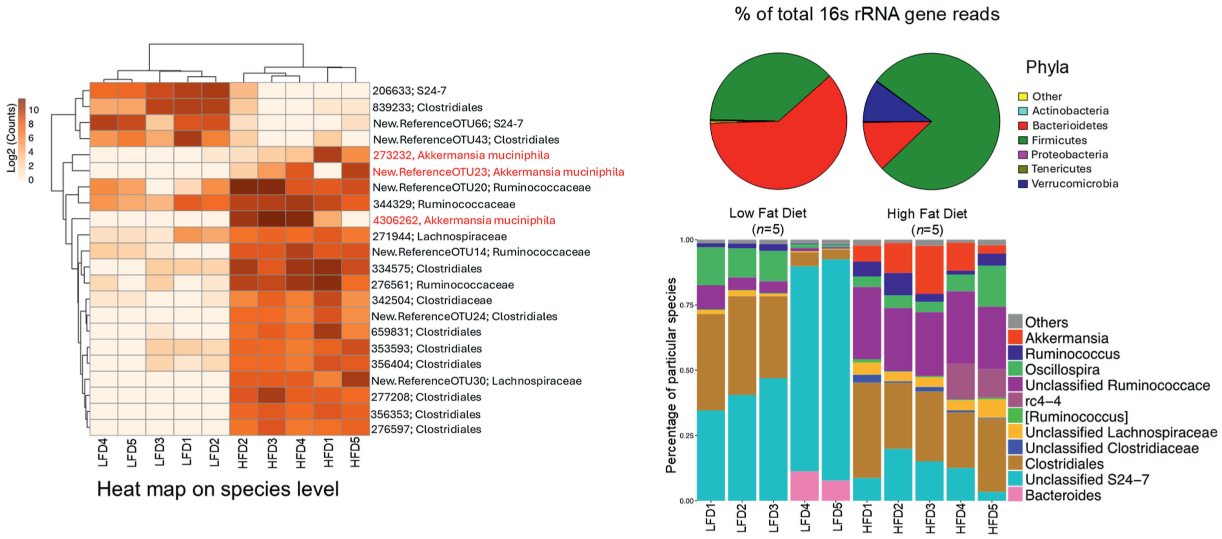

Figure 3 Microbiome composition and diversity in mice with HFD-induced obesity. The percentage of total 16s rRNA gene reads in mice fed on low fat and high fat diet (HFD) that map to various phyla (heat map) The pie and stack bar plots reveal differences in major bacterial phyla in mice fed on low fat diet and HFD.

(lactate) plays a dual role in tumor progression. In an acidic environment, lactate suppresses the function of CD4 and CD8 T cells and the tumor's immune escape is facilitated by Tregs and TAMs[173-175]. However, in the absence of acidic conditions, lactate induces the anti-tumor activity of cytotoxic CD8 T cells[176]. Like lactate, succinate also delineates both anti-tumor and pro-tumor activities. Succinate produced by a tumor helps the immunosuppressive actions of TAMs, while CD8 T cell-derived succinate enhances the cytotoxicity of tumor cells[177,178]. Future studies will be required to reach prudent conclusions for therapeutic strategies that target the metabolic−immune interactions in cancer.

9. Therapeutic implications and strategies for obesity-induced cancer

Although patients with obesity or obesity-induced T2DM exhibit an elevated prevalence for the initiation and growth of cancer, the molecular mechanisms that link obesity-associated disorders and microbiome dysbiosis with the progression of cancer remain to be determined. The identification of the shared pathophysiology among these processes is complicated by the latent period between the initiation of cancer and its development. The question also remains whether reducing obesity can effectively reduce the risk of cancer or *vice versa*. We will discuss our mechanistic insights into therapeutic options for patients with obesity-associated cancers.

Radiotherapy generally provides a first-line treatment option for cancer, either alone or in combination with chemotherapy or surgery. However, obesity-associated cancer is less susceptible to radiotherapy than other cancers and the underlying mechanisms are not well understood. Although radiation effectively treats multiple tumors, resistance to radiation therapy leads to failure in therapeutic approaches and facilitates metastasis[179]. Triple-negative breast cancer is less sensitive to radiation therapy, while obese individuals are more prone to prostate cancer[180]. In breast cancer patients, obesity and larger breast size are associated with an increased risk of dermatitis after radiotherapy[181]. Furthermore, the serine protease inhibitor SERPINE1 correlates with the progression of obesity-related breast cancer and provides a reliable prognostic marker for patient resistance to radiotherapy.[179,182]

In addition to radiotherapy and chemotherapy, exercise therapy effectively mitigates obesity-related weight gain and associated breast cancer[183]. The American Cancer Society recommends that exercise training is safe for individuals who are undergoing cancer treatment and helps to effectively maintain a healthy body weight[184]. Dietary factors correlated with metabolic processes influence the risk of obesity-associated cancer progression, while dietary patterns and nutritional interventions reduce the risk of meta-inflammation and oncogenesis[185]. The intake of saturated fat correlates with an increased risk of cancer progression and chronic inflammation, while poly-unsaturated fatty acids (PUFA) exhibit anticancer characteristics[186-188]. Intake of omega 3 FAs and an increased ratio of omega 3 and omega 6 FAs correlates with a lower risk of obesity-related breast cancer[189]. Moreover, natural phytochemicals such as polyphenols, and stillbenes exhibit significant anti-tumorigenic effects under conditions of obesity[190].

Oral antidiabetic drugs such as metformin lead to a decreased risk of breast, pancreatic, and colorectal cancers[191,192]. In obese mice, administration of metformin inhibits tumor growth in breast and endometrial cancers[189]. However, metformin shows limited or no potential benefits in randomized clinical trials when used as an adjuvant therapy[193,194]. Other therapeutic approaches for the treatment of these cancers may include the use of the tetrahydrolipostatin lipase inhibitor orlistat, which reduces the absorption of dietary fat and functions as an anti-obesity drug. In clinical trials, the administration of orlistat together with a low-calorie diet induced more weight loss and fewer obesity-related health complications than the diet alone[195]. Orlistat also significantly increases oxysterol metabolism in obese individuals[196] and exhibits anti-tumorigenic activities against various solid tumors[197,198]. Thus, orlistat may prove beneficial for managing obesity and reducing the risk of cancers associated with metabolic disorders.

Recently, microbiota-based therapies have been used to treat metabolic disorders and associated carcinomas. Microflora-based therapy is considered a promising therapeutic strategy in the field of metabolic diseases and cancer, as it possesses fewer side effects than other therapeutic options[15]. Importantly, microorganisms provide a powerful source of metabolic machinery for chemotherapeutic agents[199]. For example, gut-microbiota-derived metabolites such as indole-3-carboxaldehyde, propionate, and kynurenic acid are protective against the adverse effects of radiotherapy[200]. In addition, the peptidoglycan synthesized by *Enterococcus* species increases the antitumor efficacy of anti-PD-L1 antibodies by improving the immunocompetence of cancer patients. Dietary fiber produced by the gut microbiota produces SCFAs, which have the potential to manage obesity and cancer. Moreover, SCFAs increase the efficacy of $CD8^+$ T cells, leading to successive immune checkpoint therapy[201].

Promising new therapies under development target the insulin, adipokine, and inflammatory signaling pathways for the treatment of obesity-related cancer. Therapies that target glucagon-like peptide-1 (GLP-1) may prove effective for the treatment of obesity and T2DM. In addition to controlling weight gain and glucose homeostasis, therapies based on long-acting GLP-1 agonists appear to decrease the incidence of cardiovascular diseases such as stroke and myocardial infarction[202], while cells that overexpress the GLP-1 receptor (GLP-1R) contribute significant therapeutic benefits in hepatic diseases. In colorectal cancer, GLP-1R agonists block cell cycle progression, decrease cell proliferation, and block PI3K/Akt/mTOR signaling to promote tumor cell apoptosis[203]. GLP-1R agonists also attenuate the growth of prostate cancer by inhibiting ERK signaling[204] and exhibit anti-proliferative effects on breast cancer cells treated with conditioned media from obese AT-derived stem cells, which promotes cancer growth and proliferation[205]. Although GLP-1 therapy shows promising results for the treatment of obesity, diabetes, and cancer, careful selection of GLP-1R agonists and long-term safety monitoring will be required before the potential adoption of such agents for the treatment of obesity-related cancers.

Chimeric antigen receptor (CAR) T-cell therapy represents a revolutionary breakthrough in cancer treatment in murine and human models[206,207]. CAR-T cells primarily target the B cell lineage antigen CD19 and provide a significant treatment option for treating patients with B cell non-Hodgkin lymphomas and acute B cell lymphoblastic leukemia[208]. These results have opened the door to using CAR-T cells against other inflammatory diseases, including nonalcoholic steatohepatitis and heart failure[209,210]. A novel and exciting offshoot of CAR-T cell therapy is the engineering of autologous T cells to acquire the thermogenic metabolic profile of brown fat, which might increase their resting energy expenditure without the risk of mitochondrial uncoupling. Thus, researchers are investigating the effect of thermogenic T cells that target BAT as a potential therapeutic option for the treatment of obesity[211]. However, the development and delivery of thermogenic T cells remain a promising experimental model that needs more work.

10. Concluding remarks

Obesity is accompanied by metabolic disorders and increased risks of various cancers, highlighting the critical importance of understanding the interwinding mechanisms that link obesity and cancer. Dysregulation of adipocytes and infiltrating immune cells in the AT results in chronic inflammation, which plays a crucial role in the progression of obesity-associated cancers. However, the underlying mechanisms for the progression of obesity-associated cancers remain unclear. Obesity is a multifactorial condition in which the complex interplay between AT immune cells and cancer cells, and the adipokines and cytokines they produce, provides a suitable milieu for cancer growth that is further exacerbated by the pro-tumorigenic effects of obesity-related metabolic dysregulation. In the future, a critical understanding of the pathogenesis of obesity, metabolic syndrome, and cancer progression will be required for the development of effective therapeutics to treat these conditions. Several approaches, including improved insulin signaling, reprogramming and modulating immune cell metabolism, and the use of recent therapeutic options like CAR-T cell and GLP-1 therapies offer a promising roadmap for intervention in obesity-induced cancer. Amid the growing prevalence of obesity, prioritizing these strategies and the development of combination therapies will prove fruitful as preventive options for the treatment and prevention of obesity-related cancers.

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Author contributions

Ahmed Rakib wrote the first draft of the manuscript, edited it, and made all the figures. Md Abdullah Al Mamun, Mousumi Mandal, and Priti Sinha edited the review and helped in making figures. Udai P Singh conceived the ideas and designed and edited the review.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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