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REVIEW

Biological mechanism and immune response of MHC-II expression in tumor cells

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ABSTRACT Malignant tumors are a major threat to human health with the immune responses critically influenced by major histocompatibility complex (MHC) class I and II molecules. While MHC-I has been extensively studied for its role in tumor immunity, research on MHC-II, particularly MHC-II function within the tumor microenvironment, has lagged behind research on MHC-I. The expression and regulation of tumor-specific MHC-II (tsMHC-II) in tumor cells not only reflect the immunogenic landscape of the tumor microenvironment but also actively shape antitumor immune responses by modulating $CD4^+$ T cell recognition and activation. Expression of tsMHC-II is tightly controlled by intrinsic oncogenic signaling and extrinsic cytokine stimulation, positioning tsMHC-II as a key determinant of response to immunotherapy, including immune checkpoint blockade. Accordingly, tsMHC-II may serve as a predictive biomarker and a potential therapeutic target in tumor immunotherapy. This review highlights recent advances in the structure and function of MHC-II, the MHC-II regulatory mechanisms in tumors, and the emerging significance of MHC-II in guiding future immunotherapeutic strategies.

KEYWORDS MHC-II; tumor immunity; immunotherapy; tumor microenvironment

Introduction

Tumors are significant global health challenges with diverse therapeutic strategies, including surgery, chemotherapy, and immunotherapy, offering varying degrees of efficacy[1]. While surgical resection remains the most frequently used method, immunotherapy has revolutionized primary tumor and metastasis treatment by harnessing the immune system to combat tumors[2]. Despite these advances, many patients experience intrinsic or acquired resistance to immunotherapy, along with immune-related adverse events (irAEs) that limit broader application of immunotherapy[3,4]. For example, among melanoma patients treated with ipilimumab at 10 mg/kg, the incidence of severe irAEs reached 37% in the individuals with active metastases and 46% in those receiving post-surgery adjuvant therapy[5,6]. A study focusing on non-small cell lung cancer (NSCLC) indicated that irAEs associated with programmed death receptor 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitors correlated with improved radiologic responses, progression-free survival (PFS), and overall survival (OS), which were typically observed approximately 3 months after treatment initiation. As novel immunotherapies and combination regimens continue to emerge, a deeper understanding of the anti-tumor immune response, particularly the mechanisms underlying tumor recognition and immune escape by T cells, are critical for improving outcomes and expanding the applicability of these therapies.

A key mechanism underlying immune escape by tumors is the alteration of antigen-presenting pathways, which reduce tumor visibility to adaptive immune cells[7]. Central to this process are MHC molecules, which present non-self-peptides (neoantigens) to immune cells. MHC-I and MHC-II molecules are essential elements of the antigen presentation machinery. MHC-I, which present endogenously derived

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peptides to CD8$^+$ T cells, expressed on virtually all nucleated cells and essential for cytotoxic immune responses. In contrast, MHC-II, which are predominantly expressed by professional antigen-presenting cells (pAPCs), like dendritic cells (DCs), macrophages, and B cells, present exogenous peptides to CD4$^+$ T cells to drive adaptive immunity (**Table 1**)[8-17].

MHC molecule expression is regulated through complex genomic, transcriptomic, and post-translational mechanisms in tumor cells. These processes involve multiple intracellular pathways responsible for antigen processing and presentation. Cytotoxic CD8$^+$ T cells are the primary effectors of immune checkpoint inhibitor (ICI) therapies. In addition, CD4$^+$ T cells are critical for supporting CD8$^+$ T cell activation, promoting memory T cell formation. Emerging evidence underscores the integral function of CD4$^+$ T cells in mediating effective responses to ICIs[5,6,8-13,18].

Notably, tumor-specific MHC-II (tsMHC-II) expression, although less frequent, has emerged as a pivotal factor in enhancing anti-tumor immunity. Recent studies have demonstrated a strong correlation between tsMHC-II expression and favorable immunotherapy outcomes, including improved tumor rejection in preclinical models[8]. MHC-II-restricted CD4$^+$ T cells are critical for supporting CD8$^+$ T cell activation, positioning MHC-II-restricted CD4$^+$ T cells at the forefront of tumor immunotherapy research. This review explores the regulatory mechanisms and latest developments underlying tsMHC-II expression in tumor cells and highlights the tsMHC-II potential to improve the efficacy of current and future immunotherapeutic strategies.

Structure and function of MHC-II molecules

MHC-II is a heterodimer composed of α and β chains. Unlike MHC-I, which is highly polymorphic but restricted by peptide length, MHC-II can accommodate a broader array of neoantigen proteins. This diversity is due to the structure of the MHC-II binding groove, which accommodates longer

Table 1 Comparative analysis of MHC-I and MHC-II molecules in tumor immunology

Feature	MHC-I	MHC-II
Molecular Structure	Heterodimer: one α-chain (with α1, α2, and α3 domains) and β2-microglobulin	Heterodimer: α-chain and β-chain (both membrane-anchored, each with 2 domains)
Gene Loci	HLA-A, HLA-B, and HLA-C	HLA-DP, HLA-DQ, and HLA-DR
Peptide Binding Groove	Closed at both ends; binds short peptides (8–11 aa)	Open-ended groove; binds longer peptides (13–25 aa)
Cellular Distribution	All nucleated cells (except neurons, some trophoblasts)	Professional APCs: DCs, B cells, and macrophages; sometimes tumor cells (tsMHC-II)
Antigen Origin	Endogenous (intracellular proteins, including neoantigens)	Exogenous (extracellular proteins and phagocytosed material)
Presentation Target	CTLs	CD4$^+$ Th
Immunological Role	Direct CTL-mediated killing of tumor cells	Supports CTL priming, sustains immune memory, enhances CD8$^+$ *via* CD4$^+$ help, and shapes the TME
Relevance to Immune Checkpoint Therapy	Loss of MHC-I = resistance to CTLs and poor ICB response	High MHC-II = better ICB response, more TILs, and enhanced CD4$^+$ support
Immune Escape Mechanism	Downregulation or mutated of MHC-I to escape CD8$^+$ T cells killing	Silencing of CIITA or epigenetic repression to avoid CD4$^+$ T cells
Therapeutic Implication	Targeted by TCR-T and CTL therapies	CD4$^+$ TCR-T, CAR-T, and MHC-II vaccines

APCs, antigen-presenting cells; CAR-T, chimeric antigen receptor T cells; CIITA, class II transactivator; CTLs, CD8$^+$ cytotoxic T lymphocytes; DCs, dendritic cells; HLA, human leukocyte antigen; ICB, immune checkpoint blockade; TCR-T, T cell receptor-engineered T Cells; Th, helper T cell; TILs, tumor-infiltrating lymphocytes; TME, tumor microenvironment; tsMHC-II, tumor-specific MHC-II.

peptides (typically approximately 13 amino acids) and tolerates a wide variety of side chains[8,19]. These features significantly increase the repertoire of peptides that MHC-II molecules present. Specialized pAPCs, such as DCs, capture, process, and present foreign antigens. These protein antigens are degraded into small peptides and delivered to CD4$^+$ T cells *via* MHC-II. Among pAPCs, DCs are the most potent and have pivotal roles not only in presenting antigens to CD4$^+$ T cells but also in cross-presenting neoantigens to CD8$^+$ T cells. While cytotoxic CD8$^+$ T lymphocytes are the primary effectors of anti-tumor immunity, DC-mediated MHC-II presentation to CD4$^+$ T cells is essential for initiating and sustaining a coordinated and effective immune response (**Figure 1**).

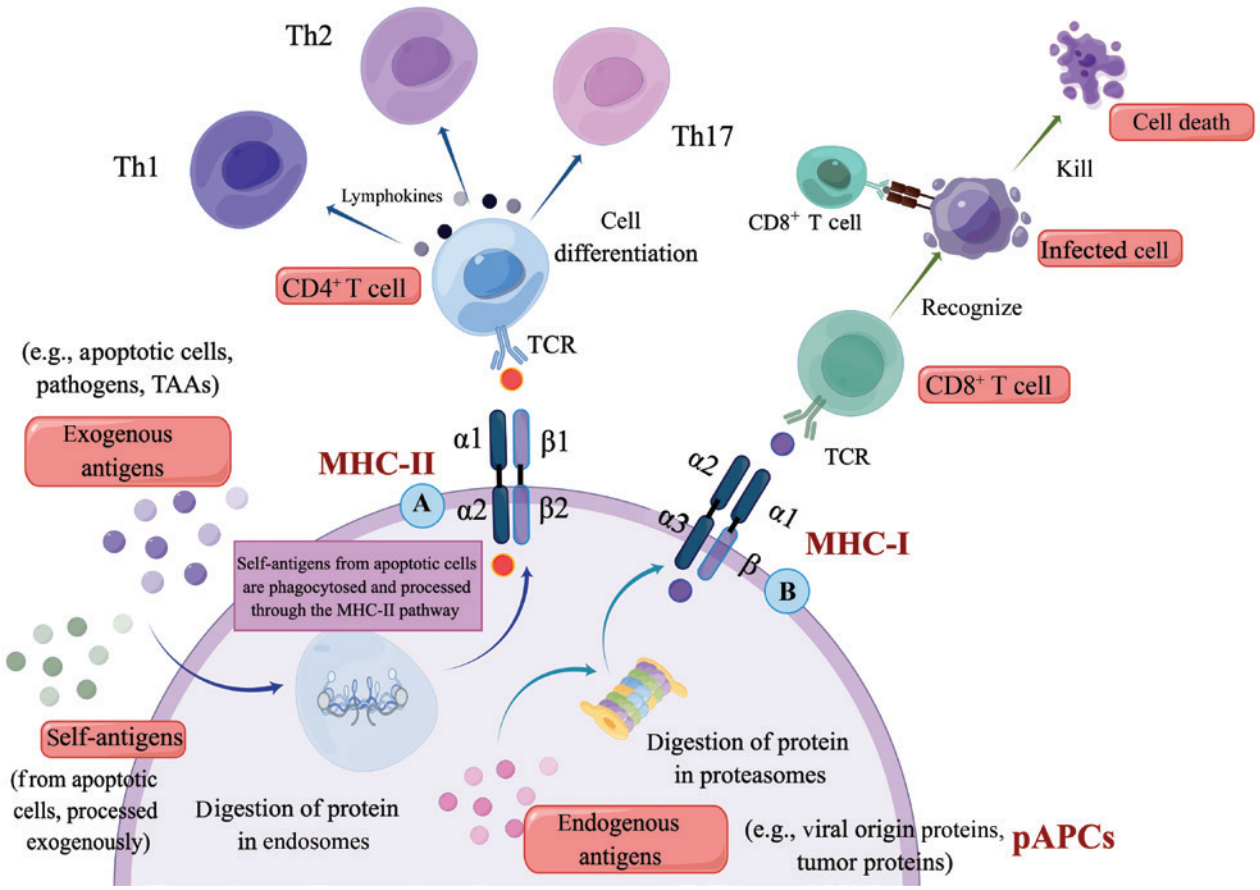

Figure 1 The structure and function of MHC. (A) MHC-II antigen presentation pathway. This pathway illustrates the process by which exogenous antigens (e.g., TAAs, apoptotic bodies, or cellular debris) are internalized by APCs through phagocytosis. These antigens are subsequently processed within endosomal compartments, where the antigens are degraded into peptides. The peptides are then loaded onto MHC-II molecules, which are trafficked to the cell surface. Peptide–MHC-II are recognized by CD4$^+$ T cells *via* the TCR at the membrane, leading to activation and cytokine secretion. This pathway is primarily involved in initiating and modulating Th cell responses. (B) MHC-I antigen presentation pathway. This pathway shows the presentation of endogenous antigens (e.g., cytosolic proteins from tumor cells or intracellular pathogens). These proteins are degraded by proteasomes into peptide fragments, which are then translocated into the endoplasmic reticulum where the proteins are loaded onto MHC-I molecules. The peptide–MHC-I complexes are transported to the cell surface, where the peptide–MHC-I complexes are recognized by CD8$^+$ CTLs *via* the TCRs. This recognition enables CTLs to target and eliminate infected or malignant cells. pAPCs may also cross-present exogenous antigens *via* the MHC-I pathway to activate naïve CD8$^+$ T cells. APC: antigen-presenting cell; CTL: cytotoxic T lymphocyte; MHC-I: major histocompatibility complex class I; MHC-II: major histocompatibility complex class II; pAPC: professional antigen-presenting cell; TAA, tumor-associated antigen; TCR, T cell receptor. The figure was created by Figdraw.

tsMHC-II expression is not limited to pAPCs in tumor immunity. In fact, tsMHC-II expression has also been detected in some tumor cells. This expression enables tumor cells to directly interact with $CD4^+$ T cells, potentially modulating the immune response. $CD4^+$ T cells recognize and bind to antigenic peptides presented by MHC-II molecules via T cell receptors (TCRs), leading to activation and subsequent differentiation. Activated $CD4^+$ T cells can differentiate into helper T (Th) cells, which secrete cytokines that regulate immune responses, promote B cell-meditated antibody production, enhance $CD8^+$ T cell activation and cytotoxic function. Once activated, $CD8^+$ T cells recognize tumor-specific antigens (TSAs) and eliminate tumor cells through cytotoxic mechanisms.

Although tumor cells do not typically express MHC-II constitutively, the presence of interferon-γ (IFN-γ) within the tumor microenvironment (TME) can induce tsMHC-II expression. tsMHC-II expression is associated with increased infiltration and activation of $CD4^+$ T cells in several tumor models. These activated $CD4^+$ T cells further produce IFN-γ, which in turn amplifies tsMHC-II expression, forming a positive feedback loop (**Figure 2**)[20]. It has been reported that tsMHC-II expression is positively correlated with elevated numbers of $CD4^+$ and $CD8^+$ tumor-infiltrating lymphocytes (TILs), improved survival outcomes, and enhanced responses to ICIs[20-22]. The regulation of MHC-II expression is mediated by the class II transactivator (CIITA), a key transcriptional regulator essential for initiating MHC-II gene transcription and its related pathways[23]. CIITA-driven tsMHC-II expression can modulate tumor cell sensitivity to PD-1 blockade, thereby enhancing the efficacy of immunotherapy and improving patient prognosis. Thus, tsMHC-II has a critical role in anti-tumor immunity by activating $CD4^+$ T cells and bridging innate and adaptive immune responses, underscoring the importance of tsMHC-II in orchestrating immune regulation and promoting therapeutic responses.

Expression and regulation of MHC-II in tumor cells

Mechanisms regulating tsMHC-II expression in the TME

Regulation of tsMHC-II expression within the TME is a complex process governed by multiple signaling pathways and molecular mechanisms. These regulatory factors collectively influence tumor cell susceptibility to immune surveillance and have pivotal role in determining the efficacy of immunotherapy. This review highlights three principal mechanisms that modulate tsMHC-II expression in the TME.

Transcriptional regulation via CIITA

The master regulator of MHC-II gene expression is CIITA. Although CIITA does not directly bind DNA, it functions as a non-DNA-binding coactivator by recruiting transcription factors to MHC-II promoters to facilitate transcription. CIITA expression is governed by four distinct promoters (pI, pII, pIII, and pIV)[24]. While pI and pIII predominantly drive CIITA expression in APCs, pIV is the primary promoter induced by IFN-γ stimulation[25].

Ectopic expression of CIITA in tumor cells leads to upregulation of MHC-II and enhances the capacity to activate tumor-specific $CD4^+$ T cells, eliciting robust and durable anti-tumor immune responses. For example, CIITA-transduced tumor cells have been shown to secrete exosomes enriched with tsMHC-II and TSAs, thereby functioning as "mini-APCs"[26]. Additionally, permanent genomic insertion of CIITA into tumor cells has demonstrated potent immune-mediated tumor rejection *in vivo*[27].

Another study reported that interleukin-1β signaling promotes CIITA expression in melanoma cells, enhancing MHC-II-mediated antigen presentation[28]. Some tumor cells exhibit insufficient responsiveness to IFN-γ and rely on alternative regulatory pathways to regulate tsMHC-II expression. One pathway involves the transcription factor, FoxO1, which can directly bind to the CIITA promoter to enhance its expression. Conversely, epigenetic modifications can suppress CIITA activity[29]. For example, *Mycobacterium tuberculosis* infection downregulates CIITA and tsMHC-II expression through Rv1198-mediated histone H3 lysine 9 trimethylation, a process driven by the bacterial antigen, ESAT-6-like protein[30]. These findings highlight how infection or tumor-associated pathways can modulate immune surveillance by altering CIITA expression and antigen presentation.

Epigenetic modulation

Epigenetic alternations in DNA packaging can result in the silencing or activation of tumor-associated genes, thereby significantly influencing tumor progression. Among the major epigenetic regulatory mechanisms, DNA methylation and histone modifications play significant role in MHC-II gene expression.

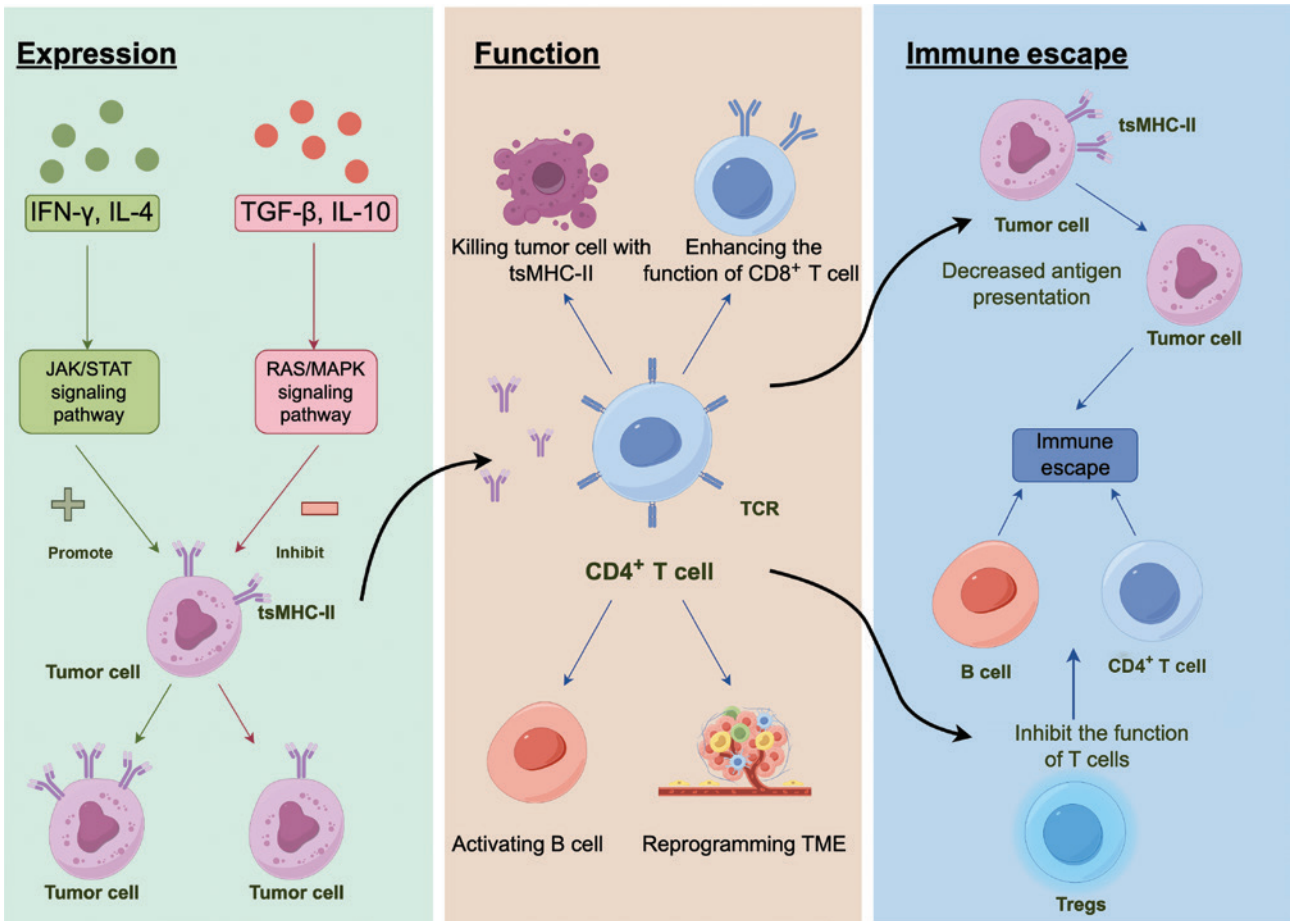

Figure 2 The specific mechanism of MHC-II in tumors. This figure summarizes the complex regulatory mechanisms, immunologic functions, and immune escape pathways associated with tsMHC-II expression in cancer. **Expression**. The regulation of MHC-II expression is shown in two signaling pathways. tsMHC-II expression on tumor cells is primarily induced by cytokines, such as IFN-γ and IL-4, through the JAK/STAT signaling pathway, which drives CIITA transcription. Conversely, immunosuppressive factors, including TGF-β and IL-10, inhibit MHC-II expression *via* the RAS/MAPK signaling pathway. **Function**. tsMHC-II enables tumor cells to present antigens to $CD4^+$ T cells when expressed, resulting in $CD4^+$ T cell activation and Th1 polarization. Activated $CD4^+$ T cells support $CD8^+$ T cell cytotoxicity, enhance dendritic cell and B cell functions, and secrete IFN-γ, which reprograms the TME toward a more inflamed and immunoresponsive state. $CD4^+$ T cells mediate cytotoxicity against MHC-II^+ tumor cells in some situations. **Immune Escape**. Downregulation or loss of tsMHC-II expression restricts antigen presentation, limits $CD4^+$ T cell priming, and promotes recruitment of Tregs, fostering an immunosuppressive microenvironment. In addition, increased IFN-γ signaling associated with tsMHC-II expression can induce PD-L1 upregulation on tumor cells, forming a negative feedback loop that dampens T cell activity. Taken together, this figure underscores the dual-edged role of tsMHC-II in shaping antitumor immunity and immune escape, highlighting the therapeutic implications. APC: antigen-presenting cell; CIITA: class II transactivator; DC: dendritic cell; IFN-γ: interferon gamma; IL-4: interleukin-4; IL-10: interleukin-10; JAK/STAT: Janus kinase/signal transducer and activator of transcription; MHC-II: major histocompatibility complex class II; PD-L1: programmed death-ligand 1; RAS/MAPK: RAS/mitogen-activated protein kinase pathway; TGF-β: transforming growth factor beta; Th1: T helper type 1 cell; TME: tumor microenvironment; Treg: regulatory T cell; tsMHC-II: tumor-specific MHC class II. The figure was created by Figdraw.

DNA hypermethylation has been observed at the promoter region of the *CIITA* gene, directly suppressing MHC-II expression[31,32]. As a key mechanism of transcriptional regulation at the chromatin level in eukaryotic cells, DNA hypermethylation is both heritable and reversible, offering a potential opportunity for therapeutic intervention. CpG islands, which are commonly located in gene promoter regions, are frequent targets of aberrant methylation and CpG island dysregulation is often associated with tumor progression.

For example, hypermethylation of the human leukocyte antigen-D related (*HLA-DR*) and human leukocyte antigen-Q related (*HLA-DQ*) genes are frequently observed in multiple tumors and correlate with immune escape and poor clinical outcomes in gastric cancer, renal cell carcinoma, and esophageal squamous cell carcinoma[31,33-36]. Inhibition of hypermethylation through gene inactivation or pharmacologic intervention has been demonstrated in colorectal and breast cancer cell lines, underscoring the potential for therapeutic strategies targeting epigenetic alterations[34,37]. However, inter-tumoral variability in methylation patterns highlights the complexity of this epigenetic modification in tumor. DNA methyltransferases (DNMTs), specifically DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L, are commonly mutated or overexpressed in tumors, further contributing to aberrant methylation[38]. Specifically, mutations in *DNMT* genes are common in human cancers. For example, mutations in the genes responsible for the isocitrate dehydrogenase (*IDH1* and *IDH2*) have been identified in acute myeloid leukemia, angioimmunoblastic T-cell lymphomas, and gliomas. These mutations lead to the production of the oncometabolite 2-hydroxyglutarate, leading to widespread DNA hypermethylation in these tumors[39-41].

Histone modifications also have a pivotal role in regulating MHC-II expression. Specifically, acetylation of histones H3 and H4 enhances transcriptional activation, while deacetylation suppresses gene expression. For example, trimethylation of H3K4 (H3K4me3) is usually associated with gene activation, whereas H3K9me2 is typically linked to gene silencing[42]. Acetylation of histones H3 and H4 at the HLA-DRA promoter is induced by IFN-γ in B-cell lymphoma cells expressing tsMHC-II[43]. Inactivating mutations in the histone acetyltransferase CBP (CREB-binding protein) result in decreased tsMHC-II expression[44,45]. Histone deacetylase (HDAC) inhibitors can restore MHC-II expression *via* CIITA upregulation in solid tumors and hematologic malignancies[43,46-48]. HDAC inhibition has been shown to enhance tsMHC-II expression in NSCLC cell lines, suggesting a potential strategy to improve the immunotherapeutic response[20,36]. HDAC inhibitors may promote antigen presentation *via* the tsMHC-II pathway by increasing histone H3 acetylation and reducing inflammation within TME[49-51]. Enhancer of Zeste homolog 2(EZH2)-driven histone methylation downregulates tsMHC-II expression in diffuse large B-cell lymphoma (DLBCL) and tumors carrying the EZH2Y641 mutation exhibit low expression of tsMHC-I and tsMHC-II[52]. Thus, this finding supports the combination of EZH2 inhibitors with ICIs, such as PD-1 blockade, to restore MHC expression and identify EZH2 mutations as potential predictive biomarker for response evaluation[53].

Cytokines and signaling pathways

Regulation of MHC-II expression involves intricate mechanisms with CIITA expression driven by IFN-γ serving as a pivotal step. IFN-γ activates Janus kinase 1/2 (JAK1/2) upon engaging with the IFN-γ receptor, which in turn triggers the phosphorylate signal transducer and activator of transcription 1 (STAT1). Phosphorylated STAT1 translocates to the nucleus, where phosphorylated STAT1 cooperates with transcription factors, such as IRF1, to activate CIITA pIV, thereby promoting MHC-II gene transcription[8].

As the master regulator of MHC-II expression, upregulated CIITA enhances the transcription of MHC-II-related genes, facilitating robust MHC-II surface expression[32]. Diminished responsiveness to IFN-γ is primarily attributed to defects within the IFN-γ signaling pathway in some tumor cells. Tumor cells may impair this pathway through mutations in JAK1/2 or repression of downstream effectors, ultimately diminishing IFN-γ-mediated MHC-II induction[54]. For example, CRISPR-Cas9-mediated knockout of the *JAK1* gene renders tumor cells unresponsive to IFN-γ, leading to a complete loss of MHC expression[55].

In addition to IFN-γ, several other cytokines, including IFN-α, IFN-β, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-4, and tumor necrosis factor-α (TNF-α), can enhance MHC-II expression, particularly in DCs[56,57]. IFN-α and IFN-β are mainly produced by virus-infected cells and activate similar JAK-STAT signaling cascades through their respective receptors, highlighting the multifactorial nature of MHC-II regulation[58]. IL-4, which is secreted by Th2 cells, induces MHC-II expression upregulation in DCs and support Th2-type immune responses, playing a critical role in immunity against parasitic infections[56]. TNF-α, which is secreted mainly by macrophages, is a proinflammatory cytokine that promotes MHC-II expression in DCs. TNF-α promotes inflammatory responses and immune cell activation and has an important role in immunomodulation and anti-tumor immunity[57]. In contrast, some innate immune signals can negatively regulate MHC-II. Activation of TLR2 signaling in gliomas downregulates MHC-II on tumor-infiltrating microglia and glioma-associated myeloid cells, thereby impairing $CD4^+$ T-cell recruitment and facilitating immune escape[59,60]. Conversely, activation of the

Ras-mitogen-activated protein kinase (RAS/MAPK) signaling pathway suppresses MHC-II expression[44]. For example, RAS/MAPK-driven MHC-II downregulation in breast cancer can be reversed by mitogen-activated protein kinase kinase (MEK) inhibitors[61]. Notably, activation of the MAPK pathway in HLA-DR$^+$ melanoma cells triggers the CIITA pIII, which is typically active in B cells[62]. These context-dependent regulations may reflect tumor-specific signaling pathways and distinct mechanisms that govern constitutive, inducible, or silenced expression of tsMHC-II.

Functional role and clinical significance of MHC-II

MHC-II expression in tumor cells is independent of MHC-I and contributes significantly to tumor immunogenicity. Rodig et al.[63] reported that tsMHC-II expression is associated with increased infiltration of CD4$^+$ T cells and improved patient prognosis. Notably, tsMHC-II expression has been identified across a wide range of tumor types, including tumors originating from the dermatologic[21,63,64], digestive[65], genitourinary[66,67], respiratory[20], neurologic[68], hematologic[69], and endocrine systems[20,22,70-74]. Interestingly, these tumor types typically lack MHC-II expression in the corresponding normal tissues, underscoring the unique immunologic phenotype of tumor cells that acquire tsMHC-II expression.

tsMHC-II is typically inducible by IFN-γ but can also be constitutively expressed in some tumor models, such as melanoma cell lines, even in the absence of exogenous stimulation (**Figure 3**)[21,71,72]. Importantly, tsMHC-II has emerged as a clinically relevant biomarker for T cell-inflamed ("hot") tumors, distinguishing "hot" tumors from non-inflamed ("cold") tumors[8]. Unlike IFN-γ signatures, which generally require sequencing-based detection, tsMHC-II can be readily detected by immunohistochemistry (IHC), offering a practical and accessible method for tumor stratification in clinical settings[75].

Overall, elevated expression of tsMHC-II is associated with improved therapeutic outcomes and is emerging as a promising predictive biomarker for immunotherapy responsiveness. Strategies designed to restore or enhance tsMHC-II expression, such as cytokine treatment, epigenetic modulators, or CIITA transduction, offer potential avenues to boost anti-tumor immunity and improve clinical efficacy.

tsMHC-II in immune regulation and prognosis

Cancer cells acquire various mechanisms to evade immune surveillance during tumor evolution, thereby facilitating sustained growth, invasion, and metastasis. A key immune escape strategy involves the disruption of antigen presentation pathways, notably through the downregulation or loss of MHC-I and MHC-II. These alterations impair the recognition of tumor cells by cytotoxic CD8$^+$ T cells and CD4$^+$ Th cells, respectively, leading to weakened cytotoxic and helper immune responses. Genetic mutations, epigenetic silencing, or transcriptional repression of MHC genes can profoundly affect antitumor immunity and reduce responsiveness to immunotherapy.

Role of tsMHC-II in tumor immune surveillance and escape

Immune escape is a hallmark of tumor progression[76,77]. MHC-I presents intracellular neoantigens to cytotoxic CD8$^+$ T cells, while MHC-II presents exogenous peptides to CD4$^+$ Th cells. Both pathways contribute independently and synergistically to effective tumor immunosurveillance[63]. Loss of MHC-I expression, which is often due to β2-microglobulin mutations, is a well-established mechanism of resistance to immune checkpoint blockade (ICB), particularly anti-PD-1 therapies (**Table 1**)[78-80]. These insights underscore the necessity to consider antigen presentation pathways when designing comprehensive immunotherapeutic strategies. Notably, increasing evidence indicates that tsMHC-II expression on tumor cells can sustain CD4$^+$ T cell-mediated immune pressure even in MHC-I-deficient tumors.

Expression of tsMHC-II is positively correlated with increased infiltration of CD4$^+$ and CD8$^+$ TILs, activation of Th1-associated cytokine pathways, formation of tertiary lymphoid structures, and upregulation of IFN-γ signaling. These immune features are further associated with favorable histopathologic markers, including reduced lymphvascular invasion. Although tsMHC-II is generally absent in poorly immunogenic tumors and often restricted to immune or stromal cells at the tumor periphery, preclinical studies demonstrate that enforced tsMHC-II expression enhances CD4$^+$ T cell recruitment[80], delays T cell exhaustion, and synergizes

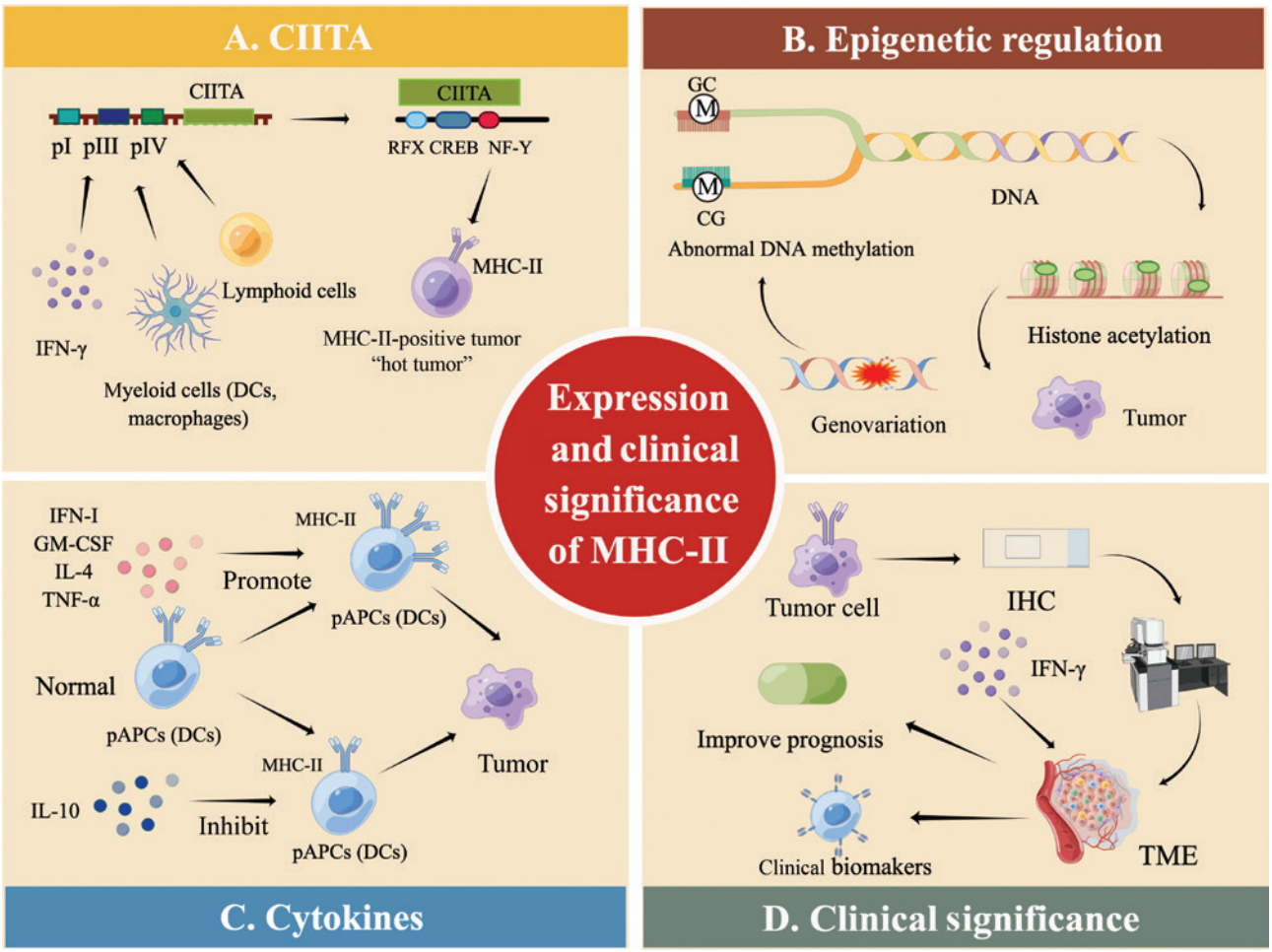

Figure 3 Expression and clinical significance of MHC-II. This figure summarizes the multifaceted regulation of MHC-II expression and the immunologic and clinical implications in TME through four distinct panels (A-D): (A) Transcriptional regulation of MHC-II *via* CIITA and its promoters. MHC-II expression in immune and tumor cells is transcriptionally controlled by CIITA. CIITA activity is modulated by four distinct promoters (pI–pIV) that are differentially regulated in various cell types. IFN-γ stimulation activates CIITA, particularly *via* pIV, leading to increased MHC-II expression in tumor cells and APCs, such as dendritic cells and macrophages. (B) Epigenetic modulation of MHC-II expression. Epigenetic mechanisms, including DNA methylation and histone acetylation, further influence MHC-II gene expression. DNA hypermethylation or histone deacetylation can silence CIITA and MHC-II expression in tumor cells, leading to immune evasion. Conversely, HATs promote open chromatin and gene transcription, favoring MHC-II upregulation. (C) Cytokine-mediated regulation in pAPCs. Cytokines have a pivotal role in modulating MHC-II expression in pAPCs. IFN-I, GM-CSF, IL-4, and TNF-α upregulate MHC-II levels by enhancing CIITA transcription or stabilizing MHC-II complexes. In contrast, IL-10 suppresses MHC-II expression and APC function, contributing to an immunosuppressive TME. (D) Clinical relevance and potential as a biomarker. TsMHC-II can be detected in tumor tissues *via* IHC. High tsMHC-II expression correlates with an inflamed TME, characterized by increased T cell infiltration and immune activation, and is associated with better patient prognosis and responsiveness to immunotherapy. Thus, tsMHC-II serves as a promising prognostic and predictive biomarker in various cancers. APCs: antigen-presenting cells; CIITA: class II transactivator; DCs: dendritic cells; GM-CSF: granulocyte-macrophage colony-stimulating factor; HATs: histone acetyltransferases; IFN-I/IFN-γ: type I/gamma interferons; IHC: immunohistochemistry; IL: interleukin; MHC-II: major histocompatibility complex class II; pAPCs: professional antigen-presenting cells; pI–pIV: promoters I to IV; TME: tumor microenvironment; TNF-α: tumor necrosis factor-alpha; tsMHC-II: tumor-specific MHC class II. The figure was created by Figdraw.

with PD-1 or lymphocyte activation gene-3 (*LAG-3*) blockade to promote tumor regression[81-83].

At the molecular level tsMHC-II expression is primarily regulated by the master transcriptional coactivator CIITA, which is modulated by IFN-γ signaling, the JAK-STAT pathway, and a variety of epigenetic factors. In chronic myeloid leukemia progenitor cells, cytokine-induced JAK signaling suppresses CIITA expression, an effect that can be reversed

by IFN-γ stimulation or JAK1/2 inhibition[84,85]. Similarly, activation of Toll-like receptor 2 (TLR2) has been shown to downregulate MHC-II expression in gliomas, thereby impairing $CD4^+$ T cell-mediated immune surveillance[86]. In addition, autophagy-related proteins (ATG), such as ATG5, regulate MHC-II-dependent antigen presentation by modulating lipid receptors trafficking in DCs[87].

Beyond established roles in natural immunity and checkpoint responses, tsMHC-I-restricted neoantigens have emerged as promising targets for engineered immunotherapies. MHC-II-restricted T cell receptor-engineered T (TCR-T) and chimeric antigen receptor T (CAR-T) cells have demonstrated preclinical efficacy against tumors expressing MHC-II-peptide complexes, particularly within $CD4^+$ T cell-enriched TMEs[88,89]. Enhancing MHC-II expression on tumor cells or APCs can augment antigen presentation and $CD4^+$ T cell-mediated help, thereby improving the persistence, trafficking, and effector function of adoptively transferred CAR-T or TCR-T cells. These strategies may overcome the immunosuppressive TME to enhance the durability of therapeutic response[90,91].

Nevertheless, tsMHC-II expression may paradoxically contribute to immune escape in some situations. For example, tsMHC-II expression by lymphatic endothelial cells has been shown to recruit regulatory T cells (Tregs) and enhance co-inhibitory signaling, thereby suppressing antitumor immune responses[92-94]. These findings highlight the context-dependent dual role of tsMHC-II, which can either promote or inhibit immune activity depending on the surrounding microenvironmental and molecular signals.

Future research should aim to elucidate the factors that determine the functional outcomes of tsMHC-II expression, such as the presence of co-stimulatory or co-inhibitory ligands, antigen specificity, and spatial compartmentalization, and to develop targeted strategies that enhance immunogenic effects while minimizing immunosuppressive activity[95]. Such approaches hold promise for advancing tsMHC-II-based immunotherapeutic interventions in tumor treatment.

Correlation between tsMHC-II molecular expression and prognosis of tumor patients

The prognostic significance of tsMHC-II expression has been increasingly recognized in various tumor types. High tsMHC-II expression on tumor cells has been confirmed to correlate with prolonged survival, enhanced T-cell infiltration, and improved therapeutic responses. This association has been documented in gastrointestinal[96-99], head and neck[100,101], respiratory[102], genitourinary[66,103,104], and hematologic tumors [105,106].

tsMHC-II expression significantly reduces tumor burden in preclinical mouse models *via* $CD4^+$ T cell-mediated mechanisms[12,107]. Clinical evidence from patients with classical Hodgkin lymphoma (CHL), melanoma, and gastric adenocarcinoma (GAC) has also shown that tsMHC-II-high tumors exhibit enhanced responsiveness to ICB, particularly anti-PD-1 or anti-PD-L1 therapies[21,63]. These findings collectively suggest that upregulating tsMHC-II in human tumors may potentiate antitumor immunity and improve ICB efficacy.

tsMHC-II has emerged as a robust biomarker for predicting responses to immunotherapy. Multiple studies have reported strong correlation between tsMHC-II expression and favorable clinical endpoints, such as PFS, OS, and enhanced infiltration of $CD4^+$ and $CD8^+$ T cells. Specifically, tsMHC-II expression serves as a reliable predictor of responses to neoadjuvant anti-PD-1/PD-L1 therapy combined with chemotherapy in HER2-negative breast cancer. While tsMHC-II-positive tumors often exhibit heightened sensitivity to monotherapy, recent work in bladder cancer and melanoma has revealed a synergistic mechanism; tumors with high tsMHC-II expression level also show more robust responses to PD-L1 inhibitors, likely due to improved $CD4^+$ T helper activation within the TME[108,109]. Conversely, tsMHC-II-negative tumors may respond better to PD-1/PD-L1 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) combination therapy, aligning with meta-analysis data showing improved outcomes in PD-L1-negative patients receiving dual checkpoint blockade.

Approximately 60% of patients who benefit from combination immunotherapy present with low baseline MHC-I/II expression and poor prognostic features in melanoma and CHL, such as elevated lactate dehydrogenase (LDH) levels[8,110,111]. Moreover, recent findings reveal that dynamic tumor-specific MHC-II expression, both baseline and inducible, serves as a predictive biomarker of checkpoint inhibitor response in melanoma[112].

Transcriptomic analyses further support the clinical utility of tsMHC-II. Notably, multigene analysis incorporating 13 key MHC-II pathway genes (e.g., *CIITA*, *CD74*, and *HLA-DPA1*) in triple-negative breast cancer (TNBC) reveals strong association with prolonged PFS and outperforms single-gene markers in predictive accuracy[113]. Furthermore, Wang et al. identified nucleophosmin (NPM1) as a negative regulator of

antigen presentation. NPM1 suppresses the expression of both tsMHC-I and tsMHC-II by repressing interferon regulatory factor 1 (IRF1), thereby promoting immune escape. Inhibition or genetic ablation of NPM1 restores MHC expression and enhances tumor-specific T-cell cytotoxicity, positioning NPM1 as a potential therapeutic target to enhance immunotherapy efficacy[114].

Taken together, tsMHC-II serves as a biomarker and a functional effector in tumor immunity. tsMHC-II integration into immunotherapy strategies, whether through ICB, adoptive T cell therapies, or antigen-targeted vaccines, offers a promising avenue to enhance treatment specificity, durability, and overall patient outcomes.

Application of tsMHC-II in tumor immunotherapy

Vaccine strategies based on MHC-II

Despite notable advances in conventional tumor therapies, which have shown encouraging outcomes in combating this life-threatening disease, ongoing research continues to focus on developing more effective and innovative treatment strategies. Among these strategies, tumor vaccines have recently emerged as promising tools[115,116]. Progress in immunology, molecular biology, and genetic engineering has enabled the development of specialized and personalized tumor vaccination approaches. Early therapeutic vaccines primarily targeted tumor-associated antigens (TAAs), which are autologous proteins aberrantly expressed or overexpressed in tumors. However, these strategies have generally failed to elicit clinically significant anti-tumor immune responses. This limited efficacy is largely attributed to central and peripheral tolerance mechanisms that restrict T cell responses to TAA-specific targets[117]. Moreover, TAAs are often expressed in normal tissues, thereby increasing the risk of autoimmune toxicity following vaccination[117]. These findings underscore the key challenges in tumor vaccine development, including insufficient tumor specificity and low immunogenicity of TAAs.

Neoantigen-based vaccines have emerged as a transformative approach in tumor immunotherapy, offering personalized strategies that target TSAs. Among these neoantigen-based vaccines, peptide-based vaccines use short peptides containing immunogenic epitopes derived from tumor antigens, which are critical for eliciting a robust immune response[102,118]. To maximize efficacy, these vaccines generally contain both $CD8^+$ and $CD4^+$ T cell epitopes. $CD8^+$ T-cell epitopes enhance tumor immunogenicity and activate CTLs *via* antigen-presentation pathways, while $CD4^+$ T-cells stimulate Th cells to support and sustain CTL function. However, the clinical effectiveness of peptide-based vaccines remains limited by various factors, such as short half-life of peptide epitopes and MHC polymorphisms, which pose significant challenges for broad clinical application[118,119].

An alternative approach is the use of DC vaccines, which aim to overcome the limitations imposed by tumor-induced immune escape. DCs play a central role in initiating immune responses because DCs capture antigens during inflammation and present the antigens to T cells. Unlike infectious diseases, tumors frequently fail to provoke a strong inflammatory response, leading to suboptimal DC activation and inadequate immune priming. DC vaccines address this issue by directly delivering tumor antigens to DCs, promoting their maturation into potent APCs and facilitating activation of antigen-specific T lymphocytes through interaction with TCRs, ultimately leading to tumor cell destruction and inhibition of tumor growth[119-122]. *In vitro* modulation of DCs enables precise control over DC activation and function, offering greater efficacy than conventional vaccination approaches.

In addition, nucleic acid vaccines, which utilize DNA or RNA to encode tumor antigens, have distinct advantages over traditional peptide-based vaccines. While peptide vaccines typically present only a single epitope, mRNA vaccines are capable of encoding entire antigens that contain multiple epitopes, thereby eliciting a broader and more potent T cell response[123]. However, significant challenges remain for prophylactic tumor vaccines, especially vaccines targeting non-viral tumors. These challenges include the identification of suitable antigens, strategies to mitigate autoimmune reactions, methods to enhance vaccine accumulation and retention in lymphoid tissues, and approaches to promote the generation of durable memory immune responses[124,125]. Furthermore, the combination of tumor antigens with appropriate adjuvants may further enhance antitumor immune responses[119-121]. **Table 2** summarizes representative therapeutic approaches and clinical trials that leverage MHC-II in tumor immunotherapy to better illustrate the translational progress of tsMHC-II-targeted approaches.

ICIs utilizing MHC-II molecules

In addition to tsMHC-II-based vaccines aimed at combating tumors, ICIs provide another strategy by modulating the host immune system. ICIs enhance the immune response to tumors by blocking inhibitory receptors or their ligands on immune cells, thereby preventing the immunosuppressive signaling that dampens T cell activation and proliferation. Factors influencing the efficacy of ICIs can be broadly categorized into two main areas: (1) tumor genomic features associated with activated T cells, such as *de novo* antigens that stimulate T cells, somatic mutations that produce these antigens, MHC molecules that determine antigen presentation, and TCRs that recognize the neoantigens; and (2) TME, including PD-L1 expression on tumor cells, the extent of T cell infiltration, and presence and function of other immune cells.

MHC-I and MHC-II expression may serve as valuable biomarkers for guiding ICI therapy, particularly when used in conjunction with other well-established biomarkers. Although PD-L1 expression and tumor mutational burden (TMB) are currently more widely accepted biomarkers for predicting efficacy, the predictive power remains limited, especially in the context of combination therapies. Therefore, the identification of novel and complementary biomarkers is critical to refining patient stratification and improving therapeutic outcomes[128] (**Figure 4**).

MHC molecules have crucial role in recognizing antigens and are essential for antigen presentation and immune signaling. MHC-II, in particular, is responsible for presenting exogenous antigens to $CD4^+$ T cells, activating Th cells, initiating humoral immune responses, and enhancing $CD8^+$ T cell activity. $CD4^+$ T cell activation requires three distinct signals: (1) recognition of antigenic peptides presented by MHC-II molecules through interaction with the TCR; (2) a co-stimulatory signal provided by the interaction between CD28 on T cells and CD80 or CD86 on APCs; and (3) cytokine signaling, which directs the differentiation of $CD4^+$ T cells into distinct functional subsets. MHC-II can further contribute to the activation and support of $CD8^+$ T cells-mediated cytotoxic responses through these mechanisms[129].

Table 2 Therapeutic strategies targeting MHC-II in tumor immunotherapy

Category	Strategy	Title	Mechanism	Tumor types	Clinical status	Reference
Vaccine	MHC-II-restricted peptide vaccines	S-6MHP–peptide vaccine (6 melanoma helper peptides + GM-CSF)	Activates $CD4^+$ T cells, promotes helper function	– Melanoma – NSCLC	Phase I/II trials	126
Vaccine	DC vaccines presenting MHC-II neoantigens	ICT-107 glioblastoma trial (Phase II, NCT01280552)	Potent activation of $CD4^+$ and $CD8^+$ T cells	– Glioma – Prostate cancer	Phase I/II	60
ICI combination	Anti-PD-1 + MHC-II vaccine	6MHP peptide vaccine + pembrolizumab trial (Phase I/II)	Enhances T cell priming, synergizes with checkpoint blockade	Breast cancer	Preclinical	127
Epigenetic enhancer	CIITA-inducing HDAC inhibitors	Preclinical agents (e.g., pracinostat)	Reactivates MHC-II pathway *via* chromatin remodeling	– Colon cancer – Melanoma	Preclinical	51
Engineered T cell therapy	MHC-II-restricted TCR-T/CAR-T	Mesothelin-CAR-T trial in pleural mesothelioma (NCT02414269)	Targets peptide-MHC-II complexes on tumor cells	– Mesothelioma – Melanoma	Preclinical	89

CAR-T, chimeric antigen receptor T cells; GM-CSF, granulocyte-macrophage colony-stimulating factor; HDAC, histone deacetylase; ICI, immune checkpoint inhibitor; ICT, immune checkpoint therapy; NSCLC, non-small cell lung cancer; S-6MHP–peptide vaccine, synthetic 6 multi-HLA-binding peptides vaccine; TCR-T, T cell receptor-engineered T cells.

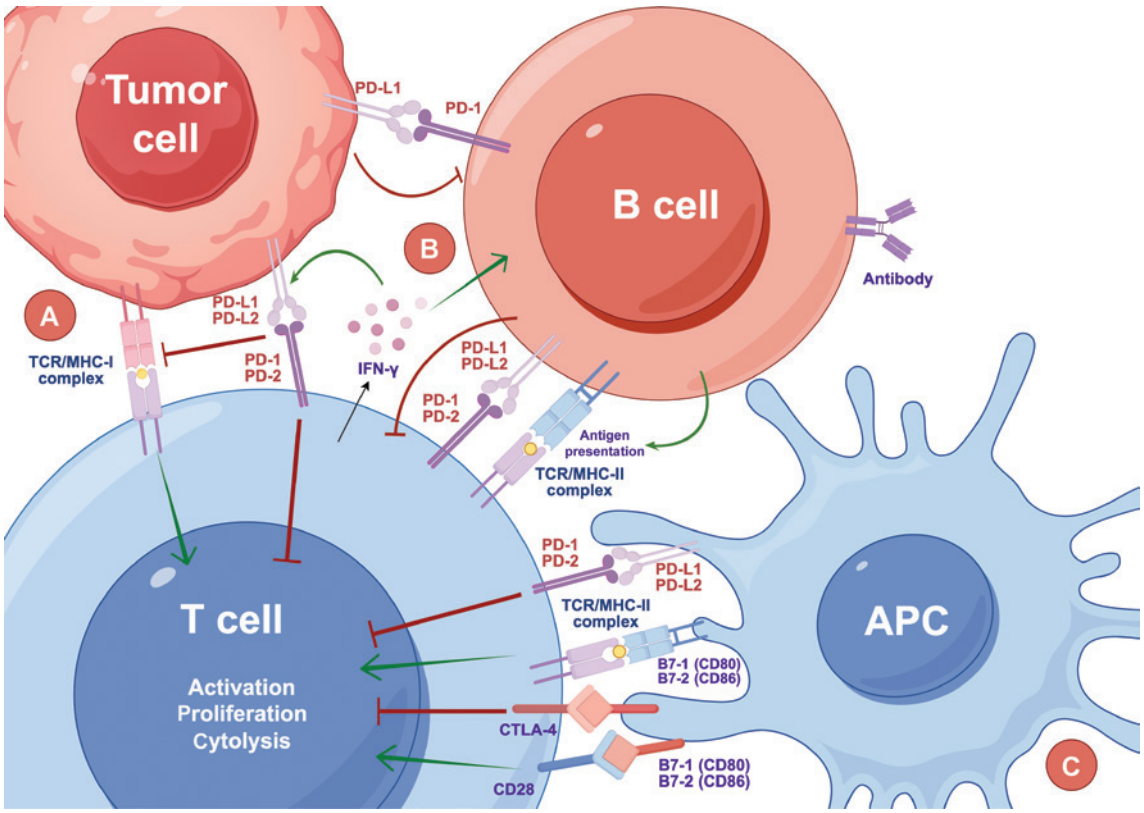

Figure 4 The role of PD-1/PD-L1 in tumor immunotherapy. This diagram illustrates the immune regulatory interactions between tumor cells, APCs, T cells, and B cells within the context of tumor immunotherapy, highlighting the role of PD-1/PD-L1 signaling. Each section is labeled as (A), (B), and (C), representing key components of the immune response. (A) Tumor cell-T cell interaction. Tumor cells express PD-L1 on the surface, which interacts with PD-1 receptors on T cells, leading to the inhibition of T cell activation, proliferation, and cytolytic activity. The TCR on the T cell is essential for recognizing tumor antigens presented by MHC-I molecules on the tumor cell surface. The engagement of PD-1 with PD-L1 prevents the activation and proliferation of the T cell, which hampers the ability of the immune system to recognize and eliminate the tumor. This immune checkpoint can be targeted for immunotherapy to block the PD-1/PD-L1 interaction, thereby enhancing anti-tumor immunity. Additionally, activated T cells secrete IFN-γ, which can increase PD-L1 expression on tumor cells, forming a feedback loop that further suppresses T cell activity. (B) B cell-T cell-tumor cell interaction. B cells can contribute to anti-tumor immunity by presenting antigens *via* MHC-II to $CD4^+$ T cells. B cells can express PD-1 similar to T cells and PD-L1 on tumor cells can interact with PD-1 on B cells, suppressing B cell activation and antibody production. IFN-γ in the TME further shapes B cell activity by enhancing antigen presentation and modulating cytokine production. This bidirectional communication between B cells, T cells, and tumor cells influences tumor antigen recognition and immune regulation. (C) APC interaction with T cells. Professional APCs, such as dendritic cells, express MHC-II and costimulatory molecules, like B7-1 (CD80) and B7-2 (CD86), which are necessary for T cell activation. The APC presents antigens through the TCR/MHC-II complex, which induces T cell activation, proliferation, and cytolysis of tumor cells. Engagement of CD28 on the T cell with B7-1/B7-2 on the APC promotes T cell activation. However, the presence of CTLA-4 on the T cell can act as a negative regulator of this response, inhibiting T cell activation. IFN-γ is also produced by activated T cells, contributing to the inflammatory tumor microenvironment. APC: antigen-presenting cell; B7-1 (CD80): B7 homolog 1, also known as CD80; B7-2 (CD86): B7 homolog 2, also known as CD86; CD28: cluster of differentiation 28; CTLA-4: cytotoxic T lymphocyte-associated protein 4; IFN-γ: interferon-gamma; MHC-I: major histocompatibility complex class I; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; TCR: T cell receptor. The figure was created by Figdraw.

Activated $CD8^+$ T cells that recognize oncogene-derived epitopes exert direct cytotoxic effects on tumor cells. Recent studies have highlighted that high-level expression of genes involved in the tsMHC-II antigen presentation signaling pathway is potential biomarkers for survival benefit in patients undergoing sindilizumab combination chemotherapy[130]. Specifically, elevated expression of these genes was strongly associated with prolonged PFS (HR = 0.32) and OS (HR = 0.36)

in the combination treatment group. Notably, even in patients with low or undetectable PD-L1 expression, those with high levels of tsMHC-II pathway-associated genes still benefited from the combination therapy. This finding suggests that combining tsMHC-II expression with PD-L1 expression could broaden the patient population benefiting from this treatment. In contrast, high-level expression of genes related to the MHC-I antigen presentation signaling pathway does not have significant association with the effectiveness of this combination regimen.

An analysis revealed that tsMHC-II expression serves as a more reliable predictor of response to ICIs than PD-L1 expression in early-stage HER2-negative breast cancer[131]. In addition, MHC I expression was identified as a robust predictive biomarker for CTLA-4 inhibitors but not for PD-1 inhibitors, whereas MHC-II expression was proved to be predictive for PD-1/PD-L1 inhibitors but not for CTLA-4 inhibitors[132]. These findings underscore the potential of MHC expression analysis in biomarker research. A composite biomarker approach that integrates MHC expression with well-established markers, such as PD-L1 expression and TMB, could enhance predictive accuracy without replacing existing markers[130].

However, it is important to note that combination ICI therapy is associated with increased risk of adverse events, including greater toxicity, higher incidence of immune-related adverse reactions compared to monotherapy, and substantially higher financial burden. Therefore, the identification and application of reliable biomarkers are essential for guiding early and personalized treatment decisions by identifying whether a patient is more likely to benefit from monotherapy or combination immunotherapy.

Potential of MHC-II in personalized immunotherapy

Current research emphasizes the potential of MHC-II in personalized immunotherapy. The tsMHC-II genotype is an independent predictor of response to anti-PD-1 immunotherapy in melanoma patients. One study demonstrated a significant negative correlation between the tsMHC-II genotype binding score and treatment outcomes, particularly among patients previously treated with anti-CTLA-4 antibodies, based on data from 144 melanoma patients receiving anti-PD-1 therapy[3,133].

Importantly, new evidence suggests that tumor cells may express tsMHC-II and higher levels of tsMHC-II expression are linked to more favorable responses to anti-PD-1 therapy. The tsMHC-II genotype and level of expression have been shown to independently predict clinical outcomes in patients with prior anti-CTLA-4 treatment[134]. Mechanistically, the MHC-II genotype affects the peptide-binding capacity of HLA molecules, high MHC-II expression is generally associated with enhanced immune responses and improved therapeutic efficacy.

Interestingly, greater MHC-II binding capacity is paradoxically associated with poorer treatment outcomes, suggesting a more complex role for tsMHC-II in modulating anti-PD-1 efficacy. Furthermore, TMB and MHC-II binding properties have been shown to negatively correlate with IFN-γ activity, potentially explaining the limited treatment response observed in some patients.

In addition to melanoma, the predictive value of tsMHC-II has been explored in other malignancies, including breast, ovarian, and pancreatic cancers[131,135-137]. In patients with HER2-negative breast cancer, the expression level of tsMHC-II (HLA-DR) on tumor cells has been shown to predict patient response to anti-PD-1/PD-L1-based neoadjuvant chemotherapy[127,131]. Targeted elimination of effector regulatory T cells significantly enhances anti-tumor immunity in high-grade serous ovarian cancer with homologous recombination deficiency, suggesting that the dynamic expression of tsMHC-II is closely related to the immunosuppressive microenvironment[137].

These findings collectively underscore the potential of tsMHC-II as a biomarker for personalized immunotherapy and indicate that MHC genotypes could serve as tumor-agnostic predictors for response to anti-PD-1 therapy in melanoma[3,126,133]. The independent association of MHC-II genotype and expression suggests that the tsMHC-II complex has a significant role in modulating responses to anti-PD-1 immunotherapy. These insights may have significant clinical implications, particularly for patients undergoing combination treatment with anti-CTLA-4 and anti-PD-1 therapies.

The development of personalized tumor vaccines based on neoantigens has become a prominent focus in tumor immunotherapy research. These vaccines are tailored to individual patients, leveraging tumor-specific somatic mutations to stimulate targeted immune responses[138]. A key advantage of neoantigen vaccines is the ability to elicit highly specific T cell responses, thereby minimizing off-target effects and reducing the risk of damage to healthy tissues. Moreover, because neoantigens are novel epitopes derived from tumor-specific mutations, neoantigens can bypass central and peripheral tolerance

mechanisms that typically limit T cell responses to self-antigens. This effect enables a more robust and tumor-specific immune response. Recent advances in neoantigen identification, vaccine design, and delivery technologies have laid the groundwork for next-generation tumor vaccines with the potential to transform therapeutic strategies in oncology.

Research progress of MHC-II molecules and the roles across tumor types

Predict neoantigens that bind to MHC-II molecules

Neoantigens arise primarily from somatic mutations in tumor cells that alter the protein-coding sequence, resulting in the generation of novel antigenic peptides absent from normal tissues. In virally driven tumors, such as HPV-positive cervical cancer and EBV-associated nasopharyngeal carcinoma, neoantigens may also originate from non-self open reading frames encoded by viral genomes[139]. These unique antigens represent ideal targets for tumor-specific immunotherapies, particularly in the development of personalized tumor vaccine.

tsMHC-II molecules facilitate the presentation of these neoantigens to $CD4^+$ T cells, thereby augmenting Th cell responses, enhancing cytotoxic $CD8^+$ T cell activity, and promoting a pro-inflammatory TME[140]. High-level tsMHC-II expression is associated with increased infiltration of immune effector cells and favorable clinical outcomes across multiple tumor types. Synthetic long peptide (SLP) vaccines, which incorporate both MHC-I and MHC-II epitopes, have been designed to leverage this mechanism by promoting efficient antigen presentation to both $CD4^+$ and $CD8^+$ T cells. Compared to short peptide vaccines, SLPs elicit more robust and durable immune responses due to prolonged antigen presentation in draining lymph nodes and enhanced Th cell activation[141].

The neoantigen-based vaccines have shown promising results in clinical trials, particularly in melanoma, where they stimulate T cell expansion, broaden the neoantigen-specific TCR repertoire, remodel the immune microenvironment, and improve tumor control[136,138].

However, the accurate prediction of MHC-II-binded-peptides remains a major technical challenge. Unlike MHC-I, MHC-II molecules bind peptides of variable lengths and display extensive polymorphism, making computational modeling of peptide binding highly complex[142-144]. Tools, such as NetMHCIIpan, use neural network-based algorithms trained on large peptide-MHC binding datasets to estimate binding affinities. However, these models often fail to account for critical contextual features, including peptide structural conformation, flanking residues, and intracellular antigen processing dynamics. Recent approaches that incorporate TIL-derived TCR data have improved prediction accuracy by considering antigen structural avidity, particularly in hepatocellular carcinoma and melanoma[143].

Despite recent advances, several limitations hinder the clinical translation of neoantigen prediction. One of the most pressing challenges is the lack of standardized and reliable methods for detecting tsMHC-II expression in patient tumor samples[145]. Conventional IHC techniques often fail to distinguish tsMHC-II expression on tumor cells from that on stromal cells or APCs. Furthermore, the limited availability of validated antibodies and the absence of uniform scoring criteria compromise the reproducibility and comparability of results across studies and clinical centers.

Moreover, the spatial and temporal heterogeneity of MHC-II expression within the TME further complicates the interpretation. Regions with strong tsMHC-II positivity may coexist alongside areas exhibiting complete loss of expression. This heterogeneity influences patterns of immune cell infiltration, neoantigen presentation, and responsiveness to immunotherapies. Notably, most of the vaccine design models do not adequately account for this variability, potentially limiting the predictive and therapeutic efficacy.

Therefore, future research should focus on enhancing both computational prediction algorithms and experimental validation pipelines, which include the integration of spatial transcriptomics, single-cell proteomics, and multi-region tumor sampling to more accurately characterize intra-tumoral heterogeneity. Additionally, the development of clinical-grade assays for precise assessment of tsMHC-II expression is essential for effective patient stratification and the design of MHC-II-targeted immunotherapeutic strategies.

Research status of MHC-II molecules in different tumor types

Given the immunologic complexity and clinical heterogeneity across tumor types, the expression and function of MHC-II molecules vary substantially among different

Table 3 Prognostic impact of MHC-II expression across tumor types

System	Tumor type	TsMHC-II expression profile	Associated clinical outcome	Reference
Cutaneous tumor	Melanoma	High tsMHC-II correlates with increased $CD4^+$ T cell infiltration and Th1 responses	High expression of MHC-II referring to: – Prolonged OS; – Enhanced response to anti-PD-1 therapy	21
Hematologic tumor	CHL	MHC-II expression retained on Reed–Sternberg cells, facilitating tumor immunogenicity	Durable and sustained responses to PD-1 blockade	69
	DLBCL	Frequent loss or downregulation of MHC-II expression, contributing to immune escape	Low expression of MHC-II referring to: – Poorer prognosis; – Reduced sensitivity to ICIs	52
Gynecologic tumor	TNBC	Upregulated MHC-II gene signature (e.g., HLA-DPA1 and CIITA)	High expression of MHC-II referring to: – Longer PFS; – Improved clinical response to immunotherapy	22
Digestive system tumor	GAC	Co-expression of tsMHC-II and *LAG-3* in TME reflects an inflamed immune phenotype	Co-expression of MHC-II and *LAG-3* in TME referring to: – Better prognosis – Potential biomarker for immunotherapy responsiveness	146

CHL, classical Hodgkin lymphoma; CIITA, class II transactivator; DLBCL, diffuse large B-cell lymphoma; GAC, gastric adenocarcinoma; HLA-DPA1, human leukocyte antigen-DP alpha 1; ICIs, immune checkpoint inhibitors; *LAG-3*, lymphocyte activation gene-3; OS, overall survival; PFS, progression-free survival; PD-1, programmed death receptor 1; Th, T helper cell; TNBC, triple-negative breast cancer; TME, tumor microenvironment.

tumors. Understanding these tumor-specific differences is critical for refining immunotherapeutic strategies and identifying tumor-specific biomarkers. To further delineate the clinical significance of tsMHC-II, **Table 3** and the following subsections summarize the prognostic associations across major tumor types, underscoring the potential utility of it as a predictive marker and tool for patient stratification in immunotherapy.

Cutaneous tumor

Melanoma is the most extensively studied tumor type in the context of tsMHC-II research. Melanoma is highly aggressive and fatal skin cancer and remains a significant challenge due to limited effective treatment options[21,110,147]. Recent studies have shown that a subset of patients with advanced melanoma benefit from therapies targeting the T-cell inhibitory receptor, PD-1. However, resistance to PD-1 monotherapy is frequently associated with the downregulation of MHC-I transcription in melanoma cells. This downregulation correlates with decreased expression of tsMHC-II and PD-L1, along with reduced infiltration of T cells into TME[110].

The primary mechanism underlying PD-1 blockade is to restore the activity of exhausted immune cells, thereby reinitiating tumor-specific immune responses. However, the effectiveness of immune-mediated tumor elimination hinges on the recognition of tumor antigens by CTLs through MHC-I presentation. Evidence suggests that the co-expression of tsMHC-I and tsMHC-II on tumor cells is essential for achieving optimal responses to anti-PD-1 monotherapy. Interestingly, approximately 60% of patients who respond to combination immunotherapy, such as anti-PD-1 and anti-CTLA-4, exhibit reduced expression of tsMHC-I and tsMHC-II on melanoma cells. This paradoxical response is often observed in patients with unfavorable baseline prognostic features, including elevated serum LDH levels[110].

Rodig et al.[63] examined the expression of tsMHC I and tsMHC-II in treatment-naïve melanoma patients and correlated these findings with transcriptomic profiles and clinical outcomes. Rodig et al.[63] reported that 43% of patients (78/181) exhibited loss of membrane-bound MHC-I expression in >50% of melanoma cells. This loss was linked to transcriptional repression of key antigen-presentation genes, including *HLA-A*, *HLA-B*, *HLA-C*, and *β2M*, and was associated with primary resistance to anti-CTLA-4 therapy. In contrast, tsMHC-II expression, defined as detection in >1% of melanoma cells, was observed in 30% of patients (55/181). This

expression pattern correlated with interferon-gamma (IFN-γ)-induced gene signatures and was predictive of a favorable response to anti-PD-1 therapy.

These findings underscore the association between tsMHC-II expression and clinical outcomes, response to ICI, and tumor rejection in preclinical models. Consequently, melanoma patients with low MHC-I expression may obtain greater benefit from first-line combination immunotherapy, such as anti-PD-1 plus anti-CTLA-4, rather than PD-1 monotherapy. Nevertheless, the utility of MHC-I expression as a predictive biomarker for anti-PD-1 therapy remains controversial and requires further investigation.

Hematologic tumor

The frequency of MHC loss varies considerably among tumor types, with DLBCL exhibiting a relatively high incidence. The loss of tsMHC-I and tsMHC-II expression has been reported in approximately 40%–60% and 20%–40% of DLBCL cases, respectively[52,148]. Ennishi et al.[52] revealed a potential association between this loss and mutations that impair the function or expression of MHC molecules. Notably, mutations in *EZH2* were frequently observed in tsMHC-I- and tsMHC-II-negative primary lymphomas. In support of this finding, *in vitro* experiments confirmed that *EZH2* mutations can lead to downregulation of MHC expression.

In addition, another study demonstrated low expression of tsMHC-II-related genes in testicular DLBCL samples derived from immune-privileged sites. The findings revealed that diminished *HLA-DR* mRNA levels are associated with decrease in infiltrating $CD3^+$ T cells and significant downregulation of genes involved in antigen presentation, T-cell activation, chemokine signaling, and components of the complement system[149]. These findings suggest that tsMHC-II has a pivotal role in orchestrating anti-tumor immune responses and its downregulation in DLBCL may occur through multiple, context-specific mechanisms.

Clinically, tsMHC-II expression correlates with the International Prognostic Index (IPI) score and OS in DLBCL patients. The loss of tsMHC-II protein expression has been linked to poor survival outcomes in patients undergoing immunochemotherapy[149]. Furthermore, studies have demonstrated that inhibition of the transcription factor, forkhead box P1 (FOXP1), restores tsMHC-II expression in activated B-cell-like (ABC) DLBCL cells[150]. FOXP1 acts as a negative regulator of CIITA, the master transactivator of tsMHC-II. FOXP1 inhibition may enhance antigen presentation and improve immune surveillance in high-risk DLBCL patients[151]. Collectively, these findings underscore the pivotal role of tsMHC-II in the immune response to DLBCL and provide a rationale for developing immunomodulatory therapeutic strategies.

CHL exhibits a critical relationship with tsMHC-II expression in the context of tumor immunotherapy. tsMHC-II expression is associated with enhanced responses to anti-PD-1 therapy in CHL. Studies have shown that tsMHC-II-positive tumor cells correlate with improved clinical outcomes, including longer PFS and OS, as well as increased infiltration of $CD4^+$ and $CD8^+$ T cells. Additionally, MHC-II expression in Hodgkin Reed-Sternberg (HRS) cells may serve as a predictive biomarker of favorable outcomes following PD-1 blockade. These findings suggest that tsMHC-II expression in HRS cells facilitates tumor recognition by the immune system and has a key role in the efficacy of immunotherapy. Roemer et al.[69] evaluated the response of relapsed or refractory CHL patients to PD-1 blockade with nivolumab in the CheckMate trial. The findings indicated that clinical responses to nivolumab were independent of MHC-I expression in HRS cells, underscoring the distinctive predictive value of tsMHC-II expression for treatment outcomes in CHL.

Gynecologic tumor

TNBC is an aggressive subtype of breast cancer that is characterized by absence of the estrogen receptor (ER), progesterone receptor (PR), and HER2 expression[152,153]. This subtype presents challenges due to aggressive behavior, high metastatic potential, frequent recurrence, and the lack of clearly defined therapeutic targets. Tumor cells may evade immune system surveillance by downregulating MHC molecules expression in TNBC. While the mechanisms underlying MHC-I and the role of immunosuppressive cells in the TME have been explored in other studies, herein we focus on the relationship between tsMHC-II expression and TNBC.

tsMHC-II expression in TNBC may influence tumor immunogenicity and responsiveness to immunotherapy. Forero et al.[22] reported that the tsMHC-II antigen-presenting pathway in tumor tissues from TNBC patients is strongly associated with PFS. The analysis of 199 TNBC cases from a public gene expression database further corroborated the link between MHC-II pathway activity and favorable prognosis. The study demonstrated that altered expression of the tsMHC-II pathway in TNBC tumor cells can stimulate anti-tumor immune responses, reduce recurrence rates, and improve PFS. Similarly, tsMHC-II expression in tumor cells was closely associated with

TILs and increased interferon signaling in TNBC[113]. Moreover, strategies aimed at enhancing tsMHC-II expression in TNBC tumor cells through genetic modification or pharmacologic interventions hold promise for improving antigen presentation and thereby augmenting the efficacy of immunotherapy.

Digestive system tumor

Epstein-Barr virus-associated gastric adenocarcinomas (EBVaGCs) are characterized by a more favorable clinical prognosis compared to other GC subtypes, which may be attributed to the persistent expression of viral antigens[154]. A hallmark of tumor immune escape is the dysregulation of antigen presentation, often mediated by mechanisms that suppress tsMHC-II expression. However, the expression of tsMHC-II is notably upregulated in EBVaGCs, suggesting a different immune landscape compared to other GCs[146].

APCs typically present peptides *via* MHC-II to initiate immune responses. Epithelial cells can also express MHC-II and function as non-professional helper APCs under inflammatory conditions, thereby contributing to antigen presentation. tsMHC-II gene expression is significantly elevated in EBVaGCs, not only compared to normal gastric tissue but also relative to other GC subtypes, highlighting a unique aspect of the TME. Remarkably, the increased MHC-II expression exceeds that observed in professional APCs by several orders of magnitude, suggesting that this upregulation is unlikely due to increased APC infiltration. This observation is supported by the concomitant upregulation of key transcriptional regulators of the MHC-II pathway, such as CIITA and regulatory factor X5[38].

Furthermore, elevated intratumorally IFN-γ levels in EBVaGCs strongly correlate with increased expression of genes involved in the tsMHC-II antigen presentation pathway, reinforcing the central role of IFN-γ in driving this enhanced immune response. The upregulation of tsMHC-II and associated pathways may contribute to the improved survival outcomes observed in EBVaGC patients, as well as the heightened sensitivity to immune checkpoint inhibitors, such as pembrolizumab[130].

Future perspectives

MHC-II has a pivotal role in anti-tumor immunity by presenting tumor-associated antigens to $CD4^+$ T cells, thereby initiating and sustaining adaptive immune responses[155]. However, many tumors evade immune surveillance by downregulating tsMHC-II expression or silencing the master regulator, CIITA. Accumulating evidence indicates that elevated MHC-II expression within TME correlates with increased immune cell infiltration, improved prognosis, and enhanced responsiveness to ICIs[21].

Recent studies have investigated genetic, pharmacologic, and cytokine-based approaches to restore MHC-II expression, thereby enhancing antigen presentation and promoting $CD4^+$ T cell priming. These strategies hold promise for synergizing with existing immunotherapies and broadening their efficacy, particularly in patient populations refractory to ICIs.

Nevertheless, critical challenges remain unresolved. Notably, the spatial and cellular heterogeneity of MHC-II expression within the TME is insufficiently characterized. Single-cell and spatial transcriptomic analyses have revealed substantial intra-tumoral variation in MHC-II expression, with certain tumor subpopulations, especially those proximal to immune cell niches, displaying enriched expression, while other regions remain MHC-II-silent[156]. This heterogeneity may influence localized differences in antigen presentation capacity, $CD4^+$ T cell engagement, and the formation of tertiary lymphoid structures. However, the underlying mechanisms and functional implications require systematic investigation.

Future research should aim to dissect the epigenetic and microenvironmental regulators of MHC-II silencing in tumor and stromal compartments, including tumor-associated macrophages and fibroblasts[157]. In particular, identifying histone modifiers or DNA methylation pathways responsible for repressing CIITA or HLA-DRA may yield novel small-molecule epigenetic modulators to restore immunogenicity[158]. Moreover, integrative multi-omics approaches, such as combining single-cell RNA sequencing, spatial transcriptomics, and proteomics, will be essential to mapping MHC-II expression landscapes and developing predictive biomarkers for patient stratification[159]. Ultimately, a comprehensive mechanistic understanding of MHC-II regulation and heterogeneity within the TME will guide the rational design of next-generation tumor immunotherapies.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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