T cell fate regulation in EBV-associated nasopharyngeal carcinoma (Review)

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Abstract. Nasopharyngeal carcinoma, a malignancy associated with Epstein-Barr virus, presents a complex immune editing landscape in which T cell fate determination carries out a central role. T cell metabolic exhaustion, Epstein-Barr virus antigen presentation and tertiary lymphoid structure remodeling are important in the context of tumor immune evasion. Although individual mechanisms have been extensively studied, their interplay and collective contribution to immune editing remain incompletely understood. The present review summarizes the current advances in nasopharyngeal carcinoma immune editing, with a focus on the molecular network underlying T cell fate decisions. How these mechanisms can be leveraged to develop novel immunotherapeutic strategies is further discussed. By integrating recent findings, the present review aims to offer new insights into the intricate immune landscape of nasopharyngeal carcinoma and to provide a theoretical basis for improving immunotherapy efficacy.

Contents

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1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor associated with Epstein-Barr virus (EBV) infection, and its distinct tumor immune microenvironment (TIME) makes it an ideal model for studying tumor immune editing. EBV carries out a key role in NPC pathogenesis and modulates the TIME (1). During NPC development, EBV infection drives multiple immune evasion mechanisms, for example, tumor cells can upregulate coinhibitory receptors to suppress IFN-γ production by $CD8^+$ tumor-infiltrating lymphocytes (TILs), thereby enhancing immunosuppressive capacity (2). Moreover, latent and lytic EBV genes, such as latent membrane protein 1 (LMP1) and EB nuclear antigen 1 (EBNA1), have been shown to contribute markedly to tumor cell proliferation, survival and immune evasion (3,4).

T cell fate in NPC immune editing is orchestrated by a variety of factors, including aberrant EBV antigen presentation, T cell metabolic exhaustion and dynamic remodeling of tertiary lymphoid structures (TLSs) within the tumor microenvironment (TME). Tumor cells infected with EBV can escape immune surveillance by inducing metabolic exhaustion in T cells, a process associated with metabolic reprogramming in the TIME (5). Single-cell RNA sequencing analyses have revealed the existence of diverse cellular subsets in NPC, which either promote or suppress antitumor immunity through intricate cellular interactions (6-8).

In terms of microenvironmental remodeling, NPC is characterized by abundant lymphocyte infiltration, indicating its potential immunogenicity. However, this also underscores the presence of sophisticated immunosuppressive mechanisms.

Tumor-associated fibroblasts and tumor-associated macrophages (TAMs) modulate T cell function through cytokine secretion and extracellular matrix (ECM) remodeling, thereby reshaping immune responses (9,10). In this context, therapeutic approaches targeting the TIME, such as immune checkpoint inhibitors (ICIs) and chimeric antigen receptor-T cell therapy, have shown promising potential but still require further refinement to enhance clinical efficacy (11-13).

In summary, immune editing in NPC is a multifaceted process involving EBV antigen presentation, T cell metabolic exhaustion and microenvironmental remodeling. These interconnected factors collectively determine T cell fate and carry out key roles in antitumor immune responses. The present review systematically explores the key molecular checkpoints, cellular interactions and structural dynamics that influence T cell fate decisions during NPC immune editing, highlighting their potential clinical implications. Rather than acting as isolated mechanisms, EBV antigen presentation, T cell metabolic exhaustion and TLS remodeling constitute a temporally ordered and mechanistically interconnected immune editing process in NPC. Persistent viral antigen exposure initiates chronic T cell activation, which progressively drives metabolic dysfunction and ultimately reshapes local immune architecture. The present review therefore emphasizes not only individual mechanisms, but also their causal relationships and dynamic progression during EBV-associated immune editing.

2. EBV latent infection and aberrant antigen presentation

Expression profile of EBV latent proteins. In NPC, the expression patterns of EBV latent proteins hold notable clinical relevance. Key EBV-encoded latent proteins, including LMP1 and latent membrane protein 2A (LMP2A), as well as EBNA1, carry out key roles in the pathogenesis and progression of NPC. LMP1 is considered the primary oncogenic driver of EBV, capable of activating multiple intracellular signaling pathways to promote cellular proliferation, survival and immune evasion (4). LMP2A contributes to the maintenance of EBV latency by inhibiting B cell differentiation and proliferation, thereby enabling the virus to evade host immune surveillance (14). Studies have demonstrated that the expression levels of these latent proteins are markedly elevated in NPC tissues compared with normal tissues, underscoring their potential as therapeutic targets (15-18).

Beyond modulating tumor cell behavior, LMP1 and LMP2A also influence host immune responses by altering the expression of major histocompatibility complex (MHC) molecules. LMP1 has been shown to downregulate MHC class I molecule expression, thereby reducing T cell-mediated tumor recognition (19). Similarly, LMP2A is implicated in the suppression of MHC class II molecule expression, hindering T cell activation and proliferation (20). Through interference with the antigen presentation machinery, these latent proteins enable EBV-infected cells to escape immune detection, facilitating persistent viral infection and tumorigenesis.

Additionally, EBV-encoded microRNAs (miRNAs) are key modulators of host antigen presentation pathways. These viral miRNAs can suppress host antiviral responses by targeting specific host genes. For example, EBV-miR-BART17-3p has been shown to impair host immunity by targeting DDX3X, thereby promoting EBV persistence and progression (21). The expression of EBV miRNAs is associated with the development of EBV-related malignancies, highlighting their functional importance in shaping the TIME.

Collectively, the expression profile of EBV latent proteins not only serves as a key factor in understanding NPC pathogenesis but also represents a promising foundation for the development of targeted therapeutic strategies. Further exploration of the functional roles of these proteins and their interactions with host immunity may provide novel directions and targets for clinical interventions.

Mechanisms of defective antigen processing and presentation. Defective antigen processing and presentation in NPC cells involve multiple molecular and cellular disruptions. Among them, the transporter associated with antigen processing (TAP) plays a key role in MHC class I-mediated antigen presentation. TAP translocates peptides derived from intracellular protein degradation into the endoplasmic reticulum, where they bind to MHC class I molecules and are subsequently presented on the cell surface for recognition by $CD8^+$ T cells. Studies have shown that TAP dysfunction in NPC cells frequently results in reduced MHC class I expression, thereby compromising antigen presentation and enabling tumor cells to evade immune detection. For example, TAP deficiency has been associated with impaired recognition and cytotoxicity by $CD8^+$ T cells, contributing to tumor progression (22,23).

EBV latent proteins also directly interfere with antigen processing and presentation pathways. LMP1 and LMP2 are highly expressed in NPC cells and disrupt the expression of MHC class I molecules and the overall antigen processing machinery. LMP1, for example, activates the NF-κB signaling pathway to suppress components of the antigen presentation system, destabilizing MHC class I molecules and promoting immune evasion by tumor cells (24). These findings suggest that EBV infection is not only a causal factor in oncogenesis but also a key mechanism through which tumor cells escape immune surveillance.

Dysfunction in the cross-presentation pathway is another key aspect of defective antigen presentation in NPC. Cross-presentation refers to the process by which antigen-presenting cells (APCs) internalize exogenous antigens and present them via the endogenous pathway to $CD8^+$ T cells. In NPC, the immunosuppressive TME and impaired APC function lead to decreased cross-presentation efficiency. Studies in EBV-positive NPC models have shown that APCs exhibit reduced cross-presentation of tumor antigens, resulting in inadequate T cell activation and further enhancing immune evasion (25-27). Therefore, impairments in the cross-presentation pathway are associated with tumor immune escape and should be considered a vital component in the study of NPC immunobiology.

In summary, the mechanisms of defective antigen processing and presentation in NPC include TAP dysfunction, EBV protein-induced suppression of antigen presentation and impaired cross-presentation (Fig. 1). These mechanisms synergistically enable NPC cells to effectively escape immune surveillance, thereby facilitating tumor progression. Understanding these defects provides key insights into the immunoevasive strategies of NPC and may inform the

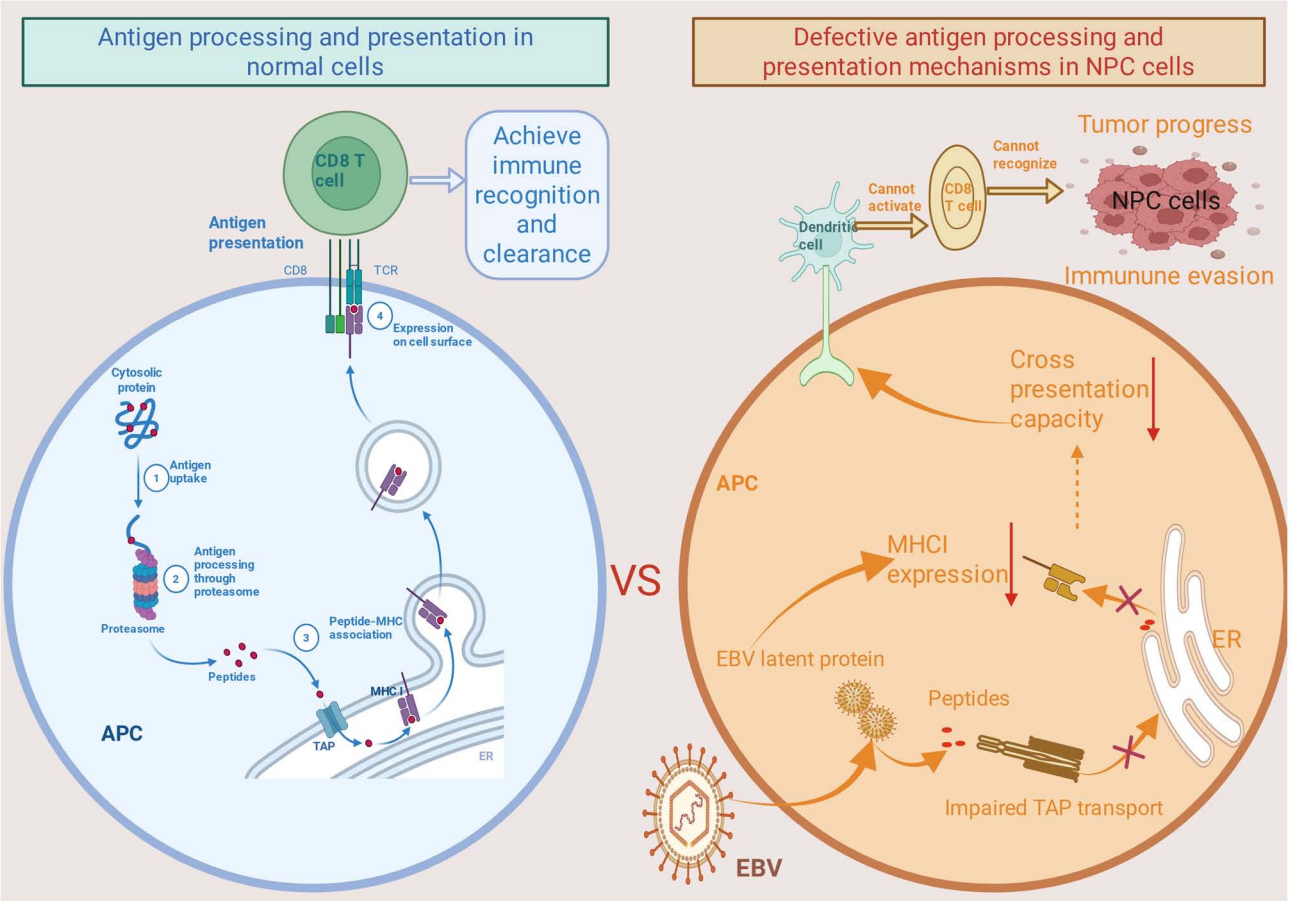

Figure 1. Schematic of defective antigen processing and presentation mechanisms in NPC cells. In normal cells, antigen processing occurs through the degradation of endogenous proteins via the proteasome. The resulting peptides are then transported to the ER, where they bind to MHC-I molecules and are subsequently displayed on the cell surface. This process ensures the recognition and clearance of abnormal cells by $CD8^+$ T cells, thereby achieving immune surveillance and elimination. By contrast, in NPC cells, EBV latent infection leads to defects in antigen presentation. The expression of EBV latent proteins impairs the function of the TAP transporter, preventing efficient peptide transport to the ER and thereby inhibiting MHC-I expression. These defects reduce cross-presentation capacity, ultimately resulting in the inability of T cells to recognize and activate NPC cells, leading to immune evasion and promoting tumor progression. MHC-I, major histocompatibility complex class I; TAP, transporter associated with antigen processing; ER, endoplasmic reticulum; APC, antigen-presenting cell; EBV, Epstein-Barr virus; NPC, nasopharyngeal carcinoma; $CD8^+$ T cell, CD8-positive T lymphocyte.

development of novel immunotherapeutic approaches targeting these pathways.

Clinical relevance of defective antigen presentation. Antigen presentation plays a key role in orchestrating immune responses, and its impairment is associated with the pathogenesis and progression of malignancies such as melanoma, lung cancer, colorectal cancer and nasopharyngeal carcinoma (28-30). In NPC, defects in antigen presentation are associated with disease staging and progression. A decline in antigen-presenting efficiency allows tumor cells to escape immune surveillance, particularly in the context of EBV-associated antigens. Studies suggest that patients with early-stage NPC often retain relatively intact antigen-presenting function, while in patients at the advanced-stage, particularly during metastasis, this ability is markedly diminished (31,32). Tumor cells may downregulate MHC molecule expression to evade recognition by T cells (33,34). These findings underscore the potential association between defective antigen presentation and NPC progression, emphasizing the need to pay clinical attention to these mechanisms for improved disease assessment and prognostic evaluation.

Moreover, the efficiency of antigen presentation has been shown to associate with patient prognosis. Patients with stronger antigen-presenting capacity generally exhibit more favorable clinical outcomes. In NPC, the responsiveness of T cell subsets is tightly associated with prognosis (35). Several studies have reported that patients with efficient antigen presentation tend to have improved responses to immunotherapies and demonstrate notably prolonged survival (36-38). This indicates the potential value of strategies aimed at enhancing antigen presentation to improve clinical outcomes in NPC.

To address the impairment of antigen presentation, several therapeutic approaches have been proposed. For example, ICIs [such as anti-programmed cell death (PD)-1/PD-Ligand 1 (PD-L1) antibodies] have shown efficacy in restoring T cell-mediated antitumor responses in multiple clinical trials (39). Additionally, targeting the TME to enhance the function of APCs has emerged as a viable strategy. Small molecules or biologics that improve APC functionality can enhance T cell recognition and killing of tumor cells, offering new therapeutic opportunities for patients with NPC (40).

In summary, defective antigen presentation has clinical implications for NPC. Understanding the underlying mechanisms not only facilitates improved diagnosis and staging but also supports the development of immunotherapeutic strategies that restore antigen presentation and strengthen antitumor immunity. Importantly, persistent EBV antigen presentation represents more than an initiating immune event. In the context of incomplete viral clearance, continuous presentation of EBV-derived antigens sustains prolonged T cell receptor engagement and chronic immune activation. This persistent activation pressure establishes the immunological conditions under which downstream metabolic stress and functional exhaustion of T cells are likely to emerge. However, it should be noted that the majority of these findings are derived from *in vitro* systems or EBV-transformed cell lines, which may not fully recapitulate the complex TIME of NPC *in vivo* (41,42).

3. Spatiotemporal dynamics of T cell activation

Molecular switches in initial T cell activation. The initiation of T cell activation relies heavily on the strength of T cell receptor (TCR) signaling and the synergistic engagement of costimulatory molecules. Upon recognition of peptide-MHC complexes by the TCR, a cascade of intracellular signaling events is triggered, regulating T cell fate and function. Protein tyrosine kinases and protein tyrosine phosphatases play opposing but coordinated roles in modulating these signals. Among them, Src homology region 2 domain-containing phosphatase (SHP) 1 and SHP2, two key protein tyrosine phosphatases, have attracted increasing attention (43-45). SHP1 generally acts as a negative regulator of T cell signaling, whereas SHP2 exhibits more complex, context-dependent roles (43). Concurrently, costimulatory molecules such as CD28 and 4-1BB augment TCR signaling and promote T cell proliferation and differentiation. Thus, the interplay between TCR signal strength and costimulation is important for effective T cell activation and function.

In the context of EBV infection, the activation threshold of virus-specific T cells plays a key role. The activation of EBV-specific T cells depends not only on TCR-antigen interactions but also on the cytokine milieu. Studies have shown that chronic EBV infection can elevate the activation threshold of T cells, leading to functional exhaustion and impaired antiviral responses (46,47). Furthermore, the clonal expansion of virus-specific T cells is directly influenced by their activation state. The quality and quantity of these T cell clones determine the effectiveness of immune responses against EBV. Investigating the activation thresholds of EBV-specific T cell clones can therefore provide valuable insights into immune escape mechanisms in EBV-associated diseases.

The cytokine microenvironment also exerts a profound influence on T cell polarization. Cytokines such as IL-2, IL-4 and IL-6 drive the differentiation of naïve T cells into various effector subsets including T helper (Th) 1, Th2 and Th17 cells. In EBV-infected settings, dysregulation of the cytokine milieu may skew T cell polarization, impairing effector function and durability (48). For example, excessive IL-6 production has been associated with T cell exhaustion and diminished antiviral capacity. Modulating the cytokine environment may therefore represent a viable strategy to enhance T cell functionality, particularly in the treatment of EBV-associated malignancies. Therefore, while persistent EBV antigen exposure is widely proposed to contribute to chronic T cell activation, direct causal evidence associating antigen persistence to specific T cell fate outcomes in patients with NPC remains limited.

Spatiotemporal distribution of TILs. TILs exhibit distinct spatial and temporal distribution patterns within the TME, with considerable heterogeneity in T cell subsets across different tumor regions. Studies in various cancer types, including breast and colorectal cancer, have revealed differences in the density and composition of T cells between the tumor core and invasive margins (49,50). For example, $CD8^+$ T cells are often more abundant at the tumor periphery than in the tumor core in breast cancer (51). In colorectal cancer, the distribution of $CD4^+$ and $CD8^+$ T cells is closely associated with tumor grade and clinical prognosis, with higher-grade tumors typically showing increased $CD8^+$ T cell infiltration (52).

This regional variation reflects the complexity of the TME and may contribute to immune evasion. Tumor cells can secrete immunosuppressive factors and alter metabolic conditions, thereby inhibiting T cell activity and infiltration. Moreover, the immune infiltration pattern is influenced by molecular features of the tumor, such as PD-L1 expression, which has been positively associated with $CD8^+$ T cell density and may predict responses to ICIs (53). Understanding the spatial organization of T cell subsets within the tumor provides key insights into TME characteristics and supports the development of personalized immunotherapy strategies.

T cell trafficking and positioning are important for mounting effective antitumor immune responses and the chemokine network carries out a central role in directing T cell migration. Chemokines secreted by various cell types bind to specific receptors on T cells, guiding their homing to tumor sites. The expression profiles of chemokines vary considerably across different TMEs, directly affecting T cell infiltration patterns. In breast and colorectal cancer, chemokines such as CXCL9 and CXCL10 associate positively with $CD8^+$ T cell infiltration, functioning through CXCR3 receptor signaling to facilitate T cell recruitment (54). Additionally, other cells within the TME, including TAMs and endothelial cells, contribute to T cell recruitment and activation through the secretion of cytokines such as IL-6 and IL-8 (52).

Beyond migration, chemokines also influence T cell effector function. For example, inhibitory signals within the TME, such as PD-L1 expression, can modulate T cell sensitivity to chemokines, thereby affecting their motility and survival (55-57). These findings suggest that targeting chemokine signaling may improve T cell localization and functionality, offering potential avenues for enhancing immunotherapeutic efficacy.

The spatial positioning of T cells within the tumor directly impacts their cytotoxic potential. TILs that localize at the invasive margin or in direct contact with tumor cells are generally more effective in exerting antitumor activity. By contrast, T cells trapped in poorly vascularized or hypoxic tumor cores often display diminished functionality. For example, in lung cancer, a higher density of $CD8^+$ T cells at the tumor margin associates with improved survival, whereas sparse $CD8^+$ infiltration in the tumor core is associated with poor prognosis (51). Furthermore, immunosuppressive components of the TME,

such as TAMs, can secrete inhibitory mediators that impair T cell positioning and function.

Optimizing T cell localization within tumors is thus a key objective in enhancing the efficacy of immunotherapy. Strategies such as adoptive T cell therapy and cancer vaccines aim to improve T cell infiltration and activity within tumors. A deeper understanding of the dynamic interactions between T cells and the TME will inform the rational design of novel immunotherapies.

Mechanisms of activation-induced cell death (AICD). The Fas/FasL pathway plays a key role in AICD, which is essential for the contraction phase of immune responses. Fas (CD95), a death receptor expressed on the surface of several cell types, binds to its ligand FasL to trigger downstream signaling cascades that activate caspases and induce programmed cell death (58). In T cells, the Fas/FasL pathway not only regulates immune homeostasis but also influences T cell fate within the TME. Tumor cells can downregulate Fas expression to escape FasL-mediated killing by cytotoxic T cells, thus promoting their survival (59). Dysregulation of this pathway is implicated in the development of autoimmunity and cancer, suggesting that modulation of Fas/FasL signaling may offer therapeutic benefit in immuno-oncology.

PD-1 is another key immune checkpoint that regulates T cell activation and survival. Expressed primarily on activated T cells, PD-1 binds to its ligands (PD-L1/PD-L2) to attenuate T cell responses and promote immune tolerance. The PD-1 pathway has been shown to contribute to AICD, especially in settings of chronic infection and cancer, where prolonged antigen exposure leads to T cell exhaustion (60). Activation of PD-1 signaling not only suppresses effector functions but also upregulates pro-apoptotic genes, thereby accelerating T cell attrition (61). Therapeutic blockade of PD-1/PD-L1 interactions has emerged as an effective strategy in cancer immunotherapy by restoring T cell function and enhancing antitumor immunity (62,63).

Mitochondrial dysfunction is another hallmark of exhausted T cells in the TME. Persistent antigen stimulation, coupled with nutrient deprivation and oxidative stress, leads to impaired mitochondrial metabolism and diminished T cell functionality. Studies have demonstrated that exhausted T cells exhibit reduced mitochondrial membrane potential and ATP production, along with elevated reactive oxygen species (ROS) levels (64). Excess levels of ROS induce oxidative damage and activate apoptotic pathways, exacerbating T cell exhaustion (65). Interventions that restore mitochondrial function and metabolic fitness may therefore rejuvenate T cell responses. For example, pharmacological agents that enhance mitochondrial bioenergetics have shown potential in improving T cell-mediated antitumor activity.

Together, these mechanisms highlight the vulnerability of T cells under chronic stimulation and within immunosuppressive TMEs. AICD involves multiple mechanisms, such as Fas/FasL, PD-1/PD-L1 and ROS accumulation, leading to T cell dysfunction and death, thereby allowing tumor cells to evade immune clearance (Fig. 2). A comprehensive understanding of AICD pathways is key for developing strategies to preserve T cell functionality and improve outcomes in immunotherapy.

4. Molecular basis of T cell metabolic exhaustion

Reprogramming of energy metabolism. Chronic antigen-driven activation is increasingly recognized as a primary upstream driver of metabolic reprogramming and exhaustion in TILs. Within the TME, exhausted T cells undergo profound metabolic reprogramming, particularly in glycolysis and oxidative phosphorylation (OXPHOS). These cells often exhibit a glycolysis-dependent metabolic profile, relying less on mitochondrial OXPHOS. This metabolic shift allows T cells to maintain ATP production under hypoxic conditions, sustaining their basic survival and minimal functionality. However, due to nutrient competition between tumor and immune cells, essential substrates become scarce in the TME, forcing T cells to adopt glycolysis as their predominant energy source. Exhausted T cells commonly produce elevated levels of lactate, while their mitochondrial OXPHOS capacity is markedly diminished. This reprogramming not only reduces energy production but also impairs T cell proliferation and promotes apoptotic susceptibility. Key signaling pathways, including mTOR and AMPK, are involved in regulating this glycolytic switch, ultimately contributing to impaired T cell effector function and antitumor activity (66,67).

Mitochondria play a central role in T cell metabolism, particularly in maintaining viability and effector function. In exhausted T cells, mitochondrial dysfunction is frequently observed, characterized by reduced membrane potential and impaired OXPHOS activity. Mitochondrial deficits contribute to energy insufficiency and facilitate progression to exhaustion. Moreover, these T cells accumulate high levels of ROS, which not only impair mitochondrial integrity but also disrupt intracellular signaling cascades. This metabolic dysfunction negatively affects cytokine production and clonal expansion, further weakening the antitumor immune response. Enhancing mitochondrial bioenergetics has been shown to restore T cell function; studies indicate that interventions targeting mitochondrial metabolism can improve T cell activity and increase antitumor immunity (64,68). Moreover, it remains challenging to disentangle whether metabolic dysfunction is a primary driver of T cell exhaustion or a downstream consequence of prolonged activation and inhibitory signaling.

Amino acid metabolism is also essential for T cell survival and function, particularly under the nutrient-limited conditions of the TME. Tumor cells can deplete specific amino acids, such as glutamine and arginine, thereby impairing T cell proliferation and cytokine secretion. Amino acid deprivation compromises metabolic fitness and alters T cell fate decisions. Furthermore, abnormal amino acid metabolism can affect epigenetic modifications, leading to transcriptional reprogramming and reduced immune competence. Strategies that replenish or modulate amino acid availability may help restore T cell function, offering novel avenues for improving the efficacy of cancer immunotherapy, especially when combined with conventional treatments (69,70). Importantly, the majority of studies examining T cell metabolic exhaustion rely on static or endpoint measurements, which may not adequately capture the dynamic and reversible nature of metabolic states during disease progression.

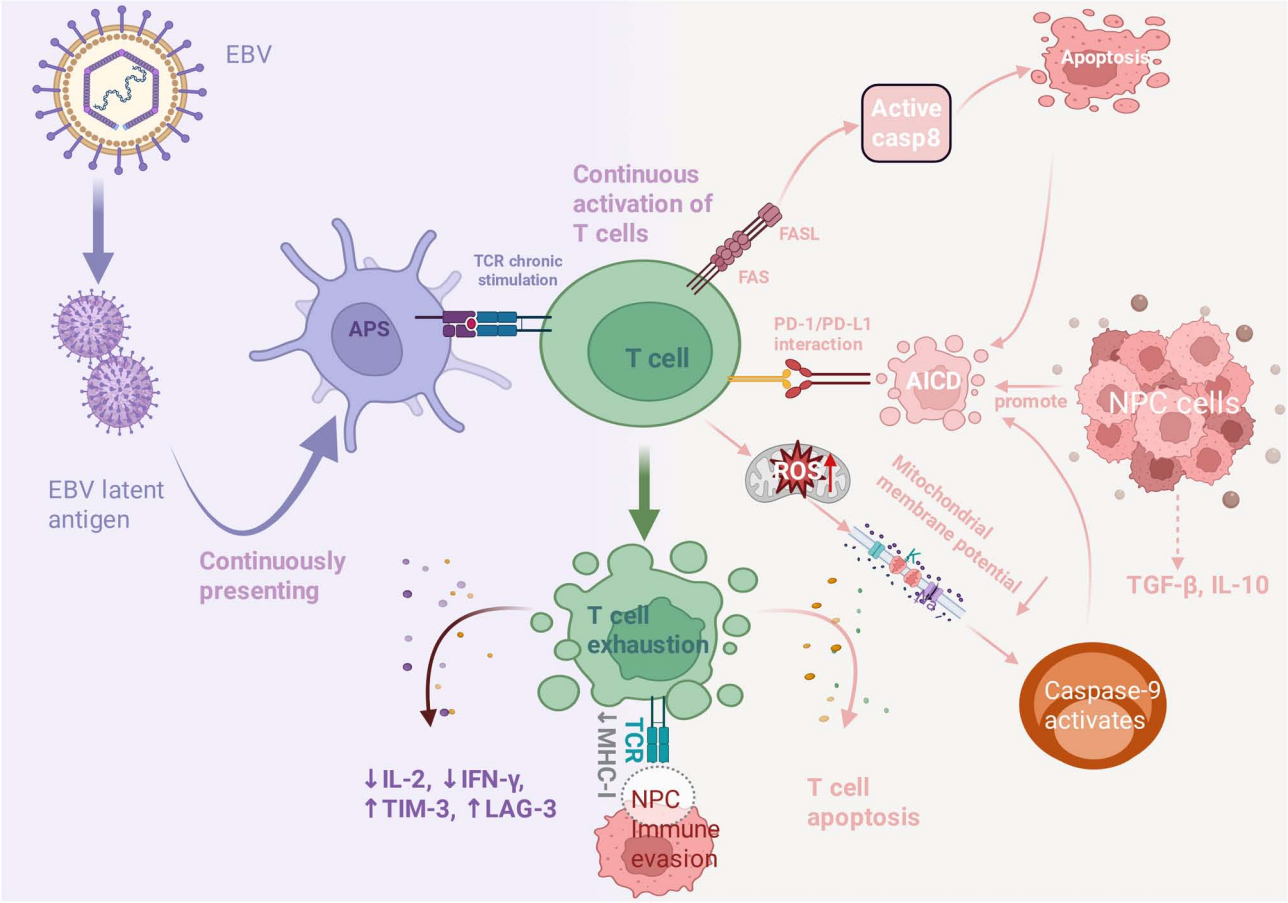

Figure 2. Schematic of AICD in T cells in NPC. EBV latent antigens are continuously presented by APCs, leading to sustained activation and exhaustion of T cells. Chronic TCR activation triggers immunosuppressive signals, resulting in T cell dysfunction (T cell exhaustion) and reduced antitumor efficacy. Activation of the PD-1/PD-L1 pathway, accumulation of ROS and changes in mitochondrial membrane potential promote AICD. These processes further enhance immune evasion by NPC cells, which secrete immunosuppressive factors such as TGF-β and IL-10, inhibiting T cell function and promoting tumor growth. EBV, Epstein-Barr virus; APS, antigen-presenting cell; TCR, T cell receptor; AICD, activation-induced cell death; PD-1/PD-L1, programmed cell death protein 1/programmed cell death ligand 1; ROS, reactive oxygen species; NPC, nasopharyngeal carcinoma.

Epigenetic regulatory networks. DNA methylation is a key epigenetic modification that influences gene expression by adding methyl groups to cytosine residues, typically within CpG islands. Recent studies have revealed that T cell exhaustion is closely associated with aberrant DNA methylation patterns (71,72). Chronic antigen stimulation in infections or cancer can induce exhaustion in $CD8^+$ T cells, accompanied by increased methylation of key regulatory genes such as PD-1, cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and T cell immunoglobulin and mucin-domain containing-3 (TIM-3). Hypermethylation of promoter regions suppresses the expression of these genes, leading to reduced effector function (73).

Moreover, the extent of DNA methylation in exhausted T cells associates with impaired proliferation, survival and memory formation. In some cases, methylation-driven upregulation of inhibitory receptors forms a negative feedback loop that deepens exhaustion and further weakens antitumor immunity (74). Reversing these epigenetic changes, using DNA methylation inhibitors or epigenetic editing tools, has emerged as a promising strategy to restore T cell functionality.

Histone modifications are another key layer of epigenetic regulation. Specific histone marks, such as H3K27me3 (associated with gene repression) and H3K4me3 (associated with gene activation), maintain transcriptional balance. In exhausted T cells, this balance is often disrupted. Downregulation of key transcription factors such as Basic Leucine Zipper ATF-Like Transcription Factor(BATF)leads to altered histone modification patterns at loci associated with exhaustion, impairing the gene expression necessary for effector function (75). Upregulation of histone deacetylases results in hypoacetylation of histones, while overactivation of histone methyltransferases such as EZH2 promotes repressive chromatin states, both contributing to T cell dysfunction (76). Thus, targeting histone-modifying enzymes presents another opportunity for epigenetic reprogramming in exhausted T cells.

Non-coding RNAs have emerged as important regulators of gene expression and metabolic reprogramming in T cells. Long non-coding RNAs, in particular, can modulate the expression of transcription factors and metabolic enzymes by binding to regulatory DNA elements or protein complexes (77). During exhaustion, the expression of various long non-coding RNAs is altered, and several are implicated in controlling glycolytic and OXPHOS-related genes. These non-coding RNAs influence T cell viability, cytokine production and cell fate decisions (78).

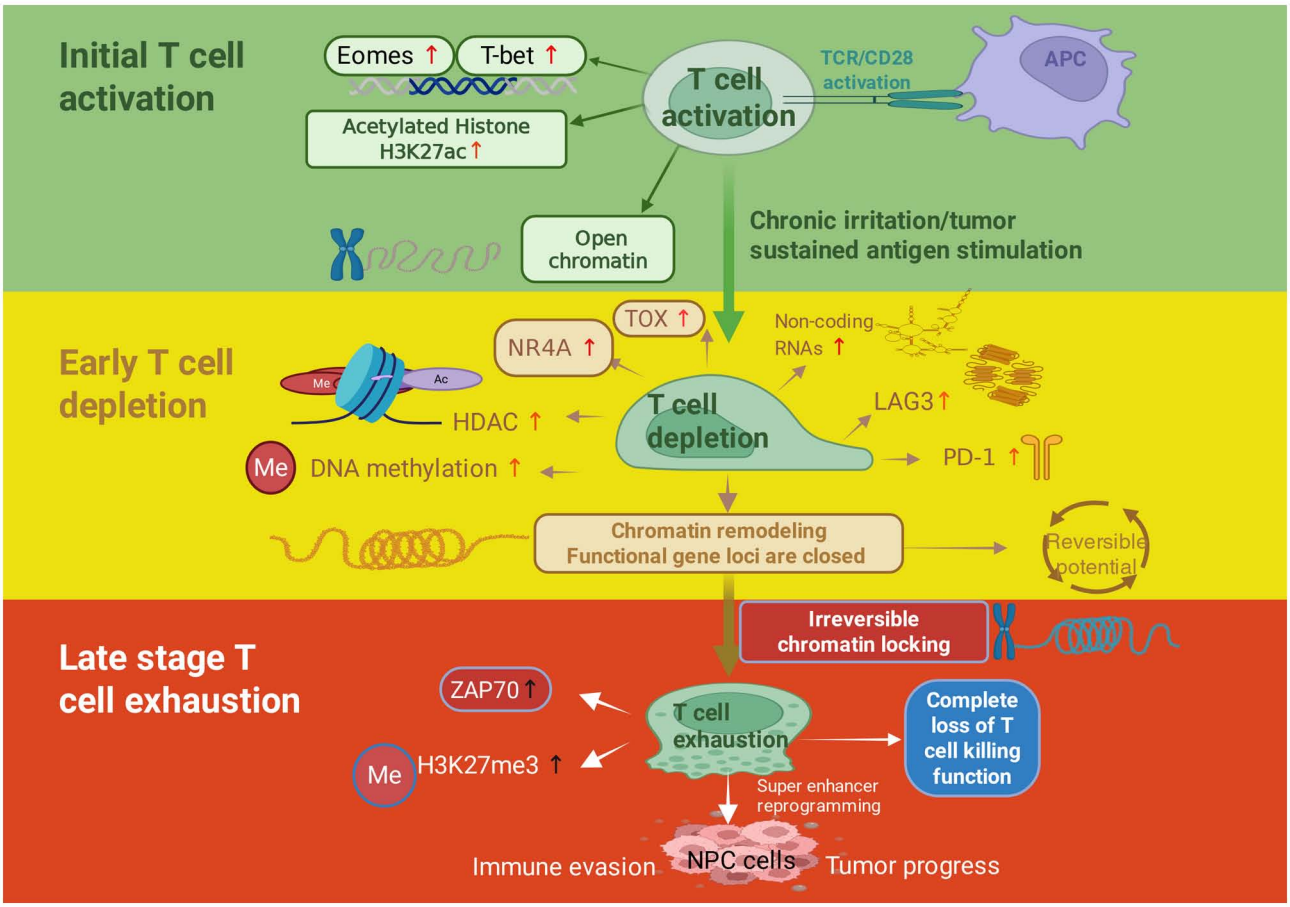

Figure 3. Schematic of the epigenetic regulatory network in the initiation and progression of T cell exhaustion. T cells undergo distinct stages in response to continuous antigen stimulation, including initial activation, early depletion and late exhaustion, with accompanying epigenetic regulatory changes. In the initial activation phase, T cells are activated through TCR/CD28 and stimulated by APCs, leading to chromatin opening and upregulation of transcription factors such as Eomes and T-bet. Chronic stimulation thereafter drives T cells into early depletion, characterized by increased expression of NR4A, TOX and non-coding RNAs, along with DNA methylation and histone modifications that result in the closure of functional gene loci. Finally, during the late exhaustion stage, chromatin becomes irreversibly locked, with increased H3K27me3, leading to a complete loss of T cell killing function and contributing to tumor progression and immune evasion. TCR, T cell receptor; CD28, co-stimulatory receptor on T cells; APC, antigen-presenting cell; Eomes, eomesodermin; T-bet, T-box transcription factor; H3K27ac, acetylation of histone H3 on lysine 27; TOX, thymocyte selection-associated high mobility group box; NR4A, nuclear receptor subfamily 4 group A; LAG3, lymphocyte-activation gene 3; PD-1, programmed cell death protein 1; HDAC, histone deacetylase; me, methylation; Ac, acetylation; ZAP70, zeta-chain-associated protein kinase 70; H3K27me3, trimethylation of histone H3 on lysine 27; NPC, nasopharyngeal carcinoma; Super enhancer, a cluster of enhancers with the potential to drive gene expression at a high level.

In summary, epigenetic regulation plays a pivotal role in the development and maintenance of T cell exhaustion (Fig. 3). Understanding the mechanisms involved may provide insight into potential therapeutic targets for reactivating exhausted T cells and enhancing immunotherapeutic outcomes.

Metabolic intervention strategies. Glycolysis inhibitors have garnered increasing attention as potential tools to reverse T cell exhaustion (79,80). Tumor cells rely heavily on glycolysis for energy production and biosynthesis, while T cells in the TME often experience metabolic exhaustion and impaired function (81). In chronic infections and cancer, elevated glycolytic activity can hinder T cell proliferation and effector cytokine secretion (82). Therefore, targeting glycolysis to alleviate metabolic stress in T cells represents a promising therapeutic strategy.

Several studies have demonstrated that glycolysis inhibitors can enhance T cell function by reducing lactate accumulation and mitigating extracellular acidification (83,84). This metabolic rebalancing facilitates improved T cell proliferation and cytokine production (85). Furthermore, glycolysis inhibition may improve energy efficiency, shifting T cells toward more sustainable mitochondrial metabolism and enhancing their cytotoxic activity. These findings support the clinical potential of glycolytic modulation, especially when used in combination with immunotherapy to improve patient outcomes.

However, challenges remain, such as ensuring drug selectivity and minimizing resistance (86). Future research should focus on optimizing glycolysis inhibitor regimens to maximize T cell recovery while minimizing off-target effects.

Mitochondria-targeted drugs offer another promising avenue for enhancing T cell function. As central regulators of energy metabolism and apoptosis, mitochondria are key for T cell survival. In exhausted T cells, mitochondrial dysfunction severely limits antitumor responses (87). Agents such as MitoTEMPO, a mitochondria-targeted antioxidant, have been shown to improve mitochondrial function, reduce ROS levels

and restore T cell energy metabolism (88). These interventions can promote T cell proliferation and effector function, supporting their use in immunotherapy.

Despite their promise, mitochondria-targeted therapies face challenges related to delivery, tissue distribution and toxicity. Continued development of safer, more effective compounds is necessary. Notably, combining these drugs with immune checkpoint blockade may yield synergistic benefits, improving both metabolic fitness and antitumor efficacy. Metabolic reprogramming represents an emerging paradigm in cancer therapy. Tumor cells often evade immune detection by altering their metabolism, which contributes to T cell exhaustion and dysfunction (82). By reprogramming T cell metabolism, researchers aim to reinvigorate immune responses against tumors.

Evidence suggests that combining metabolic reprogramming with immunotherapy enhances treatment efficacy. For example, interventions that restore T cell energy production and reduce TME immunosuppression improve cytokine production, proliferation and cytotoxicity. These effects can also potentiate the efficacy of ICIs, offering synergistic therapeutic outcomes (89).

Nevertheless, challenges remain in selecting optimal metabolic targets and integrating interventions with existing treatment protocols. Future research should aim to unravel the mechanistic basis of metabolic reprogramming and identify effective combinations with immunotherapy, ultimately offering more personalized and effective cancer treatment strategies.

5. Dynamic remodeling of TLSs

Composition and functional features of TLSs. In the TME of NPC, TLSs represent organized aggregates of immune cells typically found at the invasive margins and within the tumor core. From a temporal and mechanistic perspective, TLS remodeling emerges as a downstream consequence of sustained immune activation and T cell dysfunction during EBV-associated immune editing. Chronic inflammation, together with metabolically exhausted T cells, reshape local cytokine milieus and affect stromal cell activation and antigen-presenting niches, thereby driving alterations in TLS organization, composition and functionality (90). Histologically, TLSs resemble secondary lymphoid organs, comprising densely clustered B and T lymphocytes. Increasing evidence suggests that the presence of TLSs associates positively with clinical prognosis in NPC (91,92). Their characteristic features include high levels of lymphocytic infiltration, mature B cell follicles and active T cell responses (93). In various cancer types, the maturity, spatial distribution and cellular heterogeneity of TLSs are associated with patient survival and antitumor immune responses. Notably, in NPC, TLSs are often accompanied by the presence of high endothelial venules (HEVs), which play a key role in lymphocyte recruitment and TLS formation (94).

Within NPC-associated TLSs, B cell follicles and T cell zones exhibit a distinct spatial organization. B cells are typically concentrated within the follicular core, whereas T cells are predominantly distributed in the surrounding areas, forming a functional immunological interface. This spatial arrangement facilitates coordinated interactions between immune cell subsets. For example, T cells can activate B cells via cytokine secretion, thereby enhancing antigen-specific immune responses (94). T cells within TLSs often display a highly activated phenotype, supporting tumor-specific immunity. The structured interaction between B and T cells not only boosts immune efficiency but may also establish local immunological memory, contributing to improved clinical outcomes in patients with NPC (95). Notably, evidence regarding the functional role of TLSs in NPC is largely extrapolated from other tumor types, and their immunological impact may vary substantially depending on maturation status and cellular composition.

HEVs play a key role in the formation and maintenance of TLSs within the TME. These specialized vessels enable efficient transmigration of lymphocytes from the bloodstream into tumor tissues. Studies have demonstrated a positive association between HEV density and TLS presence in NPC, suggesting that HEVs facilitate immune cell infiltration and contribute to effective antitumor immunity (93,96). Furthermore, HEVs regulate immune cell trafficking by expressing specific chemokines that attract both T and B cells, thereby enhancing the immunological activity of TLSs. As such, HEVs represent not only structural components of TLSs but also potential therapeutic targets in immuno-oncology (94). In turn, remodeled TLSs may further modulate antigen presentation efficiency and T cell activation thresholds, forming a feedback loop that reinforces immune exhaustion or, in specific contexts, sustains localized immune responses.

Regulatory networks governing TLS formation. The lymphotoxin (LT) and LIGHT (Lymphotoxin-like, exhibits inducible expression, and competes with HSV glycoprotein D for HVEM, a receptor expressed by T lymphocytes) signaling pathways play essential roles in the initiation and maturation of TLSs. LT, a cytokine primarily secreted by $CD4^+$ T cells and other immune cells, binds to the LTβ receptor to promote lymphoid tissue development and maintenance. Studies have shown that elevated expression of LT enhances lymphocyte proliferation and differentiation and facilitates the organization of TLSs within tumors. In the TME, increased LT signaling contributes to the maturation of TLSs and enhances tumor-specific immune responses (97). LIGHT, a TNF superfamily member, can engage its receptors to activate downstream signaling cascades that promote immune cell migration and TLS formation. Overexpression of LIGHT has been shown to increase the number and function of TLSs in tumors, thereby amplifying antitumor immunity (98). Thus, targeting the LT and LIGHT pathways holds potential for modulating TLS formation in cancer immunotherapy.

The C-X-C motif chemokine ligand (CXCL) 13/C-X-C motif chemokine receptor (CXCR) 5 axis is another key regulatory pathway in TLS development and function. CXCL13, a chemokine mainly secreted by plasma cells and dendritic cells (DCs), guides the migration of B cells and certain T cell subsets toward TLS regions by binding to its receptor, CXCR5, expressed on these immune cells. Elevated expression of CXCL13 in the TME is associated with increased TLS formation. High levels of CXCL13 promote immune cell aggregation and activation within

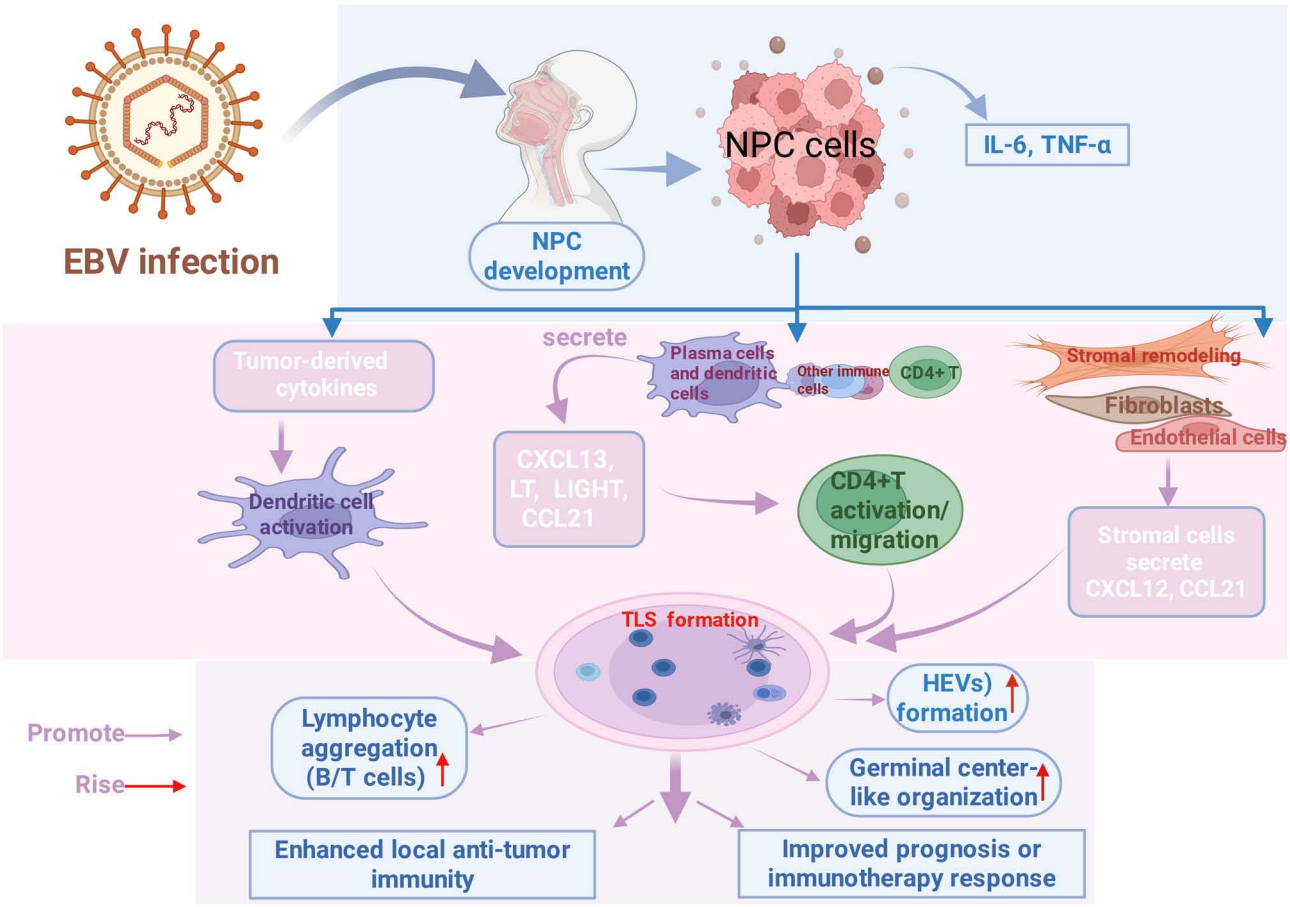

Figure 4. Schematic of the regulatory network formed by TLSs in NPC. Following EBV infection, tumor-derived cytokines activate dendritic cells, promoting the aggregation of B cells and T cells, thereby enhancing local antitumor immunity. During the progression of NPC, various immune cells (for example, plasma cells, dendritic cells) and stromal cells (for example, fibroblasts, endothelial cells) participate in the activation and migration of $CD4^+$ T cells by secreting chemokines such as CXCL12 and CCL21. This process promotes the formation of HEVs and the organization of germinal center-like structures, ultimately improving prognosis or enhancing responses to immunotherapy. TLSs, tertiary lymphoid structures; EBV, Epstein-Barr virus; NPC, nasopharyngeal carcinoma; B/T cells, B lymphocytes and T lymphocytes; CXCL12, C-X-C motif chemokine ligand 12; CCL21, C-C motif chemokine ligand 21; HEVs, high endothelial venules; $CD4^+$ T, CD4-positive T lymphocyte.

the tumor and facilitate the germinal center reaction, thereby enhancing the humoral immune response (99). This mechanism has been confirmed in multiple types of cancer, including breast and lung cancer, where high CXCL13 expression associates with improved clinical outcomes (100-102). The CXCL13/CXCR5 signaling axis not only supports TLS formation but also amplifies their immunological function, making it a promising focus for future translational research and clinical application.

Stromal cells provide essential structural and functional support during TLS formation and maintenance. These cells, including fibroblasts and endothelial cells, produce cytokines and chemokines that regulate immune cell recruitment and activation. In the TME, stromal remodeling and activation are key for maintaining the structural integrity of TLSs. Specific stromal cell subsets have been identified that secrete chemokines such as CXCL12 and CCL21, which promote lymphocyte migration and survival, thereby facilitating TLS development (103). In addition, stromal cells interact with immune cells to regulate their activation and proliferation, thus influencing the efficacy of antitumor immunity. In several types of cancer, stromal cell phenotypes have been associated with TLS maturity, well-structured TLSs often coincide with high stromal activity and cytokine production, which are predictive of improved prognosis. Therefore, as shown in Fig. 4, stromal cells not only serve as a scaffold for TLSs but also act as dynamic regulators of their immunological function, offering potential targets for therapeutic intervention.

Association of TLSs with therapeutic responses. Recent studies have revealed a strong association between TLSs and clinical responses to immunotherapy across various cancer types (104-106). The density of TLSs within the TME has emerged as a promising biomarker for predicting immunotherapy efficacy. For example, in melanoma, the presence of TLSs associates positively with intratumoral immune responses and overall patient survival (94). Furthermore, TLS density is associated with increased infiltration of $CD8^+$ T cells and B cells, suggesting that TLSs may enhance immune responses by supporting effector cell accumulation. High TLS density has also been associated with improved responses to ICIs, particularly anti-PD-1 therapy, in renal cell carcinoma and non-small cell lung cancer (103). As such, TLSs serve not only as prognostic indicators but also as a potential basis for personalized treatment strategies.

The maturation status of TLSs is another key factor influencing tumor prognosis and immunotherapeutic responsiveness. Mature TLSs are typically characterized by well-organized germinal centers, dense lymphocyte aggregates and active immune signaling. In clear cell renal cell carcinoma, mature TLSs have been associated with improved survival and enhanced responsiveness to immunotherapy (107). Moreover, mature TLSs often promote plasma cell differentiation and antibody production, features associated with favorable outcomes in several cancer types (103). Evaluating TLS maturity may thus provide valuable insights for clinical prognosis and guide treatment selection.

Artificial induction of TLS formation has emerged as a novel strategy to enhance antitumor immunity. Through the use of immune-stimulating agents or genetic engineering techniques, TLSs can be generated or amplified within tumor tissues to recruit and activate immune cells. For example, viral vectors and specific pharmacologic compounds have been shown to induce TLS formation, thereby improving T cell infiltration and the response to immune checkpoint blockade (103). Preclinical studies have also demonstrated that pharmacologic agents enhancing TLS formation can reshape the TME and boost the efficacy of immunotherapy (108-111). Thus, therapeutic induction of TLSs offers a promising approach to augment immune responses and may represent a novel avenue for clinical cancer treatment.

Recent studies have begun to provide NPC-specific evidence associating TLSs to the immunotherapy response (112,113). Analyses of NPC tumor specimens have shown that higher TLS density and more mature TLS organization are associated with increased infiltration of $CD8^+$ T cells and B cells, enhanced antigen presentation signatures and an inflamed tumor immune phenotype. Importantly, emerging clinical observations suggest that patients with NPC with TLS-enriched tumors tend to exhibit improved responses to ICIs, including higher objective response rates and prolonged progression-free survival, although these findings are primarily derived from retrospective cohorts and exploratory analyses (113,114).

However, it should be noted that current NPC-specific data remain limited in scale, and the majority of studies have not yet established a definitive quantitative association between TLS density and immunotherapy response rate. Therefore, while available evidence supports a potential association, further prospective validation is required before TLSs can be considered robust predictive biomarkers for immunotherapy responsiveness in NPC.

Importantly, accumulating evidence suggests that TLSs may exert a context-dependent, dual role in NPC. Mature TLSs characterized by organized B cell follicles, follicular DCs and germinal center-like structures are generally associated with effective antitumor immunity. By contrast, immature or dysregulated TLSs may harbor increased regulatory T (Treg) cells, exhausted T cells or immunosuppressive cytokine signals, potentially contributing to immune tolerance rather than immune activation. In NPC, where chronic EBV-driven inflammation persists, TLSs may dynamically shift between immune-supportive and immune-suppressive states, underscoring the need to evaluate TLS quality, maturation status and cellular composition rather than density alone (90,91).

6. Coordinated regulation of the immune checkpoint network

Expression characteristics of classical checkpoint molecules. In NPC, classical immune checkpoint molecules, including PD-1, CTLA-4 and TIM-3, are highly expressed and play key roles in mediating immune suppression. Studies have shown that PD-1 is expressed in ≤46.2% of NPC tumor tissues, while CTLA-4 expression is detected in 88.4% of cases (115,116). PD-1 is predominantly expressed on TILs and is associated with immune evasion mechanisms, particularly in EBV-positive NPC, highlighting its relevance in the TME (115). Additionally, TIM-3 expression has been reported in NPC and is considered to contribute to T cell exhaustion within the TME (117).

A complex interplay and synergistic effect exists among different checkpoint molecules. Co-expression of PD-1 and CTLA-4 has been identified as a major driver of immunosuppression in NPC. Their combined inhibitory effects lead to severe functional impairment of T cells in the TME (115). Moreover, high levels of TIM-3 expression, in conjunction with PD-1 and CTLA-4, further exacerbate immune exhaustion, forming a robust suppressive network that inhibits effector T cell function and promotes tumor progression and metastasis (117). These synergistic interactions not only shape the immune landscape of the tumor but also present potential targets for immunotherapeutic intervention. Notably, combinatorial blockade of these checkpoints may restore T cell function and enhance antitumor immunity.

The expression of checkpoint molecules is associated with the functional status of T cells. In the NPC microenvironment, elevated PD-1 expression often associates with T cell dysfunction and exhaustion (115). For example, TILs frequently co-express PD-1 and TIM-3 while exhibiting reduced levels of effector cytokines such as IFN-γ and TNF-α (117). This expression profile reflects a dysfunctional T cell phenotype with impaired cytotoxic capacity. Therefore, checkpoint molecule expression not only serves as a biomarker of the immunological landscape in NPC but also reflects the degree of T cell impairment, providing a rationale for targeted immunotherapeutic strategies aimed at reinvigorating antitumor T cell responses and improving clinical outcomes.

Emerging immune regulatory molecules. The discovery of novel immune checkpoints has expanded the therapeutic landscape of cancer immunotherapy. Among these, V-domain Ig suppressor of T cell activation (VISTA) and lymphocyte-activation gene 3 (LAG-3) have garnered increasing attention. VISTA primarily functions by inhibiting T cell activation and proliferation, thereby promoting immune evasion in the TME. High VISTA expression is associated with poor prognosis in various malignancies, including melanoma, non-small cell lung cancer, pancreatic cancer, colorectal cancer, ovarian cancer and acute myeloid leukemia (118-120). Several anti-VISTA therapeutic agents have entered clinical trials, showing promising preliminary results (121).

LAG-3 is another negative regulatory molecule that plays a key role in modulating T cell activity. It binds to MHC class II molecules and suppresses T cell proliferation and cytokine production. Numerous studies have associated LAG-3

expression with immunosuppressive states in the TME, and blockade of LAG-3 signaling has been shown to enhance T cell effector function and antitumor activity (122-124). As a result, monoclonal antibodies targeting LAG-3 have demonstrated therapeutic potential in clinical trials across various cancer types.

Members of the B7 family are also key regulators of immune responses in NPC. This family includes costimulatory molecules such as B7-1 (CD80) and B7-2 (CD86), as well as inhibitory molecules such as PD-L1. Within the NPC microenvironment, B7 molecules interact with receptors on T cells to modulate their activity and function, influencing the immune evasion capacity of tumor cells. It has been reported that NPC cells upregulate CD80 and CD86 expression to enhance costimulatory signaling, which paradoxically may promote tumor progression by inducing chronic T cell stimulation and subsequent exhaustion (125).

Furthermore, inhibitory B7 family members such as PD-L1 suppress T cell activation and proliferation, thereby enhancing tumor immune evasion. In NPC, elevated PD-L1 expression has been associated with tumor aggressiveness and poor prognosis. ICIs targeting the PD-1/PD-L1 axis have demonstrated encouraging efficacy in clinical trials, offering new hope for NPC treatment (121). CD28 is a key costimulatory receptor on T cells that interacts with CD80 and CD86 to promote T cell activation and expansion. Alterations in the CD28/CD80/CD86 axis in NPC may considerably influence immune responses within the TME. Studies have shown that NPC cells can upregulate CD80 and CD86 to enhance costimulatory signaling, which may paradoxically contribute to immune exhaustion and tumor progression. This dysregulation can impair T cell proliferation and contribute to a dysfunctional immune phenotype (122,126).

Moreover, changes in CD28 expression have been observed in patients with NPC, with low CD28 expression being associated with tumor aggressiveness and poor clinical outcomes. Targeting the CD28/CD80/CD86 network may therefore represent a promising strategy to enhance antitumor immune responses in NPC. Novel therapeutic approaches aiming to modulate this axis are currently under development to improve the efficacy of immunotherapies in this context (121).

Mechanisms of resistance to checkpoint blockade. The emergence of antigen-loss variants is a major mechanism of resistance to immune checkpoint blockade therapy. Tumor cells may acquire mutations or deletions that result in the loss of surface antigens, rendering them invisible to T cells. For example, in melanoma, treatment with anti-PD-1 antibodies has been shown to select for tumor cells with MHC class I mutations or deletions, impairing antigen presentation and facilitating immune escape (127). In addition, tumors may selectively retain variants that are poorly recognized by T cells, further compounding resistance to immune checkpoint inhibition.

Adaptive changes in TCR signaling also contribute to therapeutic resistance. Tumor cells can suppress TCR signaling pathways through metabolic reprogramming, leading to impaired T cell function. For example, enhanced tumor metabolism may induce a high metabolic burden in T cells, rendering them unable to proliferate or function effectively in the hypoxic and nutrient-deprived TME. These impairments are often associated with downregulation of TCR signaling components (128). Therapeutic strategies that restore or modulate TCR signaling may therefore improve responses to checkpoint inhibitors.

The compensatory expansion of immunosuppressive cell populations, such as Treg cells and TAMs, also plays a key role in mediating resistance. These cells secrete suppressive cytokines such as IL-10 and TGF-β, which inhibit effector T cell activity and facilitate immune evasion. In some cancer types, a notable increase in Treg frequency has been observed following checkpoint blockade, thereby limiting therapeutic efficacy (129). Targeting these immunosuppressive populations, through Treg depletion or TAM inhibition, may offer a viable strategy to overcome resistance and improve the efficacy of immune checkpoint blockade.

7. Immunoregulatory functions of myeloid cells

Polarization of TAMs. In the TME of NPC, TAMs exist primarily in two phenotypic states: M1 and M2. The dynamic balance between these subtypes plays a key role in tumor progression. M1 macrophages are generally considered antitumorigenic due to their ability to produce proinflammatory cytokines such as TNF-α and IFN-γ, thereby promoting effective antitumor immune responses. By contrast, M2 macrophages support tumor growth and metastasis by secreting anti-inflammatory cytokines (for example, IL-10) and promoting angiogenesis, which contribute to an immunosuppressive TME (130). Studies have shown that the ratio of M1 to M2 macrophages in NPC is regulated by various signals within the TME (131,132). As the tumor progresses, this balance often shifts toward the M2 phenotype, thereby facilitating immune evasion and accelerating tumor development (133). Understanding the dynamic plasticity of TAMs in NPC is important for elucidating immune escape mechanisms and may provide potential targets for novel immunotherapeutic strategies.

Colony-stimulating factor 1 (CSF1) and its receptor CSF1R play key roles in the recruitment and polarization of macrophages in the TME. In NPC, tumor cells secrete CSF1 to recruit surrounding macrophages and promote their differentiation into the M2 phenotype, thereby enhancing tumor growth and dissemination (134). Activation of the CSF1/CSF1R signaling pathway has been directly associated with an increase in TAMs, which not only contributes to immune suppression within the TME but also associates with poor clinical outcomes (135). Thus, inhibition of CSF1R signaling may serve as an effective strategy to reprogram macrophage polarization and boost antitumor immunity.

The interaction between macrophages and T cells is another key regulatory mechanism in the NPC microenvironment. M1 macrophages activate T cells by producing proinflammatory cytokines and presenting antigens, thereby enhancing CTL responses. Conversely, M2 macrophages suppress T cell activity and facilitate immune escape (136). In NPC, an increase in M2 macrophages has been associated with reduced infiltration and functional impairment of $CD8^+$ T cells, suggesting an association between TAM polarization and T cell efficacy (137). Furthermore, macrophages secrete

immunosuppressive cytokines such as IL-10 and TGF-β, which promote the differentiation of Treg cells, thereby further inhibiting $CD8^+$ T cell function (138). Enhancing the functional crosstalk between macrophages and T cells may therefore offer a promising strategy for improving the efficacy of immunotherapy in NPC.

Functions of myeloid-derived suppressor cells (MDSCs). MDSCs are key immunosuppressive components of the TME and have gained increasing attention in the context of NPC. Composed of immature myeloid cells, MDSCs exhibit potent immunosuppressive activity. In patients with NPC, MDSCs are notably expanded, and their presence is associated with tumor progression and poor prognosis (139). Based on surface markers, MDSCs can be divided into two main subsets: Monocytic MDSCs and granulocytic or polymorphonuclear MDSCs. Monocytic MDSCs are particularly abundant in the peripheral blood of patients with NPC and suppress T cell activity via the secretion of inhibitory cytokines such as IL-10 and TGF-β, thereby promoting tumor growth and metastasis (140). Additionally, MDSCs contribute to immunosuppression by depleting L-arginine and generating ROS, impairing effective antitumor immune responses (141).

In NPC, MDSC accumulation is associated with tumor metabolic states. MDSCs begin to accumulate early during tumor development, and both their numbers and suppressive capacity increase as the tumor progresses, further exacerbating immune evasion and leading to worse clinical outcomes (140). Therefore, understanding the phenotypic and functional characteristics of MDSCs is important for the development of targeted therapeutic strategies.

L-arginine metabolism plays a pivotal role in MDSC-mediated immunosuppression. In the NPC microenvironment, MDSCs express high levels of arginase-1, which depletes local L-arginine, thereby impairing T cell proliferation and activation. Studies have shown that arginine metabolism not only impacts T cell function but also supports the survival and suppressive function of MDSCs (139,142-144). Arginine depletion disrupts amino acid synthesis in T cells, weakening their immune responses and facilitating immune evasion by tumor cells.

Moreover, L-arginine metabolism is associated with MDSC phenotype and function. MDSCs activate downstream signaling pathways such as STAT3 and NF-κB to promote their immunosuppressive activity. They also secrete proinflammatory cytokines such as IL-6, which sustain the immunosuppressive nature of the TME (141). Thus, targeting arginine metabolism represents a promising avenue to enhance the efficacy of immunotherapy in NPC.

Therapeutic strategies targeting MDSCs have potential in cancer immunotherapy. By eliminating or functionally inhibiting MDSCs, researchers aim to reduce immunosuppression and potentiate antitumor immune responses. Several studies have demonstrated that MDSC-targeted therapies can improve responses to immune checkpoint blockade (145-148).

One approach involves the use of specific drugs to inhibit MDSC development and function. Small-molecule inhibitors targeting MDSC metabolic pathways, such as arginine and fatty acid metabolism, have been shown to reduce MDSC numbers and restore T cell function (149). Furthermore, clinical trials suggest that combining ICIs with MDSC-targeting agents may notably enhance patient survival and quality of life. Collectively, therapies aimed at modulating MDSCs offer a promising strategy for improving outcomes in NPC and future research should focus on optimizing these approaches to maximize their clinical benefit.

Functional impairment of DCs. DCs are APCs that play a central role in initiating and regulating immune responses. Impaired DC maturation is frequently associated with disease progression, particularly in the context of tumors and chronic viral infections (150,151). For example, EBV infection has been shown to downregulate key molecules involved in DC maturation, resulting in impaired antigen presentation and weakened T cell responses (152). Moreover, DC maturation is dependent on several signaling pathways, including Toll-like receptor (TLR) and IFN pathways. Although TLR activation enhances DC maturation and functionality, chronic inflammation often suppresses these pathways, leading to DC dysfunction (153,154). Additionally, metabolic alterations, such as reduced expression of lactate dehydrogenase, can impair the energy metabolism and antigen-presenting capacity of DCs, contributing to immune evasion in the TME (155).

DCs are a heterogeneous population composed of conventional, plasmacytoid and monocyte-derived DCs, each exhibiting distinct antigen presentation and T cell activation capacities. Conventional DC1s are particularly efficient in cross-presenting tumor antigens to $CD8^+$ T cells, whereas conventional DC2s are primarily involved in $CD4^+$ T cell priming and regulation (156,157). Plasmacytoid DCs play a key role in antiviral immunity by producing type I IFNs, but they often exhibit functional exhaustion in the TME, leading to diminished antigen presentation (158). This suggests that the composition and function of DC subsets considerably influence antigen presentation and immune responses in different immunological contexts. In NPC and other conditions such as chronic viral infection, DC dysfunction can hinder T cell activation and limit the overall effectiveness of antitumor immunity (152,159).

In NPC therapy, DC-based vaccines have garnered attention as a promising immunotherapeutic approach. Given the central role of EBV in NPC, DC vaccines can stimulate antigen-specific immune responses against viral antigens. For example, a CD137L-expressing DC vaccine has demonstrated favorable tolerability and partial tumor responses in clinical trials, with some patients achieving measurable tumor regression (160,161). Recent studies also suggest that combining optimized DC vaccines with other immunotherapeutic modalities, such as ICIs, may further enhance therapeutic efficacy (162-165). However, clinical application of DC vaccines in NPC remains in the early stages and further large-scale trials are required to evaluate their efficacy, safety and optimal combination strategies to offer more effective immunotherapeutic options for patients with NPC.

8. Metabolic features of the TME

Effects of hypoxia and acidification. Hypoxia is a common feature of the TME and markedly influences T cell function through the regulation of hypoxia-inducible factor 1α (HIF-1α).

As a central regulator of cellular responses to hypoxia, HIF-1α is associated with T cell survival and function. Although HIF-1α activation under hypoxic conditions promotes T cell survival, it may also impair their effector function. Hypoxia can inhibit T cell proliferation and cytotoxicity, with HIF-1α altering cellular metabolism by regulating glycolytic pathways and mitochondrial activity. Specifically, HIF-1α activation reduces intracellular NADPH levels, compromising antioxidant capacity and contributing to T cell dysfunction (166). Furthermore, HIF-1α modulates apoptotic signaling pathways, further affecting T cell survival and function. Thus, HIF-1α not only facilitates T cell adaptation to hypoxia but may also contribute to immune evasion in the TME (167,168).

Lactate accumulation, a result of aerobic glycolysis by tumor cells, leads to acidification of the TME and suppresses immune cell function. Studies have demonstrated that lactate notably reduces T cell cytotoxicity and cytokine production and promotes T cell exhaustion (169-171). Mechanistically, lactate impairs intracellular energy metabolism and increases oxidative stress, leading to diminished T cell activity. Additionally, lactate inhibits immune cell migration and infiltration into the tumor site, further limiting their effectiveness. The suppressive effects of lactate extend beyond T cells to macrophages and other immune cells, highlighting its role as a key factor in tumor-induced immunosuppression. Therefore, targeting lactate metabolism may represent a promising strategy to improve the efficacy of cancer immunotherapy.

The acidic TME also influences the expression of immune checkpoints, thereby modulating T cell responses. Acidic conditions have been shown to upregulate the expression of checkpoint molecules such as PD-L1, enhancing immune evasion by tumor cells (172). The increased expression of PD-L1 under acidic conditions is associated with HIF-1α stabilization, which further reinforces immunosuppression. An acidic pH also impairs T cell activation, further limiting antitumor immunity. Thus, modulating the acid-base balance of the TME, particularly by neutralizing acidosis to suppress immune checkpoint expression, may improve responses to immunotherapy. Notably, metabolic exhaustion is not merely a passive consequence of chronic activation but actively constrains T cell effector function, survival capacity and migratory behavior. Metabolically compromised T cells exhibit diminished cytokine production and altered chemokine responsiveness, which in turn influence their spatial distribution and persistence within the TME. These functional impairments provide a mechanistic association between metabolic stress and subsequent immune architectural remodeling (173-175).

Nutrient competition and metabolic suppression. Tryptophan metabolism plays an important role in immune regulation, and alterations in this pathway can directly affect T cell function and fate. Tryptophan catabolism via metabolites such as kynurenine and quinolinic acid exerts immunomodulatory effects, particularly in the TME where tumor cells actively deplete tryptophan to inhibit T cell proliferation and activity (176). Abnormal tryptophan metabolism has been associated with T cell exhaustion and reduced antitumor efficacy, ultimately impairing immune responses in patients with cancer (177). Moreover, tryptophan metabolites can modulate immune checkpoint expression, promoting T cell exhaustion. These findings suggest that targeting tryptophan metabolism may provide novel strategies for enhancing cancer immunotherapy.

The adenosine signaling pathway is another key regulator of T cell metabolism and is commonly associated with immunosuppression in the TME. Adenosine, generated by tumor metabolism, suppresses T cell proliferation and cytokine secretion through activation of downstream pathways such as cAMP and AMPK (178). Elevated adenosine levels in the TME contribute to T cell dysfunction and facilitate immune escape by tumor cells (179). Therefore, targeting the adenosine signaling axis offers a promising approach to reinvigorate exhausted T cells and restore effective antitumor responses.

Glutamine is an essential nutrient for T cell activation and function. It supports T cell proliferation, cytokine production and differentiation. In the TME, competition for glutamine between tumor and immune cells results in reduced availability, particularly impairing T cell metabolic capacity in chronic tumors and infections (180,181). Glutamine metabolism also influences systemic energy metabolism and intracellular signaling pathways, affecting T cell development and function (182,183). Thus, therapeutic strategies targeting glutamine metabolism may enhance T cell-mediated antitumor immunity.

Combination strategies for metabolic intervention. Indoleamine 2,3-dioxygenase (IDO) inhibitors have emerged as promising agents in cancer immunotherapy, particularly for reversing immune suppression in the TME by blocking tryptophan metabolism (184-186). IDO inhibitors reduce Treg activity and enhance effector T cell function. Preclinical studies have shown that agents such as D-1-methyl-tryptophan and INCB024360 notably enhance antitumor immune responses in mice, especially when combined with ICIs (85,187,188). Clinical trials have further suggested that IDO inhibitors may improve outcomes in patients with treatment-resistant tumors, highlighting their potential value as components of combinatorial immunotherapy.

CD73, an ectoenzyme involved in adenosine generation, plays a central role in mediating immunosuppression in the TME. Therapeutic strategies targeting CD73 aim to inhibit adenosine production, thereby enhancing T cell cytotoxicity and reversing immune suppression. CD73 inhibitors such as AB928 have been shown to promote T cell proliferation and effector function, particularly when used in combination with PD-1/PD-L1 blockade, resulting in improved antitumor responses (81). In addition to boosting immune responses, CD73 targeting also reduces tumor metastasis and recurrence, suggesting broad therapeutic potential across multiple types of cancer.

Combining metabolic modulation with immune checkpoint blockade has demonstrated synergistic effects in cancer therapy. Tumor cells often reprogram their metabolism to suppress T cell function, leading to immune exhaustion. Intervening in metabolic pathways, through administration of metabolic intermediates or inhibition of key enzymes, can restore T cell activity and enhance the efficacy of ICIs (189). This combined approach may overcome the immunosuppressive barriers of the TME and improve clinical outcomes.

Future studies should focus on elucidating the precise mechanisms underlying various metabolic pathways and optimizing combinatorial strategies with checkpoint inhibitors to develop more effective immunotherapies.

9. Characteristics of EBV-specific immune responses

Clonal dynamics of EBV antigen-specific T cells. In NPC, the clonal dynamics of EBV-specific T cells are important to understanding the TIME and the therapeutic response. EBV infection triggers antigen-specific T cell responses with distinct phenotypic features. Studies have demonstrated that EBV-specific $CD8^+$ and $CD4^+$ T cells exhibit altered proportions and often show an exhausted phenotype, with $ISG15^+$ $CD8^+$ T cells being highly enriched in EBV-positive tumors. The infiltration of antigen-specific T cells in the TME is associated with disease progression (190).

Analysis of T cell clonal dynamics has revealed a notable association between TCR repertoire diversity and disease status. Decreased TCR diversity is commonly observed during tumor progression and is associated with increased tumor burden and immune evasion. High-throughput TCR sequencing enables precise monitoring of TCR repertoire shifts, revealing the expansion or contraction of specific clones before and after treatment (191). Moreover, the clonal expansion of EBV-specific T cells reflects dynamic changes in the TME, highlighting their role in tumor immune surveillance.

In terms of memory T cell maintenance, EBV-specific memory T cells are often sustained at high frequencies following primary infection, particularly in healthy EBV carriers. This indicates their key role in controlling EBV persistence and EBV-related malignancies (192). Notably, EBV has evolved mechanisms to modulate T cell metabolism and activation, thereby facilitating immune evasion. These findings suggest that therapeutic strategies aimed at enhancing EBV-specific memory T cell responses may improve antitumor immunity.

In summary, the clonal dynamics of EBV antigen-specific T cells not only reflect their phenotypic adaptations to latent viral antigens but also reveal the association between TCR repertoire diversity and disease progression. These insights provide potential biomarkers and therapeutic targets for NPC and deepen understanding of immune evasion mechanisms in EBV-associated malignancies.

Role of humoral immune responses. Humoral immunity plays a pivotal role in controlling EBV infection. Changes in EBV-specific antibody profiles have been associated with tumorigenesis, disease progression and patient prognosis. In patients with NPC, the presence and titers of EBV-specific antibodies, such as viral capsid antigen IgA/IgG and EBNA IgA/IgG, serve as important biomarkers for disease monitoring (193). Elevated antibody levels are frequently observed in patients with NPC, particularly in those with disease recurrence, indicating their potential as early warning indicators for disease progression and the therapeutic response (194). Furthermore, the diversity of EBV-specific antibody profiles may reflect the immune status of the host and may be influenced by changes in the TME (195).

Neutralizing antibodies play an important protective role during EBV infection by recognizing and binding viral envelope proteins, thereby preventing viral entry and replication. In NPC, the generation of EBV-specific neutralizing antibodies not only aids viral clearance but also enhances antitumor immune responses by promoting $CD8^+$ T cell activation and cytotoxicity (196). High levels of neutralizing antibodies have been associated with favorable clinical outcomes, suggesting their importance in limiting EBV-associated tumor progression (16).

B cells, as the primary source of antibodies, also contribute to immune regulation within the TME. In NPC, B cells exert multiple functions through antibody production, cytokine secretion and T cell modulation. EBV infection promotes B cell activation and expansion, enhancing antiviral immunity. Within the TME, B cells can form germinal center-like structures that facilitate affinity maturation and the production of tumor-specific antibodies, potentially suppressing tumor growth and metastasis (197). Additionally, B cells interact with T cells via antigen presentation and secretion of immunoregulatory factors, further enhancing antitumor immunity (198). Therefore, B cell activity and abundance are key determinants of NPC prognosis.

Virological mechanisms of immune evasion. EBV is a major etiological factor in NPC, and viral genetic variation plays a key role in immune evasion. Mutations in several regions of the EBV genome have been implicated in the ability of the virus to evade host immune surveillance, including alterations in the PD-1/PD-L1 signaling pathway. In EBV-positive tumors, upregulation of PD-L1 on tumor cells suppresses the function of EBV-specific T cells, allowing for immune escape (199). Additionally, EBV mutations can affect antigen presentation, reducing TCR recognition of viral epitopes and impairing effective immune responses (200). Thus, viral genetic variation contributes to both oncogenicity and immune evasion.

EBV-encoded miRNAs also play a central role in modulating host immunity. EBV miRNAs, such as those from the BART and BHRF1 families, downregulate host immune-related gene expression, suppressing cytokine production and immune cell activation. For example, BART10-3p targets multiple host genes to inhibit antiviral responses and promote tumor cell survival (201). These mechanisms not only facilitate immune evasion but may also promote tumorigenesis within the EBV-positive microenvironment.

Latency is another immune evasion strategy used by EBV. During latency, the virus remains hidden in B cells with limited antigen expression, meaning that infected cells are difficult to detect and eliminate. Latent-to-lytic reactivation can trigger acute immune responses and, in some cases, immune-mediated pathology such as EBV-associated lymphoproliferative disorders (202). Furthermore, reactivation may contribute to tumor progression by impairing immune cell function within the TME. Understanding the immunological consequences of EBV latency and reactivation is key for developing novel therapeutic strategies against EBV-associated malignancies.

In summary, the virological mechanisms underlying EBV-mediated immune evasion are complex and multifaceted (as detailed in Fig. 5). Future studies are warranted to further

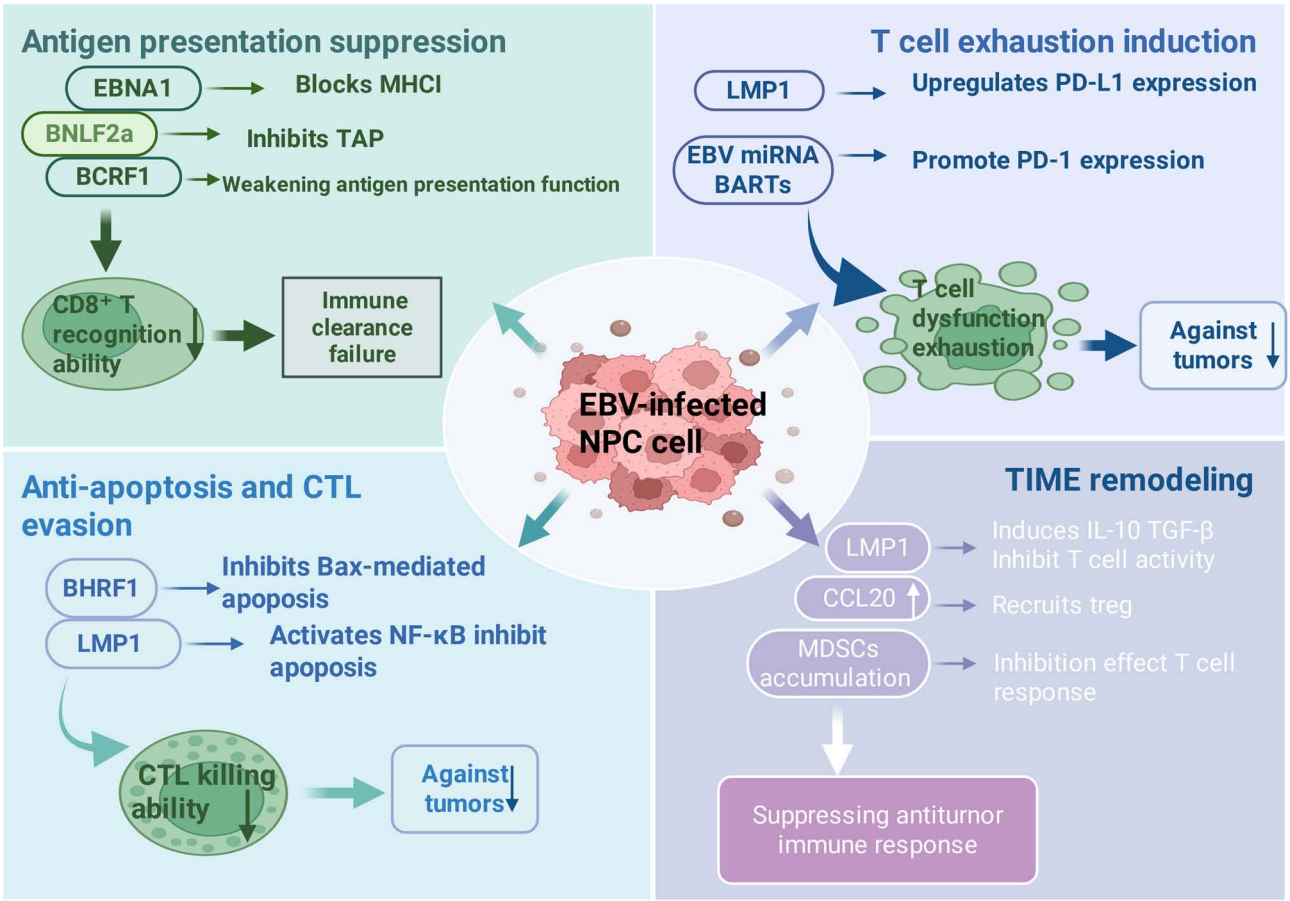

Figure 5. Schematic diagram of the virological mechanisms of immune evasion by EBV. After EBV infection of NPC cells, immune evasion is achieved through multiple mechanisms that suppress antitumor immune responses. The molecular mechanisms include: i) Antigen presentation inhibition: EBV proteins (EBNA1, BNLF2a and BCRF1) block the function of MHC class I molecules and TAP transport, weakening the recognition capacity of $CD8^+$ T cells. ii) Anti-apoptosis and CTL evasion: BHRF1 and LMP1 inhibit apoptosis (for example, by blocking Bax) or activate the NF-κB pathway, assisting tumor cells in evading CTL-mediated killing. iii) Induction of T cell exhaustion: LMP1 and BARTs mRNA upregulate the PD-L1/PD-1 signaling pathway, leading to T cell dysfunction. iv) Remodeling of the TIME: Through the secretion of factors such as IL-10, TGF-β and CCL20, EBV recruits Tregs and MDSCs, further suppressing T cell activity and creating an immunosuppressive microenvironment. EBV, Epstein-Barr virus; NPC, nasopharyngeal carcinoma; EBNA1, Epstein-Barr nuclear antigen 1; BNLF2a, BamN-terminal latent protein family member 2a; BCRF1, BamC-terminal reading frame 1; BHRF1, BamHI rightward reading frame 1; LMP1, latent membrane protein 1; BARTs, BamHI-A rightward transcripts; MHC-I, major histocompatibility complex class I; TAP, transporter associated with antigen processing; CTL, cytotoxic T lymphocyte; PD-L1, programmed cell death ligand 1; PD-1, programmed cell death protein 1; Treg cell, regulatory T cell; MDSCs, myeloid-derived suppressor cells; CCL20, C-C motif chemokine ligand 20; TIME, tumor immune microenvironment.

elucidate these pathways, which may uncover novel targets and strategies for cancer immunotherapy.

10. Dynamic process of immunoediting

Characteristics of the elimination phase. During the elimination phase of NPC, effective early immune surveillance plays an important role. This early immune response primarily depends on specific immune cells, such as $CD8^+$ T cells and natural killer (NK) cells, which are key for recognizing and eliminating tumor cells. For example, in studies of chronic hepatitis B virus infection, effective immune surveillance in the acute phase was marked by rapid activation of virus-specific T cells and efficient viral clearance (203). Similarly, in NPC, EBV infection triggers the expression of viral antigens by tumor cells, thereby activating host immune responses.

The TME in early NPC harbors a variety of immune cells that secrete cytokines and express activation markers to enhance T cell-mediated surveillance. The effectiveness of this early immune response not only determines the extent of tumor cell clearance but also influences the formation of immune memory. Thus, enhancing early immune surveillance may represent a promising strategy for NPC treatment.

Immunogenic cell death (ICD) is a key component of immune-mediated tumor clearance, particularly in NPC. ICD promotes the release of tumor antigens through specific death signals, thereby triggering robust immune activation. Studies have shown that chemotherapeutic or radiotherapeutic stress can induce ICD via the release of molecules such as HMGB1 and ATP, which recruit DCs and activate T cells (204-207). In chronic hepatitis B virus models, $CD3^+$ macrophages are activated during viral clearance and produce large amounts of TNF-α and other proinflammatory mediators, enhancing ICD and immune activation (208). Similarly, in NPC, ICD-inducing chemotherapeutic agents have been shown to improve tumor immunogenicity and promote T cell activation and expansion.

The activation of innate immunity during the elimination phase involves complex multilayered mechanisms. Tumor-derived danger signals (for example, damage-associated molecular patterns) are recognized by innate immune cells such as macrophages and DCs via pattern recognition receptors (for example, TLRs), leading to the production of inflammatory cytokines and the recruitment of additional immune effectors (204). Moreover, innate cells such as NK and NK T cells are rapidly activated and secrete interferons and TNF-α, which boost T cell-mediated responses. This innate immune activation not only modulates the TME but also lays the groundwork for adaptive immunity (209). Overall, the rapid and effective activation of the innate immune system is essential for successful tumor elimination and long-term immune memory formation in NPC.

Transition of the equilibrium phase. The equilibrium phase represents a key transitional stage in NPC development, where immune selection pressure shapes the dynamic interactions between tumor cells and immune cells. Initially, host immunity attempts to control tumor growth via CTLs and NK cells. However, as tumors evolve, immune pressure leads to the emergence of escape mechanisms, such as the upregulation of immune checkpoint molecules (for example, PD-1 and CTLA-4), which suppress T cell activity and facilitate immune evasion (210). Furthermore, cytokines such as IL-6 and TGF-β within the TME promote T cell exhaustion, weakening antitumor responses (211).

Tumor heterogeneity, a hallmark of cancer, is particularly pronounced in NPC. It arises not only from genetic variation within tumor cells but also from the diverse composition and function of immune cells in the TME. Various immune subpopulations (for example, M1 vs. M2 macrophages, effector vs. Treg cells and B cell subsets) exert dual roles in tumor progression. M1 macrophages support antitumor immunity, whereas M2 macrophages promote immunosuppression and tumor growth (212). These diverse immune cell interactions, along with differential cytokine secretion and antigen expression, lead to TIME remodeling and increased tumor heterogeneity (213).

Immunoediting is a key mechanism by which tumors modulate antigen expression in response to immune pressure. Tumor cells may selectively lose or downregulate specific antigens to reduce their immunogenicity and avoid recognition by T cells (214). This process contributes to the emergence of immune-evasive tumor subclones with enhanced survival and suppressive capabilities. In NPC, changes in EBV-associated antigen expression may impair T cell recognition and hinder effective immune responses (215). These dynamic alterations in the antigenic landscape influence disease progression and therapeutic efficacy, underscoring the need to consider immunoediting features when designing treatment strategies.

Establishment of the escape phase. Immune escape is a defining feature of advanced tumor progression, particularly in EBV-associated types of cancer such as NPC. The evolving TME plays a key role in establishing immunosuppression. EBV-infected tumor cells upregulate immune checkpoint molecules such as PD-L1 to inhibit T cell responses, thereby facilitating immune evasion (216).

The interactions between tumor cells and infiltrating immune cells within the TME are central to immune escape. EBV-positive tumor cells secrete both proinflammatory and immunosuppressive cytokines that reprogram surrounding immune cells. TAMs and Treg cells are often enriched in the TME, secreting immunosuppressive cytokines such as IL-10 and TGF-β to reinforce local immunosuppression (217).

Metabolic reprogramming is another mechanism by which tumors escape immune surveillance. Tumor-derived metabolites such as lactate inhibit T cell function and promote a suppressive microenvironment conducive to tumor survival and growth (218). Chronic EBV antigen exposure leads to progressive $CD8^+$ T cell dysfunction, characterized by high expression of inhibitory molecules (for example, PD-1, LAG-3) and diminished cytokine secretion and proliferative capacity (180).

T cell exhaustion, a hallmark of chronic infection and cancer, is often irreversible. It results from persistent antigen stimulation, suppressive signaling and metabolic stress in the TME (219). In NPC, nutrient competition within the TME, particularly involving glucose and glutamine, exacerbates T cell exhaustion and impairs antitumor immunity.

Stromal remodeling also contributes to immune escape and the establishment of immune privilege. Tumor-associated stromal cells such as fibroblasts and myeloid cells interact with tumor cells to reshape the ECM and modulate immune cell infiltration (220). In NPC, EBV-infected cells secrete cytokines that recruit and activate Treg cells, which secrete TGF-β and IL-10 to suppress effector T cell functions and maintain immune privilege (217). Additionally, tumor cells secrete matrix metalloproteinases that degrade ECM components, promoting tumor invasion and altering immune cell localization and activity (221). Therefore, targeting stromal remodeling and reversing T cell exhaustion may represent promising strategies for overcoming immune escape in NPC and enhancing immunotherapy efficacy.

11. Therapeutic strategies and clinical translation

Limitations of current immunotherapies. Immunotherapy has emerged as a promising treatment modality for NPC, yet pronounced limitations remain. Notably, the response rate to anti-PD-1 inhibitors in patients with NPC is relatively low. Clinical trials have revealed that despite substantial infiltration of $CD8^+$ T cells in the TME, therapeutic efficacy remains suboptimal. This discrepancy is largely attributed to the prominent immunosuppressive signals within the TME, which restrict the effectiveness of PD-1 blockade (222). Single-cell omics analysis of 50 patient samples demonstrated that NPC cells enhance the development and suppressive function of Treg cells via the CD70-CD27 interaction, leading to the inhibition of $CD8^+$ T cell activity (222). Such immunosuppressive mechanisms highlight the complexity of the TME and the challenges of monotherapy targeting PD-1.

Regarding treatment resistance, tumor cells employ diverse immune evasion strategies. Overexpression of CD70 in NPC cells impairs $CD4^+$ T cell metabolism and function, driving T cell exhaustion (222). Moreover, metabolic reprogramming within the TME has been identified as a key contributor to T cell dysfunction, thereby promoting tumor progression and

metastasis (223). Comprehensive investigation into these resistance mechanisms is important to inform the development of novel therapeutic approaches that can enhance immunotherapy outcomes.

The development of reliable biomarkers for predicting the immunotherapy response remains challenging. Although PD-L1 expression is widely used as a predictive marker, its prognostic accuracy is contentious (224). Radiomic features derived from magnetic resonance imaging have demonstrated superior predictive performance compared with PD-L1 scoring in patients with NPC, indicating the need to explore more robust and prospective biomarkers (224). Additionally, the composition of the gut microbiome has emerged as a potential modulator of immunotherapy efficacy, with specific microbial communities associating with treatment responses in NPC (225). Future research should focus on multi-dimensional biomarker integration to improve response prediction and facilitate personalized treatment.

In summary, despite the potential of current immunotherapies in NPC, low response rates, complex resistance mechanisms and biomarker limitations underscore the urgent need for comprehensive strategies that consider the TME, metabolic pathways and novel biomarkers to improve therapeutic efficacy and patient outcomes.

Novel combination therapeutic strategies. Combining immunotherapy with radiotherapy has shown promising synergistic effects in NPC treatment. Radiotherapy enhances tumor immunogenicity by inducing ICD, leading to the release of tumor antigens and the activation of antitumor immune responses. This promotes the infiltration and activation of immune cells, particularly T lymphocytes (226). Studies have demonstrated that the combination of anti-PD-1 antibodies with radiotherapy improves the TME by facilitating T cell recruitment and activation, resulting in improved clinical responses (227-230). Furthermore, radiotherapy can alleviate immunosuppressive elements in the TME, thereby enhancing the efficacy of ICIs and offering more effective therapeutic options for patients with NPC (231). Nonetheless, further clinical trials are warranted to optimize combination regimens and assess safety profiles.

Epigenetic modulators have gained increasing attention in augmenting immunotherapy. In NPC, epigenetic drugs can modulate interactions between tumor and immune cells, thereby influencing immune responses. Certain epigenetic agents suppress immunosuppressive cytokines within the TME, enhancing immune cell activity and boosting immunotherapy efficacy (232). Additionally, epigenetic regulation of T cells can restore their functionality and reverse exhaustion states, strengthening antitumor immunity (233). These advances suggest that combining epigenetic therapy with immunotherapy may improve clinical outcomes in NPC.

Targeting metabolic pathways in combination regimens offers another promising avenue. Metabolic reprogramming underpins tumor cell survival and proliferation; thus, inhibiting these pathways can suppress tumor growth and enhance immune responses. Studies indicate that metabolic interventions can remodel the TME, improving T cell function and augmenting their antitumor activity (234-237). Moreover, metabolic inhibitors combined with immune checkpoint blockade have shown potential in increasing tumor immunogenicity and immune cell infiltration, leading to superior therapeutic outcomes (238). Successful implementation of these strategies may provide novel treatment options and markedly improve survival and quality of life for patients with NPC.

Prospects for personalized therapy. Personalized therapeutic strategies based on TCR repertoire analysis hold potential for NPC treatment. TCR profiling enables the identification of tumor-specific antigens and stratification of patients according to their T cell reactivity, thereby guiding optimal therapy selection. The diversity of the TCR repertoire is associated with immune escape mechanisms and can predict potential responsiveness to immunotherapy (239). Furthermore, TCR-based approaches can be integrated with other modalities, such as ICIs, to amplify overall antitumor immunity and improve clinical efficacy. This individualized approach enhances treatment precision and potentially reduces adverse effects, thereby improving patient quality of life.

The development of neoantigen vaccines also shows considerable potential in personalized NPC therapy. These vaccines aim to elicit robust immune responses against tumor-specific neoantigens, facilitating the immune recognition and elimination of cancer cells. Neoantigen vaccines have been shown to enhance $CD8^+$ T cell responses and improve tumor immune surveillance, contributing to prolonged patient survival (239). Ongoing research focuses on optimizing neoantigen identification and vaccine delivery systems to enhance immunogenicity and safety (240). Incorporating genomic data allows for the design of tailored vaccines that further augment therapeutic efficacy and immune responsiveness (241).

The microbiome plays a key role in modulating host immunity, particularly in the context of NPC immunotherapy. The composition of the microbiome influences treatment responses, including sensitivity to immune checkpoint blockade (239). Modulation of the microbiota may enhance T cell function and strengthen antitumor immunity. Specific microbial communities have been reported to promote proliferation and activation of immune effector cells, thereby improving treatment outcomes (242). Future studies should explore interventions such as dietary modifications, probiotics or other microbiome-targeted therapies to optimize microbial composition and enhance survival in patients with NPC (243). Consequently, the majority of proposed therapeutic strategies discussed in the present review should be considered hypothesis-generating, and their clinical applicability requires validation in well-designed prospective studies.

Despite increasing insight into immune dysregulation in EBV-associated NPC, the clinical translation of these findings remains limited. ICIs, particularly targeting the PD-1/PD-L1 axis, have demonstrated clinical benefit in a subset of patients; however, primary resistance and heterogeneous response rates remain important therapeutic challenges. These limitations suggest that immune checkpoint blockade alone may be insufficient to fully reverse the complex and dynamic immune editing processes occurring in this disease.

One major therapeutic bottleneck is the persistent antigenic pressure imposed by EBV (244). Chronic EBV antigen presentation sustains prolonged TCR signaling, which drives

continuous immune activation and ultimately promotes T cell dysfunction. Current immunotherapeutic strategies largely focus on downstream reinvigoration of exhausted T cells, while the upstream viral antigen burden is rarely addressed. Future therapeutic approaches may benefit from targeting EBV latency programs, modulating viral antigen processing and presentation, or integrating antiviral strategies to reduce chronic immune stimulation and delay or prevent T cell exhaustion.

A second important limitation lies in the metabolic exhaustion of TILs. Accumulating evidence indicates that mitochondrial dysfunction, redox imbalance and impaired glucose and lipid metabolism fundamentally constrain T cell effector capacity and persistence within the TME. However, metabolic fitness is not routinely evaluated in clinical practice, and biomarkers reflecting T cell metabolic status are lacking. Future research should prioritize the identification of metabolic signatures predictive of immunotherapy responsiveness and explore metabolic interventions, such as modulation of mitochondrial function or antioxidant pathways, as rational combinatorial strategies alongside ICIs.

TLS remodeling further complicates therapeutic decision-making. Although the presence of TLSs has been associated with improved outcomes in several types of cancer, their functional heterogeneity in NPC remains poorly characterized. Emerging evidence suggests that TLSs may exhibit both immunostimulatory and immunosuppressive properties depending on their maturation state, cellular composition and spatial organization. Therefore, simply promoting TLS formation may not uniformly enhance antitumor immunity. Future studies should focus on stratifying TLS phenotypes and defining their functional relevance in NPC, which may inform patient selection and therapeutic timing.

Collectively, these observations highlight the need for stage-adapted and mechanism-guided therapeutic strategies. Rather than targeting isolated immune components, effective clinical translation may require combinatorial approaches that simultaneously address persistent antigen exposure, metabolic exhaustion and immune architectural remodeling. Longitudinal studies integrating immune profiling, metabolic assessment and spatial transcriptomic analysis of TLS dynamics may be important in translating mechanistic insights into precision immunotherapy for EBV-associated NPC.

12. Conclusion

NPC, which is characterized by high incidence and mortality rates, according to the latest GLOBOCAN 2022 estimates, nasopharyngeal carcinoma accounts for 120,000-130,000 new cases and more than 70,000 mortalities worldwide each year, with a marked geographic predominance in East and Southeast Asia, has long attracted attention due to the complexity of its immune evasion mechanisms (245). The present review has comprehensively examined the intricate molecular networks involved in T cell fate decisions during immune editing, with particular focus on the interplay among aberrant EBV antigen presentation, T cell metabolic exhaustion and TLS remodeling. These key processes not only deepen understanding of NPC immune escape but also lay a foundation for future immunotherapeutic strategies.

First, as a pivotal oncogenic factor in NPC, EBV considerably disrupts antigen presentation, thereby impairing T cell activation and function. Detailed analysis of EBV antigens reveals multiple immune evasion mechanisms within the TME, including altered antigen presentation and secretion of immunosuppressive factors, collectively diminishing T cell recognition of tumor cells. Insight into these processes enhances comprehension of NPC pathogenesis and offers valuable guidance for vaccine development targeting EBV-associated antigens.

Second, T cell metabolic exhaustion represents another key aspect. Within the metabolically hostile TME, T cells endure profound metabolic stress that compromises their effector functions. Emerging evidence suggests that metabolic reprogramming is important for sustaining T cell survival and activity in tumors. Thus, future research should prioritize strategies to modulate T cell metabolic states to restore their antitumor functionality and improve immunotherapy efficacy.

Furthermore, remodeling of TLSs in the TME has garnered increasing interest (91,112). TLS formation not only affects T cell aggregation and activation but may also play a key role in tumor progression. Investigating the mechanisms underlying TLS development and their specific functions in NPC may offer more comprehensive therapeutic insights.

In summary, immune evasion in NPC is governed by a complex and interdependent network. Future studies should focus on dynamically dissecting these processes to facilitate the design of combination therapies that concurrently target multiple immune escape pathways. Additionally, establishing robust predictive models for treatment responses may aid the development of personalized precision immunotherapy, ultimately enhancing patient survival and quality of life. By integrating multidisciplinary findings, a more holistic understanding of NPC immune evasion can be achieved and clinically actionable frameworks to drive advances in NPC treatment can be provided.

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Authors' contributions

LZ, SD and DC wrote the manuscript and created the figures. DC collected and organized literature. LZ and SD proofread the manuscript. ZM and BC are responsible for the study design, research fields, drafting and finalizing the manuscript. All

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Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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