

From Etiology to Targets: Molecular Vulnerabilities and Precision Therapy in Nasopharyngeal Carcinoma Driven by Risk Factors

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Nasopharyngeal carcinoma (NPC) is the only malignancy etiologically linked to Epstein-Barr virus (EBV), with a high prevalence in specific geographic regions and ethnic populations. The host genetic predisposition, viral oncogenesis and environmental factors interact in a complex manner, collectively contributing to disease pathogenesis and forming a multifactorial etiological network. Accumulating evidence supports a triangle model, where these factors not only initiate and promote tumor progression, but also maintain long-term biological vulnerability, rendering the tumor responsive to various therapeutic interventions. EBV-encoded proteins, including Epstein-Barr nuclear antigen 1 (EBNA1), latent membrane protein 1 (LMP1) and latent membrane protein 2A (LMP2A), promote malignant transformation by stimulating oncogenic signaling pathways, enhancing immune evasion and modifying the tumor microenvironment. Host determinants, such as polymorphism of human leukocyte antigens (HLA), extracellular vesicle-mediated communication, and apolipoprotein B mRNA editing catalytic polypeptide-like 3 (APOBEC3), further modulate disease susceptibility. Environmental factors, including dietary toxins and chronic inflammatory stimulation, exacerbate all these pathogenic processes. Viral, genetic and microenvironmental signals are integrated into sustained survival and metastasis programs through persistent activation of key signaling pathways, notably nuclear factor kappa B (NF- κ B) and phosphatidylinositol 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/AKT/mTOR). Also, metabolic reprogramming, epigenetic modification, and immunological inhibition contribute to a dynamic vulnerability network that links disease etiology to treatment options. Based on this model, recent studies have shifted toward a precision medicine paradigm that prioritizes molecular stratification over traditional anatomical staging, grounded in the mechanistic interplay between therapeutic sensitivity and oncogenic drivers, thereby enabling personalized treatment strategies.

Keywords: nasopharyngeal carcinoma; Epstein-Barr virus; etiological triad; molecular vulnerabilities; immune checkpoint inhibitors

Introduction

Nasopharyngeal carcinoma (NPC) is an epithelial tumor originating from the mucosal surface of the nasopharynx [1]. Distinct from other head and neck cancers, NPC exhibits geographic and ethnic distributions, along with host susceptibility, suggesting that its pathogenesis involves complex interactions among environmental factors, host characteristics, and viral infection [2]. Although the global incidence is low, NPC remains a major health concern in endemic regions, such as Southern China, Southeast Asia, North Africa and parts of the Arctic [3,4]. This uneven distribution implies that the occurrence of NPC is not induced by one particular carcinogenic factor but rather by a combination of risk factors. The widely accepted triangle model attributes this epidemiological pattern to a dynamic interaction between latent Epstein-Barr virus (EBV) infection, hereditary genetic predisposition, and environmental or lifestyle exposure to carcinogens [5,6]. In most cases of non-keratinizing NPC, EBV is regarded as the primary bio-

logical agent. Moreover, EBV DNA circulating in the body has been used as a major biomarker in monitoring therapy, classification of prognosis, and screening [7,8]. However, given the relatively low NPC incidence and the widespread prevalence of EBV in the general population, EBV alone is insufficient to initiate malignant transformation, highlighting the critical roles of host and environmental cofactors.

Genetic susceptibility is another significant vertex in the triangle model. Genome-wide association studies have identified multiple loci associated with the risk of NPC, especially in the human leukocyte antigen (HLA) region, suggesting that host responses to EBV-associated oncogenesis are mediated by immune surveillance and antigen presentation [9]. Additional susceptibility genes related to inflammation, cell-cycle regulation and DNA repair have also been discovered [10,11]. Some individuals may be more susceptible to chronic mucosal inflammation due to some genetic variations, long-term viral latency and genomic damage caused by carcinogens. Environmental exposures constitute the third part of the model. Epidemiologi-

ical studies have linked Cantonese-style salted fish and preserved food consumption, tobacco smoking, occupational dust exposure, formaldehyde, and air pollution to an increased risk of NPC [12]. Multiple factors, such as exposure to nitrosamines, oxidative stress, epithelial injury and chronic inflammation, collectively create an environment conducive to malignant transformation. Therefore, it is advisable to consider NPC as a disease caused by long-term biological interplay between innate susceptibility and external stressors. Despite significant advancements, contemporary review remains frequently hindered by a fragmented writing paradigm. Most etiological evaluations treat environmental, genetic, and viral factors as independent variables [13,14]. While informative, this descriptive approach emphasizes association over mechanism, describing risk factors without elucidating how these factors change tumor biology in a clinically actionable manner.

Molecular reviews have predominantly centered on canonical signaling pathways or the carcinogenic properties of EBV-encoded proteins, expanding our understanding of NPC-relevant routes, including nuclear factor kappa B (NF- κ B), Janus kinase/signal transducer and activator of transcription (JAK/STAT), phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), and mitogen-activated protein kinase (MAPK) [15,16]. Latent membrane protein 1 (LMP1), latent membrane protein 2 (LMP2), and Epstein-Barr nuclear antigen 1 (EBNA1) are recognized as potent regulators of immune evasion, proliferation, and metastasis [17]. However, pathway-centered analyses often characterize these events as separate intracellular processes and fail to connect these molecular modifications to the initial risk exposures responsible for their emergence. A similar restriction applies to therapeutic reviews, many of which concentrate on concurrent reporting of developments in immune checkpoint inhibitors, anti-epidermal growth factor receptor (EGFR) treatment, intensity-modulated radiation, platinum-based chemotherapy, and new adoptive cell approaches [18,19,20]. Despite their clinical significance, these reviews often overlook a crucial translational question regarding the drivers of differential treatment responsiveness and resistance. Without integrating molecular dependencies and etiological drivers, treatment selection may remain empirical rather than biologically guided.

The foregoing observations necessitate a shift in conceptual framework. We propose that risk factors of NPC function not merely as upstream contributors to illness; more importantly, they imprint long-lasting molecular marks on malignant and premalignant cells, including epigenetic reorganization, metabolic pathways, DNA damage patterns, immune evasion phenotypes, viral-host synthetic interactions, and pathway dependencies [21]. In essence, host genetics, environmental carcinogens, as well as EBV infection, not only trigger carcinogenesis but also generate distinct molecular vulnerabilities that sustain tumor persis-

tence, with direct therapeutic implications. Redox-targeted therapy can be applied when carcinogenic exposure leads to oxidative stress dependency. EBV latency-associated anti-apoptotic rewiring may create susceptibility to viral-context synthetic lethality, and impaired antigen presentation may guide biomarker-driven optimization of immunotherapies. Hence, the connection between the etiology and the treatment lies in identifying risk factor-associated molecular fingerprints and translating them into actionable targets. In this Review, we define these persistent, etiologically acquired molecular dependencies as molecular vulnerabilities. Specifically, molecular vulnerabilities are molecular alterations shaped by EBV infection, host genetic susceptibility, and/or environmental exposure. These alterations are indispensable for tumor maintenance and progression but relatively dispensable in normal tissues, thus offering a therapeutic window for targeted intervention. Departing from a conventional module-based narrative, we examine how external drivers of NPC generate innate molecular vulnerabilities and explore their integration into precision medicine frameworks, with the goal of providing a broader roadmap for next-generation management of NPC in terms of etiology, mechanism and therapeutic action.

The Etiological Triad: Host, Virus, and Environment

The three oncogenic drivers of NPC—environmental exposure, EBV infection and host susceptibility—do not operate in isolation but converge to establish a pro-tumorigenic microenvironment that promotes tumor growth, immune evasion and epithelial transformation. Recent genomic and translational studies have expanded this classical framework, providing new insights into how oncogenic factors generate targetable molecular vulnerabilities.

Host Genetic Susceptibility: From Genome-Wide Association to Functional Interpretation

The genetic background of the host is one of the most important determinants of NPC susceptibility, as evidenced by familial clustering, ethnic disparities, and endemic population clustering [22]. Variations within the HLA locus make a prominent impact on immune surveillance and presentation of antigens [23], and are the most consistently associated with NPC risk, a relationship particularly prominent in hematopoietic or infectious malignancies. According to some early genome-wide association studies (GWAS), there are several loci associated with NPC on chromosome 6p21.3, which has crucial HLA genes [24]. Subsequent evidence has further implicated major histocompatibility complex, class I, A (HLA-A) among Southern Chinese populations [25].

Recent integrative genomic and whole-exome sequencing studies have extended the concept of susceptibility beyond immunological loci. Zeng et al. [26] identified three germline variations linked to the risk of

NPC: a common rs2276868 in ribosomal protein L14 (RPL14), a rare rs5361 in selectin E (SELE), and a common rs1050462 in major histocompatibility complex, class I, B (HLA-B). These results suggest that NPC predisposition involves mechanisms beyond immune regulation. Notably, RPL14 is implicated in protein arginine methyltransferase 5 (PRMT5)-driven DNA damage repair and reduced drug sensitivity in hepatocellular cancer, raising the possibility that inherited RPL14 variation may influence treatment resistance and genome maintenance in NPC [27]. E-selectin, an endothelial adhesion protein that interacts with CD44 to enable shear-resistant attachment and motility of circulating tumor cells, is encoded by SELE [28]. SELE mutations in NPC may affect leukocyte trafficking, inflammatory recruitment, or metastatic spread within the nasopharyngeal microenvironment. HLA-B polymorphisms further underscore the significance of adaptive immune recognition in influencing host responses to EBV latency.

Transcriptome-based methods have also acquired extra functional information. Liang et al. [29] performed integrative transcriptome-wide association studies (TWAS) with expression quantitative trait loci colocalization in 1577 cases of NPC and 6359 Southern Chinese controls, identifying a causative susceptibility variant in vesicle-associated membrane protein 8 (VAMP8). VAMP8 regulates endocytosis, secretory trafficking, and fusion of vesicles, biological processes that are closely associated with the recycling of membrane receptors, antigen processing and cytokine production. Functional studies on colorectal cancer have confirmed that VAMP8 knockdown exerts pro-apoptotic, pro-ferroptotic, anti-autophagic, and anti-proliferative effects, accompanied by blockade of the JAK/STAT3 pathway [30]. Moreover, centromere protein N (CENPN) in NPC enhances paclitaxel resistance by suppressing autophagy through the cAMP response element-binding protein (CREB)-VAMP8 signaling pathway [31]. All these findings indicate that inherited VAMP8 dysregulation may contribute to NPC vulnerability, treatment, and cellular stress adaptability. These germline variants create host-derived vulnerabilities that may be exploitable therapeutically: RPL14 variation could influence DNA repair capacity and drug sensitivity, while VAMP8 dysregulation may affect vesicular trafficking and immune signaling pathways.

The host-bacteria interaction represents another emerging frontier in NPC research. Using 16S ribosomal RNA gene sequencing on 343 nasopharyngeal tissues and 36 normal nasopharyngeal tissues, Tan et al. [32] identified four risk-related bacterial genera, *Bacteroides*, *Alloprevotella*, *Parvimonas*, and *Dialister*, as potential prognostic biomarkers for NPC. Additional evidence indicates that oral microbiota dysbiosis can regulate the EBV latency-lysis conversion [33], facilitating viral entry into nasopharyngeal epithelial cells and promoting malignant transformation. It is worth noting that genetic and

microbiological factors are associated with the prognosis of anti-programmed cell death protein 1 (PD-1) immunotherapy in NPC [34]. Besides, changes in the microbiota may lead to toxicities related to treatment such as oral mucositis, implying an obvious relationship between the composition of microorganisms and tolerance to treatment [35]. These observations open avenues for microbiota-modulating therapies aimed at reducing toxicity, improving quality of life, and enhancing efficacy of therapy. Collectively, these studies demonstrate that NPC susceptibility genes are not merely statistical risk indicators, but functionally involved in vesicular trafficking, immunological response, virus-host interaction and homeostasis of epithelial tissue. Importantly, these inherited pathways may constitute biological vulnerabilities in established tumors, thereby providing a functional bridge between genetic vulnerability and precision therapeutic strategies.

EBV Infection and Its Oncogenic Strategies

EBV is the most well-known biological cause of non-keratinizing NPC. Instead of engaging in productive lytic replication, EBV often remains as a latent episome in tumor cells [5]. Latency type II is pertinent to NPC and defined by a limited viral expression program, comprising EBV-encoded short RNAs, EBNA1, LMP1, LMP2A, LMP2B, and several viral microRNAs (mRNAs) [36]. This latency pattern confers several oncogenic advantages: EBNA1 restricts immunological visibility while preserving the viral episome during cell division; LMP2A can alter epithelial survival pathways and imitate B-cell receptor signaling in lymphoid environments; and viral non-coding RNAs alter the immunological and transcriptional networks of the host. Among these, LMP1 is the best-characterized EBV oncoprotein and functions as a constitutively active receptor-like molecule that recruits signaling molecules associated with tumor necrosis factor receptors and continuously activates NF- κ B [37,38], thereby promoting proliferation, resistance to apoptosis, angiogenesis, cytokine production, epithelial-mesenchymal transition, and metastatic dissemination. Additionally, LMP1 engages in extensive signaling crosstalk with the PI3K/AKT, MAPK, and JAK/STAT pathways [39,40].

Emerging evidence also underscores the genetic heterogeneity of EBV, with interpatient heterogeneity and geographical variations in incidence attributed to distinct virus subtypes or sequence variants. Certain viral gene changes modulate oncogenic potential through effects on epithelial tropism, latency regulation, and immune evasion, a finding that may partially explain why EBV infection is widespread worldwide while NPC remains largely endemic. The EBV-encoded latent proteins (EBNA1, LMP1, and LMP2A) are not merely viral oncogenes; they create virus-specific molecular dependencies that are selectively expressed in tumor cells, providing a unique therapeutic window for direct antiviral targeting and EBV-directed immunotherapies.

Environmental Exposures: From Epidemiology to Mechanism

Environmental factors remain important cofactors in the development of NPC. Conventional preserved foods, especially salt-cured fish and nitrosamine-rich products, have been traditionally linked to increased incidence of NPC [41], possibly through carcinogen-induced chronic mucosal irritation and DNA damage. Tobacco smoking is another well-validated risk factor; epidemiological data indicate that current smokers have a substantially increased risk, with odds ratios reaching 3.10 in some cohorts [42]. Smoking introduces reactive oxygen species, mutagenic aldehydes and polycyclic aromatic hydrocarbons, which collectively compromise local immunity, inflammatory signaling, and genetic stability. Regional exposures can also affect disease clustering. High ambient nickel exposure has been proposed as one of the potential risk modifiers in various areas of Southeast Asia [43]. Nickel compounds also induce oxidative stress, alter epigenetic regulation, and interfere with DNA repair mechanisms, while formaldehyde exposure, indoor air pollution and occupational dust exert similar adverse effects in susceptible populations [44]. Thus, environmental carcinogens not only initiate mutations, but also generate long-lasting stress-adaptation systems, including oxidative stress dependency and chronic inflammatory pathway addiction, that later support tumor survival. These environment-derived vulnerabilities may be therapeutically exploitable through redox-modulating agents or anti-inflammatory interventions.

A Triangular Interaction Model of Vulnerability Generation

A key unresolved question is why some risk factors can serve as therapeutic targets whereas others, despite similar epidemiological associations, cannot. The model we propose is a conceptual and mechanistic framework rather than a validated computational model or clinical decision tool. The core principle of this model is that not all risk factors generate targetable vulnerabilities—only those that create persistent, tumor-specific molecular addictions do. For example, oxidative injury due to long-term smoking leads to addiction to the antioxidant machinery, or EBV-induced hyperactivation of NF- κ B results in dependence on inflammatory survival pathways, both of which are potentially targetable. Conversely, exposures that only cause transient damage without establishing lasting molecular reprogramming are unlikely to yield actionable dependencies. The triangular interaction among host genetics, EBV and environment determines the type of specific dependency profile that emerges in each tumor. This framework explains the biological heterogeneity of NPC despite its uniform anatomical diagnosis, and provides a rational basis for moving beyond traditional staging toward etiology-based molecular stratification, where treatment decisions are guided by molecular imprints left by causative exposures.

To illustrate this framework visually, we present a schematic diagram that delineates the causal trajectory from etiological exposures to molecular vulnerabilities and ultimately to therapeutic strategies (Fig. 1).

Molecular Vulnerabilities Created by Oncogenic Drivers

Environmental exposure, EBV infection, and host genetics are the three oncogenic variables. Beyond initiating carcinogenesis, they collectively establish long-lasting molecular dependencies in tumor cells, addictions that offer therapeutic potential.

EBV-Encoded Proteins: Vulnerability and Therapeutic Targeting

EBV latent proteins are specific therapeutic targets, as they are essential to the oncogenic maintenance of NPC. These viral proteins are primarily absent in normal tissues and preferentially produced in tumor cells, providing a favorable therapeutic window, in contrast to many host oncogenic drivers [45]. Among them, the viral nuclear antigen EBNA1 plays a central role in EBV episomal maintenance and replication, which ensures replication and faithful segregation of episomal viral DNA throughout host cell division. This enables persistent viral latency [46], while simultaneously limiting its own antigen processing and presentation to partially evade immune detection.

EBNA1 has become one of the most appealing direct antiviral targets due to its constant expression in almost all EBV-positive NPC [47]. In the first-in-human clinical study of the small-molecule EBNA1 inhibitor VK-2019 in patients with EBV-positive NPC, Colevas et al. [48] demonstrated that VK-2019 altered immune cell biomarkers and reduced EBV genome copy number and viral gene expression in tumor samples, based on integrated pharmacokinetic and pharmacodynamic investigations. These results demonstrate that pharmacologic disruption of EBNA1 may influence the tumor immunological milieu and viral persistence. Targeted protein degradation strategies have been further investigated in recent translational research. Rather than inhibiting disease-relevant proteins, proteolysis-targeting chimeras (PROTACs) recruit endogenous ubiquitin ligases to induce target protein degradation. In humanized mouse models, Liu et al. [49] found that combining anti-PD-1 treatment with the EBNA1-targeting PROTAC degrader EP-1215 restored interferon (IFN) signaling, improved T-cell infiltration, and decreased EBNA1-positive tumors. These findings imply that EBNA1 degradation may enhance immunotherapy sensitivity, reverse immunological suppression, and disrupt viral maintenance.

Other EBV latent membrane proteins are also actionable targets. LMP1, a constitutively active receptor-like protein that activates carcinogenic signaling through the CD40 pathway, has been explored as an immunotherapeu-

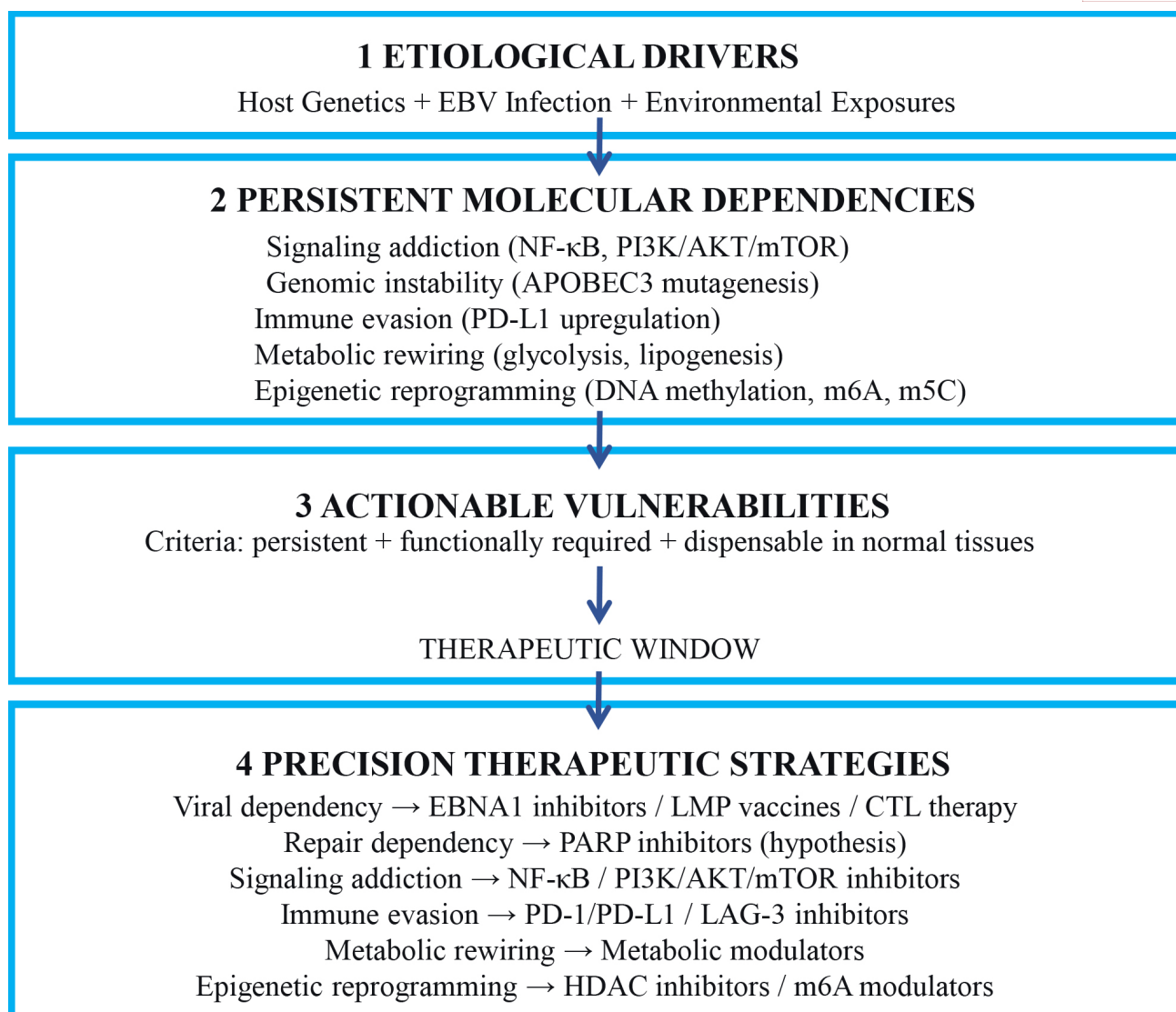


Fig. 1. Etiology-driven molecular vulnerabilities and therapeutic strategies in nasopharyngeal carcinoma. EBV, Epstein-Barr virus; NF-κB, notably nuclear factor kappa B; PI3K/AKT/mTOR, phosphatidylinositol 3-kinase/protein kinase B/mechanistic target of rapamycin; APOBEC3, apolipoprotein B mRNA editing catalytic polypeptide-like 3; m6A, N6-methyladenosine; m5C, 5-methylcytosine; PD-L1, programmed death-ligand 1; EBNA1, Epstein-Barr nuclear antigen 1; LMP, latent membrane protein; CTL, cytotoxic T lymphocyte; PD-1, anti-programmed cell death protein 1; LAG-3, lymphocyte activation gene-3; HDAC, histone deacetylase. Figure created using Microsoft PowerPoint (version 2024; Microsoft Corporation, Redmond, WA, USA).

tic vaccine due to its high immunogenicity. Cytotoxic T cells (CTLs) are CD8 effector T cells that recognize antigenic peptides presented by major histocompatibility complex class I molecules and are directly involved in the destruction of cancerous or infected cells through the release of granzymes and perforin [50]. This rationale is directly translatable to EBV-C. Pan et al. [51] developed a recombinant adeno-associated virus tumor vaccine encoding the epitopes of CTLs, the latent membrane proteins of the EBV, and the fusion heat shock protein gene. This chimeric structure elicits potent cytotoxic lymphocyte activity *in vitro* and mediates tumor elimination in animals of syngeneic species [51]. In addition, Lin et al. [52] demonstrated that the EBV-

LMP1 vaccine inhibited tumor progression and metastases *in vivo* by inducing activated T cells (activated CTLs) and LMP1-specific T cells. LMP2A, which mimics the B-cell receptor signaling and promotes epithelial cell survival, has also emerged as a candidate immunotherapeutic target. Sun et al. [53] reported that the virus Ankara (MVA)-LMP2A vaccine generated high levels of LMP2A-specific CTLs that prevented the occurrence of NPC and exhibited a cytotoxic effect towards target cells. These findings provide a strong biological rationale for the development of CTL-based preventive and therapeutic vaccines.

Importantly, latent viral antigens maintain immunogenicity despite EBV-mediated immune evasion, allowing

dual immune-targeting modalities, such as vaccination platforms, to boost endogenous antiviral immunity and adoptive T-cell transfer; nevertheless, their clinical translation remains challenging. In an international randomized phase III study for recurrent or metastatic NPC, gemcitabine, carboplatin, and EBV-specific autologous CTLs demonstrated a favorable safety profile but failed to improve overall survival compared with chemotherapy alone [54]. Several interconnected mechanisms account for this phenomenon: the highly immunosuppressive NPC microenvironment, characterized by dense infiltration of regulatory T cells and M2-polarized macrophages, EBV-mediated antigen presentation defects, and T-cell exhaustion, all of which limit the efficacy of adoptively transferred CTLs [47,55,56]. Of note, this does not invalidate EBV antigen-targeting strategies; rather, it suggests that single-modality immunotherapy is insufficient and that combination with TME-modulating agents, such as immune checkpoint inhibitors, may be essential to overcome these barriers. Concurrent efforts in vaccine optimization are also underway. A modified MVA-EL recombinant vector with tailored sequences from Chinese EBV strains effectively re-stimulates CD4-positive memory T-cell responses *in vitro* and selectively reactivates LMP2-specific CD8-positive memory T-cell responses, supporting its potential as a therapeutic NPC vaccine [57]. These results show that EBV-encoded proteins play two essential roles: they serve as key factors in the development of NPC while constituting a distinct class of tumor-specific therapeutic targets. Future success requires integrating direct viral targeting, immunological activation, and reversal of microenvironmental repression into cohesive therapeutic approaches.

EBV-Induced Host Collateral Damage as Therapeutic Vulnerabilities

Beyond viral proteins, EBV infection causes significant changes in the stability of the host DNA. Among the most notable examples is the activation of the apolipoprotein B mRNA editing catalytic polypeptide-like 3 (APOBEC3) family of cytidine deaminases [58], which serve as components of the innate antiviral defense. Tumor suppressors and oncogenes in NPC typically have APOBEC-associated mutations, which produce a mutagenic milieu that promotes intratumoral heterogeneity and tumor progression. Crucially, prolonged APOBEC activity induces dependence on specific DNA repair pathways, such as homologous recombination and base excision repair, rather than being a passive bystander event [59]. APOBEC-mediated cytidine deamination primarily generates U:G mismatches, necessitating efficient base excision repair (BER) for genomic integrity. Oxidative stress may further compromise BER capacity, thereby amplifying APOBEC-driven mutagenesis and promoting the accumulation of DNA damage. Moreover, persistent oxidative stress contributes to remodeling of the tumor immune

microenvironment by sustaining chronic inflammatory signaling and immunosuppressive cell polarization, highlighting the functional interplay among genomic instability, redox imbalance, and antitumor immunity [60,61]. This dependency presents a theoretical opportunity for synthetic lethality. Inhibition of PARP plays a role in ovarian cancer models with high APOBEC3B expression [62], though its relevance to NPC remains unknown. While genomic profiling has revealed APOBEC-associated mutational signatures in NPC [63,64], direct evidence linking APOBEC burden to PARP inhibitor sensitivity in NPC is currently lacking. Therefore, APOBEC-driven mutagenesis should be viewed as a mechanistic hypothesis, warranting dedicated investigation using NPC-specific models.

Signaling Network Reprogramming and Druggable Nodes

The extensive signaling network rewiring that characterizes NPC is orchestrated by EBV latent proteins, persistent inflammation, and reciprocal crosstalk within the tumor microenvironment. This not only promotes tumor progression but also creates stable pro-survival pathways that are promising therapeutic targets. Activation of the NF- κ B pathway is one of the most consistent molecular aberrations in NPC. As well-known upstream activators of NF- κ B signaling, EBV-encoded proteins, especially LMP1, cause the persistent transcription of genes related to angiogenesis, proliferation, inflammation, and resistance to apoptosis [65]. NF- κ B signaling modifies tumor stroma in addition to tumor cells. According to recent research, tumor vascular endothelial cells enhance immune escape in NPC by activating the NF- κ B pathway and upregulating programmed death-ligand 1 (PD-L1) [66]. These findings reveal that NF- κ B signaling plays a role in both extrinsic immunosuppressive remodeling and intrinsic tumor survival. Loss of endogenous negative regulators, comprising NF-kappa-B inhibitor alpha (NFKBIA), cylindromatosis (CYLD), and tumor necrosis factor alpha-induced protein 3 (TNFAIP3), promotes aberrant NF- κ B activation [63,67]. Anti-apoptotic and pro-inflammatory gene transcription is maintained, prolonging pathway activity when these regulatory factors are silenced, mutated, or repressed. As a result, NPC cells become dependent on NF- κ B signaling for tumor maintenance while gaining a selective survival advantage. This pathway addiction provides a strong rationale for NF- κ B-directed therapeutic intervention.

The PI3K/AKT/mechanistic target of rapamycin (mTOR) axis is another significant carcinogenic change in NPC, with aberrant activation accelerating cell cycle progression, protein synthesis, and metabolic reprogramming, ultimately contributing to therapy resistance. PI3K/AKT/mTOR signaling in NPC is controlled by both microenvironmental crosstalk and tumor-intrinsic pathways. For instance, interactions between complement C1q-positive macrophages and tumor cells promote car-

cinogenesis by inducing DNA hypermethylation via the PI3K/AKT pathway [68], thereby linking signal transmission, immunological infiltration, and epigenetic modification within a single carcinogenic mechanism. Additional regulators of this pathway have also been identified. For instance, knockdown of transferrin receptor 1 (TFRC) inhibits NPC progression by downregulating PI3K/AKT/mTOR signaling [69]. These results imply that both canonical kinase inhibitors and upstream modulators may have therapeutic benefit and reinforce the crucial role of this pathway in sustaining malignant phenotypes. The PI3K/AKT/mTOR pathway thus represents a host-derived vulnerability that supports tumor growth and therapy resistance; its inhibition by mTOR or PI3K inhibitors offers a potential therapeutic approach, although clinical efficacy may depend on pathway activation status and combination strategies.

Oncogenic signaling networks are stabilized by epigenetic reprogramming. Numerous epigenetic aberrations are present in NPC cells, including pronounced DNA methylation changes, disrupted histone modifications, and altered N6-methyladenosine (m6A) RNA methylation [70]. These epigenetic modifications modulate gene expression programs associated with immune evasion, epithelial plasticity and stress response, and critically, the reversibility of epigenetic regulators renders them attractive therapeutic targets.

Metabolic-Epigenetic-Immune Crosstalk Networks

The EBV-associated NPC is characterized by the reprogramming of immune signaling, metabolism and epigenetic regulation in a coordinated manner. These processes do not operate independently but rather through dynamic interactions that collectively support tumor growth, cell survival, and immune evasion. Central to this metabolic rewiring is the Warburg effect, characterized by a shift toward aerobic glycolysis [71], which enhances ATP synthesis, biosynthesis, and hypoxia resistance, all conducive to aggressive tumor growth. This metabolic reprogramming is directly induced by some EBV-encoded products. Latent LMP1 activates the FGFR1 pathway in epithelial cells of the nasopharynx [72], promoting aerobic glycolysis and malignant transformation. In addition, EBV-miR-BART1-5p stimulates glycolysis and angiogenesis in NPC simultaneously via phosphatase and tensin homolog (PTEN)-independent activation of adenosine monophosphate-activated protein kinase/mechanistic target of rapamycin/hypoxia-inducible factor 1 (AMPK/mTOR/HIF1) [73]. These findings indicate that the virus may utilize either coding or non-coding proteins to alter the host metabolism. A strong connection exists between lipid production and the metabolic reprogramming induced by EBV. Sterol regulatory element-binding protein 1 (SREBP1)-mediated lipogenesis is activated by LMP1 [74], which boosts NPC cell proliferation and tumor growth. Glycolytic

reprogramming and lipid accumulation facilitate membrane biogenesis, signaling mediator production, and energy storage. All these observations imply that the EBV coordinates an overall anabolic activity instead of having separate effects on metabolism.

The tumor immune microenvironment is further shaped by metabolic rewiring. Elevated glycolytic flux leads to lactate accumulation, extracellular acidification and competition for nutrients, including glucose and amino acids, all of which induce T-cell exhaustion, suppress cytokine secretion and impair the function of CTLs. As a result, the tumor microenvironment becomes immunologically “cold” or functionally inactive, which reduces immunotherapy response and limits the effectiveness of immune surveillance.

Another crucial aspect of this network is epigenetic regulation. EBV encodes several regulatory RNAs that modify host gene expression programs. In NPC, BamHI-A rightward transcripts (BART) long non-coding RNAs (lncRNAs) have been implicated in aberrant host gene regulation [75], facilitating tumor immune evasion and promoting tumor progression through post-transcriptional and epigenetic modulators. Emerging evidence has also underscored the involvement of RNA epigenetics in EBV-associated NPC. EBV facilitates immune evasion by suppressing Toll-like receptor 9 (TLR9) through altered m6A modification [76]. Additionally, EBV promotes NPC metastasis by introducing 5-methylcytosine (m5C) to intercellular adhesion molecule 1 (ICAM1) RNA through NOP2/Sun RNA methyltransferase 2 (NSUN2) and Y-box binding protein 3 (YBX3) [77]. These results show that EBV may regulate innate immunity, cell adhesion, and metastatic spread via RNA methylation machinery. Additionally, host-derived adipokines such as adiponectin and resistin have also been implicated in NPC progression through modulation of AMPK, NF- κ B, and MAPK signaling pathways [78,79].

More generally, chromatin and transcriptional regulation are linked to nutritional availability through metabolic-epigenetic interplay. Important epigenetic processes are controlled by cellular metabolites incorporating α -ketoglutarate, S-adenosylmethionine, and acetyl-coenzyme A [80], which directly affect DNA methylation, demethylation, and histone acetylation. Thus, EBV-driven metabolic alterations may indirectly reshape the epigenetic landscape, resulting in persistent transcriptional programs that promote immunological tolerance and survival. This integrated network explains how EBV infection, host signaling, and environmental stress converge to sustain tumor persistence. Therefore, NPC is not driven by isolated molecular defects, but by a coordinated system of immune suppression, metabolic rewiring, viral dependence, and epigenetic plasticity, offering multiple therapeutic entry sites, such as immunological microenvironment reprogramming, lipid

metabolism targeting, glycolysis suppression, and epigenetic treatment.

Several metabolism- and epigenetic-targeted agents have been clinically investigated in NPC. mTOR inhibitors have been evaluated but yielded modest responses [81]. HDAC inhibitors exhibit synergistic effects with PD-1 blockade in preclinical NPC models [82]. IDO inhibitors have been explored in combination with ICIs, though their role in NPC requires further validation. From an etiology-driven perspective, EBV-induced metabolic reprogramming (glycolysis via LMP1-FGFR1 [72]; lipogenesis via LMP1-SREBP1 [74]) represents virus-specific vulnerabilities, whereas mTOR and HDAC inhibitors target host pathways with broader applicability. Distinguishing these categories reinforces the etiological framework and provides a rational basis for combination strategies.

Harnessing Molecular Vulnerabilities: From Targeted Therapy to Immunotherapy

Therapeutic development has evolved in parallel with the elucidation of etiological and genetic vulnerabilities in NPC, shifting from empirical therapy selection to host genetic instability, virus-driven dependencies, and immune evasion mechanisms.

Targeting Host Genomic Vulnerabilities

Host-derived molecular vulnerabilities present more therapeutic entry sites. One of the most relevant activities is mutagenesis of APOBEC3 enzymes, which induces DNA damage, genomic instability, and replication stress, thereby enhancing dependency on DNA repair mechanisms. Although this concept has not yet been clinically validated in NPC, emerging evidence from other tumors demonstrates that APOBEC3B-high tumors have elevated levels of replication stress and may be preferentially sensitive to PARP inhibitors [62]. The EGFR pathway represents another host-targeted strategy. Monoclonal antibodies such as cetuximab have been employed to determine inhibition of EGFR, as EGFR is overexpressed in NPC [83]. Nevertheless, primary and acquired resistance, due to compensatory signaling activation and route redundancy, limits long-term efficacy, and clinical outcomes remain low and often short-lived. Recent advances in antibody-drug conjugates (ADCs) have revitalized this medicinal route. Phase III studies of dual-targeting ADCs produce promising results, including EGFR×HER3-directed agents [84]. These bispecific strategies are designed to mitigate antigen heterogeneity and improve tumor selectivity.

Immune Checkpoint Inhibitors: Clinical Progress and Biological Basis

Immune checkpoint blockade has emerged as a pivotal therapeutic strategy in NPC. EBV-associated malignancies frequently exhibit upregulation of the PD-1/PD-L1 axis

via a multitude of mechanisms, including viral latent gene expression, inflammatory signaling, and epigenetic regulation. PD-L1 transcriptional induction is predominantly driven by LMP1-mediated activation of NF- κ B signaling [66]. Large-scale studies have solidified the clinical evidence for ICIs. The JUPITER-02 study demonstrated significant survival benefits with PD-1 inhibition in recurrent or metastatic NPC, which made PD-1 inhibition the backbone of standard therapy, establishing PD-1 blockade as the standard-of-care backbone, with durable responses and a manageable safety profile [85]. Emerging strategies include dual blockade of PD-1 and lymphocyte activation gene-3 (LAG-3). Phase Ib/II trials combining toripalimab with LBL-007 have shown manageable safety and promising antitumor activity in advanced solid tumors, particularly in cold tumors [86]. A major unresolved question is why EBV-positive NPC is more sensitive to ICIs. One hypothesis posits that the production of viral antigens amplifies interferon signaling and basal immune recognition; alternatively, EBV may directly induce PD-L1 expression via the interferon regulatory factor and NF- κ B pathways. These mechanisms are not mutually exclusive. Interestingly, these models may predict patterns of immune infiltration, cytokine profiles, and treatment-responsive biomarkers.

Immunotherapy-Based Combination Strategies

Immunotherapy is used in conjunction with conventional and cutting-edge therapies to enhance treatment effectiveness. A notable advance is the combination of immunotherapy with reduced-intensity chemotherapy. The Sun Yat-sen University group's clinical research has shown that combining modified cisplatin-based chemotherapy with PD-1 inhibition can increase response rates while preserving tolerability [87]. Combinations based on radiotherapy are also undergoing refinement. By improving antigen presentation and driving immune cell infiltration, low-dose radiation treatment has been suggested to alter the tumor microenvironment [88], thereby converting cold tumors into hot tumors and increasing tumor susceptibility to immune checkpoint blockade. EBV-targeted mRNA vaccine systems are also in the early phases of development, with therapeutic vaccines encoding EBV latent antigens designed to elicit robust T-cell responses against tumor-specific viral epitopes [89]. Studies in animal models have revealed feasibility [90,91], although long-term efficacy and durability remain to be established. These combination strategies recognize that the therapeutic vulnerabilities in NPC are multifaceted: radiotherapy enhances antigen presentation, chemotherapy reduces immunosuppressive burden, and mRNA vaccines boost EBV-specific T-cell immunity.

Resistance Mechanisms and Strategies to Overcome Them

Resistance is still a significant clinical problem despite advancements in treatment. Primary resistance to immune checkpoint inhibitors is frequently associated with infiltration by immunosuppressive myeloid cells, a non-inflammatory tumor microenvironment, and impaired antigen presentation. Acquired resistance may arise from loss of tumor antigen expression, activation of alternative immune checkpoints, or T-cell exhaustion. EBV also actively contributes to immune evasion [56]. By reducing the processing and presentation of antigens, EBNA1 demonstrates a “molecular stealth” approach, thereby diminishing CTL recognition and promoting immune tolerance. Viral mRNAs reinforce an immunosuppressive niche by further suppressing immunological signaling pathways. Resistance to targeted therapies, particularly EGFR inhibition, is driven by compensatory activation of parallel signaling pathways, such as PI3K/AKT and MAPK cascades [92,93,94], in addition to receptor heterogeneity and epigenetic reprogramming. Collectively, these resistance mechanisms reflect the remarkable adaptability of NPC. Multi-layered approaches that concurrently target viral dependencies, host vulnerabilities, and mechanisms of immune escape are likely required to achieve effective therapy. This adaptive resistance landscape highlights that the molecular vulnerabilities of NPC are not static; successful precision therapy must anticipate and counteract acquired dependencies through rational combination and sequential strategies targeting both EBV-driven and host-adaptive pathways.

An Integrated Roadmap: From Etiology to Precision Medicine

The growing recognition of NPC as an etiologically driven malignancy has catalyzed a conceptual shift from descriptive risk categorization to mechanism-based precision oncology. An integrative treatment roadmap may be developed by connecting persistent molecular dependencies to extrinsic carcinogenic influences.

An Evidence-Based Decision Framework for Etiology-Driven Therapy

As an organized framework for making decisions, we suggest an etiology-driven therapy approach (Fig. 2). The main idea is that downstream therapeutic vulnerabilities, intermediate molecular subtypes, and upstream risk exposure profiles should all be taken into consideration for therapeutic selection. This approach follows a decision-tree-like process: it first establishes the spectrum of risk factors, which includes genetic susceptibility, environmental exposure, and EBV infection status; it then converts these baseline inputs into molecular subtypes that are defined by immune infiltration status, metabolic phenotypes, viral dependency patterns, and epigenetic profiles; and it subsequently

connects these stratified subtypes to immune-based or targeted therapeutic approaches. For instance, combining immune checkpoint inhibition and microenvironment remodeling may be more beneficial for EBV-high tumors with immune-excluded microenvironments. Tumors exhibiting strong genomic instability profiles may be more appropriate for DNA damage response-targeted techniques. Despite its simplicity, this framework offers a logical model for incorporating diverse clinical and biochemical data into individualized treatment decisions.

Progress in Personalized Therapy Based on Molecular Subtyping

The personalized treatment of NPC is determined by its molecular classification. Metabolic classifiers are an example of such a strategy [95]: tumor metabolism can be stratified into distinct subtypes, most notably oxidative phosphorylation or glycolysis [96], which may differentially influence immunotherapy response. The tumor microenvironment (TME) categorization offers another important dimension. NPC immunological phenotypes have been identified as Type D (immune-desert tumors) and Type A (immune-inflamed tumors) [97]. Retrospective analyses suggest that Type A cancers respond better to immune checkpoint drugs than Type D, because they tend to infiltrate more T-cells. For Type D malignancies, which present stromal barriers and immune exclusion, non-coding RNA-based diagnostic methods may be applicable; additionally, combination therapies with enhanced antigen presentation or recruitment of immune cells hold great therapeutic potential [98,99]. LncRNAs, miRNAs and circular RNAs (circRNAs) regulate EBV–host interactions, immune evasion, and metabolic adaptation. Non-coding RNA signatures may serve both as indicators of therapeutic vulnerability and as diagnostic markers. Collectively, these molecular subtyping strategies remain exploratory at present, and prospective validation is required to establish their utility in guiding treatment decisions. A summary of molecular subtypes, their biomarkers, recommended therapies, quantitative evidence, evidence levels, and supporting clinical trials is provided in **Supplementary Table 1**.

The Continuum of Prevention, Screening, and Treatment

A comprehensive approach to NPC management should integrate prevention, early detection, and treatment across a temporal continuum.

Primary prevention refers to reducing exposure and preventing infection. A major translational priority is the development of vaccines to prevent EBV infection. Prophylactic and therapeutic vaccination systems targeting EBV latent antigens are under active investigation; however, no licensed EBV vaccine is available, and evidence of strong T-cell immunity to EBV is preliminary [89,100]. In terms of public health, such strategies hold potential to sig-

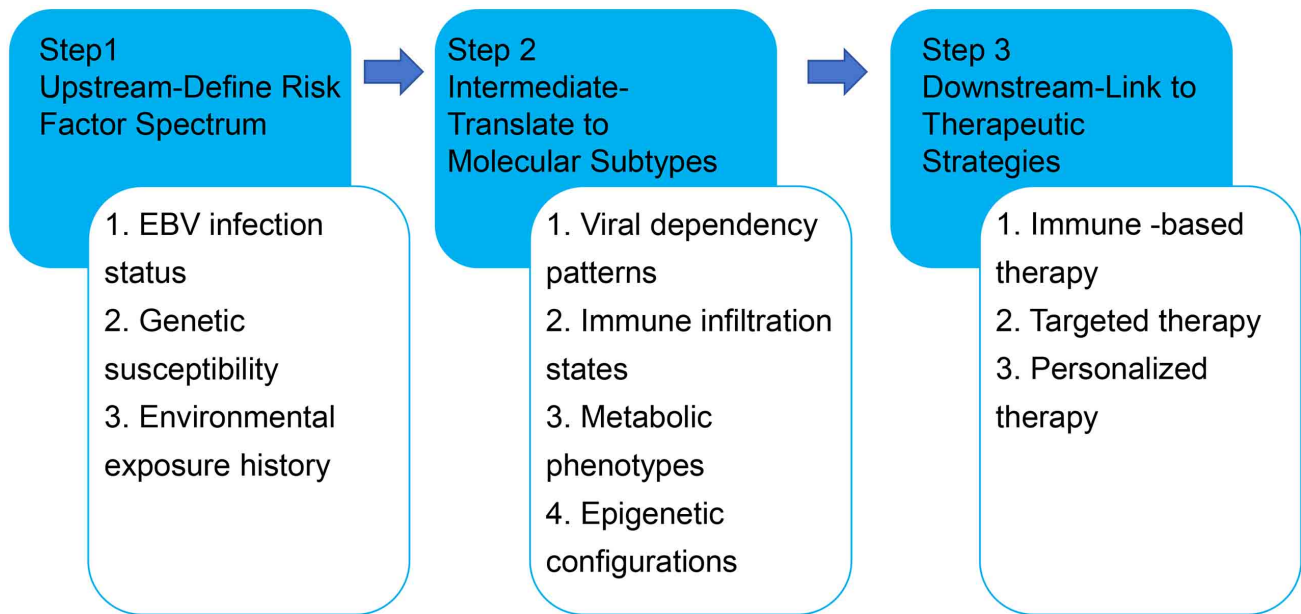


Fig. 2. Schematic framework of the etiology-driven therapeutic strategy. Figure created using Microsoft PowerPoint (version 2024; Microsoft Corporation, Redmond, WA, USA).

nificantly reduce NPC incidence in endemic regions. Environmental prevention also remains critical. Epidemiological studies have consistently shown that salted fish, preserved food, and tobacco exposure are associated with increased NPC risk [101]. Reducing these exposures may help prevent the acquisition of molecular dependencies, although stable viral and epigenetic changes may not reverse once malignant transformation has occurred.

Secondary prevention refers to early detection and screening. Circulating EBV DNA has been established as a major biomarker for NPC screening and monitoring. Emerging non-coding RNA-based methods (lncRNAs, miRNAs, circRNAs) also hold promise as biomarkers for early detection [98,99].

Tertiary prevention refers to treatment and resistance management. For patients with established NPC, treatment should be guided by molecular subtyping and therapeutic vulnerabilities. The distinction between reversible metabolic/inflammatory pathways and irreversible genetic/epigenetic alterations has important implications for treatment timing and combination strategies.

Challenges and Future Directions

Effective molecular subtyping of NPC necessitates a combination of genomic, transcriptomic, epigenomic, proteomic and microbiome data, a challenge for which machine learning and artificial intelligence can offer an effective solution through pattern recognition and predictive modeling. Although multi-omics data integration remains a substantial hurdle [102], these innovative approaches may reveal dependencies that are undetectable by single-layer studies. A further major impediment is the paucity of re-

liable NPC-specific experimental models. The complexity of EBV latency, immune microenvironmental interactions, and genetic heterogeneity of host cells are often poorly represented in current cell lines and xenografts, thereby limiting translational relevance and constraining functional validation of emerging targets. Therefore, the development of more physiologically accurate models, including patient-derived organoids and humanized mice, is an urgent priority. Overall, NPC exemplifies an etiology-driven cancer in which internal molecular factors are closely linked to external causal factors. Further progress will require integrating clinical oncology, molecular biology, and epidemiology to translate mechanistic discoveries into practical, individualized treatment strategies.

Conclusion

The triangular model of NPC comprises environmental exposure, host susceptibility and EBV infection, explaining the epidemiological features of NPC and revealing vulnerabilities for systemic treatment. Each component confers distinct biological vulnerabilities amenable to therapeutic targeting. These represent core oncogenic and immune-evasive events mediated by EBV proteins (EBNA1, LMP1, and LMP2A). Host-driven processes such as APOBEC3 mutagenesis lead to genomic instability and potential DNA repair needs. Meanwhile, viral stress response and cellular stress response are incorporated into the survival mechanisms of the organism through signaling pathways, such as NF- κ B. All these elements converge into an interdependent, cascading intervention framework that integrates molecular dependencies with etiological factors. This approach facilitates the transition from conven-

tional TNM staging to etiology-based molecular stratification, whereby treatment selection depends not on the morphological classification but on the biological effects of risk exposures.

Availability of Data and Materials

Not applicable.

Author Contributions

XFZ is the sole contributor to this manuscript. The author confirms sole responsibility for the conception and design of the study; the acquisition, analysis, and interpretation of data; the preparation of the manuscript; and for being accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.24976/Discover.Med.202638213.241>.

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