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Review

Targeting the Tumour Microenvironment in Nasopharyngeal Carcinoma: Therapeutic Advances and Challenges

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Abstract

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy of the nasopharynx, characterised by a distinct regional and racial prevalence and a strong association with Epstein-Barr virus (EBV) infection. EBV is not only the primary aetiological agent of NPC but also a key driver of its unique immunosuppressive tumour microenvironment (TME). Although most patients with early-stage disease can be cured by radiotherapy, factors such as recurrence and/or metastasis, late diagnosis, and drug resistance remain the principal barriers to effective treatment. The TME constitutes a dynamic, multicellular ecosystem that critically regulates tumour progression, and has therefore emerged as a promising therapeutic target. In this review, we summarise current research on the TME of NPC, with particular emphasis on EBV-driven remodelling mechanisms, discuss the translational potential of various TME-targeted strategies, and highlight the key challenges that remain to be addressed in clinical translation. We aim to provide a comprehensive overview and valuable insights for future investigation.

Keywords: nasopharyngeal neoplasms; tumour microenvironment; targeted therapy

1. Introduction

Nasopharyngeal carcinoma (NPC) is an epithelial tumour that arises from the nasopharyngeal mucosal lining, typically originating in the pharyngeal recess[1]. According to data from the International Agency for Research on Cancer (IARC), NPC exhibits an overall low global incidence, accounting for approximately 0.6% of all cancer diagnoses in 2024[2]. However, it displays a strikingly skewed geographical distribution, with more than 70% of newly diagnosed cases concentrated in East and Southeast Asia. This unique epidemiological pattern is principally associated with genetic susceptibility, environmental exposures, and Epstein-Barr virus (EBV) infection[3]. Indeed, primary EBV infection is intimately linked to the pathogenesis of NPC, and the vast majority of non-keratinizing NPC cases in endemic regions are EBV-associated[4].

Biologically, NPC diverges from most other epithelial carcinomas due to this pervasive EBV involvement. The persistent co-existence of EBV-infected malignant epithelial cells and dense infiltrates of host immune elements establishes a unique, highly heterogeneous, and profoundly immunosuppressive tumour microenvironment (TME) that facilitates immune evasion and promotes oncogenesis[5]. During this EBV-driven TME remodelling, multiple molecular and cellular mechanisms act synergistically. Single-cell transcriptomic profiling has revealed that a subset of malignant cells in EBV-positive NPC co-express epithelial and immune-related genes; this phenotypic hallmark correlates positively with the expression of co-inhibitory receptors on $CD8^+$ tumour-infiltrating lymphocytes (TILs) and impairs interferon-gamma (IFN-γ) production, directly evidencing

tumour-intrinsic immunosuppressive capacity[6]. Beyond latent viral programs, the EBV lytic cycle also contributes substantially to disease progression. The EBV-encoded transcriptional activator Zta recruits circulating monocytes and drives their differentiation toward a tumour-associated macrophage (TAM)-like phenotype, thereby reinforcing the supportive niche[7]. At a systemic level, EBV coordinates immune evasion through multifaceted programs, including viral antigen silencing, compensatory checkpoint induction, exosomal non-coding RNA-mediated remote immunosuppression, cytotoxic T-cell exhaustion, metabolic reprogramming, and the erection of dense stromal physical barriers. These multi-layered programs constitute the biological foundation for both primary and acquired resistance to immune checkpoint blockade (ICB)[8]. For instance, anti-programmed cell death protein-1 (PD-1) monotherapy demonstrates only modest clinical efficacy in patients harboring high baseline plasma EBV DNA copy numbers[9]. Consequently, EBV acts not merely as the primary etiological trigger of NPC, but also as the central architect of its distinctive TME.

The TME is now recognized as a dynamic, co-evolving ecological system where reciprocal crosstalk between neoplastic cells and surrounding stromal constituents fundamentally governs tumour proliferation, treatment resistance, neovascularization, and immune surveillance escape[10, 11]. Because of this profound lymphocytic infiltration and virus-driven stromal plasticity, the TME provides an exceptionally rich, actionable landscape for targeted intervention[12].

In this review, we comprehensively summarize contemporary insights into the TME of NPC, dissect the molecular networks underlying EBV-driven microenvironmental remodeling, evaluate the translational efficacy and clinical limitations of emerging TME-targeted modalities, and outline critical challenges that must be surmounted to improve outcomes in patients with advanced disease.

2. Treatment strategies targeting TME

2.1 Tumour-infiltrating immune cells

Aberrant immune cell infiltration is one of the most prominent biological hallmarks of NPC, actively supporting continuous tumour proliferation and progression[13]. Tumour-infiltrating immune cells comprise diverse lineages, including T lymphocytes, B lymphocytes, macrophages, dendritic cells (DCs), and myeloid-derived suppressor cells (MDSCs). Driven by the chronic infiltration of dysfunctional and exhausted $CD8^+$ T lymphocytes and impaired effector T cells, the prominent upregulation of suppressive inhibitory immune checkpoint pathways—most notably PD-1 and its cognate ligand, programmed death-ligand 1 (PD-L1)—enables NPC cells to efficiently evade host immunosurveillance[14]. Consequently, in light of this immunosuppressive milieu and its pervasive aetiological link to EBV, immunotherapeutic modalities targeting immune cells in the TME have emerged as primary translational priorities in NPC[15].

2.1.1 T lymphocytes

The pronounced immunosuppression within the NPC microenvironment renders immunotherapy an imperative rather than an alternative option, making the reinvigoration of intratumoural cytotoxic T-cell responses a principal therapeutic objective. Owing to EBV-driven oncogenic reprogramming, NPC cells constitutively overexpress PD-L1. Upon receptor engagement, PD-1/PD-L1 signalling dampens cytotoxic T-cell activity, establishing a clear mechanistic rationale for checkpoint blockade[16, 17]. Multiple therapeutic monoclonal antibodies—including pembrolizumab, nivolumab, camrelizumab, spartalizumab, tislelizumab, toripalimab, and atezolizumab—have been clinically evaluated, yielding objective response rates (ORRs) ranging from 13% to 43% as monotherapies[18]. Combining checkpoint inhibitors with systemic chemotherapy or radiotherapy substantially amplifies objective antitumour efficacy. For example, camrelizumab combined with gemcitabine and cisplatin achieved an ORR of up to 91% in recurrent or metastatic disease[19], and toripalimab plus chemotherapy reduced the risk of death by 37% relative to gemcitabine–cisplatin alone in the randomized phase 3 JUPITER-02 trial, thereby demonstrating definitive overall survival advantages[20]. More recently, landmark phase 3 trials—specifically the CONTINUUM and DIPPER trials—have successfully expanded PD-1 blockade from recurrent or metastatic settings into the curative-intent management of high-risk locoregionally advanced NPC, demonstrating that integrating sintilimab into chemoradiotherapy or administering adjuvant camrelizumab significantly improves event-free survival[21, 22] (Table 1).

Nevertheless, the broad heterogeneity in monotherapy responses (13%–43%), alongside primary and acquired resistance, continues to limit the long-term clinical benefit of immune checkpoint blockade, underscoring the urgent need for innovative combination regimens. Beyond variations in baseline plasma EBV DNA copy numbers and trial eligibility criteria, this clinical divergence is governed by distinct microenvironmental resistance programs. Primary resistance is predominantly driven by minimal

tumour PD-L1 expression, defective human leukocyte antigen (HLA) antigen presentation, and an immune-desert or "cold" TME characterised by sparse cytotoxic lymphocytic infiltration or the physical exclusion of effector cells by dense stroma[23]. Acquired resistance, conversely, typically entails the compensatory upregulation of alternative co-inhibitory checkpoints, such as T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and lymphocyte-activation gene 3 (LAG-3). In the context of NPC, EBV infection further complicates the resistance landscape. EBV-encoded latent proteins, along with their non-coding RNAs, inflammatory cytokines, hypoxia-inducible factors, oncogenic signalling pathways, and transcription factors, converge to regulate PD-L1 transcription in NPC. For instance, EBV-encoded proteins such as LMP1 can enhance PD-L1 expression either directly or via exosomal secretion, thereby reinforcing immunosuppressive signalling[24]. Because these multilayered circuits render PD-L1 a dynamic rather than a static biomarker, directly targeting EBV-encoded latent antigens—particularly the latent membrane proteins—has emerged as a compelling strategy to overcome resistance and restore antitumour immunity[25]. Targeting EBV latent membrane protein 2 (LMP2) provides a viable approach to counter T-cell exhaustion. Recently, an ionizable lipid nanoparticle (LNP) was developed to deliver LMP2-mRNA to tumour-draining lymph nodes, effectively activating cytotoxic $CD8^+$ T lymphocytes[26, 27]. This formulation promoted memory T-cell expansion and reversed $CD8^+$ T-cell exhaustion by downregulating inhibitory co-receptors, demonstrating synergistic antitumour efficacy when combined with anti–PD-1 therapy in preclinical models[27]. However, clinical-grade scalability, targeted delivery efficiency, and systemic stability warrant further prospective investigation.

Chimeric antigen receptor T-cell (CAR-T) therapy represents another promising avenue. In this approach, autologous T lymphocytes are isolated from the patient, genetically engineered to express target-specific chimeric antigen receptors (CARs), expanded *ex vivo*, and reinfused to specifically mediate targeted cytolysis[28]. While targeting the EBV lytic glycoprotein gp350 showed preclinical efficacy in xenograft models[29], and early clinical trials targeting LMP1 have demonstrated tolerable safety profiles, broad clinical efficacy in solid NPC lesions remains constrained. Key translational barriers include dense stromal physical barriers that impede T-cell infiltration, a highly immunosuppressive milieu that precipitates rapid CAR-T exhaustion, and the risk of on-target off-tumour toxicities. To overcome these hurdles, recent preclinical strategies have developed TCR-like CAR-T cells equipped with inducible IL-18 release (TRUCKs) targeting LMP2A peptides to amplify cytotoxicity and bystander immune recruitment[30], alongside CRISPR-, base-, and prime-editing approaches to resist T-cell exhaustion[31]. However, both strategies remain at the preclinical stage, constrained by HLA restriction, lack of validation in solid NPC models, and potential genome-editing genotoxicity or chromosomal rearrangements.

Complementary therapeutic strategies focus on enhancing endogenous antigen presentation and depleting suppressive subsets. For instance, a clinical study utilized EBV LMP2-derived epitope peptides to pulse autologous dendritic cells as a therapeutic DC vaccine. Following ultrasound-guided intranodal injection into inguinal lymph nodes, epitope-specific $CD8^+$ cytotoxic T lymphocyte (CTL) responses were elicited or boosted in five of nine fully evaluable patients with advanced NPC, with detectable *ex vivo* cytotoxicity against target cells[32]. Pharmacologically, sorafenib promotes major histocompatibility complex class I (MHC-I) antigen presentation by downregulating the cystine/glutamate antiporter SLC7A11, thereby enhancing T-cell-mediated cytotoxicity against NPC cells *in vivo*[33] (Table 2). Additionally, disrupting the CD70–CD27 axis impairs the metabolic fitness and suppressive activity of regulatory T cells, acting synergistically with anti-PD-1 blockade *in vivo*[34]. These findings highlight the therapeutic rationale of combining checkpoint inhibitors with antigen-restoring or Treg-depleting agents.

2.1.2 Natural killer cells

Natural killer (NK) cells are innate cytotoxic lymphocytes with an innate ability to lyse tumour cells without the need for prior antigenic sensitization, playing a fundamental role in tumour immunosurveillance[35]. Research has demonstrated that EBV-infected B cells are more susceptible to NK-mediated lysis during the lytic phase than during the latent phase. In NPC, however, NK cell function is frequently impaired by the immunosuppressive TME. For instance, EBV-encoded proteins and the upregulation of co-inhibitory ligands such as B7-H3 may counteract NK-mediated lysis during both late lytic and latent phases[36, 37]. This interplay constitutes a critical axis in NK-mediated tumour control.

Interferon-beta (IFN-β) upregulates tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) expression on NK cells, increases their cytotoxicity against NPC cells *in vitro*, and induces soluble TRAIL (sTRAIL) secretion, thereby

eliminating micrometastatic disease[38, 39]. Therapeutic strategies aimed at enhancing NK cell function can act synergistically with anti-PD-1 therapy to improve efficacy. Specifically, PD-1 blockade in IFN-β-activated NK cells promotes sTRAIL secretion, enabling effective lysis of TRAIL-sensitive NPC cells[40]. In addition, polyinosinic-polycytidylic acid (poly-IC), a toll-like receptor 3 (TLR3) agonist, has been demonstrated to augment the efficacy of cetuximab-based immunotherapy by increasing NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) and facilitating cross-talk between NK cells and dendritic cells[41]. Beyond canonical biological agents, exploratory preclinical studies have also investigated traditional Chinese medicine (TCM) formulations as complementary immunomodulators; for instance, in rodent models, the herbal formula Fuyuan Decoction was reported to increase peripheral NK cell counts and mitigate metastasis[42] (Table 2). However, translating NK cell-based therapies into solid NPC lesions remains hampered by EBV-induced suppressive ligands, poor tumour homing, and rapid functional exhaustion within the stroma, while clinical validation for herbal formulations remains absent[43]. Future research should prioritise overcoming these obstacles to fully realise the therapeutic potential of NK cells in NPC.

2.1.3 Macrophages

Macrophages, referred to as TAMs within the tumour microenvironment, participate in both innate and adaptive immune responses and exhibit notable phenotypic plasticity and heterogeneity[44]. In murine models, TAMs facilitate tumour progression through diverse mechanisms. Therefore, therapeutic strategies that either deplete TAMs or reprogram their phenotype are under active investigation[45]. At the preclinical discovery stage, natural immunomodulatory macromolecules have been explored for this purpose; for instance, Sargassum fusiforme polysaccharides (SFPS) were shown in murine models to stimulate peritoneal macrophages to secrete pro-inflammatory cytokines, upregulate IgM expression, and elicit antitumour effects[46].

The heterogeneity of TAMs enables their polarisation into distinct phenotypes under different stimuli. M1 macrophages are pro-inflammatory and tumour-inhibiting, whereas M2 macrophages are anti-inflammatory and tumour-promoting. Given that M2-polarized macrophages predominate within the TAM population, modulating intracellular signalling to reorient TAM polarisation toward an M1-like immunostimulatory phenotype is essential in immunotherapy[47]. In a recent study, the selective BCL-2 inhibitor APG-2575 was used to polarize M2-like immunosuppressive macrophages toward an M1-like immunostimulatory phenotype, remodeling the tumour immune microenvironment and improving T-cell immunity[48]. These findings indicate the potential for combination with immunotherapy. Additional studies have also identified new therapeutic directions by targeting M1 macrophage polarization. Ubiquitin-specific processing protease 7 (USP7) deubiquitinated tripartite motif-containing 24 (TRIM24) to stabilize TRIM24 expression and increased short palate, lung and nasal epithelium clone 1 (SPLUNC1) expression by upregulating STAT3, reprogramming macrophages to M1 phenotype[49] (Table 2).

Substantial obstacles persist in targeting TAMs[50]. Single-cell profiling highlights pronounced TAM heterogeneity in NPC, encompassing distinct pro-angiogenic and immunosuppressive subsets. Consequently, non-selective TAM depletion strategies risk systemic toxicities and opportunistic infections, while clinical trials evaluating TAM-reprogramming agents in NPC remain scarce, necessitating subset-specific biomarkers for precise intervention.

2.1.4 Other Immune Cells

Beyond T lymphocytes, NK cells, and TAMs, other immune cell populations—including B lymphocytes, DCs, and MDSCs—also contribute significantly to the immunosuppressive architecture of the NPC microenvironment. Among these, dendritic cells and B lymphocytes account for approximately 7% and 40% of the infiltrating immune population in NPC, respectively, revealing a cellular composition that is markedly distinct from other head and neck cancers and highlighting the cellular heterogeneity of the TME of NPC[51]. Tumour-infiltrating B cells (TIBs) frequently aggregate to form tertiary lymphoid structures (TLS), which serve as local hubs for anti-tumour humoral immunity and correlate with favorable prognoses and enhanced responsiveness to immune checkpoint blockade. Conversely, regulatory B cells within the NPC niche can secrete immunosuppressive cytokines such as IL-10 and TGF-β, promoting $CD8^+$ T-cell exhaustion and collaborating with regulatory T cells[52].

Dendritic cells—the primary professional antigen-presenting cells—are often functionally impaired in EBV-driven NPC. Latent membrane proteins (such as LMP1) locally expressed or secreted via exosomes can downregulate co-stimulatory molecules on DCs, disrupting effective cross-presentation to naïve T cells and dampening primary anti-tumour immunity[53].

Concurrently, MDSCs are massively recruited into the NPC stroma via chemokine axes, where they

act as potent immunosuppressors. MDSCs impair effector T-cell proliferation through the high-level production of arginase-1 (Arg-1), inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS), while concurrently establishing a positive feedback loop that expands immunosuppressive Tregs, impairs DC maturation, and induces epithelial–mesenchymal transition (EMT) through direct cell–cell contact[54]. These observations indicate that these under-represented immune populations possess both unique and interconnected features that actively reinforce therapeutic resistance, warranting deeper spatiotemporal characterization to unlock novel combinatorial targets.

2.2 Cancer-associated fibroblasts

In addition to infiltrating immune cells, the TME of NPC harbours a rich stromal compartment that actively communicates with neighbouring parenchymal cells and infiltrating lymphocytes, thereby profoundly influencing tumour behaviour. Among these stromal components, cancer-associated fibroblasts (CAFs) represent one of the most abundant cell types in the TME, comprising a diverse cell population of varied origins. In NPC, CAFs are not merely passive bystanders but active participants in orchestrating tumour progression. Beyond orchestrating tumour invasion, metastasis, and extracellular matrix (ECM) remodelling, CAFs engage infiltrating immune cells in the TME through a multidimensional secretory network that harbours substantial potential for targeted intervention[55]. Importantly, miRNAs and tumour-derived exosomes serve as key mediators of cancer cell–CAF crosstalk, activating signalling pathways such as nuclear factor-kappa B (NF-κB), driving CAFs toward a pro-tumourigenic phenotype, and enhancing both chemoresistance and radioresistance[56, 57]. This virus-modulated stromal communication establishes a permissive microenvironment that supports tumour growth, immune evasion, and therapeutic resistance.

Signal transducer and activator of transcription 3 (STAT3) activation emerges as a key therapeutic target in this context[58], as interleukin-6 (IL-6) secreted by CAFs triggers STAT3 signalling in NPC cells. Given the clinical challenges of directly drugging STAT3 with conventional small molecules, preclinical studies have screened natural alkaloids as alternative inhibitors; notably, berberine was shown to suppress this CAF-driven STAT3 activation, thereby inhibiting NPC cell proliferation and tumourigenicity in nude mice[59]. Furthermore, disulfiram/copper (DSF/Cu) suppresses the expression of alpha-smooth muscle actin (α-SMA), induces apoptosis via ROS/mitogen-activated protein kinase (MAPK) and ferroptosis cascades, and inactivates CAFs, effectively synergizing with cisplatin (CDDP) both *in vitro* and *in vivo*[60]. In parallel, CAFs secrete fibroblast growth factor 5 (FGF5) to activate downstream FGFR2/Nrf2 signalling, which attenuates cisplatin sensitivity in NPC cells and highlights the FGF5/FGFR2 axis as an exploitable target to overcome chemoresistance[61]. Additionally, cylindromatosis lysine 63 deubiquitinase (CYLD), an endogenous NF-κB inhibitor, restricts fibroblast and endothelial stromal cell infiltration into the TME of NPC[62] (Table 2).

Despite these encouraging observations, the translation of CAF-targeted strategies into clinical practice faces substantial hurdles. Specifically, CAFs exhibit marked functional heterogeneity, current evidence remains largely restricted to *in vitro* and rodent models, and non-selective stromal ablation risks impairing physiological tissue homeostasis[56]. Moreover, the considerable methodological heterogeneity across studies limits inter-study comparability. Overcoming these obstacles will require the identification of CAF subtype-specific biomarkers, the development of more selective targeting modalities, and rigorous clinical validation.

2.3 Epithelial–Mesenchymal Transition (EMT) and Stromal Plasticity

Beyond the immunological landscape, the NPC microenvironment is governed by profound stromal plasticity, wherein resident and recruited mesenchymal components dynamically reshape the tumour architecture to promote progression and therapeutic resistance. Central to this matrix-remodeling network are CAFs and mesenchymal stem/stromal cells (MSCs)[63]. MSCs, acting as multipotent progenitors within the tumour stroma, do not merely provide structural support. Rather, they engage in active paracrine crosstalk and shed specialized exosomes that accelerate the EMT cascades in neighboring epithelial tumour cells[64].

EMT represents a cornerstone program of cellular plasticity, empowering epithelial cancer cells to shed their adhesion molecules, acquire mesenchymal markers, and display heightened migratory and invasive phenotypes necessary for metastatic dissemination[65]. In NPC, this phenotypic switch is heavily potentiated by the chronic inflammatory milieu and EBV latency products. A prime mechanistic link is established by EBV-encoded microRNAs, such as EBV-miR-BART7-3p, which directly target and suppress the core tumour suppressor PTEN, thereby persistently activating pathways that drive EMT and distant metastasis[66]. Beyond its role in metastasis, EMT is also associated with chemotherapy and radiotherapy resistance, and

is closely linked to the acquisition of cancer stem cell (CSC) properties[67, 68]. Consequently, therapeutic interventions targeting the EMT process offer a promising new avenue for preventing metastatic dissemination.

Because clinically approved targeted agents that directly and selectively block EMT transcriptional drivers remain scarce, numerous exploratory *in vitro* and rodent investigations have turned to TCM- and plant-derived bioactive compounds as multi-target modulators of EMT-permissive microenvironments (often driven by upstream mediators like TGF-β1)[69]. For instance, curcumol upregulates E-cadherin while suppressing N-cadherin[70]; epigallocatechin gallate (EGCG) targets core EMT proteins[71]; oridonin restrains EMT through AKT/STAT3 inhibition[72]; asiatic acid downregulates claudin-1 via STAT3 suppression[73]; and caffeic acid phenethyl ester reverses mesenchymal traits through NF-κB inactivation[74] (Table 2). However, the translation of these botanical agents remains restricted by severe pharmacokinetic hurdles—including poor aqueous solubility, rapid metabolic clearance, and a complete lack of phase II/III clinical validation.

Consequently, targeting stromal plasticity and EMT in NPC remains a formidable challenge. The inherent reversibility and high heterogeneity of the EMT spectrum risk inducing unintended mesenchymal–epithelial transition (MET) at metastatic niches, while dense desmoplastic stroma impairs systemic drug delivery[75]. Future clinical strategies must move beyond treating EMT as a static tumour cell trait; instead, they must focus on dual-targeting the MSC/CAF-driven matrix network alongside tumour-intrinsic drivers, coupled with robust biomarkers to monitor spatial and temporal plasticity.

2.4 Lipid Metabolism and Cancer-Associated Adipocytes

Notably, the metabolic reprogramming that accompanies EMT—particularly alterations in lipid metabolism—has emerged as another critical dimension of TME-driven tumour progression. Adipocytes are stromal cells present across numerous anatomical sites, and cancer-associated adipocytes (CAAs) function as active participants in the TME of NPC[76]. Upon tumour invasion, adjacent stromal adipocytes undergo profound reprogramming, delipidation, and dedifferentiation into fibroblast-like cells expressing the CAF marker S100A4 (FSP-1)[77], while in the NPC microenvironment, EBV infection further drives extensive lipid metabolic reprogramming[78]. Rather than acting as passive energy reservoirs, these CAAs function as active metabolic partners that continuously release excessive free fatty acids into the microenvironment, establishing an exogenous energy depot that fuels tumour expansion and survival[79, 80].

Capitalizing on this lipid-rich milieu, NPC cells intrinsically rewire their lipid metabolism to sustain oncogenic signalling and therapeutic resistance[81]. Upregulation of fatty acid oxidation (FAO)—orchestrated by regulators such as PGC1α and the rate-limiting enzyme carnitine palmitoyltransferase 1A (CPT1A)—is intimately coupled to cell cycle progression, EMT, and radioresistance[82-84]. Furthermore, sterol regulatory element-binding transcription factor 1 (SREBP1) acts as a master regulator of lipogenesis, driven upstream by EBV-encoded LMP1[78, 85]. Preclinical investigations have sought to disrupt this axis; pharmacological agents like the selective SREBP inhibitor fatostatin or the botanical compound luteolin effectively blunt LMP1-driven mTOR–SREBP1 activation and downstream lipogenesis[78]. Concurrently, luteolin independently induces G1 cell-cycle arrest in NPC cells via the Akt–GSK-3β pathway[86]. In parallel, dehydrogenase/reductase member 2 (DHRS2) serves as an endogenous metabolic regulator that restricts cell growth and migratory capacity[87], a pathway targeted by trichothecin (TCN) to perturb lipid homeostasis and suppress tumour progression *in vivo*[88]. Additionally, disrupting downstream effectors like the CPT1A–Rab14 axis successfully re-sensitizes refractory NPC cells to ionizing radiation[81], highlighting the therapeutic potential of targeting tumour-intrinsic lipid pathways alongside systemic lipid profiles[83, 84] (Table 2).

Beyond fueling cancer cells and interacting with CAAs, this aberrant lipid metabolism exerts profound metabolic suppression on infiltrating immune cells within the TME[83]. High levels of extracellular fatty acids and lipid metabolites impair effector T-cell mitochondrial fitness, drive $CD8^+$ T-cell exhaustion, and concurrently promote the survival and immunosuppressive polarization of TAMs.

Nonetheless, translating systemic lipid-targeting strategies into clinical practice remains exceptionally challenging. Because physiological tissue homeostasis and the functional persistence of effector T lymphocytes strictly rely on intact fatty acid oxidation and lipid remodeling, non-selective metabolic inhibition risks severe systemic toxicities and compromised antitumour immunity. Consequently, future clinical translation relies on developing tumour-selective delivery platforms that exploit NPC-specific metabolic vulnerabilities.

2.5 Vascular Endothelial Cells

Beyond supporting tumour cell survival and immune evasion, deregulated lipid metabolism crosstalks intimately with the stromal vasculature to fuel neoangiogenesis and systemic dissemination. Vascular endothelial cells (VECs) serve as fundamental orchestrators of neovascularisation and haematogenous metastasis. Because malignant progression depends strictly upon sustained vascularization to satisfy escalating metabolic demands, anti-angiogenic intervention has long been pursued as a core therapeutic paradigm[89]. Recent evidence further indicates that judicious regimens can induce structural and functional tumour vessel normalisation, thereby alleviating interstitial fluid pressure, restoring perfusion, and markedly potentiating concurrent chemotherapy or immunotherapy[90].

In NPC, neovascularisation extends beyond classical vascular endothelial growth factor (VEGF)-dependent sprouting to encompass vasculogenic mimicry (VM)—a non-endothelial perfusion modality wherein highly plastic, EBV-infected malignant epithelial cells de novo assemble fluid-conducting, matrix-rich vascular channels. Mechanistically, this phenotypic switching is orchestrated by aberrant activation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR)/hypoxia-inducible factor-1alpha (HIF-1α) signalling cascade, partially driven by EBV-encoded latent membrane protein 2A (LMP2A)[91]. Importantly, this EBV-driven VM cascade reciprocally remodels the local immune niche; hyperactivation of the AKT/mTOR/HIF-1α axis governs the secretion of C-C motif chemokine ligand 5 (CCL5) and colony-stimulating factor 1 (CSF-1), which cooperatively recruit circulating monocytes and polarise them into protumourigenic M2c-like macrophages; these stromal infiltrates, in turn, accelerate VM channel assembly via matrix metalloproteinase-9 (MMP-9) secretion[92].

As the primary pro-angiogenic driver, VEGF is frequently overexpressed alongside its cognate receptor tyrosine kinases in NPC, establishing the VEGF–VEGFR axis as the principal target of early therapeutic interventions[93]. In parallel, the fibroblast growth factor (FGF) family and fibroblast growth factor receptors (FGFRs) play indispensable compensatory roles during pathological angiogenesis[94]. Although incorporating the humanized anti-VEGF-A monoclonal antibody bevacizumab into definitive chemoradiotherapy proved clinically feasible, therapeutic durability remains severely compromised by emerging refractory resistance, resulting in modest overall survival gains[95, 96] (Table 1). Translational studies have elucidated that this intrinsic and acquired resistance to VEGF-targeted blockade in NPC is largely driven by compensatory, tumour-derived FGF2 upregulation. The FGF2–FGFR1–MYC signalling axis functions as an alternative salvage pathway that bypasses canonical VEGF–VEGFR2–MYC signalling to preserve endothelial viability and drive neovascular proliferation under sustained VEGF inhibition. Accordingly, genetic ablation of FGF2 restores sensitivity to anti-angiogenic drugs (AADs) and halts metastatic dissemination, whereas dual VEGFR/FGFR inhibition with lenvatinib potently prunes aberrant microvasculature and overcomes AAD resistance in patient-derived humanized murine models[97]. In addition, alternative perfusion modalities such as EBV-driven VM provide functional, VEGF-independent microcirculation that circumvents conventional vascular pruning[91]. Complementing multi-kinase inhibitors, exploratory preclinical investigations have characterized diverse botanical extracts and bioactive phytochemicals. Root extracts from Actinidia eriantha Benth repress endothelial tube formation *in vitro* by co-downregulating VEGF-A and VEGFR2 expression[98], the combination of Hedyotis diffusa Willd and Andrographis paniculata curbs angiogenesis by downregulating AKT1 and upregulating VEGFA expression[99], and andrographolide induces G2/M phase arrest while suppressing VEGF-dependent invasion[100] (Table 2). Nevertheless, developing these multi-component natural products into verifiable therapeutics is critically impeded by ambiguous pharmacokinetic profiles, uncharacterized multi-target toxicology, and an absence of randomized clinical validation. From a translational standpoint, effectively overcoming anti-angiogenic resistance will require not merely multi-target kinase suppression, but multifaceted paradigms that simultaneously eradicate non-canonical VM networks and mitigate hypoxia-induced metastatic rebound.

Rational combination regimens pairing anti-angiogenic compounds with immune checkpoint inhibitors have exhibited notable therapeutic synergy. In patients with recurrent or metastatic NPC refractory to first-line platinum or PD-1 inhibitors, camrelizumab combined with the VEGFR2 inhibitor apatinib yielded objective response rates of 65.0% and 34.4%, respectively[101]. Furthermore, the triplet regimen comprising gemcitabine, apatinib, and toripalimab (GAT) demonstrated robust antitumour activity with a manageable safety profile in refractory cohorts[102], reinforcing the mechanistic rationale established by pivotal randomized phase 3 trials that evaluated checkpoint inhibitors integrated with standard

systemic chemotherapy[103, 104] (Table 1). In parallel, exploratory preclinical investigations have evaluated natural bioactive monomers, with gambogic acid suppressing endothelial angiogenesis and reshaping the immunosuppressive milieu when combined with chemotherapy *in vitro*[105], while triptolide radiosensitizes NPC cells in animal models via NF-κB inhibition[106]. Nonetheless, clinical translation of these monomers remains severely hampered by critical toxicology liabilities—exemplified by the severe hepatotoxicity and exceptionally narrow therapeutic window of triptolide—along with undefined human pharmacokinetics. Engineering advanced nanocarrier platforms and undertaking chemical scaffold optimization represent essential prerequisites to alleviate off-target organ toxicities before prospective clinical translation can be realistically pursued.

Significantly, tumour-derived exosomes—nanoscale extracellular vesicles shuttling regulatory biomolecules to govern intercellular crosstalk in NPC[107] —also act as indispensable drivers of angiogenic remodeling. Exosomal miR-9 modulates endothelial migratory behavior and vessel branching by targeting midkine (MDK) and suppressing PDK/AKT signalling[108]. Conversely, exosomal limb-bud and heart (LBH) inhibits neovascular proliferation by transcriptionally silencing VEGFA expression[109]. These non-invasive nano-messengers highlight valuable prognostic utility and uncover novel molecular avenues for anti-angiogenic drug discovery.

Despite these therapeutic avenues, anti-angiogenic intervention in NPC faces significant translational constraints. First, the "vessel normalisation window" induced by anti-angiogenic regimens is inherently transient and narrow, severely complicating the optimal sequencing and timing of combination chemotherapy or immunotherapy. Second, durable clinical responses are thwarted by the rapid induction of bypass pro-angiogenic cascades, while non-endothelial perfusions such as VM inherently bypass VEGF-restricted therapies. Surmounting these obstacles necessitates validating dynamic biomarker platforms to identify the normalisation window in real time, developing selective multi-kinase inhibitors, and implementing multi-modal combination strategies designed to extinguish both canonical and non-canonical microcirculations.

2.6 Inflammation, ECM Remodeling, and Other TME Components

The abnormal vasculature in the TME not only facilitates nutrient supply and metastatic dissemination but also contributes to chronic inflammation and extracellular matrix remodelling. In the tumour microenvironment, tumour cells secrete a range of pro-inflammatory cytokines and inflammatory mediators that exert multifaceted effects on tumour cell proliferation, immune evasion, angiogenesis, metastasis, and drug resistance[110]. Beyond the cellular and vascular components discussed above, the TME of NPC is also shaped by inflammatory mediators, ECM-remodeling enzymes, and CSCs. These elements are functionally interconnected. NF-κB-driven inflammation promotes ECM degradation via MMPs, sustains CSCs, and facilitates lymphangiogenesis, forming a self-reinforcing loop that drives tumour progression and therapy resistance. The NF-κB signalling pathway is centrally involved in regulating these immune and inflammatory responses[111]. Because systemic administration of synthetic NF-κB or broad-spectrum MMP inhibitors has historically been hampered by severe dose-limiting toxicities in clinical trials, preclinical research in NPC has largely pivoted toward screening pleiotropic TCM-derived natural compounds *in vitro* and in animal models. Vitexin, a natural flavonoid glycoside, exerts antitumour and anti-inflammatory activity by downregulating constitutive NF-κB signalling[112], whereas casticin engages the PKR/JNK/NF-κB cascade to trigger caspase-1-dependent inflammasome activation and pyroptosis in NPC cells[113].

Beyond promoting inflammatory circuits, NF-κB signalling orchestrates ECM remodeling by transcriptionally upregulating MMPs, which serve as primary enzymatic effectors of basement membrane degradation and metastatic extravasation[114]. *in vitro*, the alkaloid matrine impedes NPC cell migration and invasion by dampening MMP expression and enzymatic activity[115].

In addition to promoting invasion via ECM degradation, the inflammatory and stiffened remodeling TME critically sustains the self-renewal and therapeutic resistance of CSCs. Within this niche, parthenolide, a natural sesquiterpene lactone, acts as an active agent targeting CSCs to suppress proliferation, attenuate stemness, and restore apoptosis sensitivity via inhibition of the NF-κB/COX-2 pathway in NPC cells[116]. Beyond regulating CSCs and inflammation, certain TME-derived factors also exert modulatory effects on lymphatic metastasis—another critical route of NPC dissemination. Pigment epithelium-derived factor (PEDF) has emerged as a key regulator in this context. Serving as a potent endogenous inhibitor of angiogenesis, PEDF also suppresses lymphangiogenesis and lymphatic metastasis in NPC[117] (Table 2). Nevertheless,

translating these ECM- and microenvironment-modulating agents into clinical regimens remains hindered by formidable pharmacological challenges. Systemic disruption of ECM homeostasis or non-selective MMP inhibition risks destabilizing physiological tissue architecture and precipitating severe musculoskeletal toxicities, as documented in historical clinical trials. Moreover, the therapeutic efficacy of natural monomers such as parthenolide is currently restricted to preclinical *in vitro* models, constrained by suboptimal metabolic stability, lack of human pharmacokinetic validation, and potential off-target liabilities.

3. Discussion

The TME of NPC comprises a highly convoluted, multicellular ecosystem governed by reciprocal crosstalk across distinct mechanistic axes, rendering it a compelling paradigm for both therapeutic intervention and precision prognostic stratification. However, translating these multifaceted biological discoveries into actionable clinical regimens encounters several formidable translational roadblocks.

Foremost among these challenges is the marked spatial and temporal heterogeneity inherent to the NPC microenvironment, which varies substantially across individual patients and distinct clinical stages. This heterogeneity complicates the identification of universally effective therapeutic targets and underscores the imperative need for patient stratification based on granular TME signatures. In parallel, the dynamic nature of EBV-driven immune evasion and adaptive resistance mechanisms highlights the necessity of developing real-time monitoring strategies and adaptive treatment regimens. Intrinsically weak viral or neoantigen immunogenicity, profound effector T-cell exhaustion, the persistence of multi-layered immunosuppressive networks across heterogeneous patient subsets, and suboptimal delivery routes collectively constrain the durability of immunotherapy. Although standard systemic chemotherapy (principally gemcitabine plus cisplatin) has long anchored the first-line treatment armamentarium for recurrent or metastatic NPC, disease progression remains nearly inevitable and overall survival benefits remain modest[118]. In terms of clinical maturity, anti-PD-1 ICB combined with chemotherapy currently represents the only TME-targeted strategy supported by mature Phase III evidence, whereas anti-angiogenic combinations, DC vaccines, and CAR-T therapies remain in Phase I/II clinical evaluation, and interventions targeting CAFs, EMT, lipid metabolism, or TCM-derived monomers remain strictly confined to preclinical models. Furthermore, the rapid emergence of bypass angiogenic pathways presents a major obstacle to sustained vascular-targeted therapy, while potential on-target and off-target treatment-related toxicities further circumscribe the safe therapeutic window in clinical practice.

Looking forward, several research priorities merit particular attention. First, the identification and validation of robust predictive biomarkers—beyond static PD-L1 expression, most notably dynamic plasma EBV DNA clearance, intratumoural TLS/B-cell signatures, and exhausted $CD8^+$ TIL-to-myeloid ratios—will be essential for precise patient selection and dynamic response monitoring. Multi-omics approaches, including single-cell transcriptomics and spatial proteogenomic profiling, offer unprecedented opportunities to dissect TME heterogeneity and guide personalised therapy. In addition, exosome-mediated intercellular communication—orchestrating both metabolic vulnerabilities (such as macrophage ferroptosis)[119], and metastatic remodeling via non-coding RNAs[120, 121] —offers promising non-invasive liquid biomarkers and targets for therapeutic exploration, though achieving high-purity isolation and overcoming exosome heterogeneity remain major translational hurdles. Second, the development of more effective tumour-selective drug delivery systems, particularly those capable of overcoming stromal barriers, penetrating tumour tissues, and mitigating the systemic off-target toxicities of preclinical metabolic and botanical modulators, remains a pressing need. Ionizable LNPs represent a promising example in this regard[27, 122]. Third, as the highest-priority direction for future clinical trials, the therapeutic potential of mechanistically guided combination strategies—such as dual checkpoint blockade (e.g., co-targeting PD-1 and TIGIT/LAG-3) or ICBs paired with vessel-normalising anti-angiogenic agents, metabolic modulators, or EBV-targeted LNP-mRNA vaccines—warrants systematic investigation in well-designed, biomarker-driven clinical trials. The schematic overview of these forward-looking therapeutic avenues is illustrated in Figure 1. Although the preponderant volume of current evidence remains anchored at the preclinical and animal model phase, these innovative avenues hold immense promise for expanding the repertoire of actionable targets in refractory NPC (Tables 1 and 2). Establishing deep mechanistic clarity regarding the co-evolution of distinct TME constituents will ultimately transform combination paradigms from empirical trials into rationally stratified, personalized interventions.

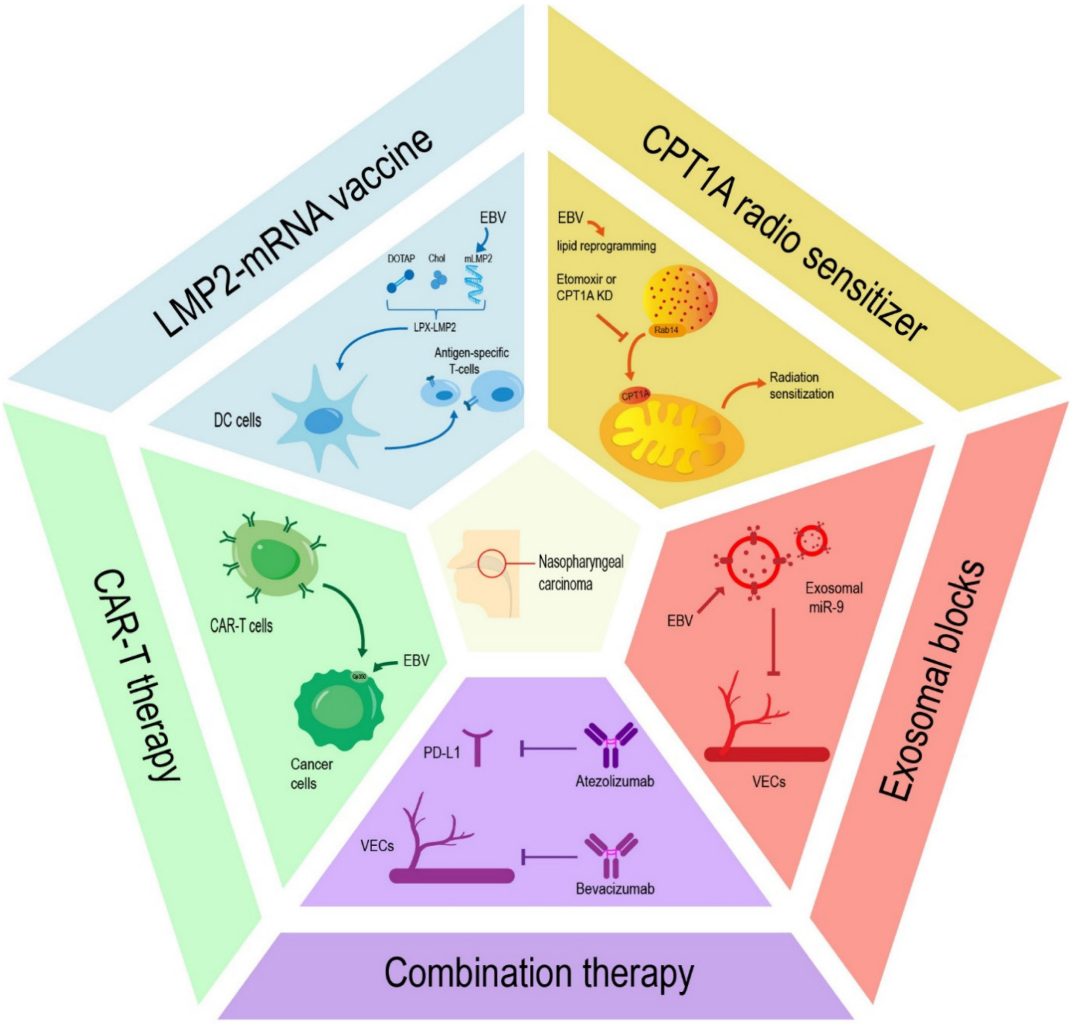

Figure 1. Strategies with future potential targeting TME in NPC.

Table 1. Clinical trials targeting the NPC microenvironment

Target	Trial ID	Study	Condition	Phase	Efficacy & Survival Outcomes	Toxicity Profile
T lymphocytes	NCT02054806	Pembrolizumab	R/M NPC	1	ORR: 25.9%; mPFS: 6.5 mo; mOS: 16.5 mo	Grade ≥3 TRAEs: 29.6%
	NCT02488759	Nivolumab	R/M NPC	1/2	ORR: 20.5%–20.8%; mPFS: 2.4–2.8 mo; mOS: 17.1 mo	Grade ≥3 TRAEs: 22.2%
	NCT02721589	Camrelizumab	R/M NPC	1	ORR: 34.0%; mPFS: 5.6 mo (1-yr PFS: 27.1%); mOS: NR	Grade 3–4 TRAEs: 16.1%
	NCT02605967	Spartalizumab	R/M NPC	2	ORR: 17.1%; mPFS: 1.9 mo; mOS: 25.2 mo	Grade 3–4 TRAEs: 16.8%
	CTR20160872	Tislelizumab	R/M NPC	1/2	ORR: 42.9%; mPFS: 10.4 mo; mOS: NR	Manageable (mainly Grade 1–2 AEs)
	NCT02915432	Toripalimab	R/M NPC	2	ORR: 20.5%; mPFS: 1.9 mo; mOS: 17.4 mo	Grade 3–5 TRAEs: 14.2%
	NCT02825940	Atezolizumab	R/M NPC	1	ORR: 10.0% (DCR: 65.0%); survival not published	Manageable preliminary safety
Dendritic cells	NCT03282617	CD137L-DC-EBV-VAX	R/M NPC	1	Induces EBV-specific T-cell responses; survival not published	Favourable safety; no DLTs
Combination therapy	NCT03121716	Camrelizumab combination trial	R/M NPC	1	ORR: 91.0%; 6-mo PFS: 86.0%; 1-yr PFS: 61.4%	Grade 3–4 TRAEs: 87.0% (mainly hematologic)
	NCT03581786	Toripalimab combination trial	R/M NPC	3	ORR: 78.8% vs. 67.1%; mPFS: 21.4 vs. 8.2 mo (HR 0.52); 3-yr OS: 64.5% vs. 49.2% (HR 0.63)	Grade ≥3 TEAEs: 89.7% (Grade ≥3 irAEs: 9.6%)
	NCT00408694	Bevacizumab combination trial	Loco-regionally advanced NPC	2	2-yr LRC: 83.7%; 2-yr PFS: 74.7%; 5-yr OS: 79.5%; 7-yr OS: 69.7%	Late Grade 3 TRAEs: 36.4% (no Grade 5 bleeding)
	NCT04547088, NCT04548271	Camrelizumab combined with apatinib	R/M NPC	2	ORR: 65.0% & 34.4%; mPFS: 10.4 mo (platinum-resistant) & 4.4 mo (PD-1-resistant)	Grade ≥3 TRAEs: 65.3%
	NCT04073784	Gemcitabine combined with apatinib	R/M NPC	1/2	Promising synergistic ORR and durable PFS in refractory cohorts	Manageable AEs (hematologic and nasopharyngeal necrosis)

Table 2. Effects and mechanisms of TME-targeted therapies in nasopharyngeal carcinoma

Target	Study	Effect	Related mechanisms	Model & Evidence Level	Translational Bottlenecks / Limitations
Immunotherapy					
T lymphocytes	Lipid-based LMP2-mRNA vaccine	T-cell exhaustion reversal	PD-1/PD-L1	Preclinical *in vivo* (murine models; Level 5)	Delivery efficiency and clinical-grade scalability
	CAR-T cell	Promote antitumour responses	EBV lytic antigen gp350	Preclinical *in vivo* (murine xenografts; Level 5)	Stromal barriers and on-target off-tumour toxicity
	Sorafenib	Facilitate killing of NPC cells	EGFR/SLC7A11/MHC-I	Preclinical *in vivo* & *in vitro* (Level 5)	Systemic toxicity and acquired resistance
	LMP2-DC Vaccine	Elicits EBV-LMP2 Response	Intranodal DC antigen presentation of EBV LMP2 epitopes	Clinical Phase I/II pilot study (human patients, n=9; Level 4)	Complex preparation and patient-to-patient variability
NK cells	IFNβ with PD-L1/PD-1 blockade	Enhance NK cell activity	PD-L1/PD-1, TRAIL	Preclinical *in vitro* (patient-derived NK & NPC cells; Level 5)	Limited *in vivo* validation and rapid functional exhaustion
	Poly-ICLC combined with cetuximab	Induce the immune response	TLR3, EGFR	Preclinical *in vitro* (NPC cell lines & PBMCs; Level 5)	Lack of randomized clinical trial validation
	Fuyuan decoction	Promote the release of NK cells	Inhibits CTC-endothelial interplay and enhances NK surveillance	Preclinical *in vivo* (rodent metastasis models; Level 5)	Undefined pharmacokinetics and multi-target complexity
Macrophages	Sargassum fusiforme polysaccharides	Stimulates cytokine secretion	TLRs/NF-κB	Preclinical *in vivo* (CNE-bearing mice; Level 5)	Lack of precise subset targeting
	BCL-2 inhibitor APG-2575	Polarize toward M1 phenotype	NF-κB/NLRP3	Preclinical *in vivo* & *in vitro* (murine models; Level 5)	Potential off-target systemic toxicities
	USP7	Polarize toward M1 phenotype	JAK/STATs, TRIM24/SPLUNC1	Preclinical *in vitro* & *in vivo* (xenografts; Level 5)	Preclinical stage only, lacks human data
CAFs	Berberine	Inhibition of STAT3 activation	STAT3, IL-6	Preclinical *in vivo* & *in vitro* (nude mouse xenografts; Level 5)	Low bioavailability and rapid metabolism
	Disulfiram/Copper	Induce apoptosis	ROS/MAPK, Ferroptosis	Preclinical *in vivo* & *in vitro* (rodent models; Level 5)	Narrow therapeutic window and systemic stability
	CYLD	Inhibit infiltration	NF-kB	Preclinical *in vivo* & *in vitro* (Level 5)	Complex stromal interactions in human tumours
MSCs	Curcumol	Induce EMT arrest	TGF-β1	Preclinical *in vivo* & *in vitro* (xenografts; Level 5)	Poor aqueous solubility and fast clearance
	Epigallocatechin gallate	Inhibit EMT	EMT-related proteins	Preclinical *in vitro* (NPC cell lines; Level 5)	Low stability and limited *in vivo* efficacy
	Oridonin	Inhibit EMT	AKT/STAT3	Preclinical *in vitro* (NPC cell lines; Level 5)	High systemic toxicity and narrow therapeutic index
	Asiatic acid	Suppress STAT3, claudin-1	JAK/STAT, Wnt/β-catenin	Preclinical *in vitro* (NPC cell lines; Level 5)	Strictly *in vitro* evidence, lacking animal validation
	Caffeic acid phenethyl ester	Reverse EMT-like changes	NF-κB	Preclinical *in vitro* & *in vivo* (Level 5)	Poor metabolic stability
Adipocytes	Luteolin, Fatostatin	Inhibit SREBP1 activity	LMP1/ SREBP1	Preclinical *in vitro* & *in vivo* (Level 5)	Pharmacokinetic limitations in clinical application
	Trichothecin	Reprogram lipid homeostasis	DHRS2	Preclinical *in vivo* & *in vitro* (murine xenografts; Level 5)	Toxicity profile needs thorough clinical evaluation
	Knockdown of Rab14	Overcome radioresistance	CPT1A	Preclinical *in vivo* & *in vitro* (xenografts; Level 5)	Requires targeted delivery systems to avoid systemic lipid disruption
VECs	Lenvatinib	Inhibit the tumour vasculature	VEGFR2, FGFR1	Preclinical *in vivo* (patient-derived humanized mice; Level 5)	Acquired resistance and hypertension toxicity
	Actinidia eriantha benth	Angiogenesis suppression	Co-downregulates VEGF-A and VEGFR2 expression	Preclinical *in vitro* (endothelial & NPC cells; Level 5)	Crude extract standardization challenges
	HDW combined with AP	Inhibited NPC cell proliferation and viability	AKT1, VEGFA	Preclinical *in vitro* & network pharmacology (Level 5)	Mechanistic complexity of herbal combinations
	Andrographolide	Downregulation of MMP-9, VEGF	NF-κB	Preclinical *in vitro* (NPC cell lines; Level 5)	Poor oral bioavailability
	Gambogic acid	Suppress angiogenesis	CD47, STAT	Preclinical *in vitro* & *in vivo* (Level 5)	Significant hepatotoxicity liabilities
	Triptolide combined with radiotherapy	Induce anti-angiogenesis activities	NF-κB	Preclinical *in vivo* & *in vitro* (murine xenografts; Level 5)	Exceptionally narrow therapeutic window and severe toxicity
Inflammasome	Casticin	Induce pyroptosis	PKR/JNK/NF-κB	Preclinical *in vitro* (5-8F NPC cell line; Level 5)	Lack of *in vivo* confirmation
Cancer stem cell	Parthenolide	Induce cell death	NF-κB/COX-2	Preclinical *in vitro* (5-8F NPC cell line; Level 5)	Poor pharmacokinetic properties
lymphatic vessel	PEDF	Inhibit lymphangiogenesis	NF-κB	Preclinical *in vivo* & *in vitro* (murine footpad model; Level 5)	Delivery barriers into dense lymphatic stroma
ECM	Matrine	Inhibit NPC migration and invasion	NF-κB/MMPs	Preclinical *in vitro* (NPC cell lines; Level 5)	Moderate potency requiring high systemic dosage

Abbreviations: HDW, Hedyotis diffusa Willd; AP, Andrographis paniculata.

In summary, the NPC microenvironment presents a vast array of actionable therapeutic vulnerabilities, continuously offering compelling opportunities for translational innovation. Dedicated mechanistic investigations into this complex ecosystem, coupled with large-scale, rigorously designed prospective clinical trials, will be indispensable to fully translate these targeted strategies into durable patient survival benefits.

4. Conclusion

In conclusion, the EBV-orchestrated tumour microenvironment of nasopharyngeal carcinoma functions as a central determinant of immune escape, stromal plasticity, neovascularisation, and therapeutic resistance. While anti-PD-1-based chemo-immunotherapy and anti-angiogenic combinations have successfully transitioned into clinical practice, the vast majority of interventions targeting CAFs, cellular metabolism, exosomes, and natural product pathways remain at the preclinical stage. Bridging this translational gap will require rigorous evidence stratification, the routine clinical integration of dynamic biomarkers—most notably plasma EBV DNA kinetics, TLS signatures, and spatial multi-omics—and the execution of biomarker-driven prospective trials evaluating rational combination regimens and precision nanomedicine delivery platforms.

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Author contributions

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Competing Interests

The authors have declared that no competing interest exists.

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