INTERNATIONAL JOURNAL OF MEDICAL SCIENCE AND DENTAL HEALTH
(ISSN: 2454-4191)
www.ijmsdh.org (2026)

Received: 17 Aug 2026
Revised: 28 Aug 2026
Accepted: 10 Sep 2026
Published: 16 Sep 2026

Volume 12 Issue 09, 2026
Page No - 149-154
DOI - 10.55640/ijmsdh-12-09-17

Article Citation: Dr. Ario Kusuma. (2026). Immunological Landscape and Chemokine Networks in Nasopharyngeal Carcinoma: Mechanisms of Treg-Mediated Suppression and Therapeutic Implications. International Journal of Medical Science and Dental Health, 12(09), 149-154. https://doi.org/10.55640/ijmsdh-12-09-17

Immunological Landscape and Chemokine Networks in Nasopharyngeal Carcinoma: Mechanisms of Treg-Mediated Suppression and Therapeutic Implications

Dr. Ario Kusuma
Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Abstract

Background: Nasopharyngeal carcinoma (NPC) is distinct among head and neck malignancies due to its strong association with Epstein-Barr virus (EBV) infection and a unique tumor microenvironment (TME) characterized by heavy lymphocytic infiltration. Despite advances in intensity-modulated radiotherapy, recurrence remains a significant challenge, largely attributed to immune evasion mechanisms.

Methods: We conducted a comprehensive review and synthesis of recent genomic, proteomic, and single-cell transcriptomic studies regarding NPC. This analysis focuses on the interplay between tumor cells, the viral component (EBNA1), and the immune infiltrate, specifically Regulatory T cells (Tregs) and chemokine signaling networks.

Results: Analysis reveals that the NPC microenvironment is highly immunosuppressive despite being "immune hot." EBV nuclear antigen 1 (EBNA1) actively recruits Tregs, while tumor cells upregulate CD70 to enhance Treg suppressive capacity via the CD70-CD27 axis. Furthermore, the chemokine landscape is dysregulated; elevated KIF18B expression correlates with immune evasion, and the LIF-CXCL9 axis in tumor-associated macrophages impairs CD8+ T cell infiltration. Conversely, NK cells play a crucial role in recruiting type 1 conventional dendritic cells (cDC1) to prime anti-tumor immunity.

Conclusion: The efficacy of immunotherapy in NPC is contingent upon overcoming specific chemokine barriers and Treg-mediated suppression. Targeting the CD70-CD27 interaction and restoring CXCL9 expression represent promising strategies to sensitize recurrent NPC to checkpoint blockade.

Keywords: Nasopharyngeal carcinoma, Tumor microenvironment, Regulatory T cells, Chemokines, Epstein-Barr virus, Immunotherapy, Single-cell transcriptomics.

Introduction

Nasopharyngeal carcinoma (NPC) represents a distinct entity within the spectrum of head and neck squamous cell carcinomas. It is characterized by a unique geographical distribution, with a remarkably high incidence in Southern China, Southeast Asia, and Northern Africa, earning it the moniker "Cantonese cancer" [1]. Unlike other head and neck cancers primarily driven by tobacco and alcohol consumption, NPC pathogenesis is inextricably linked to latent infection with the Epstein-Barr virus (EBV), alongside genetic susceptibility and environmental factors [1, 2]. This viral etiology contributes to a tumor microenvironment (TME) that is heavily infiltrated by immune cells, distinguishing NPC as an "immune hot" tumor.

Despite the radiosensitivity of NPC and significant improvements in survival rates attributable to the widespread adoption of intensity-modulated radiation therapy (IMRT) and concurrent chemoradiotherapy, treatment failure remains a critical clinical hurdle [3]. Approximately 20% to 30% of patients experience locoregional recurrence or distant metastasis [4]. The management of recurrent NPC is particularly challenging; re-irradiation is limited by the tolerance of surrounding critical neurological structures, and systemic therapies often yield diminishing returns due to chemoresistance [4]. Consequently, there is an urgent need to elucidate the biological mechanisms underpinning tumor persistence and progression.

The evolution of NPC staging systems reflects an increasing recognition of the complexity of the disease, yet current TNM classifications do not fully capture the biological heterogeneity of the tumor or the immune contexture that dictates treatment response [3]. Recent advances in single-cell transcriptomics and multi-omics have unveiled a complex ecosystem within the NPC TME. This environment is not merely a bystander but an active participant in disease progression, characterized by a paradox: the presence of abundant immune infiltrates that fail to mount an effective anti-tumor response [5].

This failure of immune surveillance is orchestrated by a network of suppressive cellular interactions and cytokine signaling pathways. Central to this process are Regulatory T cells (Tregs), which are disproportionately enriched in NPC tissues compared to peripheral blood. The recruitment and activation of these suppressive cells are often driven by EBV-encoded products, such as nuclear antigen 1 (EBNA1), and specific host factors like KIF18B [6, 8]. Furthermore, the migration and positioning of immune cells are governed by a complex language of chemokines. The dysregulation of chemokine axes, such as CXCL9/CXCR3, can effectively exclude cytotoxic T cells from the tumor core, rendering immune checkpoint inhibitors ineffective [16].

Understanding the interplay between viral antigens, chemokine networks, and immune suppression is essential for developing next-generation immunotherapies. This article synthesizes current knowledge regarding the immunological landscape of NPC, with a specific focus on the mechanisms of Treg accumulation and the chemokine networks that regulate the immune architecture. By dissecting these pathways, we aim to identify novel therapeutic targets that could reverse immune tolerance and improve outcomes for patients with recurrent or metastatic disease.

Methods

To provide a comprehensive synthesis of the immunological landscape in NPC, a narrative review approach was employed. We analyzed primary research articles, clinical trial data, and review papers focused on the tumor microenvironment of nasopharyngeal carcinoma. The literature selection process prioritized studies utilizing high-resolution techniques, such as single-cell RNA sequencing (scRNA-seq), flow cytometry, and multi-omics analysis, to ensure the inclusion of the most granular biological data available.

Key inclusion criteria involved studies investigating the role of Epstein-Barr virus in immune modulation, the specific contribution of chemokine networks (CXCL, CCL families) to cell trafficking, and the functional characterization of tumor-infiltrating lymphocytes (TILs), particularly Tregs and B cells. We specifically examined the interactions between tumor cells and the immune stroma, focusing on molecular pathways that facilitate immune evasion. The synthesis of findings was organized thematically to construct a coherent narrative regarding the architectural and functional deficits of the anti-tumor immune response in NPC. Particular attention was paid to identifying mechanistic links between specific molecular markers (e.g., KIF18B, CD70) and clinical prognosis.

Results

The Architectural Heterogeneity of the TME

Recent applications of single-cell transcriptomics have fundamentally altered our understanding of the NPC microenvironment. Unlike the monolithic view provided by bulk sequencing, single-cell analysis reveals a TME characterized by profound heterogeneity [10]. The immune infiltrate in NPC is predominantly composed of T cells and B cells, with a smaller fraction of myeloid lineage cells. However, the functional state of these cells is highly variable.

Analysis of intercellular networks at single-cell resolution demonstrates that malignant cells in NPC actively reshape the stromal compartment [10]. This remodeling creates a niche that supports tumor survival while physically and chemically excluding effective cytotoxic responses. Of particular interest is the interaction between tumor cells, viral infection, and the microenvironment. Transcriptomic profiling indicates that EBV-positive tumor cells exhibit distinct gene expression signatures related to antigen processing and presentation, yet they successfully evade recognition through the downregulation of critical surface markers and the upregulation of inhibitory ligands [11].

B-Cell Lineage and Pan-Cancer Perspectives

While T cells have traditionally received the majority of research attention, recent pan-cancer analyses highlight the critical role of B cells in the TME. In NPC, B cells are not merely antibody-producing factories but exist as phenotypically distinct subtypes with varying functions [9]. Single-cell dissection reveals subsets of B cells that possess regulatory properties (Bregs), which can suppress T cell proliferation and cytokine production. Conversely, the presence of organized tertiary lymphoid structures (TLS) containing mature B cells is often associated with a more favorable prognosis, suggesting that the spatial organization of B cells determines their functional impact [9]. The duality of the B cell compartment underscores the complexity of the immune response, where the balance between pro-tumor Bregs and anti-tumor plasma cells can tip the scales of disease progression.

Mechanisms of Treg-Mediated Immunosuppression

A defining feature of the NPC microenvironment is the accumulation of FoxP3+ Regulatory T cells (Tregs). These cells act as potent suppressors of the adaptive immune response, and their abundance is frequently correlated with poor clinical outcomes. The mechanisms driving this Treg enrichment are multifaceted, involving both viral and host factors.

Viral Induction of Tolerance: The Epstein-Barr virus plays a direct role in shaping the immune landscape. EBV nuclear antigen 1 (EBNA1), a protein essential for viral replication and maintenance, has been shown to favor the accumulation of Tregs [8]. EBNA1 modulates the cytokine milieu, promoting the secretion of transforming growth factor-beta (TGF-β) and CCL20, which acts as a chemoattractant for CCR6+ Tregs. This viral manipulation ensures that the very cells designed to eliminate the infection are suppressed, allowing the virus-driven tumor to thrive.

The CD70-CD27 Axis: Beyond viral factors, direct cell-to-cell contact mechanisms contribute to immune suppression. Recent studies have identified the interaction between CD70 on tumor cells and CD27 on Tregs as a critical pathway [7]. In NPC, tumor cells frequently overexpress CD70. Upon binding to CD27 expressed on regulatory T cells, this interaction not only promotes the proliferation of Tregs but also enhances their suppressive activity. This creates a feed-forward loop where the tumor actively reinforces the barrier against immune attack.

KIF18B and Immune Evasion: At the molecular level, the expression of Kinesin Family Member 18B (KIF18B) has emerged as a significant biomarker. Multi-omics analysis reveals a strong association between elevated KIF18B expression and unfavorable prognosis in NPC patients [6]. High levels of KIF18B are correlated with increased Treg infiltration and a reduction in CD8+ effector T cells. This suggests that KIF18B may function as a regulator of the immune architecture, potentially through the modulation of cytoskeleton dynamics that influence chemokine secretion or surface receptor presentation [6].

Chemokine Orchestration of the Immune Microenvironment

The trafficking of immune cells into the TME is governed by a complex system of chemokines and cytokines. In NPC, this system is frequently co-opted to support tumorigenesis and metastasis.

General Chemokine Dysregulation: Chemokines are critical mediators of inflammation and immunity, but in the context of cancer, they can facilitate tumor growth and metastasis [12, 13]. The "chemokine axis" involves specific ligand-receptor pairs that dictate the migration of cells. In prostate and other cancers, these axes are well-defined drivers of pathogenesis [13], and similar patterns are observed in NPC. The CC chemokines, interacting with receptors such as CCR5, CCR7, and CCR9, display a dichotomy of function, capable of exhibiting both pro-cancer and anti-cancer properties depending on the context [15].

The LIF-CXCL9 Axis: A specific mechanism of immune exclusion in NPC involves the interplay between Leukemia Inhibitory Factor (LIF) and the chemokine CXCL9. CXCL9 is a critical chemoattractant for CXCR3+ CD8+ T cells, which are necessary for tumor cell killing. However, studies indicate that LIF regulates CXCL9 expression in tumor-associated macrophages (TAMs) [16]. High levels of LIF suppress CXCL9 production, thereby preventing the recruitment of cytotoxic T cells into the tumor core. This blockade effectively impairs the efficacy of anti-PD1 therapies, as the effector cells are physically absent from the tumor bed [16].

NK Cell-Mediated Recruitment of cDC1s: Conversely, natural killer (NK) cells play a vital role in establishing a

permissive immune environment. NK cells are capable of stimulating the recruitment of type 1 conventional dendritic cells (cDC1s) into the TME [17]. cDC1s are essential for cross-priming CD8+ T cells and initiating the anti-tumor immune cycle. This recruitment is mediated through specific chemokine signals, indicating that NK cells act as architects of the immune response, bridging innate and adaptive immunity.

Integrated Analysis of Chemokine Networks and Metabolic Reprogramming (Expanded Analysis)

To fully grasp the intractability of recurrent NPC, one must look beyond individual ligand-receptor interactions and consider the integrated network of chemokines as a system of metabolic and spatial control. The synthesis of the reviewed literature suggests that NPC tumors establish a "chemokine barrier" that is not merely exclusionary but metabolically exhausting for infiltrating lymphocytes.

The chemokine landscape in NPC is spatially stratified. The interactions described in the literature—specifically the axis involving CCL20-CCR6 and CXCL9/10/11-CXCR3—create distinct micro-niches. While EBNA1 promotes CCL20 to recruit Tregs [8], the simultaneous suppression of CXCL9 via the LIF axis [16] creates a zone of immune privilege. This is not a passive absence of signals but an active repulsion of effector phenotypes. When CD8+ T cells do manage to penetrate the stroma, they often encounter a chemokine milieu that forces them into a state of metabolic stress. The interplay between cytokines and chemokines [13] regulates not just migration but cellular metabolism. Pro-inflammatory chemokines typically signal T cells to adopt glycolytic metabolism necessary for effector function. However, the dominant cytokine profile in the NPC TME, rich in TGF-β and devoid of robust CXCL9 signaling, likely restricts this metabolic switch, locking T cells in a state of anergy or senescence.

Furthermore, the role of tumor microenvironment signaling [14] extends to the modulation of the extracellular matrix (ECM), which physically traps chemokines or creates gradients that mislead immune cells. In NPC, the dense stromal reaction often seen in histology may act as a reservoir for chemokines like CXCL12, which tends to promote the retention of myeloid-derived suppressor cells (MDSCs) and exclusion of T cells. The review by Goenka et al. [14] highlights that therapeutic strategies must address these signaling matrices. In NPC, this implies that simply blocking a checkpoint like PD-1 is insufficient if the chemokine gradient required to bring the T cell to the antigen-presenting cell is disrupted.

The "Alliance" of Chemokines and Cytokines described in broader cancer contexts [13] is particularly relevant to the viral nature of NPC. Viruses are evolutionary masters of chemokine mimicry. While EBV is a latent infection in these tumors, the expression of viral microRNAs and proteins like LMP1 and EBNA1 fundamentally alters the host cell's secretome. This results in a "pseudo-inflammatory" state where chemokines that normally signal tissue repair (and thus suppression of autoimmunity) are chronically upregulated. This explains the observation of "unfavorable prognosis" linked to KIF18B and other markers [6]; these are likely downstream effectors or co-conspirators in this viral hijacking of the chemokine system.

Therefore, the failure of immune surveillance in NPC is a tri-partite failure:

1. Recruitment Failure: Due to LIF-mediated suppression of CXCL9 [16].

2. Differentiation Failure: Due to NK cell impairment reducing cDC1 recruitment [17].

3. Suppression Dominance: Due to the EBNA1-driven and CD70-mediated expansion of Tregs [7, 8].

This integrated view suggests that the TME of NPC functions as a "chemokine sink," trapping suppressive cells while repelling or disarming effector cells. The implications for therapy are profound: agents that can "normalize" the chemokine vasculature or disrupt the metabolic support for Tregs (potentially via KIF18B inhibition) may be required as prerequisites for successful checkpoint blockade.

Discussion

The immunological landscape of Nasopharyngeal Carcinoma is a testament to the sophisticated co-evolution of viral mechanisms and host immune responses. The data synthesized in this review highlights a crucial paradox: NPC is an inflamed, "hot" tumor that nevertheless maintains a deeply immunosuppressive microenvironment. This contradiction is resolved by understanding the specific qualitative defects in the immune infiltrate, largely driven by chemokine dysregulation and Treg dominance.

The EBV Imprint on Immunity

The role of EBV cannot be overstated. Unlike non-viral cancers where mutational burden often drives immunogenicity, in NPC, the virus itself dictates the immune tone. The finding that EBNA1 actively recruits Tregs [8] suggests that the virus has evolved to exploit the host's tolerance mechanisms to protect the transformed cell. This viral latency program creates a baseline of suppression that is difficult to overcome with standard therapies. The link between viral proteins and host biomarkers like KIF18B [6] further illustrates the depth of this integration, suggesting that

viral status should be a primary consideration in stratifying patients for immunotherapy.

The Chemokine Gatekeepers

The review identifies the chemokine network as a critical gatekeeper of immune efficacy. The observation that LIF regulates CXCL9 [16] provides a mechanistic explanation for "cold" tumor regions within the ostensibly "hot" NPC TME. If macrophages are programmed to withhold T cell recruiting signals, then systemic T cell activation (e.g., via vaccination or checkpoint blockade) will fail to translate into intratumoral killing. Similarly, the dependence of cDC1 recruitment on NK cells [17] points to a fragility in the antigen presentation machinery. If NK cells are excluded or exhausted, the dendritic cell bridge to adaptive immunity collapses.

Clinical Implications for Recurrent Disease

The high recurrence rate in NPC [4] despite aggressive radiochemotherapy is likely fueled by these residual immunosuppressive niches. Radiation can induce immunogenic cell death, theoretically releasing antigens and priming the immune system. However, in the presence of the CD70-CD27 axis [7] and high Treg/chemokine barriers, this potential is nullified. The surviving tumor clones are likely those that have most effectively established this suppressive shield.

Consequently, treatment of recurrent NPC requires a paradigm shift from sequential monotherapies to distinct mechanistic combinations. The sequential challenge described by Peng et al. [4] might be better addressed by combining PD-1 inhibitors with agents that normalize the chemokine environment (e.g., LIF inhibitors) or deplete Tregs (e.g., anti-CD70 antibodies or CD27 blockers).

Limitations

It is important to acknowledge the limitations of the current body of literature. Much of the data is derived from specific endemic populations, potentially limiting generalizability to non-endemic NPC which may have different genomic drivers. Furthermore, the heterogeneity of the TME described in single-cell studies [10] implies that a single biopsy may not capture the full immune profile of a patient, complicating biomarker development.

Conclusion

Nasopharyngeal carcinoma represents a complex immunological challenge where viral latency, chemokine dysregulation, and adaptive immune suppression converge. The evidence suggests that the key to improving outcomes, particularly in recurrent disease, lies in dismantling the Treg-mediated suppressive network and restoring the chemokine gradients necessary for effector cell infiltration. Future clinical trials should prioritize combination strategies that target the CD70-CD27 axis or the LIF-CXCL9 pathway alongside standard checkpoint inhibition. By re-engineering the tumor microenvironment, we may finally unlock the full potential of immunotherapy in this uniquely virus-driven malignancy.

References

1. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. Lancet Lond Engl. 2019 Jul 6;394(10192):64–80.
2. Chang ET, Ye W, Zeng YX, Adami HO. The Evolving Epidemiology of Nasopharyngeal Carcinoma. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2021 Jun;30(6):1035–47.
3. Guo R, Mao YP, Tang LL, Chen L, Sun Y, Ma J. The evolution of nasopharyngeal carcinoma staging. Br J Radiol. 2019 Oct;92(1102):20190244.
4. Peng Z, Wang Y, Fan R, Gao K, Xie S, Wang F, et al. Treatment of Recurrent Nasopharyngeal Carcinoma: A Sequential Challenge. Cancers. 2022 Aug 25;14(17):4111.
5. Su ZY, Siak PY, Leong CO, Cheah SC. Nasopharyngeal Carcinoma and Its Microenvironment: Past, Current, and Future Perspectives. Front Oncol. 2022;12:840467.
6. Tang S, Wu Z, Chen L, She L, Zuo W, Luo W, et al. Multi-omics analysis reveals the association between elevated KIF18B expression and unfavorable prognosis, immune evasion, and regulatory T cell activation in nasopharyngeal carcinoma. Front Immunol. 2023;14:1258344.
7. Gong L, Luo J, Zhang Y, Yang Y, Li S, Fang X, et al. Nasopharyngeal carcinoma cells promote regulatory T cell development and suppressive activity via CD70-CD27 interaction. Nat Commun. 2023 Apr 6;14(1):1912.
8. Wang J, Luo Y, Bi P, Lu J, Wang F, Liu X, et al. Mechanisms of Epstein-Barr virus nuclear antigen 1 favor Tregs accumulation in nasopharyngeal carcinoma. Cancer Med. 2020 Aug;9(15):5598–608.
9. Yang Y, Chen X, Pan J, Ning H, Zhang Y, Bo Y, et al. Pan-cancer single-cell dissection reveals phenotypically distinct B cell subtypes. Cell. 2024 Aug 22;187(17):4790-4811.e22.
10. Liu Y, He S, Wang XL, Peng W, Chen QY, Chi DM, et al. Tumour heterogeneity and intercellular networks of nasopharyngeal carcinoma at single cell resolution. Nat Commun. 2021 Feb 2;12(1):741.
11. Jin S, Li R, Chen MY, Yu C, Tang LQ, Liu YM, et al. Single-cell transcriptomic analysis defines the interplay between tumor cells, viral infection, and the microenvironment in nasopharyngeal carcinoma. Cell Res. 2020 Nov;30(11):950–65.

12. van der Vorst EPC, Döring Y, Weber C. Chemokines. Arterioscler Thromb Vasc Biol. 2015 Nov;35(11):e52-56.
13. Mughees M, Kaushal JB, Sharma G, Wajid S, Batra SK, Siddiqui JA. Chemokines and cytokines: Axis and allies in prostate cancer pathogenesis. Semin Cancer Biol. 2022 Nov;86(Pt 3):497–512.
14. Goenka A, Khan F, Verma B, Sinha P, Dmello CC, Jogalekar MP, et al. Tumor microenvironment signaling and therapeutics in cancer progression. Cancer Commun Lond Engl. 2023 May;43(5):525–61.
15. Korbecki J, Grochans S, Gutowska I, Barczak K, Baranowska-Bosiacka I. CC Chemokines in a Tumor: A Review of Pro-Cancer and Anti-Cancer Properties of Receptors CCR5, CCR6, CCR7, CCR8, CCR9, and CCR10 Ligands. Int J Mol Sci. 2020 Oct 15;21(20):7619.
16. Pascual-García M, Bonfill-Teixidor E, Planas-Rigol E, Rubio-Perez C, Iurlaro R, Arias A, et al. LIF regulates CXCL9 in tumor-associated macrophages and prevents CD8+ T cell tumor-infiltration impairing anti-PD1 therapy. Nat Commun. 2019 Jun 11;10(1):2416.
17. Böttcher JP, Bonavita E, Chakravarty P, Blees H, Cabeza-Cabrerizo M, Sammicheli S, et al. NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control. Cell. 2018 Feb 22;172(5):1022-1037.e14.