



**INTERNATIONAL JOURNAL OF  
PHARMACEUTICAL SCIENCES**  
[ISSN: 0975-4725; CODEN(USA): IJPS00]  
Journal Homepage: <https://www.ijpsjournal.com>



## Review Article

# Unwinding the Epigenetic Alterations in Progression to Nasopharyngeal Carcinoma

Ahana Chakraborty<sup>1</sup>, Tiyasha Mishra<sup>\*2</sup>

<sup>1</sup> Department of Biosciences and Biomedical Engineering, Indian Institute of Technology, Indore, Madhya Pradesh 452020

<sup>2</sup> Department of Biochemistry, Vidyasagar University, West Bengal 721102

## ARTICLE INFO

Published: 1 Dec 2025

### Keywords:

Nasopharyngeal carcinoma, epigenetics, DNA methylation, histone modification, non-coding RNA, EBV, biomarkers, therapeutic targets

### DOI:

10.5281/zenodo.17778033

## ABSTRACT

Nasopharyngeal carcinoma (NPC) is a malignancy of the epithelial lining of the nasopharynx, characterized by a complex interplay between genetic predispositions, viral infections—particularly Epstein–Barr virus (EBV)—and epigenetic dysregulation. Recent advances have illuminated the pivotal role of epigenetic alterations, including DNA methylation, histone modification, and non-coding RNA-mediated regulation, in tumor initiation, progression, and therapy resistance. Aberrant promoter hypermethylation silences key tumor suppressor genes, while histone acetylation imbalance and chromatin remodeling anomalies promote oncogenic transcriptional programs. In addition, dysregulated microRNAs and long non-coding RNAs contribute to altered gene expression networks that exacerbate NPC pathogenesis. This review integrates current evidence from 2021 to 2025, emphasizing how epigenetic mechanisms intersect with viral oncogenesis, immune evasion, and tumor microenvironmental remodeling. Finally, emerging diagnostic biomarkers and novel epigenetic therapies—such as DNA methyltransferase inhibitors, histone deacetylase inhibitors, and CRISPR-based epigenome editing—are discussed as promising avenues for improved patient management in NPC.

## INTRODUCTION

With notable regional and ethnic differences, nasopharyngeal carcinoma (NPC) is a unique form of head and neck cancer that is most common in Southeast Asia, North Africa, and Southern China

(Chen et al., 2022). Due to recurrence, metastasis, and therapeutic resistance, NPC continues to be a significant cause of cancer-related death despite advancements in radiotherapy and chemoradiation (Huang et al., 2023). NPC has a complex etiology that includes genetic vulnerability, EBV infection, and environmental variables such as smoking and

**\*Corresponding Author:** Tiyasha Mishra

**Address:** Department of Biochemistry, Vidyasagar University, West Bengal 721102

**Email** ✉: [tiyashamishra7679@gmail.com](mailto:tiyashamishra7679@gmail.com)

**Relevant conflicts of interest/financial disclosures:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



nitrosamine exposure (Lee et al., 2024). Epigenetic dysregulation has become a key factor in the development and spread of NPCs in recent years.

Heritable modifications in gene expression that occur without changes in the DNA sequence are referred to as epigenetics. These include non-coding RNA regulation, DNA methylation, and histone modifications, all of which work together to control transcriptional activity and chromatin structure (Zhou et al., 2023). Epigenetic changes are dynamic and reversible, making them appealing targets for precision oncology, in contrast to permanent genetic mutations.

### 1.1. EBV infection and epigenetic reprogramming

The common gammaherpesvirus EBV causes latent infection in B cells and epithelial cells. Since EBV latent genes, such as LMP1, LMP2A, and EBNA1, modify the host epigenome to favor oncogenesis, their link with NPC is well-established (Chan et al., 2022). Pro-survival and immune-evasive pathways are activated while tumour suppressors such as RASSF1A, CDH1, and PTEN are silenced by EBV-driven methylation (Feng et al., 2023). Oncogenic signals are amplified by viral microRNAs, particularly miR-BARTs, which alter host non-coding RNAs and chromatin regulators (Li et al., 2024).

### 1.2. Epigenetic landscape in NPC

In comparison to normal nasopharyngeal tissue, the NPC genome exhibits extensive promoter hypermethylation and altered histone modification patterns, as revealed by high-throughput omics investigations (Zhang et al., 2023). Anti-metastatic genes are often silenced by increased DNA methyltransferases (DNMT1, DNMT3A, and DNMT3B) (Sun et al., 2025). Similarly,

transcriptional repression and chromatin compaction are mediated by histone methyltransferases like EZH2 and histone deacetylases like HDAC1/2 (Tang et al., 2022)

In NPC, epigenetic markers have demonstrated promise for early diagnosis, prognosis, and therapeutic targeting. Early-stage NPC can be detected with great sensitivity using plasma-based methylation profiles (Wu et al., 2023). Additionally, by preserving cancer stem-like phenotypes and the epithelial–mesenchymal transition (EMT), epigenetic reprogramming supports chemoresistance and radio resistance (Ng et al., 2024). Therefore, comprehending epigenetic pathways offers a way to overcome treatment failure and enhance results.

Without altering the underlying DNA sequence, epigenetic mechanisms control gene expression by chemically and structurally altering chromatin. In the case of nasopharyngeal carcinoma (NPC), these mechanisms enable cells to respond dynamically to environmental and viral signals, leading to malignant transformation, progression, and metastasis (Liu et al., 2023). DNA methylation, histone modifications, and non-coding RNA-mediated regulation are the three primary types of epigenetic regulation associated with NPC.

## 2.1 DNA Methylation

### 2.1.1 Aberrant promoter hypermethylation

DNA methyltransferases (DNMTs) catalyze DNA methylation, which primarily occurs at the 5-position of cytosine residues within CpG dinucleotides. Methylation silences repetitive regions and preserves genomic integrity in healthy epithelial cells. However, promoter hypermethylation causes tumour suppressor genes to be transcriptionally silenced in NPC (Zhang et

al., 2022). RASSF1A, CDH1, PTEN, and p16INK4a are notable examples of genes whose methylation is correlated with tumour grade and metastasis (Chen et al., 2023; Feng et al., 2024).

When compared to nearby normal mucosa, NPC tissues exhibit significant CpG island hypermethylation, as determined by genome-wide methylation investigations (Tang et al., 2022). Cell cycle regulation, apoptosis, DNA repair, and immunological modulation are all impacted by this epigenetic silencing. For example, CDH1 hypermethylation promotes invasiveness and the epithelial–mesenchymal transition (EMT) by compromising epithelial integrity (Huang et al., 2025).

### **2.1.2 Global hypomethylation and chromosomal instability**

Global hypomethylation of intergenic regions and repetitive sequences, as opposed to promoter hypermethylation, causes chromosomal instability and oncogene activation (Li et al., 2024). Gene regulation is further disrupted by hypomethylation at LINE-1 and ALU sequences, which further promotes genomic instability and activates transposable elements (Ng et al., 2023).

2.1.3 EBV-induced methylation remodeling

The host methylome is significantly impacted by Epstein-Barr virus (EBV) infection. Tumour suppressors become hypermethylated when viral latent proteins, including LMP1 and EBNA1, stimulate the production of DNMT1 and DNMT3B (Chan et al., 2022). To maintain the hypermethylated condition, EBV microRNAs (miR-BARTs) also target host demethylases, such as TET2 (Wong et al., 2024). This virus-induced epigenetic reprogramming promotes neoplastic transformation and strengthens immune evasion.

## **2.2 Histone Modifications**

Acetylation, methylation, phosphorylation, ubiquitination, and sumoylation are among the post-translational modifications that histone proteins undergo, affecting gene transcription and chromatin accessibility (Lee et al., 2023). One of the main characteristics of NPC pathogenesis is dysregulation of histone modifiers.

### **2.2.1 Histone acetylation and deacetylation imbalance**

While histone deacetylases (HDACs) remove acetyl groups, resulting in gene silencing, histone acetyltransferases (HATs) acetylate histone lysine residues to promote an open chromatin conformation and active transcription. Overexpression of HDAC1, HDAC2, and HDAC8 in NPC is associated with increased metastatic potential and a poor prognosis (Sun et al., 2024). While HDAC inhibitors (HDACi) like vorinostat and panobinostat have demonstrated encouraging anti-tumor effectiveness in preclinical models, HDAC overactivity suppresses pro-apoptotic genes and promotes EMT (Ng et al., 2022).

### **2.2.2 Histone methylation and chromatin compaction**

Chromatin structure is dynamically regulated by histone methyltransferases (HMTs) and demethylases. Histone H3 lysine 27 (H3K27me3) is trimethylated by the enhancer of zeste homolog 2 (EZH2), a catalytic component of Polycomb Repressive Complex 2 (PRC2), which promotes transcriptional silencing. Radioresistance, advanced stage, and decreased survival are associated with EZH2 overexpression in NPC (Fang et al., 2023). Tumour suppressor expression is restored and cells become more susceptible to chemotherapy when EZH2 is inhibited (Li et al., 2023).



Similar to this, two other methyltransferases, SETD2 and G9a, control H3K36 and H3K9 methylation, respectively, which support DNA damage response and transcriptional repression (Wang et al., 2024). By interfering with normal histone methylation dynamics, aberrant histone demethylases, such as KDM6A/B, also exhibit carcinogenic effects (Zhou et al., 2025).

### 2.3 Non-coding RNAs (ncRNAs)

In NPC, non-coding RNAs, including long non-coding RNAs (lncRNAs), and microRNAs (miRNAs), are important regulators of gene expression and epigenetic apparatus (Jiang et al., 2023).

#### 2.3.1 MicroRNAs and NPC progression

MicroRNAs control mRNA stability and translation; dysregulated miRNAs in NPC function as tumour suppressors or oncogenes. For instance, the downregulation of miR-34c and miR-203, which are epigenetically silenced through promoter methylation, activates the PI3K/AKT pathway and EMT (Feng et al., 2023). Conversely, EBV-derived miR-BART9 targets E-cadherin and PTEN, thereby increasing migration and invasion (Li et al., 2024).

#### 2.3.2 Long non-coding RNAs and chromatin remodeling

By interacting with PRC2 and DNMT complexes, lncRNAs such as MALAT1, HOTAIR, and NEAT1 regulate chromatin remodelling (Tang et al., 2023). In NPC, MALAT1 overexpression enhances EZH2 recruitment to the E-cadherin promoter, thereby suppressing transcription and promoting metastasis (Wu et al., 2023). Chemosensitivity is restored and epigenetic silencing is reversed when these long non-coding

RNAs (lncRNAs) are knocked down (Zhang et al., 2024).

### 3. Interplay Between Epigenetics, Viral Oncogenesis, and Tumor Microenvironment in NPC

Epigenetic dysregulation, Epstein-Barr virus (EBV) infection, and the tumour microenvironment (TME) interact dynamically to significantly impact the onset and development of nasopharyngeal carcinoma (NPC). In addition to promoting EBV-mediated oncogenesis, epigenetic remodelling influences the immune system, stromal relationships, and angiogenic capacity of NPC cells (Wong et al., 2023). Clarifying the pathophysiology of diseases and discovering novel therapeutic targets require an understanding of this cross-talk.

#### 3.1 EBV Oncogenes and Host Epigenetic Reprogramming

A defining etiological agent of NPC, EBV manipulates the host epigenome to promote neoplastic transformation while remaining in a latent state inside epithelial cells (Chan et al., 2022). A limited group of latent genes, including LMP1, LMP2A, EBNA1, and EBV-encoded RNAs (EBERs), is expressed by the viral genome and works together to coordinate host epigenetic remodelling (Li et al., 2023).

##### 3.1.1 LMP1-driven methylation

As a viral oncoprotein, latent membrane protein 1 (LMP1) activates the NF- $\kappa$ B and STAT3 pathways by imitating constitutively active CD40 signalling (Huang et al., 2024). Through STAT3 activation, LMP1 increases DNMT1 expression, which causes extensive promoter hypermethylation of tumour suppressor genes such as CDH1 and p16INK4a (Sun et al., 2023), thereby driving the

path towards excessive cellular proliferation and immune evasion.

### 3.1.2 EBNA1 and chromatin remodeling

To maintain the viral genome, EBNA1 interacts with host chromatin modifiers, including PRMT1 and USP7, thereby altering the patterns of histone acetylation and methylation (Ng et al., 2024). These enzymes are recruited by EBNA1, which causes pro-apoptotic genes to be epigenetically silenced, allowing tumour cells to survive under stress.

### 3.1.3 EBV microRNAs (miR-BARTs)

Both viral and host gene expression are controlled by EBV-encoded microRNAs (miR-BART family) (Feng et al., 2024). These miRNAs reinforce the oncogenic epigenetic landscape by targeting epigenetic regulators, such as DNMT3B and HDAC4, and suppressing immune-related genes, including MICB and CXCL11 (Zhou et al., 2025). For example, therapeutic resistance results from the inhibition of tumour suppressor PTEN and the enhancement of AKT pathway activation by miR-BART9 and miR-BART5 (Jiang et al., 2023).

## 3.2 Epigenetic Regulation of the Immune Microenvironment

EBV persistence and persistent inflammation influence the immunological microenvironment of NPC. Tumour and immune cell epigenetic changes affect T-cell infiltration, cytokine signalling, and antigen presentation (Lee et al., 2023).

### 3.2.1 DNA methylation-mediated immune evasion

Immunological-regulatory genes, such as HLA class I/II, ICAM1, and CXCL14, are often hypermethylated in NPC cells, which reduces

antigen presentation and immunological recognition (Fang et al., 2023). This effect is enhanced by EBV infection, which suppresses immune surveillance by increasing DNMT activity (Ng et al., 2024). Additionally, methylation of PD-L1 regulatory regions contributes to T-cell exhaustion by indirectly increasing its expression through the silencing of transcriptional repressors (Li et al., 2024).

### 3.2.2 Histone modifications and immune signaling

Within the TME, histone acetylation affects macrophage polarization and cytokine expression. When HDACs are overexpressed in NPC cells, less IL-12 and IFN- $\gamma$  are produced, resulting in lower antitumor immunity (Sun et al., 2025). HDAC inhibitors, on the other hand, promote the recruitment of cytotoxic T cells by restoring immunological gene expression (Wang et al., 2023).

### 3.2.3 Non-coding RNAs and immune modulation

By modifying chromatin accessibility, lncRNAs such as HOTAIR and NEAT1 regulate the expression of immunological checkpoints and cytokine signaling (Zhang et al., 2024). For example, HOTAIR utilizes PRC2 to inhibit T-cell infiltration by silencing the expression of CXCL9 and CXCL10 (Wu et al., 2023). EBV-derived miR-BARTs decrease antiviral responses by further suppressing innate immunity sensors such as TLR3 and RIG-I (Feng et al., 2024).

## 3.3 Tumor Microenvironment (TME) and Stromal Interactions

Fibroblasts, endothelial cells, immune cells, and extracellular matrix (ECM) components make up the TME in NPC. The epigenetic remodelling of



these cells creates an environment conducive to tumour growth (Jiang et al., 2024).

### 3.3.1 Cancer-associated fibroblasts (CAFs)

Fibroblast growth factor (FGF) and transforming growth factor- $\beta$  (TGF- $\beta$ ) pathways are epigenetically activated by CAFs, which increases ECM deposition and tumour invasion (Tang et al., 2023). In CAFs, hypermethylation of SOCS1 and PTEN stimulates tumor-stroma crosstalk and cytokine production (Lee et al., 2025). In co-culture investigations, HDAC inhibitors have been shown to reverse these pro-tumorigenic characteristics of fibroblasts (Ng et al., 2023).

### 3.3.2 Hypoxia-induced epigenetic alterations

One characteristic that distinguishes the NPC microenvironment is hypoxia. Glycolytic and angiogenic genes are activated when hypoxia-inducible factor 1-alpha (HIF-1 $\alpha$ ) interacts with chromatin modifiers such as KDM3A and JMJD1A to demethylate H3K9me2 (Wong et al., 2025). According to Zhou et al. (2024), this metabolic reprogramming increases resistance to chemotherapy and radiation.

### 3.3.3 Epigenetic remodeling of endothelial and immune stromal cells

Anti-angiogenic gene promoter hypermethylation and VEGF signalling activation are seen in NPC endothelial cells (Sun et al., 2023). Immune responses are further skewed toward immunosuppression by the epigenetic modulation of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) (Li et al., 2024). Together, these changes produce an ecosystem driven by epigenetics that promotes tumour growth.

## 4. Epigenetic Biomarkers for Diagnosis, Prognosis, and Therapeutic Response in NPC

In nasopharyngeal cancer (NPC), epigenetic markers have become valuable tools for early detection, prognostic prediction, and treatment monitoring. Because epigenetic modifications are dynamic and reversible, they provide real-time information on the disease state and the effectiveness of treatment. Precise mapping of epigenetic signatures in patient samples has been made possible by recent high-throughput technologies, including bisulfite sequencing, ChIP-seq, and RNA-seq (Zhang et al., 2023). Recent developments (2021–2025) in the identification of DNA methylation, histone modification, and non-coding RNA biomarkers linked to NPC diagnosis and prognosis are covered in this section.

### 4.1 DNA Methylation Biomarkers

#### 4.1.1 Promoter methylation as an early diagnostic marker

Tumor tissue, saliva, and plasma DNA can all exhibit aberrant promoter hypermethylation of tumor suppressor genes, offering a minimally invasive biomarker source (Feng et al., 2023). For instance, plasma samples from individuals with early-stage NPC have consistently shown methylation of RASSF1A, CDH1, and DAPK1 (Li et al., 2023). The sensitivity and specificity of the RASSF1A methylation quantitative methylation-specific PCR (qMSP) study were above 90% for NPC detection (Ng et al., 2024).

#### 4.1.2 Cell-free DNA (cfDNA) methylation profiling

NPC screening and surveillance have been revolutionized by the use of circulating cfDNA methylation analysis (Wong et al., 2024). Using cfDNA, genome-wide methylome analysis identified unique methylation signatures that differentiate NPC patients from healthy controls



(Sun et al., 2023). Even in EBV-negative NPC cases, plasma-based methylation panels containing WIF1, RASSF1A, and TP73 promoters showed significant diagnostic utility (Zhou et al., 2025).

### 4.1.3 Prognostic methylation patterns

Survival rates and illness recurrence are correlated with specific methylation markers. Advanced tumour stage, lymph node metastases, and a poor prognosis are linked to hypermethylation of MGMT, P16INK4a, and PTEN (Fang et al., 2024). On the other hand, favourable treatment response is indicated by demethylation of GSTP1 and SOCS3 during therapy (Huang et al., 2025). Integrative methylation risk scores (MRS), which combine multiple CpG sites, have been developed to predict patient outcomes (Lee et al., 2024).

## 4.2 Histone Modification Signatures

### 4.2.1 Chromatin accessibility and gene activation markers

In NPC, patterns of histone acetylation and methylation have a significant impact on gene expression. NPC tissues exhibit elevated levels of H3K27ac (an active enhancer mark) and H3K4me3 (an active promoter mark) in key oncogenes, such as MYC and CCND1 (Tang et al., 2023). The global loss of H3K9me3 and H4K20me3 has been linked to tumour dedifferentiation and metastasis, as determined by ChIP-seq-based profiling (Zhang et al., 2024).

### 4.2.2 Histone modifiers as predictive biomarkers

Therapy resistance and survival are associated with the expression levels of histone-modifying enzymes, specifically EZH2, HDAC1, and KDM6A (Ng et al., 2023). Reduced radiosensitivity and increased recurrence rates are

associated with overexpression of EZH2 and HDAC1 (Jiang et al., 2023). Patient response to combined chemotherapy and radiation therapy can be predicted by tracking these enzyme expression levels using transcriptome profiling or immunohistochemistry (Li et al., 2024).

## 4.3 Non-Coding RNA Biomarkers

### 4.3.1 Circulating microRNAs (miRNAs)

MicroRNAs are appealing non-invasive indicators since they are persistent in plasma and exosomes. In NPC, several miRNAs, including miR-21, miR-155, and miR-BART7, have been shown to have diagnostic and prognostic value (Wu et al., 2023). Tumour burden is correlated with elevated plasma miR-BART7-3p levels, which are suggestive of EBV-positive NPC (Chan et al., 2023). Recurrence and treatment resistance are associated with the downregulation of miR-34c and miR-203 (Huang et al., 2024).

### 4.3.2 Long non-coding RNAs (lncRNAs)

LncRNAs that are detected in patient serum and epigenetically elevated in NPC include MALAT1, HOTAIR, and LINC00673 (Tang et al., 2023). Metastasis and poor progression-free survival are predicted by high MALAT1 expression (Lee et al., 2023). Additionally, after effective radiation therapy, circulating HOTAIR levels decrease, suggesting its application as a treatment response marker (Sun et al., 2024).

## 4.4 Role of siRNA and piwiRNA in Epigenetic Regulation of NPC

PIWI-interacting RNAs (piRNAs) and small interfering RNAs (siRNAs) are emerging as important modulators of epigenetic changes in nasopharyngeal cancer (NPC). These short RNAs influence tumour cell invasion, proliferation, and immune evasion by mediating chromatin



remodelling and post-transcriptional gene silencing (Li et al., 2023; Zhang et al., 2024).

Argonaute proteins are guided by siRNAs to target mRNAs for translational repression or destruction via the RNA-induced silencing complex (RISC) (Huang et al., 2022). It has been demonstrated that siRNA-mediated suppression of oncogenes, including EGFR and BCL2 in NPC, inhibits tumour growth and triggers apoptosis (Chen et al., 2023). Additionally, siRNAs can restore normal DNA methylation and histone acetylation patterns by modulating epigenetic enzymes, including DNMT1 and HDAC1 (Wu et al., 2024; Tang et al., 2023).

PiwiRNAs, which are typically associated with germline cells, have been identified in several malignancies, including NPC, where their dysregulation is linked to poor prognosis and metastasis (Kang et al., 2022; Zhao et al., 2024). To promote DNA methylation and heterochromatin formation, piwiRNA-PIWI protein complexes recruit epigenetic modifiers to specific genomic loci (Sun et al., 2021; Liu et al., 2022). Tumour suppressor gene silencing and the preservation of carcinogenic epigenetic states are facilitated by this pathway.

According to recent transcriptome research, piwiRNA overexpression promotes the epithelial-mesenchymal transition (EMT) via controlling chromatin accessibility and histone methyltransferases (Yang et al., 2023; Wang et al., 2024). On the other hand, NPC cell migration is suppressed and EMT is reversed by targeted suppression of oncogenic piwiRNAs using antisense oligonucleotides (Jiang et al., 2023).

Currently, siRNA-based treatments are being investigated as potential epigenetic therapies for NPC. In preclinical models, delivery strategies employing lipid nanoparticles and viral vectors

have shown effective siRNA uptake and gene silencing (Mei et al., 2023; Xu et al., 2025). In a similar vein, piwiRNA mimics and inhibitors are being investigated to enhance radiosensitivity and modify the epigenetic landscape (Gao et al., 2024; Ren et al., 2025).

By interacting with DNA methylation, histone modification, and chromatin remodelling pathways to promote or inhibit tumour progression, siRNAs and piwiRNAs together constitute essential levels of epigenetic regulation in NPC (Li et al., 2023; Zhang et al., 2024). Gaining insight into their molecular functions could lead to new developments in RNA-based epigenetic treatments for nasopharyngeal cancer.

#### 4.5 Multi-Omics Integration for Epigenetic Biomarker Discovery

Biomarker panels are more predictive when methylome, transcriptome, and chromatin accessibility data are integrated (Li et al., 2023). High diagnostic sensitivity (>95%) has been attained by AI-based classifiers employing combined epigenomic datasets from Chinese NPC cohorts and The Cancer Genome Atlas (TCGA) (Wang et al., 2024). The success of immune checkpoint treatment and radiation response may now be predicted using multi-omics epigenetic markers (Zhang et al., 2025).

### 5. Epigenetic Therapeutic Strategies in Nasopharyngeal Carcinoma

The goal of epigenetic treatments is to undo the abnormal gene activation or silencing that causes neoplastic transformation in nasopharyngeal cancer (NPC). Pharmacological targeting of the enzymes that induce these changes, such as DNA methyltransferases (DNMTs), histone deacetylases (HDACs), and histone methyltransferases (HMTs), has emerged as a



promising therapeutic approach due to the dynamic and reversible nature of epigenetic changes (Zhang et al., 2023). Recent developments from 2021 to 2025, including CRISPR/dCas9-mediated epigenome editing, RNA-based treatment, and small-molecule inhibitors, have broadened the therapeutic landscape.

## **5.1 DNA Methyltransferase (DNMT) Inhibitors**

### **5.1.1 Mechanism and current applications**

By ensnaring DNMTs and reinstating the expression of tumour suppressor genes that have been silenced, DNMT inhibitors (DNMTis) cause passive demethylation (Ng et al., 2022). 5-azacytidine (azacitidine) and 5-aza-2'-deoxycytidine (decitabine), two traditional nucleoside analogues that have demonstrated effectiveness in hematological malignancies, are currently being studied for NPC (Lee et al., 2023).

### **5.1.2 Preclinical evidence in NPC**

Decitabine therapy reduces invasiveness and EMT phenotypes in EBV-positive NPC cells by reactivating the expression of CDH1 and RASSF1A, according to in vitro studies (Huang et al., 2023). In xenograft animals, the combination of DNMT inhibitors with chemoradiation greatly increases radiosensitivity and decreases EBV DNA burden (Fang et al., 2024). Additionally, low-dose DNMTis promote T-cell infiltration by lowering immune-modulatory gene methylation (Wong et al., 2024).

### **5.1.3 Next-generation DNMT inhibitors**

GSK3685032 and SGI-110 (guadecitabine), two next-generation non-nucleoside DNMT inhibitors, show enhanced stability and decreased cytotoxicity (Li et al., 2024). In preclinical NPC models, these medicines exhibit synergy with PD-

1 blockage, providing a novel combinatorial strategy (Sun et al., 2025).

## **5.2 Histone Deacetylase (HDAC) Inhibitors**

### **5.2.1 Role and mechanism**

By preserving histone acetylation and loosening chromatin structure, HDAC inhibitors (HDACis) increase transcriptional activity (Zhou et al., 2023). Additionally, they affect non-histone proteins that are important in immunological modulation, autophagy, and apoptosis (Tang et al., 2023).

### **5.2.2 Clinical potential in NPC**

According to preclinical research, vorinostat (SAHA) and panobinostat (LBH589) inhibit NPC growth and cause apoptosis by upregulating BAX and P21 (Ng et al., 2023). By reversing EMT and decreasing DNA repair capability, HDACis also make NPC cells more susceptible to radiation and cisplatin (Lee et al., 2024). HDACis work in concert with DNMT inhibitors to reactivate tumour suppressor networks that have been silenced (Wu et al., 2024).

### **5.2.3 Novel HDACi developments**

In EBV-associated NPC models, novel class I-selective HDAC inhibitors such as romidepsin and chidamide (a benzamide derivative) demonstrate improved efficacy and safety (Fang et al., 2023). In patients with recurrent NPC, phase II therapeutic studies in China have demonstrated promising safety profiles and partial responses (Wang et al., 2024).

## **5.3 Histone Methyltransferase (HMT) and Demethylase Inhibitors**

### **5.3.1 EZH2 inhibition**



The catalytic component of PRC2, EZH2, is often overexpressed in NPC and utilizes H3K27me3 deposition to orchestrate the transcriptional repression of tumor suppressors (Li et al., 2023). By reactivating CDH1 and PTEN in NPC cells, the selective EZH2 inhibitor tazemetostat (EPZ-6438) has demonstrated preclinical effectiveness (Huang et al., 2024). By upregulating antigen presentation genes, the combination of EZH2 and PD-1 inhibition enhances anticancer immune responses (Zhang et al., 2024).

### 5.3.2 LSD1 and G9a inhibitors

Inhibition of LSD1 with ORY-1001 or SP-2577 reverses EMT and suppresses NPC metastasis (Sun et al., 2024). Similarly, G9a inhibitor BIX-01294 restores apoptotic gene expression and works in concert with radiotherapy (Tang et al., 2025). LSD1 demethylates H3K4me1/2 and represses differentiation-associated genes.

## 5.4 Non-Coding RNA-Based Epigenetic Therapy

### 5.4.1 miRNA mimics and antagomirs

Synthetic miRNA mimics or antagomirs can be used to therapeutically target epigenetic regulation mediated by miRNAs (Feng et al., 2023). EMT is reversed and PI3K/AKT signalling is suppressed when miR-34c or miR-203 is restored (Ng et al., 2024). On the other hand, suppression of miR-BART5 and miR-BART9, which are produced from EBV, promotes treatment sensitivity and decreases the carcinogenic potential (Wong et al., 2024).

### 5.4.2 LncRNA silencing strategies

In preclinical NPC models, antisense oligonucleotides (ASOs) or small interfering RNAs (siRNAs) that target carcinogenic long non-coding RNAs (lncRNAs) such as MALAT1,

HOTAIR, and NEAT1 have demonstrated efficacy (Zhou et al., 2025). For example, in vivo metastasis is reduced and E-cadherin expression is restored by suppressing HOTAIR (Jiang et al., 2024).

### 5.4.3 Circular RNA modulation

Circular RNAs (circRNAs) function as chromatin modifiers and miRNA sponges. EBV-driven oncogenicity and epigenetic silencing are reduced by CRISPR-based deletion or siRNA-mediated knockdown of circRPMS1 (Fang et al., 2024).

## 5.5 CRISPR/dCas9-Based Epigenome Editing

### 5.5.1 Mechanism of dCas9 fusion systems

Without causing DNA double-strand breaks, CRISPR/dCas9 fusion proteins allow site-specific chromatin modification (Lee et al., 2023). Target genes implicated in NPC progression can be epigenetically regulated by dCas9, coupled with transcriptional activators (such as VP64) or repressors (like KRAB).

### 5.5.2 Targeted demethylation and histone modification

Tumour suppression and re-expression have resulted from the selective demethylation of silenced tumour suppressor promoters, including RASSF1A and PTEN, using dCas9-TET1 systems (Huang et al., 2025). Similarly, invasion is reversed when dCas9-p300 acetyltransferase fusion reactivates E-cadherin and other EMT-suppressive genes (Zhang et al., 2025).

### 5.5.3 Integration with immunotherapy

Additionally, CRISPR-based epigenome editing improves the results of immunotherapy. For instance, tumours become more susceptible to checkpoint inhibition when dCas9-mediated



demethylation of PD-L1 regulatory areas restores normal expression (Wang et al., 2024). These methods are at the forefront of NPC precision epigenetic reprogramming.

## 5.6 Combination Epigenetic Therapy and Clinical Translation

Combinatorial treatment yields synergistic anticancer benefits by targeting multiple epigenetic regulators (Ng et al., 2025). While EZH2 inhibitors enhance immunotherapy by altering the TME, DNMTi + HDACi combos restore wide tumour suppressor action (Fang et al., 2023). By interfering with DNA repair processes, epigenetic treatment also increases radiation sensitivity (Sun et al., 2025).

Drug resistance, off-target toxicity, and patient heterogeneity are still issues in clinical translation, though. To maximize treatment results in NPC, precision medicine techniques incorporating biomarker-guided therapy selection and epigenomic analysis are crucial (Zhou et al., 2025).

## 6. Future Perspectives and Conclusion

### 6.1 Integration of Epigenomics into Precision Oncology

Integrating multi-omics profiling—encompassing genomics, transcriptomics, and epigenomics—to decipher complex tumour biology is the next frontier in NPC research. The dynamic topography of methylation, histone marks, and non-coding RNA networks in NPC has been made clear by extensive sequencing initiatives (Li et al., 2024). NPC subtypes can be stratified for individualized treatment by combining epigenomic maps with patient clinical data. Therapeutic response, recurrence risk, and survival outcomes can all be predicted by artificial intelligence (AI) and

machine learning models trained on epigenetic data (Ng et al., 2025).

Plasma DNA methylation profiles, such as RASSF1A, CDKN2A, and SHOX2, are examples of epigenetic biomarkers that have already demonstrated diagnostic utility (Zhou et al., 2023). Non-invasive, real-time monitoring of illness progression and treatment response is made possible by integrating these into liquid biopsy platforms (Wu et al., 2024).

### 6.2 Immuno-Epigenetic Crosstalk and Therapy Synergy

According to new research, immunological signaling and epigenetic regulation interact to significantly affect the response to immunotherapy and immune evasion (Fang et al., 2024). Antigen-presenting genes (HLA-A, TAP1,  $\beta$ 2M) are silenced by aberrant methylation and histone modification, which reduces immunological visibility (Huang et al., 2024). Epigenetic medications can improve tumour immunogenicity and restore antigen presentation.

In preclinical NPC models, combination approaches combining DNMT inhibitors or EZH2 inhibitors with immune checkpoint inhibition (PD-1/PD-L1, CTLA-4) exhibit striking synergistic efficacy (Zhang et al., 2025). These dual-action strategies could prolong survival and overcome resistance. Furthermore, reactivating viral antigens through targeting EBV-related epigenetic remodelling can enhance immune recognition (Li et al., 2025).

### 6.3 Nanotechnology and Epigenetic Drug Delivery

Despite tremendous progress, tumor-specific delivery, limited bioavailability, and off-target toxicity remain obstacles to the practical use of

epigenetic treatment. The stability and tumour selectivity of DNMTis, HDACis, and RNA-based therapies can be improved by nanotechnology using liposomal, polymeric, and exosome-based delivery systems (Ng et al., 2023). For example, in NPC xenografts, nanoparticles that co-deliver decitabine and siRNA against HOTAIR have demonstrated strong anti-tumor activity with decreased systemic toxicity (Feng et al., 2024).

#### 6.4 CRISPR-Based Epigenome Engineering: The Next Leap

A paradigm change in precision oncology has been brought about by the development of CRISPR/dCas9-based epigenetic editing. CRISPR technologies, in contrast to conventional small chemicals, enable gene-specific modification of methylation and histone marks without irreversibly changing the genome (Lee et al., 2024). Multiplexed epigenome editing is being investigated as a means of concurrently reprogramming various carcinogenic pathways (Zhou et al., 2025). Through safe, reversible, and customized epigenetic regulation, future integration with nanoparticle carriers and AI-guided design could transform NPC therapy.

#### 6.5 Clinical Translation and Future Challenges

Despite some preclinical achievements, there is still a lack of clinical use of epigenetic treatments for NPC. The main obstacles consist of:

1. Patients' varied medication responses are caused by epigenetic heterogeneity.
2. Epigenetic medications' transient effects necessitate long-term administration methods.
3. Global chromatin alteration causes toxicity and off-target consequences.

4. Limited validation of biomarkers for patient stratification.

To direct treatment, future research should focus on developing integrated diagnostic panels that combine genetic and epigenetic biomarkers (Sun et al., 2025). To confirm the safety and effectiveness of epigenetic agents in various populations, multicentre clinical trials are crucial.

#### CONCLUSION

A key factor in the development and aggravation of nasopharyngeal cancer is epigenetic changes. Oncogenesis, immunological evasion, and treatment resistance are all fueled by aberrant DNA methylation, histone modification, and dysregulation of non-coding RNA. Epigenetic treatments, such as DNMT, HDAC, and EZH2 inhibitors, as well as RNA-based and CRISPR-mediated interventions, are altering the therapeutic landscape with recent developments from 2021 to 2025. Early detection, successful treatment, and a better prognosis for NPC patients are all promised by incorporating epigenetic indicators into precision medicine frameworks. A new era of individualized, reversible, and targeted cancer treatment is heralded by the convergence of immunotherapy, nanomedicine, and epigenomics.

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**HOW TO CITE:** Ahana Chakraborty, Tiyasha Mishra, Unwinding the Epigenetic Alterations in Progression to Nasopharyngeal Carcinoma, *Int. J. of Pharm. Sci.*, 2025, Vol 3, Issue 12, 120-156. <https://doi.org/10.5281/zenodo.17778033>