The Role of PTEN in Nasopharyngeal Carcinoma

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Abstract

Nasopharyngeal carcinoma (NPC) is an aggressive head and neck tumor that is influenced by a variety of molecular factors during its pathogenesis. Among these, the phosphatase and tensin homolog (PTEN) plays a crucial role in regulatory networks. This article systematically reviews the multifaceted functions of PTEN in NPC, including its roles in inhibiting cell proliferation, regulating migration and invasion, promoting autophagy and apoptosis, and influencing resistance to radiotherapy. Molecular factors such as long non-coding RNA, microRNA (miRNA), and circular RNA can modulate PTEN through various pathways, thereby impacting the biological behavior of NPC. In addition, PTEN is involved in regulating the tumor microenvironment of NPC, and its interaction with the Epstein-Barr virus has also recently become a focus of research. A comprehensive understanding of the PTEN regulatory network provides a foundation for future personalized and targeted therapeutic strategies. This study expands our understanding of the pathogenesis of NPC and suggests new directions in the field of tumor biology and NPC treatment.

Keywords: nasopharyngeal carcinoma; PTEN; tumor suppressor gene; signaling pathways

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy of the nasopharyngeal mucosal epithelium, predominantly squamous cell carcinoma. It shows regional variation in incidence, with higher rates reported in northern Africa, southeast Asia, and southern China. Males are more commonly affected, typically in middle- to old-age [1,2]. Key risk factors include prolonged smoking, alcohol consumption, Epstein-Barr virus (EBV) infection, familial predisposition, and environmental factors [1,3,4]. Treatment modalities involve surgical resection for early-stage NPC, with radiotherapy being the mainstay, particularly for advanced or inoperable cases [5–7]. Chemotherapy, either alone or in conjunction with radiotherapy, is employed to manage or reduce tumor size [7,8]. Additionally, targeted therapies such as epidermal growth factor receptor (EGFR) inhibitors now offer viable treatment options [9]. In summary, a comprehensive treatment approach for NPC encompasses a combination of surgery, radiotherapy, chemotherapy, and targeted therapy [1,7], and our ultimate goal is to develop personalized treatment strategies to enhance patient survival rates and quality of life.

The protein encoded by phosphatase and tensin homolog (PTEN) belongs to the phosphatidylinositol 3-kinase/lipid phosphatase family. It is characterized by a lipid phosphatase domain and a C2 domain, which impart unique functionality [10]. PTEN regulates cell signaling pathways by dephosphorylating phosphatidylinositol-3,4,5-trisphosphate (PIP3) on the cell membrane, thereby inhibiting the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway [10]. The PI3K/Akt pathway participates in processes such as cell growth, proliferation, and survival. Moreover, the inhibitory role of PTEN helps to prevent abnormal cell proliferation and cancer development [10]. PTEN is thus commonly recognized as a tumor suppressor gene, and its loss or defect is common in various cancer types [10–12]. Dysfunction of PTEN leads to overactivation of the PI3K/Akt pathway, thereby promoting cell growth and survival and favoring tumorigenesis [10,11,13]. Mutations in the PTEN gene, or defects in its expression, have been associated with various cancer types including breast [14,15], prostate [16,17], and lung [18,19] cancer. Research also suggests that PTEN may have predictive value in cancer prognosis [11,20]. Beyond its role in tumor suppression, PTEN is also involved in regulating biological processes such as apoptosis, the cell cycle, and DNA damage repair, thus making it a protein of extensive research interest in cell biology and cancer studies [10].

PTEN plays a crucial role as a tumor suppressor in NPC. Current studies indicate that abnormal cytosine phosphoguanosine oligonucleotide (CpG) island methylation of PTEN is a significant early event in NPC and may be a potential diagnostic biomarker [20]. Additionally, PTEN gene mutations impact the prognosis of second head
and neck neuroendocrine carcinoma (NEC) by influencing signal transduction pathways for p53, MAPK, PI3K-Akt, myelin, and neurotrophic factor [21]. The PTEN mutation frequency reported in nasopharyngeal squamous cell carcinoma (NPSCC) is 11%, and is associated with unfavorable prognosis [22]. These findings further emphasize the critical role of PTEN in the pathogenesis of NPC. A deeper understanding of the mechanisms of PTEN action should provide a solid foundation for the personalized treatment of NPC.

2. The Protein Structure of PTEN

The PTEN protein is encoded by a gene consisting of 9 exons and an open reading frame of 1212 nucleotides [23,24]. It is comprised of 403 amino acids and has a relative molecular mass of 47 kDa [25]. This multi-domain protein features an N-terminal PIP2-binding domain, a catalytic phosphatase domain, a C2 lipid/membrane-binding domain, a degradation region, and a C-terminal portion [25–27] (see Fig. 1). The PIP2-binding domain is located at the N-terminus and helps to determine PTEN localization [25]. The catalytic phosphatase domain is involved in removing phosphate groups from proteins and regulating multiple intracellular signaling pathways [24,26]. The C2 domain forms part of the phosphatase core and interacts with lipids to influence the subcellular localization of PTEN [27]. Phosphorylation of S380, T382, and T383 in the degradation region determines PTEN stability. Mutations at these sites reduce the protein half-life and PTEN phosphatase activity [26]. The C-terminal portion facilitates Ca²⁺-dependent membrane recruitment of various signaling proteins, such as phosphoinositide-specific phospholipase C81 (PLC81), phosphatidylinositol 3-kinase (PI3K), and protein kinase C (PKC) [26,27] (see Fig. 1). Collectively, these domains participate in the diverse cellular functions of PTEN, regulating everything from localization to signal transduction. Additionally, the presence of PTENP1 (AS-alpha) messenger RNA (mRNA) inhibits the translation of PTEN mRNA, thereby reducing PTEN expression [26]. Conversely, the actions of PTENP1 (S) mRNA and PTENP1 (AS-beta) mRNA enhance the translation of PTEN mRNA, thereby increasing PTEN expression [26]. Hence, the structural diversity of PTEN is closely associated with its crucial role in cellular regulation. These regulatory mechanisms further highlight the importance of PTEN in maintaining cellular balance.

3. The Role of PTEN in the Pathogenesis of NPC

PTEN plays a crucial role in the occurrence and development of NPC, influencing several key cellular processes such as proliferation, migration, invasion, autophagy, apoptosis, and resistance to radiotherapy (Fig. 2). These functions manifest within a complex regulatory network centered around PTEN and include important interactions with long non-coding RNAs (lncRNAs), microRNAs (miRNAs), circular RNAs (circRNAs), and other regulatory factors. Recent studies indicate that LMP1, an Epstein-Barr virus (EBV) protein, promotes the expression of DNMT1 in NPC. This initiates the process of mitochondrial translocation, leading to epigenetic silencing of PTEN, activation of the AKT signaling pathway, metabolic reprogramming of NPC cells, and enhancement of tumor cell metabolic uptake [28]. Interestingly, research suggests that grifolin, a natural phenolic compound derived from higher fungi, can mitigate the glycolytic flux and restore mitochondrial oxidative phosphorylation function by inhibiting DNMT1 expression and activity [28]. These findings highlight the pivotal role of PTEN in the intricate regulatory network of NPC and its involvement in critical processes such as metabolic reprogramming. Not only do these studies contribute to a deeper understanding of the pathogenesis of NPC, they also provide a novel theoretical foundation for future therapeutic strategies.

3.1 Inhibition of NPC Cell Proliferation by PTEN

NPC is an aggressive head and neck tumor that is influenced by a complex interplay of molecular factors. The PTEN gene plays a pivotal role in this regulatory network. Firstly, circFIP1L1, through the miR-1253/EIF4A3 pathway, regulates NPC cell proliferation, apoptosis, and radiosensitivity [29]. EIF4A3 induces the formation of circFIP1L1, thereby stabilizing PTEN mRNA [29] and highlighting the critical role of circFIP1L1 in PTEN regulation. Secondly, miR-144-3p targets PTEN directly to enhance the PI3K-Akt signaling pathway and promote NPC cell proliferation and invasion, while inhibiting apoptosis [30]. Conversely, by downregulating miR-144, lncRNA IUR upregulates PTEN in NPC and inhibits cell proliferation [31]. Additionally, by downregulating miR-214, the novel lncRNA AMPC promotes NPC progression by downregulating PTEN [32]. The lncRNA GAS5 epigenetically silences PTEN through EZH2, thereby promoting NPC progression [33]. This suggests that lncRNAs can regulate PTEN through different pathways to exert complex effects on NPC cell proliferation.

The interactions between miR-182, miR-141, BRD7, and c-Myc are intricate. MiR-182 upregulates NPC proliferation and invasion by targeting PTEN [34]. By inhibiting the PTEN/AKT pathway, miR-141 participates in BRD7-mediated cell proliferation and tumor formation [35,36]. The dual-negative feedback loop between BRD7 expression and c-Myc activation affects NPC cell proliferation and tumor growth by targeting the oncogenic miR-141, which in turn targets PTEN [37]. The zinc finger protein YY1, by inactivating c-Myc-mediated microRNA-141 transcription, inhibits human NPC cell growth [38]. This series of interactions reveals the complexity of the cooperative action between miRNAs, BRD7, and c-Myc in the PTEN regulatory network (Fig. 2).
SPLUNC1 acts through the miR-141-PTEN/p27 pathway to regulate cell progression and apoptosis. SPLUNC1 is also known to be hindered by LMP1 [39]. This signaling axis plays a crucial role in regulating NPC cell proliferation, differentiation, and apoptosis. By increasing miR-21 expression and thereby downregulating its target PTEN, LMP1 further regulates cell growth [40]. This provides new insights into the formation of NPC and suggests potential roles for SPLUNC1 and LMP1 in the complex mechanisms that regulate PTEN. Thorough exploration of the PTEN regulatory network in NPC should uncover the various molecular regulators involved in cell proliferation and cancer progression (Fig. 2, Table 1).
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EMT, epithelial-mesenchymal transition; PI3K, phosphatidylinositol 3-kinase; EBV, Epstein-Barr virus.
3.2 Inhibition of NPC Cell Migration and Invasion by PTEN

PTEN is involved in a rich array of molecular mechanisms that regulate the migration and invasion of NPC cells. Firstly, Plac1 promotes NPC cell proliferation, migration and invasion through the Furin/NICD/PTEN pathway [41]. LASP1 and miR-92a interact with PTEN in the AKT signaling pathway to regulate the migration and invasion of NPC cells [42,43]. Overexpression of epithelial cell adhesion molecules also regulates the stemness, metastasis, and epithelial-mesenchymal transition (EMT) of NPC cells through the PTEN/AKT/mTOR pathway [44]. Additionally, miR-199a-3p inhibits the invasion and migration of NPC cells through the SCD1/PTEN/AKT signaling pathway [45]. The PTEN regulatory network involved in NPC cell migration and invasion demonstrates the complexity of interactions between multiple molecules (Fig. 2, Table 1).

Moreover, the circRNA ITCH induces upregulation of PTEN by suppressing miR-214 to slow the progression of NPC [46]. Conversely, miR-144 promotes the proliferation, migration, and invasion of NPC cells by inhibiting PTEN [47]. Further research found that Resveratrol downregulates miR-144, thereby enhancing formation of the p85α-PTEN complex and leading to S-phase arrest of human NPC cells [48]. The impact of plant compounds on the PTEN regulatory network could be a potential therapeutic approach for the inhibition of NPC cell migration and invasion. The regulatory mechanisms of PTEN involved in the migration and invasion of NPC cells also provide new research directions for the development of relevant treatment strategies and targeted drugs (Fig. 2, Table 1).

3.3 PTEN Facilitates Autophagy and Apoptosis in NPC Cells

Recent studies have unveiled the intricate molecular mechanisms involving autophagy regulation in the treatment of NPC, thus providing crucial insights for the discovery of new therapeutic approaches and prognostic biomarkers. Overexpression of LACTB2 has been shown to induce PINK1-dependent mitochondrial autophagy, thereby promoting the resistance of NPC to radiotherapy [49]. On the other hand, NOS1 prevents excessive autophagy through S-nitrosylation of PTEN [50] and activation of the AKT/mTOR signaling pathway [51], thus maintaining the intracellular autophagic balance. By binding to microRNA-21 and upregulating PTEN expression, the IncRNA MEG3 promotes autophagy and apoptosis in NPC cells [52]. However, activation of STAT3 leads to upregulation of miR-21, which in turn induces NPC proliferation by targeting the PTEN gene and suppressing apoptosis [53]. Another study showed that the RGD-modified, double-shRNA adenovirus ING4/PTEN could inhibit NPC cell growth and promote apoptosis [54]. Together, these findings highlight the significant role of PTEN in autophagy and apoptosis regulation in NPC (Fig. 2, Table 1).

3.4 PTEN Reduces Radiotherapy Resistance in NPC Cells

NPC is commonly treated with radiotherapy, but resistance to this treatment significantly impacts patient prognosis. Therefore, understanding radiotherapy resistance in NPC is crucial for developing more effective treatment strategies. Genetic variants in the PI3K-PTEN-AKT-mTOR pathway have been correlated with distant metastasis in NPC patients receiving intensive radiotherapy [55]. EIF4A3-induced circFIP1L1 inhibits NPC cell proliferation, promotes apoptosis, and enhances sensitivity to radiotherapy through the action of miR-1253 [29]. Furthermore, the overexpression of LACTB2 induces PINK1-dependent mitochondrial autophagy and drives radiotherapy resistance in NPC, suggesting that it may be a potential biomarker for predicting radiotherapy response [49]. MiR-205 and the IncRNA ANCR have been implicated in promoting radio-resistance in NPC by directly targeting PTEN [56,57]. Specifically, miR-205-5p targets PTEN through the PI3K/AKT signaling pathway, thereby regulating the epithelial-mesenchymal transition (EMT) in cisplatin-resistant NPC cells [58]. However, SZ-685C has shown promise in eliminating radio-resistance in CNE2 cells through the miR-205-PTEN-Akt pathway [59]. Recent research indicates that the primary mechanisms leading to resistance of 5-8F/Erbibux cells to cetuximab may be the amplification and overexpression of H-ras, possibly in association with excessive IGF-1R activity [60] (Table 1). Of note, PTEN gene loss or mutation does not correlate with the resistance of 5-8F/Erbibux cells to cetuximab [60]. Overall, the precise role of PTEN in the response of NPC to radiotherapy remains unclear.

3.5 PTEN Regulation of the NPC Tumor Microenvironment

The tumor microenvironment (TME) refers to the complex milieu surrounding tumor cells, comprising various cell types, extracellular matrix (ECM) components, and soluble factors [61]. This intricate network plays a crucial role in tumor initiation, progression, metastasis, and response to therapy. Among the key players in TME modulation, the PTEN emerges as a significant regulator, exerting multifaceted effects on tumor development [61,62]. RNF126 in tumor cell-derived exosomes regulates PTEN ubiquitination and degradation in the TME, thereby also influencing the immune microenvironment and promoting the progression of NPC [63]. Moreover, the polycytoxins protein Bmi-1 inhibits PTEN and induces EMT in human nasopharyngeal epithelial cells, thereby facilitating unfavorable behavior such as cell migration and invasion in the TME [64].

3.6 PTEN and Epstein-Barr Virus (EBV)

Research has shown that EBV can modulate the expression of PTEN through diverse pathways, exerting a profound impact on the onset, progression, and resistance to radiotherapy of NPC. EBV modulates PTEN by upregulating miR-BART4, which then targets PTEN and inhibits its ex-
pression. This action reduces the radiosensitivity of NPC, thereby favoring its progression [65]. The EBV-encoded miR-BART1 plays a pivotal role in modulating PTEN-dependent pathways in NPC, contributing to the induction of tumor metastasis [66,67]. Moreover, EBV-miR-BART7-3p targets and inhibits SMAD7, resulting in activation of the TGF-β signaling pathway. This activation promotes the EMT and metastasis of NPC cells, while simultaneously enhancing the stemness of tumor cells [68,69]. Additionally, EBV-miR-BART1-5p independently activates the AMPK/mTOR/HIF1 pathway, thereby inducing glycolysis and angiogenesis in NPC [70,71]. These research findings offer some insights into the intricate mechanisms by which EBV-encoded miRNAs orchestrate the regulation of PTEN and associated pathways. Fig. 2 shows the pathways affecting the initiation and progression of NPC.

3.7 The Relationship between Non-Coding RNA and PTEN

Non-coding RNAs, such as miRNAs, IncRNAs and circRNAs are important in various cellular processes due to their ability to modulate gene expression at the post-transcriptional level [72,73]. Recent research has revealed that EIF4A3-induced circFIP1L1 suppresses miR-1253/PTEN and enhances radiosensitivity in NPC [29]. These findings underscore the intricate regulatory roles played by non-coding RNAs in cancer biology and highlight their potential as therapeutic targets for improving treatment outcomes.

miRNAs are small non-coding RNAs that bind to the 3’ untranslated region (UTR) of target mRNAs, leading to mRNA degradation or translational repression [74, 75]. Several miRNAs have been found to directly target PTEN mRNA, thereby modulating its expression [30,43, 56]. PTEN can also indirectly regulate miRNA expression through feedback loops that influence downstream signaling pathways [58]. Notably, our research has revealed that miR-92a [43], miR-144 [48], miR-205-5p [56], miR-205-5p [58], miR-144-3p [30], miR-182 [34], miR-144 [47], miR-141 [35,37], and miR-199a-3p [45] promote the metastasis of NPC by targeting PTEN (Table 1).

Furthermore, IncRNAs can serve as molecular scaffolds, decoys, or guides to influence PTEN activity or localization [76,77]. They may interact with PTEN protein directly or indirectly through RNA-protein complexes, thereby modulating PTEN-mediated cellular functions. We previously reported that the novel IncAMPD downregulates PTEN via miR-214 to promote the progression of NPC [32]. Additionally, the IncRNA MEG3 binds to microRNA-21 to enhance the autophagy and apoptosis of NPC cells via PTEN up-regulation [52]. In addition, the IncRNA IUR downregulates miR-144 to modulate PTEN in NPC [31].

circRNAs are characterized by covalently closed-loop transcripts. They have recently attracted considerable attention due to their regulatory roles in gene expression [78]. Some circRNAs act as miRNA sponges, sequestering miRNAs that target PTEN mRNA to indirectly modulate PTEN expression [78]. Our earlier research found that Hsa_circ_0000345 inhibits the proliferation, migration, and invasion of NPC cells through the miR-513a-3p/PTEN axis [79]. Additionally, the circRNA ITCH hinders the progression of NPC by promoting PTEN upregulation via miR-214 [46] (Table 1).

In summary, circRNAs play a pivotal role in regulating gene expression, particularly by acting as miRNA sponges to indirectly modulate PTEN expression levels in NPC. Our findings highlight the intricate regulatory mechanisms involving circRNAs and PTEN, and offer insights for the development of novel therapeutic strategies in the treatment of NPC.

4. Conclusions and Prospects

NPC is a highly invasive tumor phenotype in the head and neck region that is characterized by a complex molecular regulatory network. Within this intricate landscape, PTEN plays a crucial role as a phosphatase gene. Comprehensive exploration of the PTEN regulatory network in NPC has revealed various molecular factors involved in processes such as cell proliferation, migration, invasion, autophagy, apoptosis, and radiotherapy resistance. Particularly noteworthy are the interactions between PTEN and IncRNAs, miRNAs and circRNAs. Future research endeavors should further elucidate the specific mechanistic roles of these non-coding RNAs in cancer development, thereby providing a solid foundation for the development of new treatment strategies. Furthermore, PTEN’s role in NPC extends beyond intracellular processes to encompass regulation of the TME. In-depth research in this field may contribute to the development of innovative therapies that target the TME to inhibit the growth and metastasis of NPC. Additionally, the interaction between PTEN and EBV has become a highly promising research area. Clarification of how EBV modulates PTEN and its downstream pathways to influence the onset and progression of NPC could provide a theoretical foundation for developing more effective viral-based treatment strategies. A recent study suggests that dynamic, contrast-enhanced Magnetic Resonance Imaging (MRI) can predict PTEN protein expression, thus serving as a prognostic indicator for progression-free survival in NPC patients [80]. Specifically, Ktrans and Kep were significantly lower in PTEN-negative NPC patients compared to PTEN-positive patients [80]. While PTEN can affect the AKT signaling pathway, sequencing results did not find a significant correlation between the loss of PTEN and activated Akt [81]. However, positive correlations were observed between activated Akt and phosphorylated epidermal growth factor receptor (p-EGFR), forkhead box protein O1 (FKHR), and Bcl-2. Neuregulin promotes p27 upregulation [81], and experimental induction of G1-phase cell cycle arrest in CNE2 cells suggests that neuregulin-induced upregulation of p27 may be due to the disruption
of Akt. Importantly, the decrease in phosphorylated Akt is unrelated to PI3K functionality or PTEN protein expression [82]. Further in-depth research into PTEN’s multifaceted regulation in NPC should lead to the development of more personalized and targeted therapeutic approaches, thereby improving patient survival rates and quality of life.

Author Contributions
YC: Conceptualization, Formal analysis, Writing – original draft. SX: Acquisition of data. YH: Conceptualization, Methodology, Funding acquisition. LH: Methodology, Funding acquisition. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate
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Conflict of Interest
The authors declare no conflict of interest.

References


Guo Q, Lu T, Chen Y, Su Y, Zheng Y, Chen Z, et al. Genetic variations in the PI3K-PTEN-AKT-mTOR pathway are associated with distant metastasis in nasopharyngeal carcinoma pa-


Cai LM, Lyu XM, Luo WR, Cui XF, Ye YF, Yuan CC, et al. EBV-miR-BART7-3p promotes the EMT and metastasis of nasopharyngeal carcinoma cells by suppressing the tumor suppressor PTEN. Oncogene. 2015; 34: 2156–2166.


