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Exosomes in Nasopharyngeal Carcinoma: From Pathogenesis to Clinical Applications

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Abstract

Nasopharyngeal carcinoma (NPC) is a malignant epithelial tumor with a unique geographical distribution, predominantly prevalent in East Africa and Asia. Despite advances in understanding its pathogenesis and risk factors, prevention and treatment efforts remain limited. Numerous studies indicate that exosomes actively participate in NPC development by delivering bioactive molecules such as non-coding RNAs and proteins to target cells. In NPC, exosomes regulate the tumor microenvironment, mediate chemoradiotherapy resistance, induce immunosuppression, promote pathological angiogenesis, and support metastasis, making them promising biomarkers. Due to their critical roles and unique biological properties, exosomes hold significant potential for diagnostic monitoring and prognostic evaluation. Although technical challenges exist in their large-scale application, exosomes offer unparalleled advantages in clinical management. This review summarizes the biological functions of exosomes in NPC and explores their prospects as clinical biomarkers.

Keywords

Nasopharyngeal Carcinoma, Exosomes, Proliferation, Metastasis, Diagnosis, Prognosis, Biomarker

1. Introduction

Nasopharyngeal carcinoma (NPC) originates from nasopharyngeal epithelial cells and exhibits distinct regional distribution. According to the International Agency for Research on Cancer (2022), global new cases and deaths from NPC in 2022 were 120,416 and 73,476, respectively. NPC accounts for only 0.6% of annual global

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cancer diagnoses but shows higher incidence in East and Southeast Asia [1]. Histologically, NPC includes keratinizing, non-keratinizing, and undifferentiated subtypes, with non-keratinizing squamous cell carcinoma being the most common and associated with Epstein-Barr virus (EBV) infection, environmental factors, and genetic susceptibility [2]. Due to the anatomical obscurity of the nasopharynx and nonspecific early symptoms, over 70% of patients are diagnosed at advanced stages [3]. The recurrence and metastasis rate of advanced nasopharyngeal carcinoma is high. At present, the conventional treatment of nasopharyngeal carcinoma includes radiotherapy, chemotherapy and surgery. Due to the deep location and complex anatomical structure of the tumor, surgical options are limited. However, local and/or regional recurrence still occurs in 10% - 15% of patients [4]. Therefore, there is an urgent need to further explore the mechanisms related to the occurrence and development of NPC, and identify specific diagnostic biomarkers and potential therapeutic interventions to improve the survival rate of NPC patients.

In recent years, the study of exosomes (EV) has become the focus of attention in the biological science and medicine communities. In-depth exploration of EV can bring a new perspective to the occurrence and development of NPC. More and more evidence shows that EV is involved in the physiological and pathological processes of NPC cells, such as proliferation, metastasis, invasion, immune system regulation, radiotherapy and chemotherapy resistance regulation, and is of great value in the occurrence and development of NPC [5]. This article reviews the role and mechanism of EV in the occurrence and development of NPC, and discusses the potential application of EV in the diagnosis and treatment of NPC.

2. Overview of Exosomes

EV is a nano-scale vesicle with a diameter of 30 - 150 nm wrapped by a phospholipid bilayer [6]. EV formation begins with invagination of the cell membrane to form the so-called primary endosome. These primary endosomes, under the regulation of the endosomal sorting complex (ESCRT), further develop into polyvesicular bodies. ESCRT plays a key role in this process by aiding primary endosomal membrane invagination. Subsequently, polyvesicular bodies, driven by dynein, move rapidly along microtubules or microfilaments within the cell and eventually fuse with the cell membrane to release EV into the extracellular environment [7] (**Figure 1**). EV production is not restricted by cell type and can be formed under a variety of physiological and pathological conditions. They are commonly found in a variety of body fluids, including but not limited to cerebrospinal fluid, saliva, breast milk, lymph fluid, bile, blood and urine [8].

EV is valued because they are more reflective of the characteristics of their source cells, and they exhibit higher permeability and stability compared with other types of vesicles, so it is critical to develop accurate EV isolation methods [9]. In the past few decades, the isolation technology of EV has improved significantly. At present, the commonly used techniques for the isolation and purification

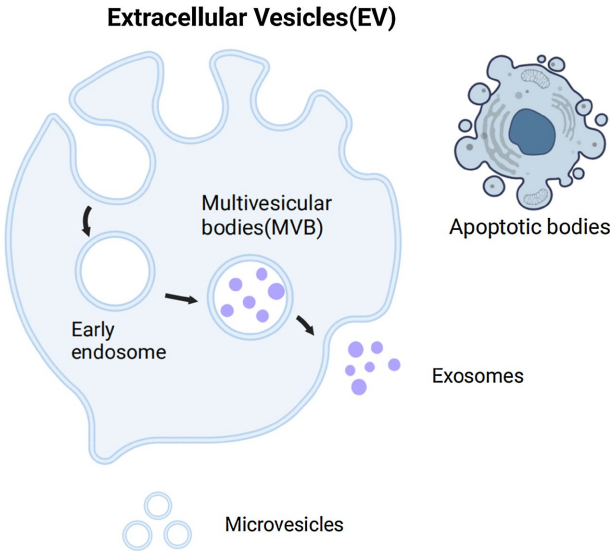

Figure 1. Extracellular vesicles are classified as three main forms: macrovesicles, apoptotic bodies, and exosomes.

of EV include ultracentrifugation, ultrafiltration, size exclusion chromatography (SEC), polymer precipitation, immunoaffinity capture technology, and microfluidic technology. By combining these techniques, more efficient separation can be achieved. As the most widely used method in EV isolation technology, ultracentrifugation is suitable for a variety of sample types. Due to its high technical maturity and low cost, ultracentrifugation is often regarded as the "gold standard" for EV isolation [10] [11]. A variety of proteins are carried on the surface of EV, including Rab-related GTPases (Rabgtpases), which are related to EV biosynthesis, and other marker proteins, such as CD9, CD81, CD63, etc. These proteins not only contribute to the identification of EV, but may also play a role in the diagnostic process of diseases [12].

The term exosome was first proposed in 1981, and the view at that time was that they were only vesicles with membrane structure [13]. However, EV was not actually observed for the first time in reticulocytes from sheep until 1983 [14]. At first, EV were not paid attention to, and EV were considered as waste products in the process of cell metabolism and lacked biological significance. After more than a dozen years of research, it has been found that EV is actually key mediators of information transfer between cells and plays a crucial role in signal transduction. They carry a variety of biologically active molecules from different cells, Including protein, DNA (such as double-stranded DNA (dsDNA), single-stranded DNA (ssDNA), mitochondrial DNA (mtDNA), etc.), RNA (such as messenger RNA (mRNA), microRNA (miRNA, miR), long non-coding RNA (lncRNA), etc.) and lipids. Under the protection of EV, these molecules can be delivered to target cells to achieve substance exchange and signal transduction, and participate in the regulation of gene expression and protein synthesis in target cells. In addition, EV can precisely activate signal transduction pathways in target cells, change the level of cytokines, promote cell proliferation, inhibit cell apoptosis, and promote cell

repair and regeneration [15]. Thus, EV plays a central role in signaling between cells. Compared with normal cells, the number of EV released by tumor cells is significantly increased. These tumor-derived EV can promote the invasion and metastasis of tumor cells by regulating the local or distal microenvironment.

During the development of NPC, EV is involved in a variety of tumor-promoting activities, such as stimulating cell proliferation, inhibiting apoptosis, enhancing tumor distal invasion and metastasis, promoting angiogenesis, epithelial-mesenchymal transition (EMT), remodeling the immune microenvironment, and inducing therapeutic resistance [5] (**Figure 2**). Of particular note, the activity of non-coding RNAs (ncRNAs) in EV plays a key role in cancer research. Therefore, EV has the potential to be predictive biomarkers and therapeutic targets for NPC. Given their characteristics, EV can also serve as delivery vehicles for drugs and functional molecules, providing a new clinical strategy for the treatment of NPC.

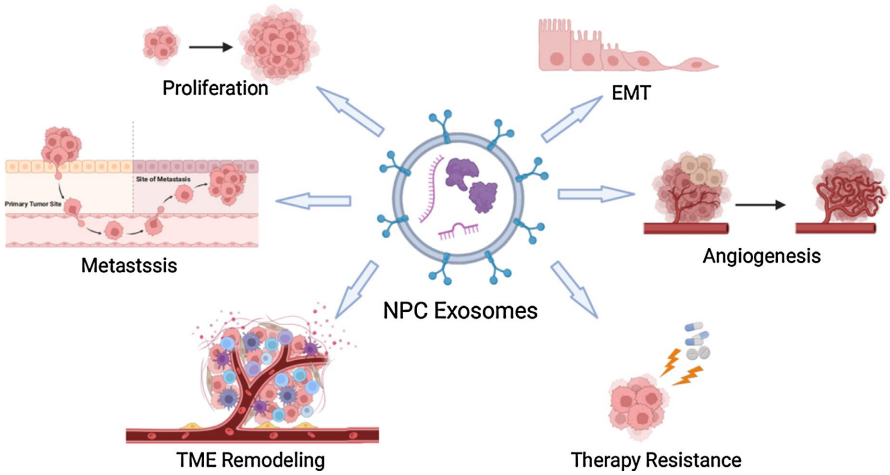

Figure 2. The mechanism of exosomes in NPC. Exosomes transport nucleic acids, proteins, and other bioactive substances, affecting various pathological processes in the occurrence and development of EC, including tumor cell proliferation, invasion and metastasis, EMT, angiogenesis, TME remodeling, and therapy resistance.

3. Role of Exosomes in the Development of NPC

3.1. Exosomes Mediate the Proliferation of NPC Cells

The high malignancy of NPC is closely related to the rapid proliferation of tumor cells. The following studies indicate that EV is involved in multiple aspects of tumor cell proliferation and apoptosis.

3.1.1. LMP1 Drives the Proliferation of Nasopharyngeal Carcinoma through EV-Mediated NF-κB/P38 MAPK Signaling Axis

Latent membrane protein-1 (LMP-1), an oncoprotein with *in vitro* transformation ability, is frequently detected in EBV-associated malignancies. It plays a central role in the initiation and progression of these tumors, acting by promoting cell proliferation and preventing NPC cell apoptosis [16]. Wu *et al.* found that EV-loaded LMP1 secreted by NPC cells upregulated the expression of a-SMA and FAP by

activating the nuclear factor-κB (NF-κB) pathway in normal fibroblasts (NFs). This process activates NFs into cancer-associated fibroblasts (CAFs). Further studies showed that activated CAFs upregulated MCT4 to promote the secretion of lactate and β-hydroxybutyric acid (β-HB) through the NF-κB pathway, while MCT1 enhanced the respiration and fuel anabolism of tumor cells. Metabolic coupling of CAFs and tumor cells promotes the proliferation, migration and radiation resistance of nasopharyngeal carcinoma cells [17]. It has been shown that NPC cells containing LMP1 have a higher proliferative capacity than those without LMP1. LMP1 increases the expression of synapsin 2 (SDC2) and synapsin 4-like (SYTL4) through the NF-κB signaling pathway, thereby promoting the formation and secretion of EV. Increasing the number of EV can promote the proliferation of recipient nasopharyngeal carcinoma cells [18]. It has also been reported that CD63, a conserved tetraester protein, increases LMP1-mediated EV release and promotes NPC cell proliferation and tumor growth [19]. The increased number of EV promotes the proliferation and tumor growth of recipient NPC cells by activating the P38 MAPK signaling pathway, a process that reveals the important role of LMP1 in EBV-associated NPC and provides potential targets for future treatment [20]. The above studies raise the possibility that LMP-1 may be a prognostic marker for NPC patients.

3.1.2. Effect of Exosome-Derived Microrna on the Proliferation of Nasopharyngeal Carcinoma

EV micrornas (mirnas) released by tumor cells are important mediators of intercellular communication in the tumor microenvironment. miRNA is a class of noncoding single-stranded RNA with a size of 21 to 24nt [21]. miRNA is highly abundant in EV and can be used as the target of miRNA sponge, which is the core of the competitive endogenous RNA (ceRNA) network. Different mirnas play the role of "oncogenes" or "tumor suppressor genes" in the occurrence and progression of tumors through the corresponding target axes [22]. miR-99a-5p is highly expressed in nasopharyngeal carcinoma cell-derived EV, and affects the proliferation and migration of nasopharyngeal carcinoma cells by regulating the expression of BAZ2A gene. The results showed that overexpression of miR-99a-5p or down-regulation of BAZ2A could significantly weaken the regulatory effect of EV on cell proliferation, migration and apoptosis ($p < 0.05$) [23]. By reducing the expression of tight junction protein (ZO-1), miR-103a-3p in EV released by NPC cells disrupted the integrity of vascular endothelium and enhanced vascular permeability *in vitro* and *in vivo*. In addition, miR-103a-3p in these EV was found to directly act on the metabolic enzyme ACOX-1 to enhance the proliferation ability of NPC cells by promoting the accumulation of lipid droplets. Therefore, EV-miR-103a-3p is considered as a potential target for the treatment of NPC [24]. EV-miR-301a-3p promotes the proliferation and invasion of nasopharyngeal carcinoma cells by targeting B cell translocation gene 1 (BTG1) mRNA, thus leading to the occurrence of nasopharyngeal carcinoma [25]. A previous study revealed that hypoxia-inducible factor-1α (HIF-1α) in adipocytes downregulates miR-433-3p expression in EV re-

leased from adipocytes under hypoxia. Down-regulation of miR-433-3p may enhance the proliferation, migration and lipid synthesis of nasopharyngeal carcinoma cells by targeting stearoyl-coa desaturase 1 (SCD1). Therefore, the HIF-1α-miR-433-3p-SCD1 signaling pathway may become a new therapeutic strategy for nasopharyngeal carcinoma [26]. Ye *et al.* found that miR-24-3p, miR-891a, miR-106a-5p, miR-20a-5p and miR-1908 were highly expressed in the serum of patients or in EV released from nasopharyngeal carcinoma cells. These miRNAs can regulate cell proliferation and differentiation process by inhibiting the signaling of microtubule affinity regulated kinase 1 (MARK1) [27].

3.2. Exosomes Are Involved in the Invasion and Metastasis of NPC

Distant metastasis of nasopharyngeal carcinoma (NPC) is currently the main factor determining the survival outcome of NPC patients. In-depth exploration of the metastasis pathway of nasopharyngeal carcinoma and identification of effective therapeutic targets are essential to improve the prognosis of patients with nasopharyngeal carcinoma and promote the progress of clinical treatment.

3.2.1. Tumor-Derived EV Drives Nasopharyngeal Carcinoma Metastasis by Regulating Macrophage Polarization

In the tumor microenvironment (TME), macrophages play a key immune role, and it has been confirmed that they can affect the process of tumor metastasis. In addition, extracellular vesicles (EV) released by stromal cells and tumor cells play a crucial role in intercellular communication in the tumor microenvironment [28]. Chen *et al.* first identified three key genes, SCARB1, HAAO, and CYP1B1, that are related to the regulatory function of macrophages in the tumor microenvironment. Studies have shown that SCARB1 expression level is positively correlated with metastasis and poor prognosis of nasopharyngeal carcinoma (NPC). Specifically, SCARB1-rich EV were able to promote ferroptosis of M1 macrophages by increasing the levels of HAAO, which resulted in reduced M1 macrophage infiltration in the tumor microenvironment. At the same time, these EV decreased the phagocytic capacity of M2-type macrophages by increasing the level of CYP1B1. Ultimately, SCARB1 in extracellular vesicles promotes the metastasis of nasopharyngeal carcinoma by synergistically regulating the function of M1 and M2 macrophages [29]. The expression of long non-coding RNA (lncRNA) TP73-AS1 is increased in nasopharyngeal carcinoma cells and tissue samples, and is closely related to poor prognosis. Studies have shown that overexpression of TP73-AS1 can promote the proliferation, colony formation and DNA synthesis of NPC cells, while its knockdown has the opposite effect. In addition, TP73-AS1 directly acts on miR-342-3p through the EV pathway, thereby promoting the polarization of macrophages to M2 type, which accelerates the progression of NPC. Therefore, TP73-AS1 is expected to become a new biomarker of NPC, and the revelation of its related mechanism provides a potential therapeutic strategy for improving the treatment prognosis of NPC patients [30]. Nasopharyngeal carcinoma-derived EV can significantly activate macrophages to release the inflammatory cytokine interleukin-6 (IL-6), which further

activates activator of transcription 3 (STAT3), thereby enhancing the malignant behavior of nasopharyngeal carcinoma cells [31]. Macrophage migration inhibitory factor (MIF) contained in EV released by nasopharyngeal carcinoma cells can be taken up by macrophages, and this process inhibits macrophage ferroptosis, thereby promoting the metastasis of nasopharyngeal carcinoma. Therefore, targeted therapy against MIF may become a potential therapeutic strategy to reduce the metastatic rate of NPC [32].

3.2.2. Hypoxia Induces HIF-1α-Dependent EV Signaling Axis to Drive EMT and Metastasis of Nasopharyngeal Carcinoma

Studies have shown that EV plays a role in conveying complex biological information under a variety of pathological conditions and are able to induce a variety of signaling responses, including hypoxia. In NPC patients, hypoxia is not only associated with the aggressive phenotype of the tumor, but also closely associated with poor prognosis. Specifically, recent studies have revealed that the expression of small RNA molecule SNHG16 in tumor-derived EV is significantly increased under hypoxia, and this change affects the progression of nasopharyngeal carcinoma by activating the miR-23b-5p/MCM6 signaling axis [32]. Shan *et al.* showed that under hypoxic conditions, the levels of matrix metalloproteinase-13 (MMP-13) in tumor-derived EV (TDE) released by the nasopharyngeal carcinoma cell line CNE2 were significantly increased, and this process was dependent on hypoxia-inducible factor-1α (HIF-1α). Further studies have found that MMP-13 can transfer from hypoxic cancer cells to normoxic cancer cells, thereby remodeling the tumor microenvironment (TME) and inducing epithelial-mesenchymal transition (EMT)-related migration and invasion in recipient nasopharyngeal carcinoma normoxic cells [33]. Aga *et al.* found that the hypoxia-inducible factor HIF-1α can be detected in extracellular vesicles (EV) and that EBV-encoded LMP1 significantly enhances the expression of HIF-1α in EV. This finding suggests that HIF-1α plays an important role in the tumor microenvironment of NPC. More importantly, HIF-1α induced changes in epithelial-mesenchymal transition (EMT) markers by decreasing E-cadherin expression and increasing N-cadherin expression, which were closely related to cell migration and invasion ability. In addition, HIF-1α is also involved in EV-mediated prometastasis of target cells, which may have an impact on the invasiveness and prognosis of NPC [34]. These findings reveal the important role of hypoxia in NPC progression in a HIF-1α-dependent manner, provide new insights into understanding the molecular mechanisms of NPC, and provide potential targets for the development of new therapeutic strategies.

3.2.3. Role of Platelet Extracellular Vesicles (PEV) in Driving Hematogenous Metastasis of Nasopharyngeal Carcinoma

Studies have shown that distant metastasis of tumors mainly includes lymphatic metastasis and hematogenous metastasis. In this process, platelets play an important role, especially in hematogenous metastasis. Platelet extracellular vesicles (PEV), as the most abundant EV in the blood, play an important role in promoting

the formation of metastasis. Nasopharyngeal carcinoma (NPC) is a highly metastatic and invasive malignant tumor, and distant metastasis is the main cause of treatment failure and death. The number of platelets is positively correlated with the distant metastasis of tumor cells, indicating that the role of platelets in tumor metastasis cannot be ignored [35]. Li *et al.* found that PEV from NPC patients induced metastasis of NPC cells by up-regulating the expression of integrin β3 (ITGB3). Up-regulation of ITGB3 enhanced protein stability and increased SLC7A11 expression by activating MAPK/ERK/ATF4/Nrf2 signaling axis, thereby inhibiting ferroptosis and promoting distant metastasis of NPC cells [36]. Many other studies have also shown that PEV can be transferred to target cells, and their cargo promotes phenotypic changes and new functions of target cells, thereby affecting tumor progression [37]. These findings not only clarify a novel role of PEV in NPC metastasis, but also have important implications for understanding the mechanism of platelet-mediated distant tumor metastasis, providing a new perspective for the diagnosis and treatment of NPC.

3.2.4. Other Relevant Mechanisms of Metastasis

Recent research advances have shown that EV-delivered miR-30a-5p in highly metastatic NPC cells enhances the migration, invasion and metastasis of low-metastatic cells, and plasma EV-miR-30a-5p level is a reliable indicator of NPC prognosis. miR-30a-5p may promote metastasis by targeting DSG2 and regulating Wnt signaling pathway. Plasma EVmiR-30a-5p is negatively correlated with DSG2 level and predicts the prognosis of patients [38]. In addition, it has been demonstrated that the expression of epidermal growth factor receptor (EGFR) is higher in tumor tissues of patients with distant metastatic nasopharyngeal carcinoma, and this high expression is associated with the reduction of reactive oxygen species (ROS) levels. More importantly, EGFR-rich extracellular vesicles from highly metastatic NPC cells enhanced the metastatic ability of low-metastatic NPC cells by reducing intracellular ROS levels through activation of the PI3K/AKT signaling pathway. These findings suggest that EGFR may be a potential target in the treatment of NPC, providing a new therapeutic strategy for reducing the metastatic rate of NPC [39]. Stromal interaction molecule 1 (STIM1) affects the enrichment of Epstein-Barr virus-encoded LMP1 in nasopharyngeal carcinoma cell-derived EV by regulating Ca^{2+} signaling. This process promotes the proliferation, migration, tube formation and vascular permeability of NPC cells through the Akt/ERK signaling pathway. Blocking EV-mediated horizontal cell-to-cell transfer of EBV-associated oncogenic signaling molecules may be an effective therapeutic strategy for nasopharyngeal carcinoma [40]. Store-operated calcium entry (SOCE) is an important extracellular/intracellular signal transduction mode, which can regulate the dynamic balance of intracellular and extracellular Ca^{2+}. Soce is closely related to epithelial-mesenchymal transition (EMT), tumor angiogenesis, invasion and metastasis, and tumor immunity of malignant tumor cells. LMP1 enhanced Ca^{2+} signaling through the activation of SOCE, thereby promoting the malignant behavior of NPC cells, including proliferation, migration and tube formation. Therefore, in-

tervention targeting LMP1 and its regulated SOCE pathway may become an effective therapeutic strategy to reduce the metastatic rate of NPC [41]. HAX1 protein is rich in EV released by nasopharyngeal carcinoma cells. HAX1 can enhance the translation efficiency of integrin β6 (ITGB6) and activate the adhesion kinase (FAK) signaling pathway, thereby affecting the formation of microvessels and promoting the metastasis of nasopharyngeal carcinoma. This finding reveals the possibility of HAX1 as a potential biomarker for NPC metastasis. The expression level of HAX1 is closely related to lymph node metastasis, metastasis classification, clinical stage and poor prognosis of nasopharyngeal carcinoma [42] [43]. Tumor cell-derived EV-RNF126 affects the immune microenvironment and promotes the growth and metastasis of nasopharyngeal carcinoma by regulating PTEN ubiquitination, which provides a basis for the screening of early markers and targeted therapy of nasopharyngeal carcinoma [44]. You *et al.* found that the content of matrix metalloproteinase-13 (MMP-13) was significantly elevated in EV released by the human nasopharyngeal carcinoma cell line CNE2. This highly expressed MMP-13 had an important effect on the function of EV, which enhanced the migration and invasion ability of NPC cells by altering the expression of epithelial-mesenchymal transition (EMT) markers, including E-cadherin, N-cadherin, and vimentin. In addition, MMP-13 also induces changes in the microenvironment, promotes the invasiveness of NPC and accelerates the progression of the disease [45].

3.3. Exosomes Promote Tumor Angiogenesis

Increased vascular permeability is conducive to tumor metastasis. EV plays a key role in the process of tumor angiogenesis. They can deliver angiogenic molecules, activate angiogenic signaling pathways, and inhibit hypoxia-inducible factors. EV released by tumor cells are essential for the formation and modification of tumor microenvironment. On the one hand, these tumor-derived EV are considered as key mediators of tumor-host interactions. On the other hand, hypoxia is a fundamental feature of solid tumors [46] [47].

3.3.1. Mechanism of Action of EV Proteins in Regulating Angiogenesis in NPC

1) A multi-molecule network of exosomes synergistically drives angiogenesis in nasopharyngeal carcinoma

Tumor angiogenesis has been shown to be mediated by a number of proteins derived from NPC-derived EV. Through EV-mediated transport of hematopoietic cell specific protein 1 (HS1)-associated protein X-1 (HAX-1) to recipient human umbilical vein endothelial cells (HUVECs), the proliferation, migration ability and angiogenesis potential of nasopharyngeal carcinoma cells were enhanced [43]. In addition, nasopharyngeal carcinoma cell-derived EV carrying phosphofructokinase isoenzyme 3 (PFKFB3) could promote the angiogenesis process. Phosphofructokinase isoenzyme 3 (PFKFB3), as a key glycolytic regulatory protein, is highly expressed in EV released by nasopharyngeal carcinoma cells. It enhances the growth,

migration and angiogenesis of NPC cells by regulating cell cycle progression and epithelial-mesenchymal transition (EMT). In addition, PFKFB3 can also reduce the apoptosis rate by activating the extracellular signal-regulated kinase (ERK) and phosphorylated protein kinase B (p-AKT) signaling pathways [48]. Proteomic analysis revealed that proteins associated with angiogenesis, for example, the expression of intercellular adhesion molecule-1 (ICAM-1) and CD44 variant isoform 5 (CD44v5) was up-regulated, while the expression of the vascular inhibitory protein thrombospondin-1 (TSP-1) was down-regulated in NPC-derived EV, which promote angiogenesis. It increases the migration and metastasis of tumor cells [49]. Nuclear EV (nEXOs) are potential tumor biomarkers. High mobility group box 3 (HMGB3) is a nuclear protein that has been found to be overexpressed in a variety of cancers and is associated with poor prognosis of tumors [50] [51]. Nuclear EV containing high mobility group box 3 (HMGB3) secreted by nasopharyngeal carcinoma cells accelerates tumor metastasis by inducing angiogenesis. Nnex-hmgb3 can be used as an important biomarker of nasopharyngeal carcinoma metastasis, which provides a new basis for clinical metastasis anti-angiogenesis therapy [52]. It was shown that the level of HMGA2 protein was higher in EV of EBV-positive NPC cells compared to EBV-negative NPC cells. HMGA2 promotes tumor angiogenesis and metastasis by up-regulating the expression of Snail, which contributes to the reduction of tight junction proteins in endothelial cells and endothelial to mesenchymal transition (EndMT). This suggests that EV-HMGA2 is a potential therapeutic target and a predictive marker for NPC metastasis [53].

2) EV regulates the expression of VEGF-A to affect tumor angiogenesis

The VEGF/VEGFR signaling pathway was identified as a major factor involved in the regulation of almost all stages of physiological angiogenesis. The VEGF/VEGFR family includes seven types of vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs), especially VEGFR-1, VEGFR-2, and VEGFR-3, which are mainly expressed on endothelial cells during angiogenesis [54]. VEGF molecule is a multifunctional pro-angiogenic factor that regulates the proliferation and migration, tubule formation, survival and permeability of NPC [55]. It is well known that VEGF has five major members in mammals, namely VEGF-A, -B, -C, -D, and placental growth factor (PlGF), which differ in their affinity for specific receptors and perform specific functions, with VEGF-C and VEGF-D molecules mainly involved in lymphangiogenesis in contrast to VEGF-A and VEGF-B. The other two VEGF types are virus-derived VEGF-E and venom-VEGF-F. These well-known cytokines are structurally related but are encoded by independent genes [56] [57]. The expression of each VEGF type is regulated by hypoxia-inducible factor (HIF) and is increased under hypoxic conditions [54]. They play a crucial role in the proliferation and migration of primary endothelial cells overexpressing VEGF. They also affect permeability, vasodilation, and stimulation of endothelial nitric oxide (NO) production [58]. miR-125a-5p was highly expressed in nasopharyngeal carcinoma tissues and cells. Guggulsterone (GS) promoted the secretion of EV-circ-

FIP1L1 in nasopharyngeal carcinoma cells. EV-circ-FIP1L1 affects tumor angiogenesis by targeting miR-125a-5p/VEGF-A axis [59]. EV-LBH (limb and heart development gene) inhibits epithelial-mesenchymal transition and angiogenesis in nasopharyngeal carcinoma by down-regulating vascular endothelial growth factor A (VEGF-A) signaling; therefore, LBH can be used as a promising therapeutic target for the treatment of nasopharyngeal carcinoma focused on VEGF-A [60]. Wang and colleagues found that the tumor homing and penetrating peptide iRGD labeled EV containing anti-BART10-5p and anti-18A could inhibit angiogenesis and proliferation of NPC cells by regulating the expression of HIF1-*α* and VEGF in a SpRY3-dependent manner [61]. Chan *et al.* found that NPC-derived EV could significantly induce angiogenesis, migration and invasion of vascular endothelial cells HUVECs [49]. Tian and colleagues found that miR-144 is highly enriched in NPC-derived EV. It can stimulate angiogenesis by inhibiting the target gene FBXW7 (encoding F-box/WD repeat containing protein 7) and promoting the expression of hypoxia-inducible factor 1*α* (HIF1*α*)-dependent vascular endothelial growth factor a (VEGF-A), ultimately enhancing the metastasis of human umbilical vein endothelial cells (HUVECs) [62]. miR-17-5p derived from EV of nasopharyngeal carcinoma cells can down-regulate BAMBI in HUVEC cells, relieve the inhibition of AKT signaling pathway, and lead to the activation of AKT, which further increases the expression of downstream VEGF-A (vascular endothelial growth factor A), thereby promoting angiogenesis in TME [63].

3.3.2. Mechanism of Exosomal Non-Coding RNA in Angiogenesis of Nasopharyngeal Carcinoma

In addition to proteins, RNA in EV has also been considered as potential tumor biomarkers [64]. Mir-6750-enriched EV inhibits premetastatic niche formation by promoting M1 polarization and inhibiting angiogenesis in macrophages. *In vitro* experiments and BALB/c mouse tumor models have shown that miR-6750 directly targets mannose 6-phosphate receptor (M6PR), remodels tumor microenvironment (TME) through SEV, and mediates the metastasis of NPC, providing a new perspective on the pathogenesis of NPC [65]. Under hypoxic microenvironment, the expression of EV-miR-455 in nasopharyngeal carcinoma cells was increased in a HIF-1*α* dependent manner. EV-miR-455 released by nasopharyngeal carcinoma cells enhanced vascular permeability and promoted metastasis by specifically targeting ZO-1. The HIF-1*α*-miR-455-ZO-1 signaling pathway may be a promising predictor of NPC metastasis and a potential therapeutic target [66]. vasculargenic mimicry (VM) is a kind of tumor blood vessel that provides blood supply for tumor growth. Its formation does not depend on vascular endothelial cells. In contrast, VM structures are formed by differentiated tumor cells such as nasopharyngeal carcinoma cells [67]. Recent studies have shown that anti-angiogenic therapy does not improve the overall survival rate of patients with nasopharyngeal carcinoma, and the presence of VM structures may be one of the reasons for resistance to anti-angiogenic therapy [68]. Irgd-labeled EV containing antagomiR-BART1-5p specifically inhibited VM and angiogenesis in NPC either *in vitro* or *in vivo*.

EBV-miR-BART1-5p promotes VM and angiogenesis *in vitro* and *in vivo* in a SPRY2-dependent manner by regulating VEGF, PI3K, Akt, mTOR and HIF1-*α* [69]. EV-miR-18a-5p of nasopharyngeal carcinoma cells promotes angiogenesis by targeting BTG anti-proliferative factor 3 (BTG3) and activating Wnt/*β*-catenin signaling pathway, and finally induces EMT and metastasis of nasopharyngeal carcinoma [70]. EV-miR-18a-5p of nasopharyngeal carcinoma cells promotes angiogenesis by targeting BTG anti-proliferative factor 3 (BTG3) and activating Wnt/*β*-catenin signaling pathway, and finally induces EMT and metastasis of nasopharyngeal carcinoma [71]. Long intergenic non-coding RNA-ROR (lincRNA-ROR) is highly expressed in serum EV of nasopharyngeal carcinoma. lnc-ROR affects the biological activities of nasopharyngeal carcinoma cells, including proliferation, migration and angiogenesis, by targeting the p-AKT/p-VEGFR2 signaling pathway. linc-ROR may be a potential therapeutic target [72]. EV-miR-205-5p enhances the EGFR/ERK signaling pathway and induces the expression of matrix metalloproteinase genes MMP2/MMP9 by targeting DSC2 (desmocollin-2) gene, thereby promoting the degradation and remodeling of extracellular matrix proteins. EV/miR-205-5p/EGFR/ERK axis may be a new therapeutic target for the intervention of nasopharyngeal carcinoma metastasis [73]. Studies have shown that miR-9 in EV is closely related to the prognosis and survival of nasopharyngeal carcinoma patients. miR-9 is lowly expressed in nasopharyngeal carcinoma tissues, and its expression level is negatively correlated with microvessel density (CD31). miR-9 can directly inhibit the expression of its target gene MDK in endothelial cells, and inhibit endothelial angiogenesis by regulating the PDK/AKT signaling pathway [74]. Zhou *et al*. found that nasopharyngeal carcinoma-derived EV long non-coding RNA (lncRNA) colon cancer associated transcript-2 (CCAT2) promotes angiogenesis by affecting the function of human umbilical vein endothelial cells (HUVEC) [75]. In addition, it has also been found that EV from EBV-positive nasopharyngeal carcinoma cells can be taken up by lymphatic endothelial cells, and can significantly promote the angiogenesis and migration ability of lymphatic endothelial cells [76]. Viral non-coding RNA (Epstein-Barr virus coding RNA, EBERs) is thought to play a key role in the progression of lymphoma and nasopharyngeal carcinoma (NPC). NPC-derived EV-loaded EBERs are recognized by cytoplasmic TLR-3/RIG-I and activate the downstream ERK1/2/AP1 axis, thereby stimulating the expression of vascular cell adhesion molecule 1 (VCAM-1) to promote angiogenesis [77]. EV secreted by NPC cells is enriched in miR-23a, which promotes the migration and generation of endothelial cells by targeting testis-specific gene antigen 10 (TSGA10), which can accelerate angiogenesis. miR-23a may become a new target for anti-angiogenesis [78].

4. Role of Exosomes in Chemotherapy and Radiotherapy of NPC and Its Effect on Drug Resistance

4.1. As an Important Target in ESCC Chemotherapy

Nasopharyngeal carcinoma (NPC) is an aggressive and highly metastatic malig-

nancy. Despite recent breakthroughs in treatment, tumor resistance to radiotherapy and chemotherapy is still a major problem in clinical treatment. The mechanisms of resistance of malignant tumors to chemotherapy drugs mainly include several aspects. First, cancer cells over-express drug efflux transporters, such as P-glycoprotein (P-gp) and multidrug resistant-related proteins (MRPs), which can pump chemotherapy drugs out of cells and reduce the intracellular drug concentration, thereby reducing the efficacy of drugs. Second, increased DNA repair capacity reduces sensitivity to chemotherapy; Third, cancer cells may inactivate chemotherapy drugs by increasing the expression of certain enzymes, such as glutathione S-transferase (GSTs), superoxide dismutase (SODs), glutathione peroxidase (GPx), etc. These enzymes are able to bind to chemotherapy drugs and form inactive complexes, thereby reducing drug binding to DNA and reducing its cytotoxicity [79] [80]. Recent studies have highlighted the important role of EV contents in tumor chemotherapy resistance.

Paclitaxel, a compound extracted from the bark of the Pacific yew tree, is an important anticancer agent and is widely used for its unique anticancer mechanism. It was also the first drug derived from a plant and approved by the US Food and Drug Administration (FDA) for chemotherapy. It is mainly used in the treatment of various types of cancer, including breast cancer, ovarian cancer, lung cancer and nasopharyngeal cancer [81]. It prevents cell division by stabilizing tubulin, thereby inhibiting tumor cell growth [82]. Although paclitaxel is effective in the treatment of malignancies, resistance to paclitaxel remains a significant obstacle to its effectiveness. Aldehyde dehydrogenase 2 (ALDH2) is highly expressed in drug-resistant nasopharyngeal carcinoma cells. Delivery of ALDH2 by EV can increase the resistance of recipient cells to paclitaxel. By blocking the release of EV, the expression level of ALDH2 and paclitaxel resistance in drug-resistant cells can be effectively reduced. Therefore, ALDH2 is not only a key molecular marker of therapeutic efficacy, but also a potential target for the development of novel anticancer strategies by blocking EV transport of ALDH2 or directly inhibiting its activity, which may overcome paclitaxel resistance and thus improve the success rate of clinical treatment [83]. Yuan *et al.* found that DEAD-box helicase 53 (DDX53) was highly expressed in paclitaxel-resistant NPC cells compared to NPC cells. Further studies have shown that DDX53 can be transferred into normal nasopharyngeal carcinoma cells through EV, and the transferred DDX53 can upregulate the level of multidrug resistance protein 1 (MDR1) in target cells, increase the pump of chemotherapy drugs from the cells, thereby reducing the accumulation of drugs in the cells and promoting paclitaxel resistance [84]. This provides a new perspective to understand NPC and may be a potential therapeutic target for NPC. In addition, extracellular vesicle (EV)-delivered microRNAs (miRNAs) have been shown to be promising biomarkers affecting cancer development. Extracellular vesicles from paclitaxel-sensitive NPC cells delivered miR-183-5p, and by targeting the mRNA of P-glycoprotein (P-gp), possibly inhibiting its expression and reducing the function of P-gp, enhanced the tumor suppressive effect of paclitaxel,

with a corresponding reduction in cell viability and tumor growth [85].

Platinum-based chemotherapy is an important treatment for nasopharyngeal carcinoma. Platinum drugs are cytotoxic agents used as first-line chemotherapeutic agents for many cancers, and their mode of action includes binding to DNA after hydrolysis of one or two chloride ions *in vivo*, thereby preventing replication and transcription, thereby hindering the growth of cancer cells [86]. However, long-term use of platinum agents may lead to the development of resistance and thus affect the therapeutic efficacy. In NPC tissues and cells, the expression of CircPARD3, SIRT1 and SSRP1 was up-regulated, and the expression of miR-579-3p was down-regulated. CircPARD3-loaded EV promoted the stemness and cisplatin resistance of EBV-miR-BART4 induced nasopharyngeal carcinoma side population (NPC-SP) cells. CircPARD3-loaded EV regulated SIRT1 through miR-579-3p, SIRT1 up-regulated the expression of SSRP1 through histone methylation, and the down-regulation of SSRP1 reversed the effect of SIRT1 on EBV-Mir-BART4-induced stemness and cisplatin resistance of NPC-SP cells. Therefore, CircPARD3-loaded EV promoted stemness and cisplatin resistance of EBV-Mir-BART4-induced NPC-SP cells by targeting miR-579-3p/SIRT1/SSRP1 axis [87]. Xia *et al.* found that over-expression of endoplasmic reticulum resident protein 44 (ERp44) reduced sensitivity to cisplatin in patients by inhibiting apoptosis and pyroptosis, a form of inflammatory cell death. More importantly, under endoplasmic reticulum stress (ERS), nasopharyngeal carcinoma cells produce EV containing ERp44 and can transfer them to neighboring cells to enhance chemotherapy resistance, suggesting that ERp44 may be a novel therapeutic target [88]. Similarly, Li *et al.* found that miR-106a-5p was transferred from cisplatin-resistant cells to susceptible NPC cells via EV and conferred cisplatin resistance to recipient NPC cells. Mechanistically, EVmiR-106a-5p targeted aryl hydrocarbon receptor nuclear transporter 2 (ARNT2) to further activate AKT phosphorylation, promote the proliferation, migration and invasion of NPC cells, and develop resistance to cisplatin treatment. EVmiR-106a-5p may be a promising diagnostic biomarker and drug target for patients with nasopharyngeal carcinoma [89]. miR-196a in EV from cancer-associated fibroblasts (CAFs) by targeting the tumor suppressors cyclin-dependent kinase inhibitor 1B (CDKN1B) and growth protein inhibitor 5 (ING5), both of which are negative regulators of cell cycle and cell proliferation. miR-196a disinhibits the cell cycle, thereby promoting the proliferation and cisplatin resistance of head and neck cancer cells, which may be achieved by altering the cellular response to cisplatin-induced DNA damage, or by affecting the apoptotic pathway [90]. These research advances provide new insights into understanding the molecular mechanisms of chemotherapy resistance in NPC and provide potential targets for the development of new therapeutic strategies.

4.2. It Plays a Role in NPC Radiotherapy by Regulating Radiosensitivity

Radiotherapy is the treatment of choice for nasopharyngeal carcinoma (NPC) due

to its high sensitivity to nasopharyngeal carcinoma (NPC). Although the survival rate of patients with nasopharyngeal carcinoma has been significantly improved with the continuous progress of radiotherapy technology, the recurrence and poor prognosis caused by radiotherapy resistance are still clinical problems to be overcome. Radioresistance is one of the major obstacles in the treatment of nasopharyngeal carcinoma. In addition, it has been found that extracellular vesicles (TEV) released by tumor cells play a key role in regulating the radioresistance of nasopharyngeal carcinoma. Ionizing radiation (IR) can cause DNA double-strand breaks (DSBS), which are usually fatal. In many cell types, IR-induced DSBS activate anti-apoptotic factors, which in turn trigger DNA damage responses. The apoptotic process regulated by p53 protein is widely considered to be the main pathway of IR-induced cell death. When DNA is damaged by IR or chemical agents, p53 protein is activated to initiate DNA repair mechanisms to protect the integrity of the genome. If DNA damage exceeds the repair capacity, cells may move toward apoptosis, a programmed cell death process [91].

EV plays a crucial role in cell-to-cell communication in the tumor microenvironment (TME). In particular, the interactions between NPC cells and tumor-associated macrophages (TAMs) play a key role in promoting tumor invasiveness and radioresistance. Nasopharyngeal carcinoma tissue-derived EVmiR-193b-3p promotes TAM activation by directly targeting mitogen-activated protein/ERK kinase kinase 3 (MEKK3), and further promotes the invasion and radioresistance of nasopharyngeal carcinoma cells [92]. Similarly, tumor-derived extracellular vesicles are delivered to radioresistant nasopharyngeal carcinoma cells through miRNA-142-5p to inhibit HGF/c-Met and EGF/EGFR pathways, thereby increasing the radiosensitivity of nasopharyngeal carcinoma cells and accelerating their apoptosis, which is of great significance for improving the therapeutic effect of nasopharyngeal carcinoma [93]. Recent studies have shown that NPC-Exos can inhibit the CD25/IL-2 signaling pathway of $\gamma\delta$T cells by carrying miR-15a, and promote the release of IL-1β, IL-6 and IL-23 from dendritic cells, thereby regulating the differentiation of $\gamma\delta$T cells into IL-17-secreting $\gamma\delta$T-17 subsets. These $\gamma\delta$T-17 cells significantly enhanced the radioresistance of tumor cells by secreting IL-17, while blocking IL-17 or inhibiting miR-15a could reverse the radioresistance. This study reveals a new mechanism by which NPC-Exos mediate radiotherapy resistance through immune microenvironment remodeling, and provides a potential therapeutic strategy for targeting miR-15a or IL-17 combined with radiotherapy [94]. CircMYC is a newly discovered circRNA in circulating EV of nasopharyngeal carcinoma patients, which is significantly expressed in radioresistant cells. Down-regulation of CircMYC increases the radiosensitivity of cells, indicating that the overexpression of CircMYC contributes to radioresistance. Luo *et al.* evaluated its diagnostic performance and reported an AUC value of 0.945, a sensitivity of 90.24%, and a specificity of 94.51%, suggesting that sEV CircMYC can be used as a biomarker to identify radioresistant nasopharyngeal carcinoma patients and radiosensitivity [95]. In addition, Wan *et al.* found that overexpression

of EV secreted by miR-34c significantly inhibited the proliferation of NPC cells, while knockdown of miR-34c significantly increased the viability of NPC cells. In addition, miR-34c promotes NPC cell apoptosis and inhibits radiotherapy resistance by targeting β-catenin. Therefore, upregulation of miR-34c or inhibition of β-catenin is an effective means to inhibit tumor progression and restore radiosensitivity [96]. It has been reported that EV from LMP1-positive NPC cells can mediate radiation resistance and inhibit apoptosis of recipient cancer cells through the activated P38 MAPK pathway. Inhibition of P38 activity can effectively restore the sensitivity of LMP1-positive EV transformed nasopharyngeal carcinoma cells to ionizing radiation [20]. miR-19b-3p was upregulated in NPC and served as an independent predictor of reduced patient survival. miR-19b-3p increases the radioresistance of NPC cells by activating TNFAIP3/NF-κB axis. TNFAIP3 knockdown reduced the radiosensitivity, while the up-regulation of TNFAIP3 expression reversed the inhibitory effect of miR-19b-3p on the radiosensitivity of NPC cells [97]. However, studies in EV are not clear. Therefore, inhibition of NF-κB activation can increase the radiosensitivity of nasopharyngeal carcinoma [98]. These findings provide new therapeutic strategies and biomarkers for radiotherapy of NPC.

4.3. Multi-Pathway Coordination of Exosomes to Reshape the Immunosuppressive Microenvironment of Nasopharyngeal Carcinoma and Its Targeted Intervention Strategy

In the context of NPC, tumor-derived EV plays an important role in shaping the immune microenvironment and regulating immune cell function, thereby affecting tumor progression and response to therapy. EV cargoes have been found to modulate immune cell function and affect tumor progression: first, EV can carry immunosuppressive molecules, such as Programmed death receptor ligand 1 (PD-L1), thereby inhibiting T cell activity and promoting immune escape of tumor cells. Second, EV were involved in the induction of immune regulatory T cells (Tregs) in the NPC microenvironment. These immunosuppressive effects inhibit the activity of T cells, leading to tumor immune escape and resistance to immunotherapy [5] [99].

Programmed death ligand 1 (PD-L1) is an immunomodulatory protein that helps tumor cells avoid immune surveillance by T cells by interacting with programmed death protein 1 (PD-1). In NPC patients, PD-L1 is expressed at high levels in plasma and in EV released by NPC cells. These nasopharyngeal carcinomas cell-derived EV carry PD-L1 and bind to the PD-1 receptor on CD8+ T cells, resulting in a decrease in the killing ability of CD8+ T cells, thereby promoting the immune escape mechanism of nasopharyngeal carcinoma [100]. A recent study revealed that $\gamma\delta$-T cell-derived EV ($\gamma\delta$-T-Exos) could effectively kill nasopharyngeal carcinoma (NPC) cells *in vitro* and inhibit NPC tumor growth *in vivo* by activating the Fas/Fas ligand (FasL) and death receptor 5 (DR5)/tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) signaling pathways. These EV

were particularly able to recognize and target CD44-positive or highly expressed cancer stem cells (CSCs) with radioresistant properties, triggering deep apoptosis of these cells. Combined with radiotherapy, γδ-T-Exos could overcome the radioresistance of CD44 positive NPC cells and significantly improve the therapeutic effect on NPC both *in vitro* and *in vivo*. Although NPC cells can secrete a large amount of tumor growth factor β to inhibit the activity of T cells, γδ-T-Exos can still maintain its direct anti-tumor effect, break through the immunosuppressive microenvironment of NPC, and thus enhance the immune response of T cells to tumors. This finding suggests that the application of γδ-T-Exos may enhance the response of NPC patients to adoptive cytotoxic T cell therapy and other immunotherapies [101]. Ye *et al.* found that EV derived from NPC could affect the proliferation and differentiation of T cells by altering the phosphorylation levels of ERK and STAT in T cells. In addition, high EV protein levels were positively correlated with lymph node metastasis and shorter disease-free survival [27]. Two years later, Ye *et al.* further found that miR-24-3p in EV affected the phosphorylation process of ERK and STAT proteins by inhibiting the expression of FGF11 gene, leading to impaired T cell function [102]. Mrizak *et al.* showed that tumor-derived EV can recruit Treg cells to the TME of NPC by transporting the chemokine CCL20. EV also recruit traditional CD4+ T cells and induce them to transform into suppressive Tregs. EV can induce treg expansion and enhance its inhibitory function, thereby creating an immunosuppressive microenvironment in the tumor microenvironment [103]. This finding reveals a unique role for tumor-derived EV in immune regulation and has important implications for understanding how tumors evade immune surveillance and treatment resistance. A study has revealed that EV released by EBV-associated NPC cells are enriched in galectin-9 (Gal-9), and these EV are capable of binding to T-cell immunoglobulin domain and mucin domain 3 (Tim-3). Through this interaction, these EV promote apoptosis of Th1 lymphocytes. It was also found that blocking the Gal-9/Tim-3 interaction by using antibodies against Tim-3 and galectin-9 significantly reduced the Th1 cytosuppression induced by NPC EV. This blocking strategy helps to maintain the immune response of T cells, which is of great significance for improving the clinical effect of NPC immunotherapy [104]. YAP1 and FAPα activity levels were significantly increased in the tumor stroma of NPC patients who developed metastasis, which was further correlated with tumor fibrosis and poor metastasis-free survival. EV released from EBV (+) NPC cells contains abundant FAPα protein and EBV-encoded latent membrane protein 1. EV containing viral products promoted the characteristics of cancer-associated fibroblasts by stimulating YAP1 signaling and the production of immunosuppressive cytokines IL8, CCL2 and IL6. In addition, stimulation of fibroblasts with these EV containing viral products promoted NPC resistance to T-cell-mediated cytotoxicity in the tumor sphere. Thus, EBV stimulates YAP1 and FAPα function in fibroblasts via EV cargo to coordinate interactions with the host and surrounding stroma, thereby creating a more immunosuppressive, anti-invasive microenvironment [105]. These findings provide a scientific basis for the de-

velopment of novel immunotherapy strategies that may help to improve treatment outcomes for NPC patients.

5. As Biomarkers, Exosomes Play an Important Role in the Early Diagnosis and Monitoring Prognosis of NPC

5.1. It Can be Used as a Biomarker for the Early Diagnosis of NPC

Early diagnosis of nasopharyngeal carcinoma is crucial for improving the prognosis of patients. However, due to the lack of obvious early symptoms and the insufficient sensitivity of conventional screening methods, early diagnosis is quite challenging. Immunoserological markers, such as IgA antibody against Epstein-Barr virus (EBV-VCA-IgA), play an important role in the early diagnosis of nasopharyngeal carcinoma. However, according to studies, the positive detection rate of EBV-VCA-IgA in nasopharyngeal carcinoma patients usually does not exceed 70%, which limits its clinical application value as a single diagnostic tool [106]. In order to improve diagnostic accuracy, it is often necessary to combine other biomarkers and assays.

Circulating nasopharyngeal carcinoma EV has altered miRNA profiles due to functional changes in the cells from which they are derived, which is of great value in the diagnosis of nasopharyngeal carcinoma. The study by Zheng *et al.* found 21 up-regulated miRNAs and 10 down-regulated mirnas in the plasma EV of NPC patients, and these differentially expressed mirnas (DE miRNAs) may serve as biomarkers for the diagnosis of NPC. In particular, miR-1301-3p is considered to be more relevant to NPC progression among these differentially expressed mirnas, indicating that miR-1301-3p in circulating EV has the potential to be a diagnostic biomarker for NPC [107]. Previous studies have shown that miR-205-5p is up-regulated in NPC tissues or plasma. miR-205-5p is considered as a potential diagnostic biomarker [108]. Jiang and colleagues found that the 3-mirNA-based model consisting of miR-134-5p, miR-205-5p, and miR-409-3p had a good diagnostic ability for NPC patients, showing an area under the ROC curve (AUC) of 0.91 in ROC analysis. Therefore, these miRNAs have shown good effects in the diagnosis and prognosis of nasopharyngeal carcinoma [109]. Zou *et al.* also found that 5 miRNAs (let-7b-5p, miR-140-3p, miR-192, mi2-5p, miR-223-3p and miR-24-3p) were significantly up-regulated in EV secreted from NPC patients. It is a marker of high sensitivity and specificity in the diagnosis of nasopharyngeal carcinoma [110]. These EVmiRNA findings further confirm the potential of liquid biopsy in cancer diagnosis and surveillance, especially when obtaining tumor tissue samples is difficult.

One study developed a model called EVum5 based on a combination of LMP1, LMP2A, and the tumor markers programmed death 1 (PD-L1), epidermal growth factor receptor (EGFR), and epithelial cell adhesion molecule (EpCAM) to identify five EV subsets. The accuracy of EVum5 in distinguishing NPC patients from healthy donors and NPG patients was 96.3% and 83.1%, respectively, which was significantly better than that of the traditional VCA-IgA assay. In addition, EV

(SUM2) (an unweighted sum of virus-specific LMP1 and lmp2a positive EV) could diagnose NPG with an accuracy of 82.6%. Overall, this work proposes a rapid, reliable and non-invasive method as well as two diagnostic markers to help more accurately distinguish NPC from NPG patients and healthy individuals in clinical practice [111]. In addition, it has been suggested that the basic leucine zipper ATF-like transcription factor 2 (BATF2) gene is involved in a variety of malignant mechanisms. The diagnostic value of BATF2 protein expression in NPC tissues has been established by immunohistochemical (IHC) microarray. The results showed that BATF2 was down-regulated in NPC. The sensitivity, specificity and AUC of plasma derived EV BATF2 in distinguishing NPC patients from healthy controls were 81%, 82% and 0.8983, respectively. The high sensitivity and specificity of sEV BATF2 suggested that it may be used as an effective auxiliary method. To improve the diagnostic accuracy of nasopharyngeal carcinoma [112]. Cyclophilin A (CYPA) is A secreted protein, and Cui *et al.* found that EV-CYPA combined with EBV-VCA-IgA levels can be used to diagnose EBV-associated NPC. It should be noted that CYPA may not be ideal as an independent indicator of NPC screening, which may be due to the multiple functions of CYPA in normal physiological processes. In clinical practice, the combined detection of EV-CYPA and EBV-VCAIgA has higher discriminatory power than EBV-VCA-IgA test alone. EV-CYPA is a novel potential biomarker for NPC, especially when EBV-VCA-IgA levels are below standard [112]. Ramayanti *et al.* found that BRAT13-3p bound to sev is a promising biomarker for minimally invasive diagnosis in hematology, with an area under the curve (AUC) value of 0.9 for BART13-3p miRNA in NPC patients. They identified patients with endemic and nonendemic NPC by measuring serum EV-bound BART13-3p levels, which could even be used as part of a screening strategy to diagnose NPC in endemic areas [113]. Liu *et al.* established a PLA-RPA-TMA method, which can detect LMP1+ or EGFR+ EV in nasopharyngeal carcinoma cells with high sensitivity and specificity, reaching 0.956 and 0.906, respectively, and found that they are effective markers for early diagnosis of nasopharyngeal carcinoma [114]. CD109 is specifically expressed in tumor tissues and highly expressed in both NPC cell lines and tumor tissues. It is also selectively enriched in tumor EV (TEV), which is a good biomarker for NPC. In particular, detection of CD109 can provide additional diagnostic information when EBV-VCA-IgA levels are below standard [115]. This combined detection method may help to improve the early diagnosis rate of NPC, thereby improving the treatment outcome of patients.

5.2. Use in Therapy

EV, as a natural vector, has been widely used in the treatment of nasopharyngeal carcinoma due to its advantages [116]. EV extracted from tumor cells is used to deliver chemotherapy drugs, which has good targeting and delivery efficiency, and the effect of drug delivery by EV is increased by 12 times. Therefore, EV has important application value as a drug carrier [117]. Ev-carried biomolecules are also

involved in the occurrence and development of nasopharyngeal carcinoma, which can not only be used as biomarkers for prognosis and efficacy monitoring, but also as predictors of response to chemotherapy and immunotherapy, as well as potential therapeutic targets. These findings provide new strategies and directions for individualized treatment of NPC.

5.2.1. Therapeutic Potential of Stem Cell-Derived EV in Nasopharyngeal Carcinoma

Mesenchymal stem cells (MSCs) are capable of differentiating into a variety of cell types and have been reported to play a variety of roles in tumor development. EV derived from human mesenchymal stem cells (MSCs) can deliver miR-34c, which can inhibit invasion, metastasis, proliferation and EMT of NPC by inhibiting β-catenin; therefore, miR-34c can be used as a strict potential therapeutic target [96]. miR-181a carried by EV released from human umbilical cord mesenchymal stem cells (hUC-MSCs) can inhibit the growth of nasopharyngeal carcinoma cells by inhibiting the activity of KDM5C [118]. The expression level of fibroblast growth factor 19 (FGF19) in EV derived from mesenchymal stem cells is high. FGF19 promotes the proliferation and metastasis of nasopharyngeal carcinoma cells by activating the FGF19-FGFR4-dependent ERK signaling pathway and regulating the epithelial-mesenchymal transition (EMT) process [119]. The protein MATN3 in urine-derived stem cell EV (USC-exos) promotes the proliferation and extracellular matrix (ECM) synthesis of nasopharyngeal carcinoma cells (NPC) by activating the TGF-β signaling pathway and increasing the phosphorylation levels of SMAD and AKT [120]. Recent studies have shown that human mesenchymal stem cells (MSCs) were artificially engineered to generate EV with high expression of miR-125a. Treatment with these miR-125a overexpressing EV attenuated NPC cell migration and vasculogenic mimicry (VM) formation. In addition, the inhibitory effects of these EV on VM formation and migration in NPC were also demonstrated *in vivo*. Overall, MSCs can be used to generate EV with high levels of miR-125a, which may be therapeutic nanoparticles against VM formation in NPC and as a supplement to anti-angiogenic therapy in the future [121]. These findings revealed that MSCS-derived EV have great potential in anti-tumor.

5.2.2. Exosomes Are Associated with the Prognosis of NPC

Recent studies have shown that extracellular miRNAs are not only potential biomarkers but also involved in cell interactions in various types of malignancies, regulating the mutual communication between cancer cells and their microenvironment. Ev-delivered miR-30a-5p from highly metastatic cells enhanced migration, invasion and metastasis of low-metastatic cells. miR-30a-5p may promote metastasis by targeting DSG2 and regulating Wnt signaling pathway. Plasma EVmiR-30a-5p is negatively correlated with DSG2 level, which predicts the prognosis of patients [38]. Dochi and colleagues performed immunohistochemical analysis of 51 NPC biopsy specimens and found that SPARC (secreted protein acidic and rich in cysteine) expression levels were significantly increased in the periph-

eral Nats of EBER-positive NPC compared with normal adjacent tissues (Nats) of EBV-negative NPC. Furthermore, increased SPARC expression in NAT was associated with worse overall survival. RNA-seq enrichment analysis of publicly available data on nasopharyngeal carcinoma and surrounding nasopharyngeal carcinoma found that the high expression of SPARC in nasopharyngeal carcinoma was related to the promotion of epithelial-mesenchymal transition [122]. A link has been identified between Exo-PD-L1 and hyperbolic alpha (M7824), a novel bifunctional therapy targeting TGF-β and PD-L1. Initially, NPC patients with plasma Exo-PD-L1 expression higher or lower than 3.5 pg/mL showed no significant differences in overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). However, a subset of patients showed changes in Exo-PD-L1 levels after the initiation of treatment. Specifically, patients with a change in Exo-PD-L1 level ≥ 60 pg/mL at week 4 had a significantly worse response to M7824 and a worse survival prognosis. The potential of Exo-PD-L1 as a biomarker to predict the response to M7824 treatment [123]. Circulating EV was extracted from 210 NPC patients. Circulating EVcirc MYC is significantly increased in NPC patients and is associated with tumor size, lymph node metastasis, TNM stage, survival rate, and disease recurrence. circMYC is an oncogene in nasopharyngeal carcinoma cells, which can promote cell proliferation and enhance the radiotherapy resistance of nasopharyngeal carcinoma cells. Circulating EVcircMYC can be used as a potential therapeutic target for nasopharyngeal carcinoma [95]. The level of CYPA in EV is much higher than that in serum of patients with nasopharyngeal carcinoma, and CYPA can be used for prognosis and monitoring of EBV-related nasopharyngeal carcinoma [124]. Furthermore, these Mir-6750-enriched EV have demonstrated anti-tumor ability by promoting M1 polarization in macrophages and inhibiting angiogenesis. From a clinical point of view, bioengineered EV enriched with miR-6750 may be adjuvants for immunotherapy, considering their ability to reverse the immunosuppressive effects of TAMs [65]. Zuo and colleagues found that aspirin significantly inhibited the secretion of LMP1 by NPC cells and promoted the expression level of miR-203 in cells and EV, which had a good therapeutic effect in the treatment of NPC. Aspirin can inhibit EMT through functional NF-κB/miR-203/CDH6 axis and significantly inhibit lung metastasis of NPC. This result suggests a potential new use of low-cost aspirin in NPC [125]. As an important mediator of intercellular communication, exosomes carry bioactive molecules such as proteins, nucleic acids and metabolites, which have shown important value in the occurrence, development and prognosis evaluation of nasopharyngeal carcinoma (NPC). Future studies need to further verify the clinical translation value of specific markers and explore the application potential of engineered exosomes in prognostic intervention.

6. Discussion

As "molecular messengers" in the tumor microenvironment, exosomes have been gradually revealed to participate in the occurrence, development, metastasis, in-

vasion and treatment resistance of nasopharyngeal carcinoma. This review systematically summarizes the key roles of exosomes in the diagnosis and treatment of NPC. 1) At the diagnostic level, the miRNA, lncRNA and protein carried by exosomes can be non-invasive monitored by liquid biopsy, and their dynamic changes are significantly related to tumor burden, lymph node metastasis and TNM stage. 2) At the therapeutic level, exosomes can not only mediate chemoresistance, but also serve as natural carriers to deliver anticancer drugs or gene editing tools. Their biocompatibility and targeting provide new strategies for breaking through the blood-brain barrier and other treatment bottlenecks. 3) In prognosis evaluation, exosome multi-omics features (such as miRNA-EBV-DNA combined markers) showed better predictive efficacy than traditional indicators through machine learning models.

However, the current research still faces three core challenges: first, the bottleneck of technical standardization. The primary obstacle to the clinical translation of exosomes is the lack of efficient and stable separation and detection system. Although emerging technologies such as microfluidic chips and nanoprobes have significantly improved the capture efficiency of exosomes, ultracentrifugation, size exclusion or immunomagnetic bead methods used in different studies still have problems such as low recovery rate and pollutant interference. Especially for low-abundance samples such as saliva and urine, it is difficult to achieve high-purity enrichment with existing technologies, resulting in insufficient sensitivity and specificity of downstream molecular detection, such as the quantification of low-frequency mutated mirRNA. In addition, precise sorting of exosome heterogeneity (e.g. tumor-derived vs. matrix-derived subsets) is not yet mature, which limits the clinical reproducibility of marker studies. Second, the depth of mechanism analysis is insufficient, and there are still many "black boxes" in the molecular network of exosome-regulated NPC. First, the molecular details of how Epstein-Barr virus-encoded ncrRNA (such as BART miRNAs) mediate host-pathogen interactions through exosomes to reshape the immunosuppressive microenvironment are not clear. Secondly, the targeted delivery mechanism of exosomal ncRNA and its synergistic effect with CTC and ctDNA need to be further verified. Moreover, functional optimization of engineered exosomes, such as surface ligand modification to enhance tumor targeting, is still limited to animal models, and the *in vivo* metabolic kinetics and long-term safety evaluation system need to be established urgently. Third, the transformation barriers of clinical application. Exosomes face multiple obstacles from basic research to clinical application. On the one hand, the existing marker studies are mostly based on single-center small sample cohorts, and lack of multi-center validation and standardized detection procedures. On the other hand, the cost-effectiveness ratio of exosome therapy has not yet met the requirements of industrialization, and tumor-derived exosomes may carry the "double-edged sword" effect of cancer-promoting components, which needs to be safely and controllable by synthetic biology methods (such as artificial exosome-drug delivery platforms). It is worth noting that the

unique anatomical location of nasopharyngeal carcinoma (adjacent to the skull base) makes the detection of cerebrospinal fluid exosomes may be the key to break through the problem of local invasion monitoring, but related research is still in the blank stage.

7. Summary and Prospect

The study of exosomes is promoting the transformation of the diagnosis and treatment mode of nasopharyngeal carcinoma to the paradigm of "dynamic monitoring-precise intervention". As an innovative tool for liquid biopsy, exosomes not only overcome the invasive limitations of tissue biopsy, but also reflect the spatiotemporal heterogeneity of tumors through multi-omics features. In terms of diagnosis, the development of portable detection equipment based on saliva/urine exosomes is expected to realize the popularization of early screening in the community. In the field of treatment, engineered exosome-drug delivery systems (such as CD63+ exosomes loaded with anti-PD-1 antibody) may break through the bottleneck of traditional chemoradiotherapy resistance. In the prognostic model, the dynamic monitoring of exosomal ncrNA-protein composite markers will provide a basis for individualized follow-up strategies.

Future research needs to focus on three major directions: 1) Technological innovation: the development of ultra-sensitive detection platforms (such as CRISPR-Cas13a combined with digital PCR technology) to achieve accurate quantification of trace exosome markers; 2) Mechanism exploration: single-cell sequencing and spatial transcriptomics were used to analyze the exosomes-mediated intercellular communication network, especially the interaction between EBV ncRNA and host genome; 3) Clinical translation: establish international consensus guidelines for the isolation and detection of exosomes, promote multi-center clinical trials to verify the universality of the marker panel, and explore the combined application strategy of exosome therapy with immune checkpoint inhibitors and oncolytic viruses. Although there are many challenges ahead, with the deep integration of interdisciplinary technologies, exosomes are expected to become the core biological vectors for the whole process management of nasopharyngeal carcinoma in the next decade, bringing better survival benefits to patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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