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Exosomes and microRNAs: Powerful mediators of cancer and their clinical applications

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Abstract

Exosomes are nanoscale extracellular vesicles secreted by nearly all cell types, playing a crucial role in intercellular communication. These vesicles transport biomolecules, including proteins, lipids, and nucleic acids, particularly microRNAs (miRNAs), which regulate post-transcriptional gene expression. In cancer, exosomes influence critical processes such as cell proliferation, angiogenesis, metastasis, and therapeutic resistance by transferring oncogenic or tumor-suppressor miRNAs to recipient cells. Their stability in biological fluids and their ability to protect molecular cargo make them promising candidates for non-invasive diagnostics and targeted therapeutics. This review explores the mechanisms of exosome biogenesis, their molecular composition, and their roles in cancer progression, alongside emerging clinical applications and challenges.

Keywords: Exosomes; MicroRNAs; Cancer; Biomarkers; Therapy; Oncogenetics

1. Introduction

Cancer is a multifactorial disease characterized by genetic and epigenetic alterations and complex interactions between tumor cells and their surrounding microenvironment. The tumor microenvironment comprises stromal cells, immune cells, extracellular matrix components, and soluble factors, all of which significantly contribute to tumor progression [1]. Over the past decade, extracellular vesicles, particularly exosomes, have emerged as key mediators of these interactions [2].

Exosomes are nanoscale vesicles formed within cells and secreted into the extracellular space. They serve as molecular messengers, transferring proteins, lipids, and nucleic acids, including miRNAs, to recipient cells [3]. miRNAs, in particular, are small non-coding RNAs that regulate post-transcriptional gene expression and are implicated in cancer-related processes such as proliferation, metastasis, angiogenesis, and therapeutic resistance [4].

The unique stability of exosomes in biological fluids and their ability to protect their cargo from enzymatic degradation make them attractive candidates for clinical applications, including non-invasive diagnostics and therapeutic delivery [5]. Studies have highlighted their ability to reshape the tumor microenvironment by transferring oncogenic signals that promote immune evasion and tumor progression [6]. Furthermore, miRNAs transported via exosomes modulate stromal and immune cells, creating an environment conducive to tumor development [7].

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2. Biogenesis and molecular composition of exosomes

Exosome biogenesis is a highly regulated process that begins with plasma membrane invagination, resulting in the formation of early endosomes [8]. These endosomes mature into multivesicular endosomes (MVEs), where intraluminal vesicles are formed [9]. The Endosomal Sorting Complex Required for Transport (ESCRT) machinery is a critical mediator of this process, although ceramide-dependent pathways also contribute [10]. MVEs eventually fuse with the plasma membrane, releasing intraluminal vesicles as exosomes into the extracellular space [11].

Exosomes contain specific biomolecules that reflect the physiological or pathological state of their cell of origin. They carry proteins such as tetraspanins (CD9, CD63, CD81), heat shock proteins, and ESCRT-related molecules [12]. Lipids like sphingolipids, ceramides, and cholesterol contribute to their structural integrity [13]. Nucleic acids, including miRNAs, messenger RNAs (mRNAs), and long non-coding RNAs (lncRNAs), are selectively packaged into exosomes, often guided by RNA-binding proteins such as hnRNPA2B1 [14]. These molecular components enable exosomes to influence recipient cell behavior, underscoring their importance in intercellular communication [15].

3. Role of Exosomes and miRNAs in Cancer

Exosomes play a pivotal role in cancer progression by acting as carriers of bioactive molecules, including oncogenic and tumor-suppressor miRNAs. By transferring these miRNAs to recipient cells, exosomes modulate various hallmarks of cancer, such as proliferation, angiogenesis, metastasis, and therapeutic resistance. These vesicles influence the tumor microenvironment, promote immune evasion, and support tumor growth and survival [16, 17]. Their ability to transport molecular signals across distant sites highlights their role in preparing pre-metastatic niches and altering stromal behavior, which are critical in advanced cancer stages [18].

3.1. Proliferation

One of the critical roles of exosomes in cancer is promoting tumor cell proliferation. Tumor-derived exosomes carrying miR-21, an oncogenic miRNA, play a central role in this process. miR-21 targets tumor suppressor genes such as PTEN, leading to the activation of the PI3K/AKT signaling pathway. This pathway enhances cell survival, proliferation, and resistance to apoptosis, creating a permissive environment for tumor growth [19, 20].

Additionally, miR-21 modulates the expression of other downstream targets, such as PDCD4 and RECK, further amplifying its effects on proliferation [21]. Studies have shown that exosomes from glioblastoma and breast cancer cells containing miR-21 are readily internalized by neighboring cells, spreading oncogenic signals and increasing tumor aggressiveness [22]. Furthermore, exosomal miR-21 has been correlated with worse prognostic outcomes, highlighting its potential as a biomarker for monitoring tumor progression [23].

3.2. Angiogenesis

Angiogenesis, the formation of new blood vessels from existing vasculature, is critical for supplying oxygen and nutrients to growing tumors. Hypoxic tumor microenvironments are particularly effective at releasing exosomes enriched with angiogenic factors, including miR-210. This miRNA stabilizes hypoxia-inducible factor-1α (HIF-1α), a master regulator of the hypoxic response in endothelial cells [24].

miR-210 suppresses anti-angiogenic pathways by targeting genes such as EFNA3 and VEGF inhibitors, leading to enhanced endothelial cell migration, tube formation, and vascular remodeling [25]. Tumor-derived exosomes carrying miR-210 have been detected in plasma, correlating with increased angiogenesis and poor prognosis in cancer patients [26].

3.3. Metastasis

Metastasis, the dissemination of cancer cells to distant organs, is a leading cause of cancer-related mortality. Exosomes facilitate metastasis by modifying both the local tumor microenvironment and distant pre-metastatic niches. A key player in this process is miR-105, which is abundantly present in exosomes derived from breast cancer cells. miR-105 disrupts endothelial tight junctions by downregulating ZO-1, a critical component of junction integrity, increasing vascular permeability and facilitating cancer cell intravasation [27].

In addition to altering vascular barriers, exosomal miR-105 influences the extracellular matrix by regulating MMP expression, further promoting cancer cell migration and invasion [28]. Notably, elevated levels of exosomal miR-105 in patient plasma have been associated with increased metastatic burden, suggesting its utility as a biomarker [29].

Furthermore, exosomes enriched with integrins such as αvβ6 have been shown to direct metastatic colonization toward specific organs, making them critical players in organotropism [30, 31].

3.4. Therapeutic Resistance

Therapeutic resistance is one of the most significant barriers to effective cancer treatment. Exosomes contribute to resistance by delivering miRNAs that reprogram recipient cells to evade therapeutic effects. For instance, miR-222, carried by exosomes derived from tamoxifen-resistant breast cancer cells, downregulates pro-apoptotic genes such as Bim and p27, enhancing cell survival under tamoxifen treatment [32].

4. Clinical Applications of Exosomes and miRNAs

Exosomes offer immense potential for clinical applications in oncology due to their molecular specificity, stability in biological fluids, and ability to deliver therapeutic agents. Their protective encapsulation of miRNAs and other molecules ensures their stability in circulation, making them ideal candidates for non-invasive diagnostic biomarkers and therapeutic delivery systems [33, 34].

Exosomes not only serve as diagnostic biomarkers but also offer promising avenues for therapeutic delivery. Their ability to encapsulate and protect therapeutic agents, such as tumor-suppressive miRNAs or chemotherapeutic drugs, has been widely documented (Table 1). For example, exosomal miR-34a has demonstrated significant tumor-suppressive effects in lung cancer models, while encapsulated doxorubicin enhances drug bioavailability and reduces systemic toxicity.

Table 1 Exosomal miRNAs in cancer diagnostics and therapy

Function	Description	Example miRNAs	References
Diagnostic biomarkers	Exosomal miRNAs serve as non-invasive biomarkers, detectable in blood, urine, and saliva. Reflect tumor stage and progression.	miR-21: Elevated in lung and breast cancer.- miR-92a: Early diagnostic marker for colorectal cancer.	[22,23]
Tumor progression	Exosomal miRNAs regulate pathways that promote cancer cell proliferation, angiogenesis, and metastasis.	miR-21:Promotes proliferation by targeting PTEN miR-105: Facilitates metastasis by disrupting endothelial barriers.	[16,19]
Therapeutic resistance	Exosomal miRNAs mediate drug resistance by altering apoptotic pathways and enhancing drug efflux mechanisms.	miR-222: Contributes to tamoxifen resistance in breast cancer. miR-125b: Enhances chemotherapy resistance in colorectal cancer.	[20,21]
Therapeutic delivery	Engineered exosomes can deliver therapeutic miRNAs or drugs to specific tumor cells, reducing off-target effects and toxicity.	miR-34a: Delivered via exosomes to inhibit tumor growth in lung cancer. Doxorubicin: Encapsulated for enhanced bioavailability.	[24,25]

4.1. Diagnostic Biomarkers

Exosomal miRNAs are promising non-invasive biomarkers for cancer diagnosis and monitoring. Their stability in biological fluids, such as blood, urine, and saliva, and their tumor-specific profiles allow for early detection of cancer [35].

For instance, miR-375 and miR-141 have been associated with prostate cancer progression. Elevated plasma levels of these miRNAs correlate with advanced disease stages, highlighting their diagnostic and prognostic potential [36]. Similarly, miR-92a, derived from colorectal cancer exosomes, is an early diagnostic marker with high sensitivity and specificity for differentiating malignant from benign conditions [37].

4.2. Therapeutic Delivery

Exosomes are natural delivery vehicles capable of transporting tumor-suppressive miRNAs and drugs directly to target cells, reducing systemic toxicity and enhancing therapeutic efficacy. Engineered exosomes delivering miR-34a have shown efficacy in suppressing tumor growth in lung cancer models by targeting MYC and BCL2 pathways [38].

Additionally, exosome-encapsulated chemotherapeutic agents such as paclitaxel and doxorubicin demonstrate improved bioavailability and reduced off-target effects compared to conventional therapies. For example, paclitaxel-loaded exosomes derived from mesenchymal stem cells exhibited superior anti-tumor activity in preclinical models of lung cancer [39, 40].

4.3. Immunotherapy

Exosome-based vaccines represent a novel approach in cancer immunotherapy. These vaccines leverage exosomes to deliver tumor-associated antigens to dendritic cells, activating robust anti-tumor immune responses. Preclinical studies have demonstrated their efficacy in melanoma and lung cancer models, where exosome-based vaccines elicited strong cytotoxic T-cell responses [41].

Additionally, exosomes derived from immune cells, such as macrophages and NK cells, have been engineered to carry immune-stimulatory molecules, overcoming tumor-induced immunosuppression and enhancing the efficacy of checkpoint inhibitors [42].

5. Conclusion

Exosomes and miRNAs have become pivotal in advancing our understanding of cancer biology, offering innovative solutions for non-invasive diagnostics and targeted therapies. Their roles in mediating intercellular communication and influencing tumor progression underscore their clinical significance. Despite ongoing challenges, including standardization of isolation techniques and targeted delivery, these vesicles hold immense promise for integration into precision oncology. Continued research and technological advancements will be critical to unlocking their full potential, paving the way for transformative approaches in cancer treatment.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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