**Review Article**

**Exosomal Communication in the Tumour Microenvironment of Non-Small Cell Lung Cancer: Implications for Progression and Therapy**

**ABSTRACT**

Non-small cell lung cancer (NSCLC) is regarded as the most prevalent form of lung cancer, accounting for approximately 85% of all cases worldwide. This type of cancer is highly affected by the tumour microenvironment (TME), where exosomal communication is a major contributor. This prompts ongoing exploration of exosomes as therapeutic tools. Research into exosome-derived biomarkers, such as miRNAs, lncRNAs, and proteins, continues because their potential in drug delivery and immunotherapy can improve NSCLC treatment. This review explored the role of exosomal communication in the NSCLC tumour microenvironment, focusing on its impact on tumour progression, immune modulation, angiogenesis, and therapy resistance. Additionally, it evaluates the potential of exosomes as biomarkers for early diagnosis and therapeutic targets in NSCLC. A comprehensive literature review was conducted using peer-reviewed studies from databases such as PubMed, Google Scholar, and Web of Science. Articles were selected based on relevance to NSCLC and exosomal communication, with focus on studies published within the last five years. Both experimental and clinical studies were analyzed to provide a well-rounded understanding of exosome-mediated mechanisms in NSCLC. Exosomes contribute to NSCLC progression by promoting tumor-stromal interactions, modulating immune responses, and enhancing angiogenesis. Tumour-derived exosomes induce cancer-associated fibroblast activation, macrophage polarization, and suppression of cytotoxic T cells, creating an immunosuppressive microenvironment which promotes cancer growth. Exosomal communication plays a critical role in NSCLC pathogenesis, influencing tumour progression, immune evasion, and angiogenesis. This presents it as a great tool to be used as biomarker for predicting tumour progression. Future research should focus on refining exosome-based diagnostic and therapeutic strategies, paving the way for personalized medicine in NSCLC management.

Key words: Lung cancer, Tumour, Non-small cell lung cancer, Therapy

**1. INTRODUCTION**

Lung cancer is one of the leading causes of cancer-related deaths worldwide, and NSCLC accounts for about 85% of all lung cancer cases. NSCLC has different variants which is categorized according to their histological features. Sub divisions are: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (Riudavets et al., 2021; Alduais et al., 2023). These subtypes have different characteristics, but they all originate from lung tissues and share similar characteristics. When this type of lung cancer is compared with another type, such as small cell lung cancer (SCLC), the major difference is that the latter grows and spreads quickly. In constrast, NSCLC usually develops more slowly and conditions are found to be chronic (Alduais et al., 2023). This may explain why it is often diagnosed at an advanced stage because early symptoms are slow, mild or even absent as reported in some patients. The obvious implication of late diagnosis is the eventual reduction in treatment options and lower survival rates (Alduais et al., 2023). Many factors have been reported to contribute to the development of NSCLC. Smoking remains the primary risk factor, but a significant number of non-smokers also develop NSCLC due to genetic and environmental influences (Hendriks et al., 2024). including smoking, environmental pollutants, genetic mutations, and chronic lung diseases Treatment options for NSCLC usually include surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy. However, despite advances in these treatments, the prognosis for NSCLC remains poor, especially in metastatic cases. One reason for treatment failure may be due to the complex TME, which supports cancer growth and makes it harder for treatments to work effectively (Wislez et al., 2022; Hendriks et al., 2024).

The TME consists of different types of cells and molecules that surround and interact with tumour cells. Immune cells, cancer-associated fibroblasts, blood vessels, and extracellular matrix components are the common examples of the TME components. The TME as a whole has a significant involvement in how cancer grows. It may also create conditions that allow cancer cells to invade nearby tissues, and spread to other parts of the body (Wislez et al., 2022; Hendriks et al., 2024). One of the most significant effects of the TME is its ability to help tumours escape attacks from host immune system. These characteristics enable cancer cells to evade immune destruction and proliferate without being destroyed (Wislez et al., 2022; Hendriks et al., 2024). Another important feature of the TME is its role in drug resistance. Many drugs are in production and are expected to kill tumour cells, but the surrounding environment can negatively affect potency by reducing drug penetration (Riely et al., 2021). Therefore, understanding the TME is essential for improving NSCLC treatment. Therapies targeting the TME, such as immune checkpoint inhibitors and anti-angiogenic drugs, have shown promising results. However, cancer cells can still find ways to adapt and resist these treatments. This is why researchers are exploring new strategies, such as targeting exosomal communication, to disrupt the interactions between cancer cells and the TME (Alduais et al., 2023).

Cells communicate with each other using different methods. It could be through direct contact, by sending signalling molecules, or through extracellular vesicles like exosomes (Lee et al., 2024). In the context of NSCLC, researches have suggested that exosomes take part in some aspects of tumour development. For example, we found out that exosomes can transfer cancer-promoting molecules to surrounding cells, which can initiate aggressive oncogenesis (Donoso‐Quezada et al., 2021). In a similar manner, exosomes from tumour cells can make fibroblasts to support cancer growth and alter immune cells (Lee et al., 2024). Furthermore, exosomes can help cancer cells leave their initial area and migrate to another place in distant organs (metastasis) (Donoso‐Quezada et al., 2021).

Despite advances so far in NSCLC treatment, survival rates remain low. Because exosomes are found in easily accessible body fluids, they have gained attention as potential biomarkers to look at in tumours like NSCLC. Scientists are also investigating whether exosomes can be used as drug carriers to deliver treatments directly to cancer cells, as well as other therapeutic potentials of exosomes.

**2. EXOSOMES AND THEIR FUNCTIONAL ROLE**

Exosomes are small extracellular vesicles which typically range in size from 30 to 150 nanometres. They arise when the membrane inside a cell’s endosome folds inward, making little sacs called intraluminal vesicles that sit inside multivesicular bodies (Shan et al., 2021). These multivesicular bodies are like the known cellular organelles packed with small vesicles that later get released outside of the cell. Exosomes have a double-layered membrane composed of proteins, fats, and nucleic acids, which help them connect with other cells. What makes them special compared to other vesicles is their unique mix tetraspanins (CD9, CD63, CD81), heat shock proteins (HSP70, HSP90), and integrins that control how they get taken up by other cells (Han et al., 2022). Because they’re so small, they can zip through body fluids like blood, urine, saliva, and even spinal fluid, letting cells communicate with each other whether they’re close by or far apart (Shan et al., 2021; Han et al., 2022).

**2.1 Exosomes Biogenesis and Release Mechanisms**

Exosomes are generated from a carefully controlled process that starts with early endosomes, which grow into late endosomes. Inside these late endosomes, the membrane folds inward to create those intraluminal vesicles mentioned earlier (Shan et al., 2021; Han et al., 2022). These will then pile up to form multivesicular bodies, which then have two options: they either fuse with lysosomes to get broken down or join up with the cell’s outer membrane to let the exosomes out (Shan et al., 2021).

The process of packing molecules into exosomes involves a few key steps. One big player in this process is the endosomal sorting complexes required for transport (ESCRT), which has both dependent and independent ways of working (Küng et al., 2022). The ESCRT system is a group of protein teams that pick out and load specific molecules into the forming vesicles. When this pathway is followed it is known as ESCRT-dependent pathway. There’s also an alternate ESCRT-free route that uses lipid molecules, ceramide, and tetraspanins to sort cargo and shape the vesicles. This is known as the ESCRT-independent pathway (Gurung et al., 2021). Then there are Rab family GTPases, especially Rab27a and Rab27b, which help steer the multivesicular bodies to dock and fuse with the cell membrane for release. Factors like low oxygen concentration, stress, or inflammation may determine how many exosomes are released, their functional impact as well as their composition (Gurung et al., 2021).



Figure 1. Exosomes and other extracellular vesicles: biogenesis and secretion in eukaryotic cells (Zhang and Yu, 2019).

First, exosomes fuse into early endosomes and multivesicular bodies (MVBs). Late MVBs fuse with either plasma membrane to release exosomes or with lysosomes for degradation. Many mRNAs, microRNAs (miRNAs), proteins, and receptors are also carried by exosomes. Microvesicles bud directly from the plasma membrane, not from MVBs. CD42, integrins, and selectin are enriched in microvesicles; microvesicles also carry multiple receptors, proteins, miRNAs, and mRNAs. Apoptotic vesicles are derived from apoptotic cells. They contain DNAs and histone besides proteins, receptors, mRNAs, and miRNAs.

**2.2 Molecular Cargo of Exosomes**

Exosomes are consisting of proteins, fats, and nucleic acids, that contribute to their function (Li et al., 2023). Their protein line-up includes membrane proteins (CD9, CD63, CD81), skeleton-like proteins (actin, tubulin), and signalling molecules (kinases, growth factors). Heat shock proteins like HSP70 and HSP90 help fold proteins right and deal with cell stress, while MHC proteins pitch in to show antigens to immune cells (Küng et al., 2022).

The lipid components in exosomes are not quite like the ones in the parent cell’s membrane. They’re loaded with sphingolipids, ceramides, phosphatidylserine, and cholesterol, which helps with membrane stability keep the membrane sturdy and help exosomes fuse with other cells (Li et al., 2023). Ceramide plays a crucial role in exosome formation by promoting membrane curvature, facilitating vesicle budding (Küng et al., 2022).

Then there are also nucleic acids: microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and messenger RNAs (mRNAs). miRNAs are tiny RNAs that controls gene activity by sticking to mRNAs and shutting them down (Küng et al., 2022). lncRNAs and circRNAs act like sponges, soaking up miRNAs to mess with cell signalling. The mRNAs in exosomes can even get turned into working proteins once they land in another cell, changing how it behaves (Küng et al., 2022). Additionally, exosomes carry DNA fragments, including single-stranded and double-stranded DNA, which may contribute to genetic transfer and mutational changes in target cells (Wei et al., 2021).

**2.3 Exosomes in Health and Disease**

Exosomes are key players in keeping cell haemostasis balanced by mediating cellular interactions. In physiological conditions, exosomes contribute to immune modulation, tissue repair, and neuronal function (Shan et al., 2021; Han et al., 2022). They may also function as antigen presenting cells, boost immune cell action, and participate in synaptic plasticity by transferring signalling molecules between neurons. In the cardiovascular system, exosomes released by endothelial cells regulate vascular function and angiogenesis. Pertaining to cancer, their angiogenetic role in this aspect may emphasize their importance in tumour growth (Küng et al., 2022).

In pathological conditions, exosomes contribute to disease progression by transferring bioactive molecules that alter the behaviour of recipient cells. In cancer, exosomes derived from tumour cells promote tumour growth, invasion, and metastasis by transferring oncogenic proteins and RNAs to surrounding stromal cells (Han et al., 2022). They also contribute to drug resistance by delivering multidrug resistance proteins and anti-apoptotic factors. In neurodegenerative diseases, exosomes facilitate the spread of misfolded proteins such as β-amyloid and α-synuclein, accelerating disease pathology. In infectious diseases, pathogens exploit exosomes for immune evasion and viral transmission (Shan et al., 2021).

**3. Exosome-Mediated Communication in the NSCLC TME**

The tumour microenvironment (TME) in NSCLC consists of a complex network of different cells and molecules interacting together. Cancer cells, stromal cells, immune cells, and extracellular matrix components are some of the cells involved. The TME provides a supportive niche that facilitates every aspect of the tumour cycle including a specific resistance to therapy (Mao et al., 2022).

**3.1 Exosome-Mediated Crosstalk Between Tumour Cells and TME**

Exosomes act as important mediators of cell-to-cell communication in NSCLC by transferring bioactive molecules, including proteins, lipids, and nucleic acids, between tumour cells and stromal cells within the TME (Shan et al., 2021). Stromal component of the TME includes cancer-associated fibroblasts (CAFs), tumour-associated macrophages (TAMs), endothelial cells, and various immune cells that dynamically interact with tumour cells. These interactions are mediated by cytokines, chemokines, growth factors, and extracellular vesicles such as exosomes, which facilitate intercellular communication within the TME (Genova et al., 2022). Exosomes are capable of influencing various biological processes and tumour-derived exosomes carry oncogenic factors that reprogram the cells they affect for further support for metastasis (Genova et al., 2022).

**3.2 Activation of CAFs to Promote Invasion and Metastasis**

There is growing evidence from reviewed articles that Tumour-derived exosomes are capable of activating Cancer-associated fibroblasts (CAFs) by transferring transforming growth factor-beta (TGF-β), miRNAs, and other signalling molecules that enhance fibroblast differentiation (Yang et al., 2021; Hu et al., 2023; Mito et al., 2023). They do this by secreting extracellular matrix proteins, growth factors, and cytokines. The tumorigenic role of CAF is well documented as they have been reported to secrete matrix metalloproteinases and fibronectin, which remodels the extracellular environment, supporting tumour invasion and metastasis (Batista et al., 2021).

**3.3 TAM Polarization and Immune Evasion**

Tumour-associated macrophages (TAMs) are immune cells present in NSCLC tumours. They can sometimes have pro tumourigenic effect through the activity of exosomes. Research shows that NSCLC-derived exosomes induce the polarization of TAMs from an anti-tumour M1 phenotype to a pro-tumour M2 phenotype which is tumorigenic (Pan et al., 2020). This is a crucial shift mediated by exosomal miRNAs and cytokines, that eventually increases inflammatory responses and promote an immunosuppressive environment for lung cancer to thrive (Yang et al., 2021; Wang et al., 2024). It is noteworthy that the eventual M2-polarized macrophages enhance tumour growth through increased angiogenesis by the secretion of vascular endothelial growth factor (VEGF) (Wang et al., 2024).

**3.4 Effects on Immune Modulation**

The major determinant of how far a NSCLC metastasizes is the nature of the immune environment. When it comes to the effect of exosome on the immune system there are different functional groups that are affected (Batista et al., 2021). For example, cytotoxic T cells are vital for recognizing and eliminating tumour cells. However, in the case of NSCLC, where it is understood that chronic inflammation from smoking or environmental exposure already primes the lung TME, tumor-derived exosomes amplify T-cell suppression by delivering PD-L1 and TGF-β (Yang et al., 2021; Hu et al., 2023). These exosomal components inhibit T-cell activation, this would then lead to impaired immune surveillance and tumour progression. This means that exosome-mediated suppression of cytotoxic T cells enables tumour cells to evade immune destruction and establish a more permissive microenvironment (Huang et al., 2022). In the TME of NSCLC, exosomes arising from tumours promote the up-regulation of Tregs by transferring immune suppressing miRNAs and cytokines, like TGF-β and IL-10. This results in a reduction of anti-tumour immune responses, thereby allowing cancer cells to proliferate and metastasize without immune interference (Huang et al., 2022).

**Another critical immune component that is affected by exosomal communication is the dendritic cell.** Dendritic cells are antigen-presenting cells that initiate adaptive immune responses by indirectly activating T cells. NSCLC-derived exosomes modulate dendritic cell activity by inhibiting their maturation and antigen-presenting capacity (Khan et al., 2023; Orooji et al., 2024). Tumour-derived exosomes carrying miRNAs and proteins interfere with dendritic cell function, reducing their ability to stimulate cytotoxic T cells. Given that in NSCLC, dendritic cells patrol the lung’s airway interface to serve as APCs, disruption in their maturation can contribute to immune evasion and further enhances tumour progression (Qiu et al., 2024).



Figure 2: Role of immune cell-derived exosomes in the stimulation of the immune response against the tumour (Zhang and Yu, 2019). Demonstration of the different potentials of exosomes as tools in immunotherapy for NSCLC. Dendritic cell-derived exosomes (Dex) and NK cell-derived exosomes (NK-Exos) activate cytotoxic responses. Additionally, highlights the role of exosomal miRNAs in modulating the immune microenvironment and enhancing therapeutic outcomes

**3.5 Effects on Angiogenesis**

Exosomes promote angiogenesis by conveying VEGF and other pro-angiogenic factors to endothelial cells (Orooji et al., 2024). In many cases tumour growth is well supported by the lung cells’ vascular-densed environment. Meta-analysis shows that exosomes facilitate endothelial cell migration and vessel formation by transferring pro-angiogenic miRNAs and proteins (Orooji et al., 2024). These molecular signals activate signalling pathways, including the phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK) pathways, which promote endothelial cell survival and vascular remodelling. In foresight this situation explains how tumour progression is enhanced by the increased nutrient availability and providing a route for metastatic dissemination (Orooji et al., 2024).

**4. EXOSOMAL COMMUNICATION AS PREDICTIVE BIOMARKERS FOR NSCLC**

In the course of diagnosis, treatment and prognosis of NSLSC, exosomes are becoming a target due to their projected roles in cancer from recent studies. **As discussed earlier, e**xosomes contain a wide variety of biomolecules. A liquid biopsy investigating some of these biomolecules may assist in the laboratory diagnosis of NSCLC. Firstly, it is noteworthy that in NSCLC, tumour-derived exosomes carry specific molecular signatures that can serve as potential biomarkers (Orooji et al., 2024). **Secondly,** In NSCLC, miRNAs (such as miR-21, miR-155, and miR-126) can also serve as potential biomarkers to diagnose or predict treatment efficacy during monitoring since their expressions are altered in NSCLC (Enomoto et al., 2022). **There are also some Proteins and metabolites** found in NSCLC-derived exosomes with biomarker potentials. Proteins such as epidermal growth factor receptor (EGFR), programmed death-ligand 1 (PD-L1), and heat shock proteins (HSPs) are frequently detected in exosomes and can indicate tumour progression, immune evasion, and response to targeted therapies (Khan et al., 2023). Additionally, metabolic components, including lipids and amino acids, present in exosomes reflect tumour-specific metabolic alterations and may serve as indicators of disease state (Huang et al., 2022).

**5. EXOSOME-BASED THERAPEUTIC STRATEGIES IN NSCLC**

The role of exosomes in NSCLC progression has led to growing interest in targeting exosome-mediated communication for therapeutic purposes. Several approaches are being explored to either block exosome biogenesis and uptake or harness exosomes as delivery vehicles for therapeutic agents (Orooji et al., 2024). Exosome-based therapies offer a promising strategy for overcoming drug resistance, enhancing immune responses, and improving drug bioavailability in NSCLC treatment.

**5.1 Targeting Exosome Biogenesis**

Since exosomes facilitate tumour progression by modulating the tumour microenvironment, blocking their biogenesis could limit their role in NSCLC.

Several molecular pathways involved in exosome formation have been identified as potential drug targets. The Endosomal Sorting Complex Required for Transport (ESCRT) machinery plays a critical role in exosome formation, and inhibitors of ESCRT components, such as ALIX and TSG101, have been explored for reducing exosome secretion (Batista et al., 2021). Additionally, small-molecule inhibitors of neutral sphingomyelinase (nSMase), an enzyme involved in ceramide-mediated exosome biogenesis, have been shown to decrease exosome release in NSCLC models (Batista et al., 2021).

Blocking exosome uptake by recipient cells is another strategy under investigation. Tumour-derived exosomes are taken up by various cell types within the TME through endocytosis or membrane fusion. Inhibitors targeting lipid raft-mediated endocytosis, clathrin-mediated endocytosis, and heparan sulfate proteoglycans have been studied to prevent exosome-mediated signalling in NSCLC (Batista et al., 2021).

**5.2 Engineering Exosomes for Drug Delivery**

Exosomes possess natural biocompatibility, low immunogenicity, and the ability to cross biological barriers, making them ideal carriers for delivering therapeutic agents to tumour cells. By engineering exosomes to carry specific drugs or genetic materials, researchers aim to develop novel treatment strategies for NSCLC. Chemoresistance remains a major challenge in NSCLC treatment, and exosome-based drug delivery systems can offer a way to improve drug efficacy. Exosomes can be loaded with chemotherapeutic drugs such as paclitaxel, doxorubicin, and cisplatin to enhance targeted drug delivery and reduce systemic toxicity. Studies have shown that loading exosomes with paclitaxel increases its uptake by NSCLC cells and improves drug sensitivity.

In addition to passive drug loading, exosomes can be surface-modified to enhance their tumour-targeting abilities. Ligand-modified exosomes expressing tumour-specific molecules, such as integrins or antibodies against NSCLC markers, have been developed to improve drug accumulation at tumour sites (Orooji et al., 2024).

**5.3 Exosomal RNA-Based Therapies (siRNA, miRNA Mimics)**

Exosomes can be engineered to carry small interfering RNAs (siRNAs) or microRNA (miRNA) mimics, that target oncogenic pathways in NSCLC. RNA-based therapies have gained interest due to their ability to silence gene expression and modulate tumour progression. It is thus believed that delivering them to tumour cells may offer a strong therapeutic opportunity. Thus far, exosome-loaded siRNAs that have been used to target oncogenes such as KRAS and EGFR have demonstrated great potential in reducing tumour growth in NSCLC models as reported in the article by Raguraman et al., 2023.

Exosomes are also being explored for their potential in cancer immunotherapy. Exosomes contain immune-modulating molecules that can either suppress or activate immune responses depending on their phenotype. Therefore, conversion of specific extracellular exosomes can be highly beneficial in promoting anti-tumour immunity for NSCLC (Zhu et al., 2017).

One approach involves using dendritic cell-derived exosomes (Dexosomes) for cancer vaccination. Another strategy involves using exosomes as carriers for immune checkpoint inhibitors. Since tumour-derived exosomes express immune checkpoint molecules such as PD-L1, there is a strong indication that they can be used as a decoy to bind and neutralize PD-1 on T cells, thereby restoring anti-tumour immunity (Kim et al., 2019; Xu et al., 2020). Engineered exosomes loaded with anti-PD-L1 antibodies or siRNAs targeting immune checkpoint pathways are being investigated for their potential to enhance immunotherapy responses in NSCLC (Samuel and Gabrielsson, 2021; Pandya et al., 2024).

Additionally, exosomal vaccines are another interesting idea being explored as a strategy to boost immune responses against NSCLC. Tumour cell-derived exosomes containing tumour antigens can be used to prime the immune system and generate anti-tumour immunity. Clinical trials are underway to evaluate the efficacy of exosome-based cancer vaccines in lung cancer patients (Naseri et al., 2020). Recent study by Meng et al. 2023 already looked into this and found that exosome based vaccine drastically reduced tumour burden in mice (Meng et al., 2023)

**6. LIMITATIONS AND FUTURE PERSPECTIVES**

Despite the promising role of exosomes in NSCLC, several obstacles hinder their widespread clinical use. One of the main challenges is the **heterogeneity of exosomes**. Exosomes derived from different cell types within the tumour microenvironment vary in size, molecular composition, and functional properties (Samara et al., 2023). This variability makes it difficult to establish consistent biomarkers and therapeutic targets. Additionally, tumour-derived exosomes may carry both pro-tumour and anti-tumour factors, making it complicating to understand their contribution in tumour progression (Samuel and Gabrielsson, 2021).

Another major limitation is the **lack of efficient exosome isolation methods**. This directly hinders assessments and study progress. Ultracentrifugation remains the most widely used method, but it is time-consuming and can result in present of other contaminants (Pandya et al., 2024). This lack of a standardized, high-throughput isolation method poses a challenge for large-scale exosome research and clinical applications (Samuel and Gabrielsson, 2021).

**Future directions**

To improve the clinical utility of exosomes, standardized protocols for isolation, characterization, and functional assessment are needed. The creation of robust and scalable isolation methods will help to enhance the purity and consistency of exosome samples. This will in turn help in their use in diagnostics and research (Huang et al., 2022).

Characterization of exosomes using advanced analytical techniques such as nanoparticle tracking analysis can also be looked into. Characterization can prove to be essential for identifying specific subpopulations of exosomes. Additionally, reliable biomarker panels can be developed to distinguish tumour-derived exosomes from normal exosomes to improve accuracy in NSCLC (Orooji et al., 2024).

Another important aspect is the standardization of functional assays to evaluate exosome-mediated effects in NSCLC. In vitro and in vivo models must be optimized to assess the biological impact of exosomes on tumour progression, immune modulation, and therapy resistance. Large-scale clinical trials will also be necessary to validate the efficacy and safety of exosome-based therapies (Rao et al., 2023).

**7. Conclusion**

Exosomal communication plays a crucial role in shaping the tumour microenvironment in NSCLC. Exosomes facilitate intercellular communication by transferring bioactive molecules such as proteins, lipids, and RNAs, influencing tumour activity and therapy resistance. Their ability to modulate stromal cells, suppress immune responses, and promote metastasis highlights their significance in NSCLC pathophysiology. The potential of exosomes as biomarkers for NSCLC is evident in their application in liquid biopsy for early detection and prognosis. Exosomal miRNAs, lncRNAs, and proteins offer non-invasive diagnostic tools with promising clinical implications. Additionally, exosome-based therapeutic strategies, including engineered exosomal drug delivery and immunotherapy, present innovative approaches to improving treatment outcomes. However, challenges such as the heterogeneity of exosomes, lack of standardized isolation methods, and unclear mechanisms of cargo transfer hinder their clinical translation. Future research should focus on refining exosome-based diagnostics and therapeutics, improving isolation techniques, and developing targeted exosome therapies. Overcoming these challenges will enhance the role of exosome research in personalized medicine, paving the way for more effective NSCLC diagnosis and treatment.

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