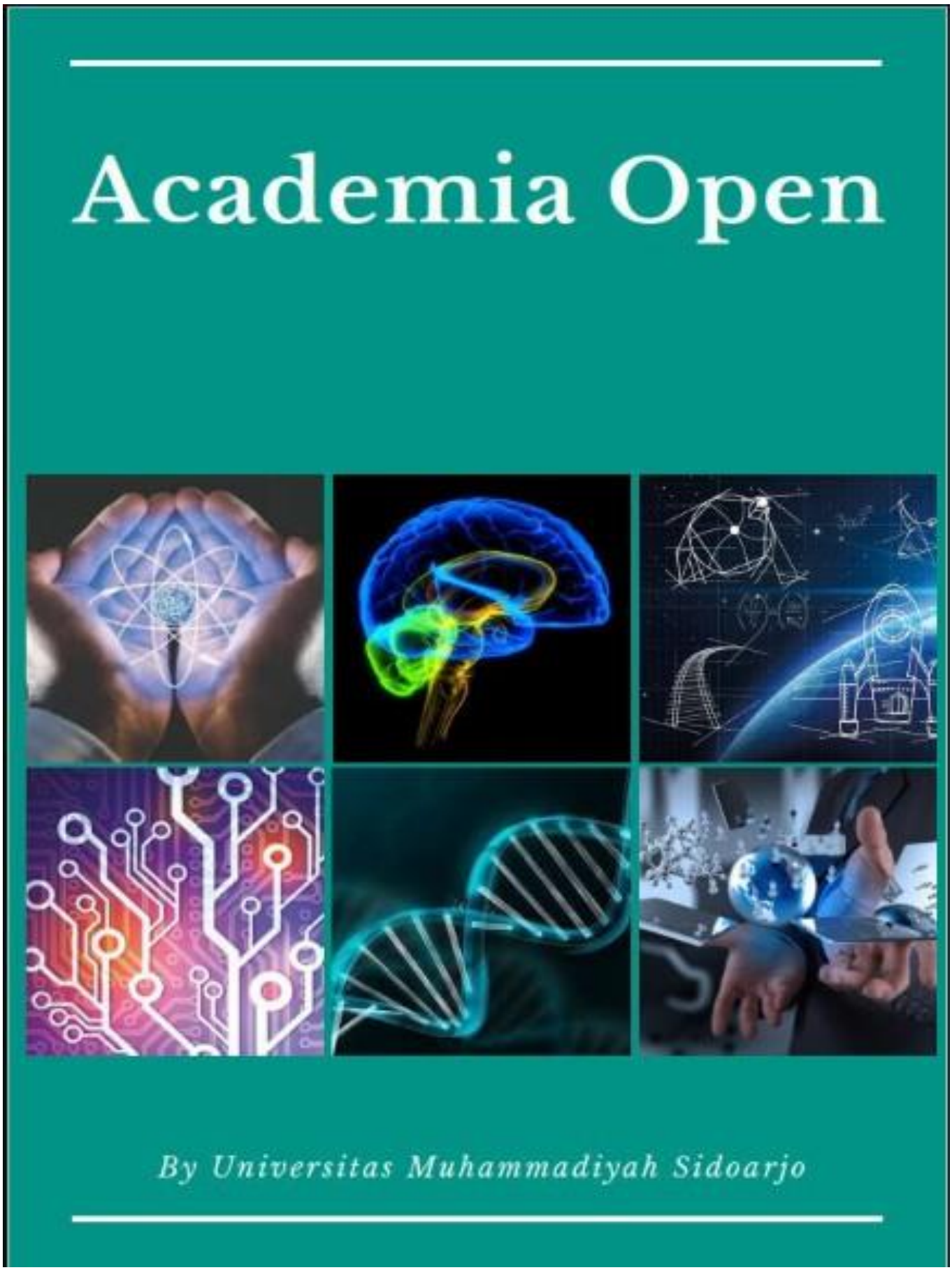

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The outer vesicles that contain abundant of microRNA play a spectacular role of dancer between immune cells and cancer cells

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Abstract

General Background: Exosomes are extracellular nanovesicles involved in intercellular communication through the transfer of proteins, lipids, and nucleic acids, particularly microRNAs. **Specific Background:** In cancer biology, immune cell-derived exosomes participate in tumor microenvironment regulation by transferring molecular cargo that can alter immune responses and tumor behavior. **Knowledge Gap:** Despite growing interest in exosome-mediated communication, the molecular mechanisms governing microRNA selection, immune modulation, and their therapeutic utilization remain incompletely understood. **Aims:** This review aims to examine the formation of exosomes, characterize their molecular cargo, and summarize the roles of immune cell-derived exosomal microRNAs in cancer-associated immune regulation and therapeutic applications. **Results:** The findings indicate that exosomal microRNAs regulate interactions between immune cells and cancer cells through pathways associated with tumor proliferation, immune evasion, macrophage polarization, dendritic cell regulation, and antitumor activity. Evidence also shows that exosomes can function as delivery platforms for nucleic acids and naturally derived anticancer compounds in experimental cancermodels. **Novelty:** This review integratescurrent evidence regarding immunecell-derived exosomes as dual mediators of tumor progression and antitumor responses while highlighting their multifunctional therapeutic potential. **Implications:** A better understanding of exosome-mediated molecular communication maysupportfuture advances in cancer diagnosis, immunotherapy development, and targeted therapeutic strategies.

Highlights:

- Immune vesicles transport regulatory microRNAs between cellular populations within tumor ecosystems.
- Molecular cargo derived from macrophages, dendritic cells, and natural killer cells participates in immune regulation pathways.
- Nanovesicle-based delivery systems demonstrate potential for nucleic acid transport and anticancer compound administration.

Keywords: Exosomes; MicroRNA; Tumor Microenvironment; Cancer Immunotherapy; Immune Cell Communication

Introduction

The past decades have been characterized by an extensive interest in human mesenchymal stem cells (MSCs) due to their regenerative potential and modulating properties; therefore, MSCs are often regarded as top of the list in the research of chronic and inflammatory diseases. They are usually characterized as pluripotent precursors cells that are involved in cellular remodelling and tissue repair [1]. As has been seen in a number of experimental systems, they can also activate immune responses in a more direct manner. [2]. These cells are not restricted to one anatomical source; reports mention their isolation from bone marrow, adipose tissue, salivary glands, Wharton's jelly, and even dental pulp. [3] which, in practice, makes their therapeutic use more flexible than was initially assumed.

More than 1,300 registered clinical trials in the National Institutes of Health database by September 2021 indicate the extent to which these cells have entered the field of regenerative medicine. The interest, however, is not centred on the cell as a whole like before, since many researchers started to look at what the cell secretes, cytokines, chemokines, growth factors, and extracellular vesicles as the real mediators of the biological effect. A substantial body of evidence indicates that several therapeutic actions attributed to MSCs can be reproduced by a vesicle population known as exosomes. [4].

Exosomes are small endosomal nanovesicles, their size usually falls between 30 and 150 nm [5] Their molecular content tends to mirror the physiological condition of the parent cell rather than being randomly assembled. They transport proteins, membrane antigens, signalling components and different forms of genetic material [6]. and in many models exosomes derived from MSCs were linked with enhanced neurovascular plasticity after stroke, maintenance of dormancy in metastatic breast cancer cells, skeletal muscle repair, faster skin wound closure and stimulation of cartilage regeneration [7] [8] [9] [10].

Their biological relevance is often linked to the tightly regulated intracellular pathway through which they are formed, a process that subsequently influences their behavior upon release from the cell. Even though the technical advancements in this field have been achieved, certain methodological problems still exist, especially those associated with the isolation practices and currently existing biomarkers, which reveal only a few subpopulations. The literature makes numerous associations with exosomes and different pathological conditions and this correlation is more pronounced in different types of cancer, as discussed in Table 1. Table 2 shows the possible therapeutic use of immune cell-derived vesicles. [11].

MicroRNAs are short molecules, approximately 22 nucleotides in length, that bind to the untranslated region at the 3′ end of the target messenger RNA (mRNA) either directly cleaving it or inhibiting its translation, thereby silencing gene expression post-transcriptionally or during translation. Tumors and their microenvironment appear to be in a state of constant flux. They are directly or indirectly affected by the abnormal production of certain molecules, which may promote or inhibit tumor growth. [12].

Exosomal origin	Exosomal cargo	Recipient cell type	Pathological setting	Result
M2 macrophages	MiR-221-3p	Tumor cells	Malignancy	Aiding tumor cell proliferation
M2 macrophages	miR-29a-3p	T lymphocytes	Tumor microenvironment	Reducing IL6, and TNF-a Promoting IL10 release
M2 macrophages	Apolipoprotein E	Tumor cells	Cancer	Increased invasive capacity of malignant cells
Myeloid-derived suppressor cells (MDSCs)	CD95L	$CD8^+$ T cells	Cancer	Induction of activation-induced cell death (AICD)
M2 macrophages	miR-21	Tumor cells	Malignancy	Development of chemoresistance
M2 macrophages	HISLA	Tumor cells	Cancer	Stabilization of HIF-1α, promotion of aerobic glycolysis, and resistance to apoptosis
M2 macrophages	miR-21-5p/miR-155-5p	Tumor cells	Tumor progression	Increased migration and metastatic potential

Table 1. **The role of immune cell-derived exosomes in cancer pathogenesis** [13]

miRNAs are key regulatory mechanisms within the tumor microenvironment, playing a pivotal role in modulating interactions between immune cells and cancer cells. When specific miRNAs are secreted in a controlled manner, the efficiency of immune pathways responsible for eliminating tumor cells may be disrupted, thereby allowing the tumor to evade immune control, it is also possible that the cancer cells can re-program themselves to avoid apoptosis through the production of aberrant miRNAs, and hence they will be able to aggressively proliferate and continue their pathological existence [14].

Exosomes of immune cells are important to deliver miRNAs to the target cells, such as dendritic cells, where miRNAs can repress gene expression and cell maturation [15]. It has been demonstrated that miR-212-3p contained in tumor exosomes suppresses the expression of the MHC-II-related transcription factor RFXAP in the dendritic cells, allowing cancer cells to avoid immune surveillance. Moreover, miR-222-3p, which is transferred through tumor exosomes, suppresses SOCS3 in

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monocytes, therefore, enhancing the polarization of M2 macrophages via the action of STAT3 and leading to the establishment of an immunosuppressive microenvironment. These results prove that miRNAs transport through exosomes is one of the important pathways through which the exosomes can control the immune response during cancer [16].

Exosome-producing cell	Molecular cargo	Recipient/tumor model	Disease context	Biological effect
Natural killer (NK) cell	DNAM1	NALM-18 leukemia cell line	Hematological malignancy	Targeted cytotoxic interaction with leukemic cells
Macrophage	MiR-7	Ovarian cancer cell	Ovarian carcinoma	Suppression of tumor cell growth
$CD8^+$ T cell	MiR-5p	Cancer-associated MSCs	Pancreatic cancer	Modulation of tumor-supportive stromal cells
M1 macrophage	HOTTIP lncRAN	Head and neck cancer cells	Head and neck carcinoma	Regulation of malignant cell behavior
Dendritic cell	Hsp70	Gastric carcinoma cell line	Gastric cancer	Activation of antitumor immune response
M1 macrophage	let-7a-5p	Lung cancer cell	Lung carcinoma	Inhibition of tumor progression
Natural killer (NK) cell	MiR-186	Neuroblastoma cells	Neuroblastoma	Reduction of oncogenic activity

Table 2. **Summary for therapeutic applications of immune cell-derived exosomes**[17]

Results and Discussion

A. Exosome Biogenesis

Understanding exosome activity is linked to understanding the fate of their components and the phenotypic and molecular changes they induce in recipient cells within cell culture systems. A single cell may contain both endogenously produced and recycled exosomes, leading, over time, to the formation of multiple exosome types due to the overlap of uptake and secretion pathways. The diversity of exosome uptake devices and pathways, along with their potential for cell-type specificity, contributes to the complexity of their role in cell-cell communication. [18].

Exosome formation occurs through the development of intracellular polyvesicles (MVBs), which contain internal vesicles known as luminal vesicles (ILVs) via a mechanism involving plasma membrane double infiltration. Upon fusion of the polyvesicles with the plasma membrane and exocytosis, the luminal vesicles are released into the extracellular environment as exosomes, ranging in diameter from 30 to 150 nm (Figure 1) [19].

In the first stage, invagination of the plasma membrane forms a goblet-like structure that captures components from the extracellular environment, including soluble proteins and cell-surface proteins, thereby generating an early endosome (ESE). In some cases, this endosome may fuse with another pre-existing early endosome. The composition and development of the early endosome may also be influenced by its interactions with the endoplasmic reticulum and the Golgi network. [20].

As maturation progresses, the early endosome transitions into a late endosome (LSE) and subsequently into a polyvesicle. It is done by infiltration of the inner membrane of the endosomes or by dual infiltration of the plasma membrane leading to the appearance of many luminal vesicles in the polyvesicles which are the future exosomes. These bodies may then amalgamate with the plasma membrane to discharge exosomes or transit through the hemolytic route.

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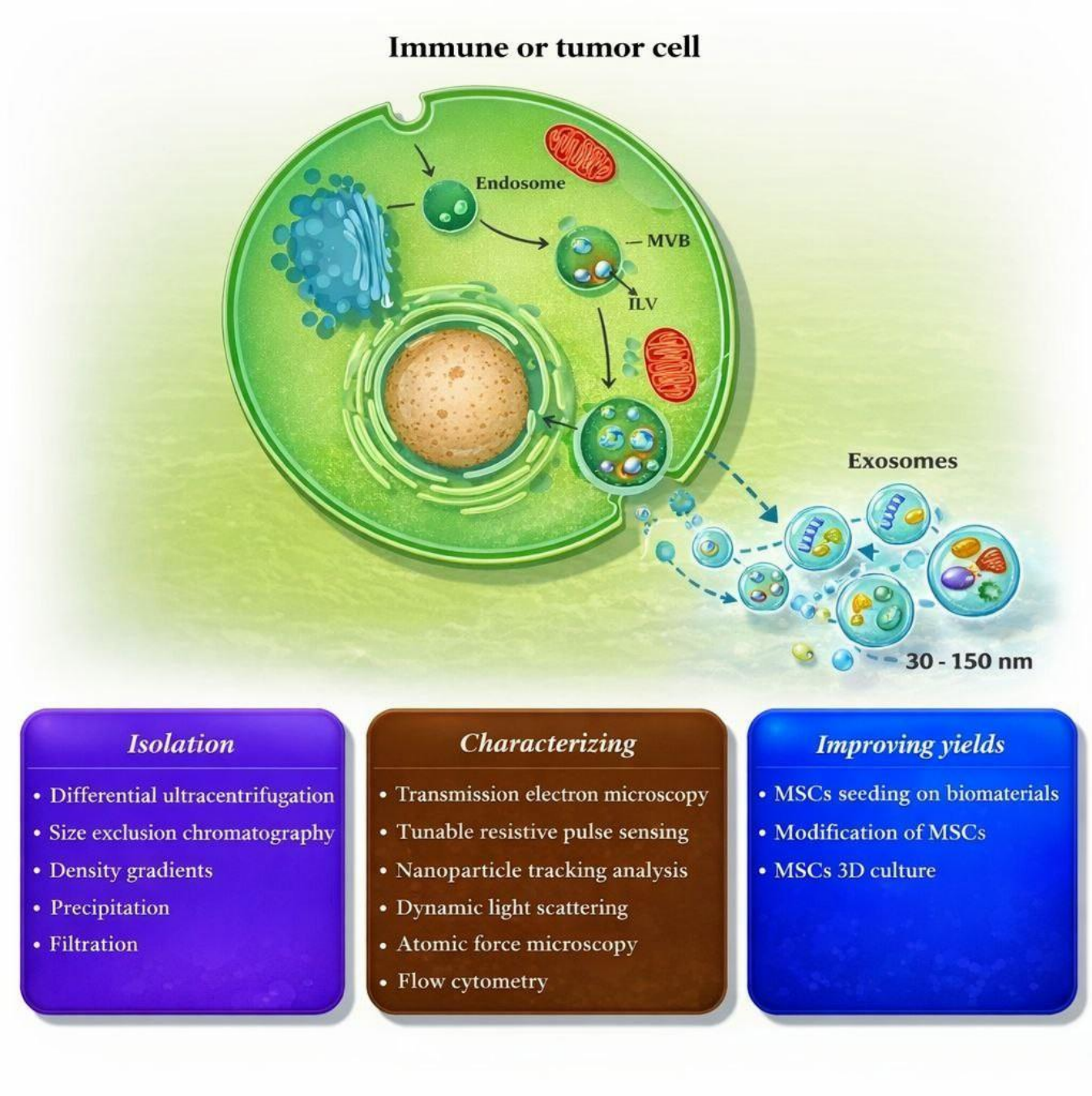

Figure 1. **The biogenesis of exosomes. The figure depicts the biogenesis of exosomes, their isolation and characterization, and associated strategies to improve exosome yields.** [21].

A polyvesicle can follow two distinct pathways: it may fuse with the plasma membrane, releasing its luminal vesicles into the extracellular ecosystem as exosomes, or it may fuse with lysosomes or phagocytes, where its contents are eventually lysed. [22].

The remarkable diversity of exosomes is attributable to their diverse cellular origins, dimensions, and structures, as well as their distinct functional roles in recipient cells. Size variations appear to be related to the amount of liquid and solid components within the vesicle or to the isolation method used, which may allow for the presence of other types of extracellular vesicles within the sample. [23]. Advanced fractionation techniques have also shown that exosomes can be composed of subgroups that differ in size, which in turn affects the nature of their payload. [24]. A single factor does not determine exosome composition; internal influences of the donor cell and external influences of the surrounding microenvironment shape it.

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These vesicles contain genetic material, along with proteins and lipids, particularly messenger RNA (mRNA) and microRNA (miRNA). The amount of RNA is significantly lower than in the original cell; the majority of it is selectively packaged as microRNA. Correspondences have been observed in the patterns of microRNAs carried in exosomes from different cell types, suggesting a precise regulatory mechanism controlling this selection process [25]. These particles are resistant to degradation by RNases in blood and other body fluids, allowing them to translocate to neighboring or distant cells and influence various biological processes, including the immune response, metabolic homeostasis, and the functions of the nervous and cardiovascular systems.

The regulation of microRNA loading within exosomes remains an open area of research. Data suggest that the process is energy-intensive and is associated with the appearance of cell-type-specific proteins. [26]. The composition of an exosome often reflects the molecular signature of the donor cell, containing a wide range of proteins, lipids, and nucleic acids. Common proteins include adhesion molecules, tetraspanin proteins, transferrin receptors, heat shock proteins, and proteins involved in the formation of polyvesicles [27].

Exosome isolation techniques have seen significant advancements in recent years. Traditional methods have primarily relied on ultracentrifugation, polymerase chain reaction (PCR), and size-based isolation. Furthermore, the lack of specific biomarkers that distinguish exosomes from other extracellular vesicles limits the accuracy of interpreting their attributed biological functions. [28].

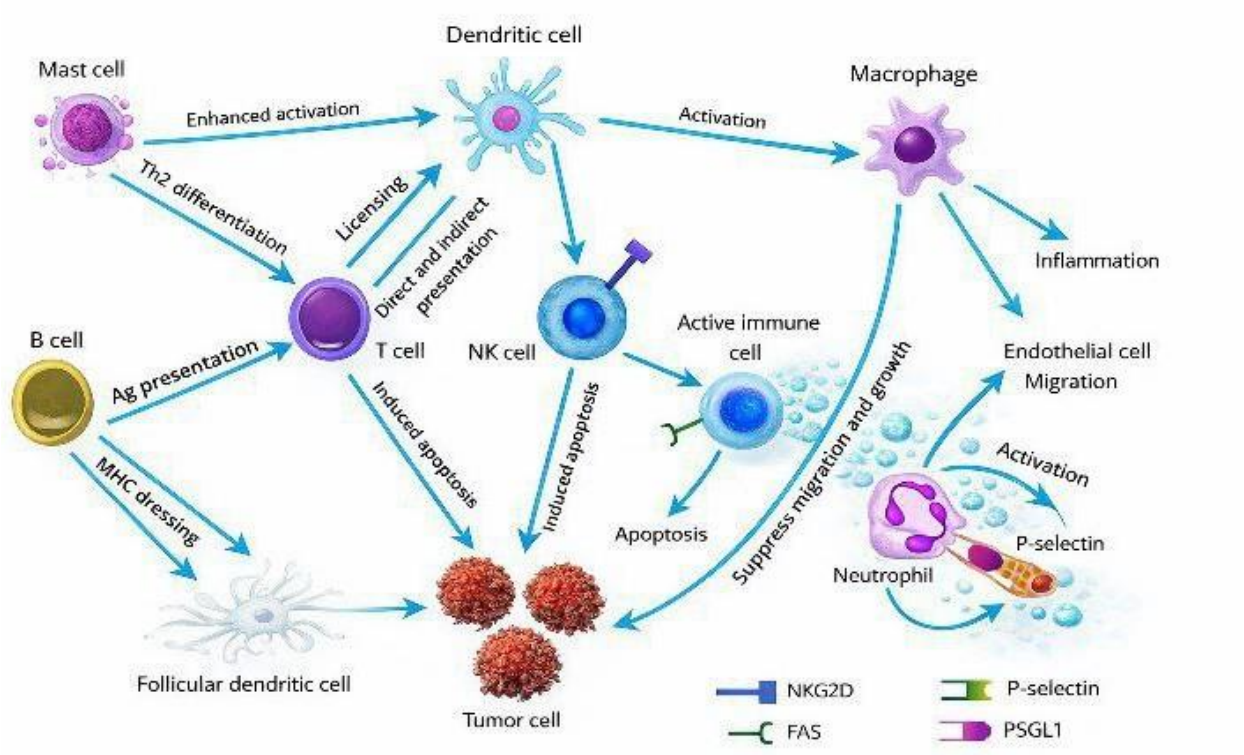

Figure 2. **Schematic diagram of immune cell interactions mediated by exosomes, the roles of dendritic cells, T cells, B cells, NK cells, macrophages, and neutrophils in immune activation, regulation, and tumor cell apoptosis.** [29].

B. Natural Killer (NK) Cell Exosomes

Decreased expression of certain functional receptors on NK cells, such as NKG2D, may suppress their activity and impair their ability to kill tumor cells, thereby reducing immune surveillance and tumor-degrading protein levels. [30]. Conversely, NK cells produce exosomes that carry cytotoxic proteins such as perforin, granzymes, granulysin, FasL/CD178, and TRAIL/CD253, as well as small antimicrobial peptides. They can directly eliminate cancer cells, such as breast cancer, melanoma, and some hematological malignancies, via the direct killing pathway. [31].

C. Macrophage Exosomes

Microenvironmental signals alter macrophage functional programs, and tumor-associated macrophages (TAMs) are influential cells in tumor growth and development. M1 macrophages exhibit a pro-inflammatory character, while M2 macrophages tend to have anti-inflammatory properties. Clinical and experimental evidence suggests that M2 may support

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tumor growth and spread, while M1 contributes to the phagocytosis of cancer cells. [32]. Macrophages can also capture antigens originating from extracellular vesicles and transport them to CD4+ or CD8+ T cells. Exosomes bind to cells via receptor/ligand interactions and adhesion molecules such as phosphatidylserine, ICAM-1, and tetraspanins. Both internal and external stimuli influence the release of a macrophage exosome. [33] The overlap of MVB and lysosome pathways affects intracellular transport, making exosomes dependent on lysosomal function [34]. Macrophage exosome payloads may change with factors such as aging and autophagy. [35] Hypoxia in solid tumors may increase their release.

LncRNAs carried within macrophage exosomes play a role in modulating the tumor microenvironment. For example, M2 macrophage exosomes have been found to carry lncRNAs such as PVT1, which acts as a "sponge" for miRNA-21-5p, and another lncRNA, AFAP1-AS1, has been shown to act as a "sponge" for miRNA-26a, promoting invasion and metastasis in some cancers. Macrophage exosomes can carry protein molecules including ERAP1 and CCL3 to facilitate phagocytic action, and TNF-a and IFN-g facilitate NO production through vesicle-dependent transport systems. Furthermore, molecules such as Integrin αMβ2 in M2 macrophage exosomes have been described as promoting hepatocellular carcinoma migration via the MMP-9 pathway. It has also been suggested that vesicles derived from M1 macrophages may redirect M2 macrophages toward an M1-like phenotype and enhance the efficacy of immunotherapies such as aPD-L1 while suppressing tumor growth [36].

D. Dendritic cell exosomes (DCs)

Dendritic cells are among the most potent antigen-presenting cells, bridging the gap between innate and adaptive immunity. When tumor antigens are presented with co-stimulatory molecules, such as CD80/CD86, via MHC class I and MHC class II to naïve T cells (CD8+ and CD4+), an early immune response can be induced [37]. DC-derived exosomes have been used in animal models and clinical trials to induce anticancer immunity, activating CD8+ and B-cell responses. A phase II clinical trial using DC exosomes in NSCLC has also been conducted [38]. Mature DC exosomes are characterized by their ability to stimulate specific T cells via peptide-MHC complexes and co-molecules such as CD86. They are rich in membrane proteins, including ICAM-1, MFGE8, and integrins, that support binding to various immune cells [39]. DC exosomes also carry NKG2D ligands, which may activate NK cells through an MHC-independent mechanism and have antitumor activity. Furthermore, they may express TLR1/2 and TLR4, which promote activation of neighboring DC cells and the release of inflammatory mediators, thereby supporting NK activation. DC exosomes contribute to the transport of miRNAs, and a clear difference in miRNAs has been observed between immature and mature DC exosomes [40]. Examples include miRNA-21, transduced from TSLP-treated DCs, which affects Th17 and Treg differentiation by suppressing Smad7 and miRNA-335; miRNA-335 transduction may support mesenchymal stem cell growth by targeting LATS1 and influencing the Hippo pathway. Directing miRNAs via DC exosomes may enhance the effectiveness of the antitumor response [41].

E. siRNA and mRNA

Multiple studies have demonstrated the potential of exosomes as effective vectors for siRNA and miRNA in cancer therapy. In HeLa (cervical cancer) and HT1080 (myofibroblast) cells, exosome-mediated siRNA delivery targeting RAD51 and RAD52 reduced RAD51 expression without affecting RAD52, resulting in G2/M cell cycle arrest, DNA damage, and significant apoptosis. In another study, the FaDu head and neck cancer cell line was treated with exosomes loaded with siRNA for the TRPP2 protein (Exo-TRPP2), which reduced protein expression and inhibited invasion, migration, and epithelial-stromal transformation of cancer cells. [42].

Exosomes loaded with short interfering RNA molecules targeting STAT3 and modified with the Angiopep-2 peptide known as Exo-An2-siRNA demonstrated high efficiency in delivering the genetic payload within the U87MG glioblastoma model. They exhibited significant persistence in serum and a clear ability to cross the blood-brain barrier. Their effect was not limited to inhibiting cell proliferation in vitro; a reduction in tumor growth was also observed in vivo, along with extended lifespan for experimental animals and minimal toxicity. [43].

F. Natural Compounds

In another direction, recent research has focused on utilizing exosomes to deliver natural compounds with anticancer properties. Their advantages appear to stem from their biocompatibility, relative safety, low immunogenicity, and suitability as cell-free nanoplatforms. It has been reported that vesicles extracted from the E. coli W3110 strain induce a long-lasting antitumor immune response resulting in complete tumor growth inhibition in living models without serious side effects. Other reports have also shown that vesicles isolated from lemon juice, grapefruit, garlic, and corn have demonstrated promising therapeutic potential in various cancer cell models in vitro [44].

In this context, the exosome-encapsulated celastrol formulation (Exo-CEL) was evaluated in non-small cell lung cancer cell lines via direct physical incubation. The results suggest apoptosis, as evidenced by elevated endoplasmic reticulum stress markers and reduced growth of A549 and H1299 cells. Oral management of Exo-CEL in C57BL/6 mouse models of lung tumors resulted in tumor growth inhibition without apparent systemic toxicity. [45]. Similarly, curcumin A-loaded bovine milk exosomes showed a marked improvement in solubility and stability when applied to MDA-MB-231 breast cancer cells, enhancing intracellular uptake and leading to increased cytotoxicity compared to free curcumin. [46].

Conclusion

These data clearly show that exosomes containing microRNAs are a key regulatory factor in the immune-cancer cell

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interaction network of tumor microenvironment. These vesicles are not merely passive carriers; in a number of experimental studies, they have been shown to modulate the pattern of the immune response by means of the transfer of regulatory molecules which can increase anti-tumor responses, although in other environments they are associated with tumor progression and other types of immune evasion. What is interesting here is that the cellular source of the exosome and the molecular cargo constituents of the exosome to a large extent affect the outcome, be it the recruitment of phagocytic cells, the activation state of natural killer cells, or the regulation of dendritic cell functionality. In addition to their biological applicability, exosomes are often discussed as nucleic acid delivery vehicles of similarly biocompatible targeting agents due to their relative biocompatibility and semi-specific targeting properties, although the protocols of their isolation and characterisation are by no means standard, and the issue of clinical safety is not yet clearly resolved. A closer molecular investigation of the mechanism of such vesicles will probably transform the existing methods of diagnosis and treatment in cancer immunotherapy instead of simply improving them.

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