

Review Article

Mesenchymal Stem Cell-Derived Exosomes: Emerging Therapeutic Strategies for Liver Diseases and Cancer

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ABSTRACT

Objective: This review aims to highlight the biological characteristics of mesenchymal stem cells (MSCs) and their derived exosomes, focusing on their therapeutic roles in liver diseases and cancer.

Material and Methods: A comprehensive literature review was conducted to evaluate MSC sources, isolation methods, and the biological functions of MSC-derived exosomes. Relevant experimental and clinical studies addressing their mechanisms of action in liver pathology and cancer were analysed.

Results: MSCs and their exosomes demonstrated significant potential in modulating immune responses, reducing inflammation and fibrosis, promoting hepatocyte regeneration, and influencing the tumour microenvironment. MSC-derived exosomes also showed advantages as cell-free therapeutic agents and targeted drug delivery systems due to their low immunogenicity and biological stability.

Conclusion: MSCs and MSC-derived exosomes represent promising therapeutic platforms for regenerative medicine and cancer treatment, with strong potential for future clinical translation.

Keywords: Liver cancer, Mesenchymal stem cells, MSC-derived exosomes, Therapeutic potential

1. INTRODUCTION

Mesenchymal stem cells (MSCs) have become a crucial element in regenerative medicine due to their unique biological properties, including self-renewal, multipotency, and immunomodulatory effects. Since their initial discovery in 1976, MSCs have been extensively researched for their ability to differentiate into various mesenchymal lineages, including osteocytes, chondrocytes, and adipocytes.^[1] Their relatively straightforward isolation from multiple tissue sources and compatibility with ex vivo expansion have made them a popular choice for clinical and therapeutic applications. At the same time, exosomes—small extracellular vesicles (40–150 nm) originating from the endosomal pathway—have been recognised as important mediators of intercellular communication, carrying diverse molecular cargos, such as proteins, lipids, and ribonucleic acids (RNAs).^[2] MSC-derived exosomes (MSC-Exos) possess regenerative and immunomodulatory properties and are increasingly being investigated as cell-free therapeutic options. Both MSCs and their exosomes show significant potential in treating numerous diseases, including chronic liver conditions and cancer. In liver disorders, MSCs help regulate immune responses, decrease fibrosis, and support hepatocyte regeneration. In cancer, MSCs can be genetically modified to deliver anti-

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tumour agents or alter the tumour microenvironment (TME), while MSC-derived exosomes provide innovative drug delivery systems with lower immunogenicity.^[3] As interest in MSC-based therapies continues to grow, it is crucial to understand their biological characteristics, mechanisms in disease models, and the evolving functions of exosomes. Additionally, developing effective methods for exosome isolation, such as ultracentrifugation, ultrafiltration, and chromatography, is vital for translating these approaches into clinical practice. This overview highlights MSC biology, their therapeutic roles in liver disease and cancer, the importance of MSC-derived exosomes, and current techniques for exosome isolation and application.

1.1. Overview of mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent stromal cells that were first identified in 1976. They possess the ability to differentiate into various lineages, such as osteocytes, chondrocytes, and adipocytes.^[4] Because of their ability to regenerate, MSCs have also become one of the cell types that have been studied the most in regenerative medicine. Numerous clinical trials have demonstrated their effectiveness in treating a range of illnesses, making them a promising therapeutic tool [Figure 1].^[5] The International Society for Cellular Therapy characterises MSCs. The International Society for Cellular Therapy characterises MSCs as adult stem cells capable of multilineage differentiation, exhibiting *ex vivo* plastic-adherent expansion, and possessing a distinct immunophenotype. MSCs have the ability for self-renewal and can develop into many mesenchymal cell lineages.^[6] Stem cell niches (SCN) are crucial for maintaining stem cell populations, controlling proliferation, and ensuring homeostasis in MSCs. These niches vary in type and location, and MSCs exhibit morphological heterogeneity, multilineage differentiation potential, and immunophenotypic markers.^[7] MSCs, due to their low maintenance and ease of isolation, have gained attention in regenerative research for therapeutic potential, particularly in aging and densely populated societies, despite ongoing research on ontogeny and niche biology.^[8]

2. SOURCES OF MSCS

MSCs are embryonic or adult tissue cells, and embryonic MSCs are the gold standard due to their multipotentiality. Ethical concerns and technical difficulties are, nevertheless, encountered. Adult-derived MSCs are the most abundant sources of pure, multipotent, and immunogenic somatic stem cells, and successful isolations have been reported from various tissues. Bone marrow–mesenchymal stem cells (BM-MSCs) are found primarily in bone and other haematopoietic tissues, but their harvesting must be performed using invasive

procedures and local anaesthesia.^[9,10] They are attracted to the wounds and tumours of tissues to promote healing and angiogenesis, stabilise blood vessels, and inhibit fibrosis. Adipose tissue–mesenchymal stem cells (AT-MSCs) can be harvested from various locations in patients through either minimally invasive or relatively simple methods. They can be expanded readily using low-cost media in culture dishes. They are also widely adopted in basic and translational research due to their relatively simple isolation and expansion.^[11,12]

3. ISOLATION METHODS OF MSCS

Numerous techniques, such as tissue digestion, the entire bone marrow adherent approach, gradient density centrifugation, and immunomagnetic bead separation, have been documented for the isolation and extraction of MSCs. The methods for isolating, extracting, and cultivating stem cells are the same in all investigations, even if different species may be used [Figure 2].^[13]

3.1. Tissue digestion

MSCs are isolated by cutting tissue, enzymatic digestion, and plastic surface proliferation.^[14] Enzymatic digestion is performed by chopping tissues into fragments, treating them with an enzymatic solution, and liberating single cells or aggregates. Cell pellets formed are plated on plates for propagation.^[15]

3.2. Gradient density centrifugation

This manual method separates cells based on their density, allowing for the isolation of MSCs from various tissues. Manual density gradient separation techniques separate cellular components by centrifuging blood samples that have been diluted and treated with an anticoagulant on a premade gradient, such as sucrose or caesium chloride. Less dense platelets, monocytes, and lymphocytes are held at the interface, which makes it easier to collect stem cells, whereas high-density erythrocytes and granulocytes sink to the bottom.^[16]

3.3. Whole bone marrow adherent method

MSCs are found in many tissues, for instance, lungs, cord blood, amniotic fluid, adipose tissue, and placenta. Friedenstein first defined the origins of MSCs by demonstrating that the adhering layer of bone marrow produced cells that resembled fibroblasts. On this, plastic adhesion served as the foundation for additional separation and description. Plastic culture dishes are used to plate bone marrow mononuclear cells. The mesenchymal stem cell-containing cell fraction sticks to the plastic. Passaging purifies the cells by washing away the non-adherent cells (haematopoietic fraction).^[17] The adherent fraction remains after this, and trypsin is added to resuspend

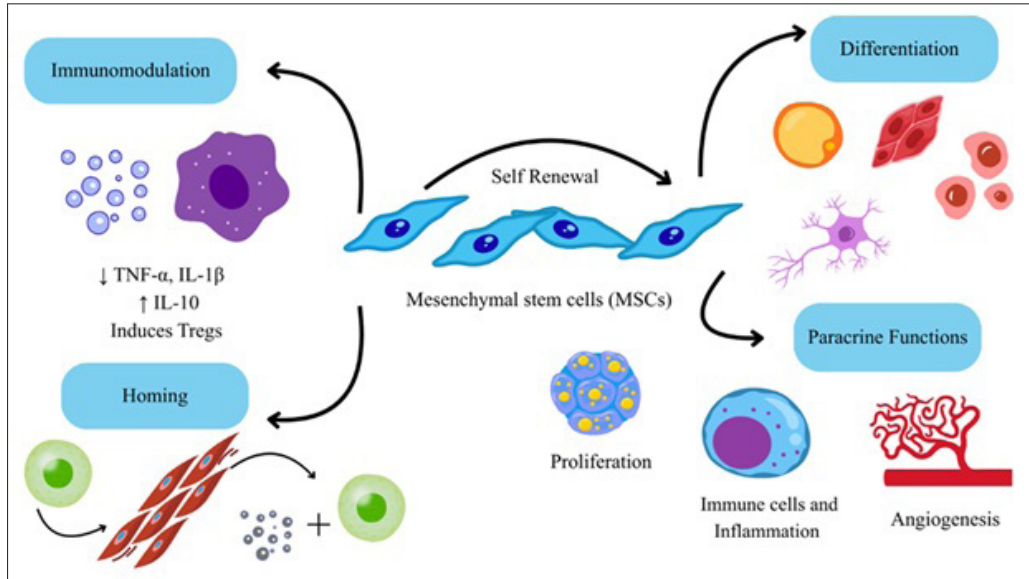


Figure 1: Overview of the fundamental biological characteristics of mesenchymal stem cells (MSCs), including their self-renewal ability, multilineage differentiation potential, immunomodulatory properties, homing behaviour, and paracrine activity. TNF: Tumour necrosis factor; IL: Interleukin.

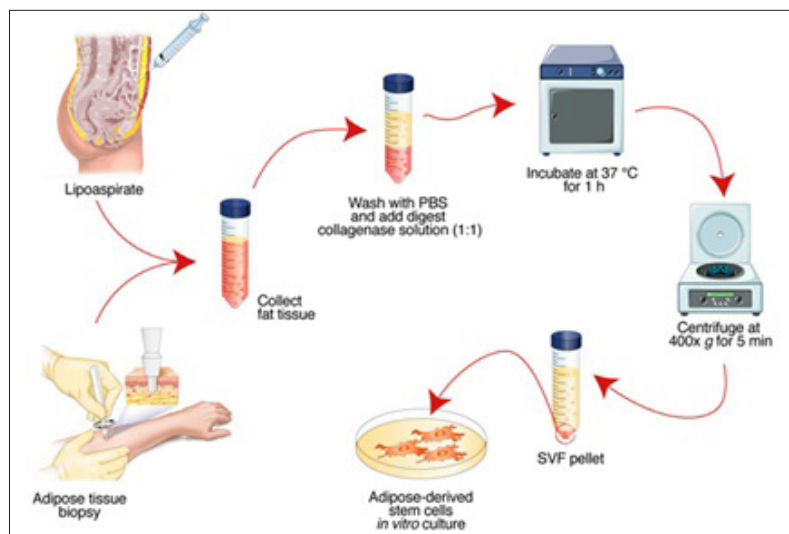


Figure 2: Main steps for generating apoptosis-associated specks (ASCs) from lipoaspirate or subcutaneous adipose tissue. PBS: Phosphate-buffered saline, SVF: Stromal vascular fraction.

it. The fraction of MSCs adheres to the plastic once more and proliferates when the resuspended cells are replated in a new culture flask. The adhering cell fraction becomes purer because of this repeating process. With every consecutive passage, the adhering cells create a population that is more homogeneous.

3.4. Immunomagnetic bead separation

Immunomagnetic separation (IMS) is an innovative immunological method that integrates the benefits of

solid-phase reagents with the heightened specificity of immunological interactions. By attaching the target substance in the sample to antibodies coated on magnetic beads, an antigen–antibody–magnetic bead immune complex is established. This complex exhibits significant magnetic responsiveness and can be mechanically controlled in the presence of an external magnetic field, facilitating the swift separation of the target antigen from other substances.^[18]

Researchers employed this technique by employing special beads coated with antibodies that bind to cell types to separate

specific groupings of Adipose stem cells from a heterogeneous population extracted from fat tissue. To make these beads, they combined them with various antibodies that identify specific stem cell markers. To cultivate these particular stem cell subpopulations in a controlled setting, scientists combined the beads with the cell solution and then used a magnet to separate the cells that adhered to the beads.^[19]

4. ROLE OF MSCS IN LIVER DISEASE

MSCs represent a significant resource for stem cell therapy and play a crucial role in the modulation of both the innate and adaptive immune systems.^[20] MSCs exhibit notable immunomodulatory properties and the ability to promote tissue repair, making them a promising therapeutic option for liver diseases. These conditions encompass inflammation, fibrosis, and metabolic dysfunction stemming from drug-induced liver injury, non-alcoholic fatty liver disease (NAFLD), and viral hepatitis (HBV/HCV), all of which can often result in liver failure. By modifying immune responses, such as blocking cytokines that encourage inflammation, MSCs can mitigate these effects, reducing fibrosis through paracrine signalling. Promoting hepatocyte regeneration [Figure 3].^[21] The need for MSC-based treatments is fuelled by the fact that HBV infection is the main cause of liver failure in China. Preclinical studies show that MSC transplantation lessens the severity of cirrhosis and fibrosis in animal models. Lowers inflammation to partially restore liver function. To shed light on the advantageous role that MSCs play in the treatment of the above mentioned liver diseases, we present an overview of the most recent studies on the molecular mechanisms underlying the MSC-dependent modulation of liver illnesses. MSC transplantation has been demonstrated in numerous studies to lower liver inflammation and encourage a partial recovery of liver function in animal models of liver cirrhosis or fibrosis. The mechanisms underlying MSCs' effects on the liver have been evaluated by basic research and disease treatment from a variety of angles.^[22] Unlike artificial liver support systems (like molecular adsorbent recirculating system (MARS) or Prometheus), which did not improve survival in patients with acute-on-chronic liver failure (ACLF), SCs offer a regenerative approach.^[23] Recent research explores MSC-derived EVs as a cell-free alternative, with bioengineering methods like parental cell modification and EV cargo loading improving therapeutic precision. MSCs can be genetically modified to release anti-tumour medications, including suicide genes, therapeutic proteins, and oncolytic viruses. These proteins suppress tumour proliferation and inhibit pro-tumour factors, making MSCs the most effective means for distributing these therapeutics.^[24] Their immunomodulatory effects can alter the TME, thereby inhibiting tumour growth. Additionally, the therapeutic window during radiation therapy may be

extended by MSCs' radioprotective qualities.^[25] They serve as effective delivery systems for therapeutic genes and chemical agents to cancers. By modifying signalling pathways such as PI3K/AKT/mTOR and WntF/ κ -catenin, MSCs can inhibit cancer dissemination.^[26] According to recent research, MSCs can realistically stop the tumour progression.^[27] MSCs have the potential to impede tumour growth, despite their influence on the progression of cancer, according to research. Combining MSCs with tumour cells increased the infiltration of monocytes, granulocytes, and T lymphocytes, a factor that promotes inflammation. The increased infiltration of inflammatory cells facilitates the communication between these immune cells and adjacent tissues.

4.1. Treatment of liver cancer using MSCs

Liver cancer is the fifth most common cancer in the US and the primary cause of cancer-related fatalities worldwide. Risk factors include hepatitis B and C viruses, fatty liver disease, alcohol-induced cirrhosis, tobacco use, obesity, diabetes, and dietary exposures. Advanced diagnosis leads to a poor prognosis—variations in the intrahepatic milieu impact liver cancer development. MSCs, with pleiotropic qualities, affect healthy and tutored livers. They can either limit or promote tumours, with theories exploring dualistic nature.^[28] The utilisation of extraembryonic MSCs in interventional medicine or corrective therapy would enhance and restructure existing treatment methodologies. Several animal studies have endorsed the use of primary extraembryonic cells in both human and animal models. Numerous recent studies have documented the beneficial effects of A-MSCs on liver disorders, including reduced inflammation, decreased fibrosis, and pathological enhancement.^[29] In liver injury models, human amniotic mesenchymal stem cells (A-MSCs) produce potent therapeutic benefits by modifying paracrine signalling and immune responses. Key pathways include: Reduced Inflammation: A-MSCs mitigate autophagic liver injury by secreting cytokines that inhibit pro-inflammatory responses mediated by Kupffer cells.^[18] A-MSCs upregulate matrix metalloproteinases (MMP-2, -9, and -13) and downregulate tissue inhibitor of metalloproteinase-1 (TIMP-1) to suppress hepatic stellate cell activation and promote extracellular matrix (ECM) remodelling, thereby mitigating fibrosis. Factors that foster regeneration: A-MSCs emit the growth factors hepatocyte growth factor (HGF) and epidermal growth factor (EGF), which promote the proliferation of hepatocytes and the regeneration of the liver.^[30]

4.2. The function of mesenchymal stem cells (MSCs) in hepatocellular carcinoma (HCC) and liver regeneration

MSCs have been found to cause regeneration of the liver, reduce fibrosis and inflammation through the production of

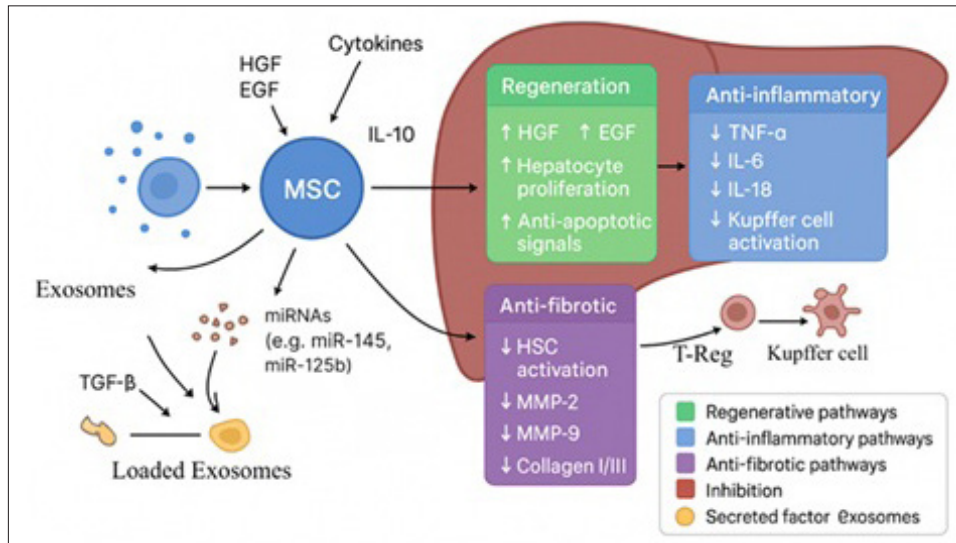


Figure 3: Integrated mechanisms through which MSCs modulate liver injury. MSCs exert anti-inflammatory, anti-fibrotic, and regenerative effects by regulating cytokines, polarizing macrophages, inhibiting hepatic stellate cell activation, and secreting paracrine growth factors. HGF: Hepatocyte growth factor, EGF: Epidermal growth factor, MSC: Mesenchymal stem cells, MMP: Metalloproteinases, HSC: Hepatic stellate cells, TNF: Tumour necrosis factor; IL: Interleukin

trophic and growth factors like HGF and EGF. Genetically modified MSCs with higher levels of HGF exhibit improved liver function, especially in the advanced stages of liver cancer.^[31,32] The activation of hepatic stellate cells (HSCs), which encourage fibrosis and the deposition of ECM components, is one of the characteristics of hepatocellular carcinoma (HCC) development.^[33] MSCs can inhibit HSC activation and pathological fibrosis by suppressing the Wnt/ β -catenin signalling pathway. They also induce remodelling of the ECM, thereby inhibiting cirrhosis and collagen deposition. MSCs have anti-tumour properties, hindering the progression of HCC by inhibiting the proliferation of cancer cells and inducing apoptosis.^[34] MSCs can inhibit tumour growth and survival by interfering with signalling pathways, but there are challenges in using them for liver cancer treatment. Current clinical trials aim to optimise MSC therapy by standardising cell sources, improving distribution methods, and tracking long-term safety indicators.^[35]

4.3. Immunomodulatory role of MSCs in the tumour microenvironment (TME)

BM-MSCs have demonstrated significant therapeutic efficacy against HCC in *in vivo* studies. The treatment of BM-MSC lowered liver damage, exhibiting reversible cellular modifications and decreased regions of cell dropout, according to histopathological analysis of chemically generated HCC models (such as DEN or 2-AAF).^[36] Additionally, MSCs were seen to proliferate in damaged areas, indicating a potential function for them in tissue regeneration

and replacement. β -catenin, the primary mediator of the Wnt signalling pathway, proliferating cell nuclear antigen (PCNA), a marker of cellular proliferation, Cyclin D, a regulator of cell cycle progression, and surviving, an anti-apoptotic protein that improves tumour survival, were among the important genes implicated in tumour progression that were downregulated at the molecular level by MSC treatment. In terms of functionality, MSC treatment resulted in a large drop in alpha-fetoprotein (AFP), a frequent biomarker of HCC, as well as a marked decrease in blood biochemical indicators of liver injury, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST).^[37] These results collectively show that MSCs have a twofold effect, repairing hepatic tissue and preventing tumour growth through paracrine signalling, apoptosis induction, Wnt/ β -catenin pathway regulation, and liver function restoration. This illustrates that MSC-based therapy could serve as a feasible treatment alternative for HCC. Within the TME, MSCs engage with immune cells and secrete soluble mediators, functioning as potent immunomodulators. Via indoleamine 2,3-dioxygenase (IDO), PGE_2 , TGF- β , and IL-10, they suppress T-cell activation, resulting in a shift from Th1 to Th2 responses, while promoting the proliferation of FOXP3⁺ regulatory T-cells (Tregs) that express glucocorticoid-induced TNFR-related protein (GITR) and cytotoxic T-lymphocyte-associated protein 4. (CTLA-4). MSCs induce a transformation of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, leading to an elevation in IL-10 and Arginase-1 levels, alongside a reduction in IL-12 and TNF- α . They reinforce a tolerogenic milieu by suppressing NK-cell

cytotoxicity and impairing dendritic cell development. These processes are similar in the immunosuppressive environment of HCC in the liver, where MSCs inhibit the production of inflammatory cytokines and decrease Kupffer cell activation. Their importance as a double-edged sword in cancer therapy is highlighted by their dual action, which reduces chronic inflammation while perhaps promoting tumour immune evasion.^[38,39]

4.4. Tumour risks and 3D MSC therapies

Numerous studies indicate that MSCs, particularly bone marrow-derived MSCs (BM-MSCs), can promote the proliferation and dissemination of cancer under certain conditions. Human BM-MSCs, for instance, have been demonstrated to promote tumour cell separation from primary locations by disabling cell-cell adhesion and downregulating E-cadherin, in part by activating ADAM10 metalloprotease. BM-MSCs and colon cancer cells co-injected into animal models increased liver metastases by almost five times *in vivo* when compared to tumour cells alone. Additionally, through upregulating MMP-2 and MMP-9, MSCs.^[14,38]

Participate in ECM remodelling, which promotes the invasion and spread of cancer cells. These results highlight the possibility that MSCs modulate adhesion, migration, and tissue remodelling pathways to encourage the dissemination of tumours, depending on the situation. Researchers are looking into three-dimensional (3D) culture systems, like spheroid cultures, which more closely resemble *in vivo* settings, to enhance the therapeutic potential of MSCs. In comparison to conventional two-dimensional cultures, MSCs cultivated in these three-dimensional settings generate greater amounts of the regenerative and antifibrotic factors IGF-1, HGF, and IL-6. These three-dimensionally grown MSCs improved fibrosis and restored liver function in liver disease models by providing better protection to hepatocytes exposed to damage (such as CCl₄), *PMC Journals of Translational Medicine*. These findings imply that 3D MSC cultivation may be a crucial tactic for improving liver regeneration medicines' overall efficacy, paracrine efficacy, and cell survival.^[40]

5. OVERVIEW OF EXOSOMES

Exosomes are membrane vesicles with a nanoscale size of 40–150 nm that are discharged by several cell types, and they are made of endocytic membranes. Exosomes are implicated in numerous physiological and pathological processes, including tumour formation, growth, and metastasis.^[41] They play essential functions in intercellular communication by transporting biomolecules, including proteins, lipids, RNA, and DNA, between cells. Due to their distinctive composition, which mirrors the metabolic condition of the originating cells, exosomes serve as potential biomarkers for disease diagnosis

and prognosis. Multivesicular bodies amalgamate with the plasma membrane to generate exosomes. The discharge is influenced by several chemical, environmental, and mechanical stimuli, including matrix separation, hypoxia, calcium ionophores, gamma irradiation, heparinase, statins, and acidosis, all of which enhance exosome release. These stimuli range from thirty-five to fifty-six. Moreover, exosome secretion is stimulated by hypoxic conditions in placental MSC growth media, K-dependent depolarization of neuronal cells, and cross-link activation of TCR/CD3 in T lymphocytes [Figure 4].^[42]

6. BIOGENESIS AND COMPOSITION OF EXOSOMES

Exosomes are created when multivesicular endosome (MVE) membranes tighten and invaginate, creating membranous vesicles that are protein-, RNA-, and genomic DNA-rich. When they fuse with the plasma membrane, they are secreted into the extracellular environment, with the help of ceramide lipids in releasing them.^[43]

Exosomes are tiny vesicles made of a lipid bilayer that contain proteins, RNAs, and bioactive lipids. It is noteworthy that the protein, peptide, and nucleic acid compositions of exosomes remain invariant regardless of the donor cell types; conversely, the lipid composition of exosomes is predominantly influenced by the producing cells. Among the plasma membrane lipids found in exosomes, sphingomyelin (SM), desaturated phosphatidylethanolamine (DS), phosphatidylserine (PS), desaturated phosphatidylcholine (PC), cholesterol (CHOL), ganglioside (GM), and some others are abundant. The primary and most comprehended component of exosome membranes is lipids. Besides being essential for the formation of exosome membranes, lipids also facilitate the maturation and release of exosomes into the extracellular milieu.^[44]

6.1. Exosome composition

The RNAs found in exosomes can range from microRNAs to ribosomal RNAs, transfer RNAs, long noncoding RNAs, and messenger RNAs. RNA cargo can alter the epigenetics and biological functions of cells. The RNA found in MSC-derived exosomes is typically linked to immune system modulation as well as the control of cell survival and differentiation. From a systemic perspective on the miRNA of MSC-derived exosomes, the predominant miRNA may facilitate angiogenesis, remodel tissue, and augment the quantity of cardiomyocytes.^[45] Numerous investigations have been conducted to determine the molecular makeup of exosomes to identify therapeutic targets and biomarkers. Proteins like CD9, CD63, and CD81 that are frequently present in exosomes

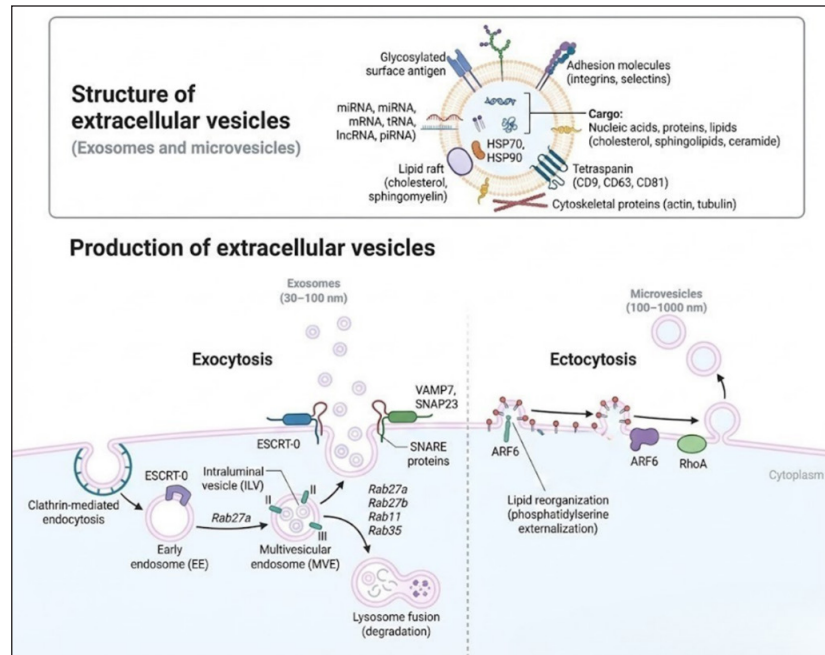


Figure 4: Overview of exosome biogenesis and composition. Exosomes originate from the endosomal system, forming intraluminal vesicles inside multivesicular bodies. After membrane fusion, exosomes are released carrying diverse molecular cargo, including proteins, RNAs, DNA fragments, and lipids.

have been identified as "exosome-specific" indicators. Since there have been reports of increased CD63-positive exosomes in cancer patients, CD63 is proposed as a cancer biomarker for diagnosis and prognosis. The clinical function of some proteins found in HCC cell-derived exosomes (HEX) has not yet been assessed.^[46] Furthermore, Integrins, major histocompatibility complex (MHC) class II proteins, heat shock proteins, tetraspanins (including CD9, CD63, CD81, and CD82), and other evolutionarily conserved proteins are incorporated into exosomes during biogenesis.^[45]

7. MECHANISM OF EXOSOMES ISOLATION

Exosomes must be carefully separated from a broad range of cellular waste and interfering substances to make it easier to research and use these special extracellular vesicles. The methods used to separate exosomes should be very effective and able to separate exosomes from different sample matrices.^[47]

7.1. Ultracentrifugation isolation method

Ultracentrifugation is employed in various strategies. Upon centrifugation of a suspension, its constituents are segregated based on the viscosity of the solvent, the applied centrifugal force, and physical attributes such as size, shape, and density. During ultracentrifugation (UC), samples experience exceptionally strong centrifugal forces, reaching up to 1,000,000 g, applied to their particle components. Analytical

and preparative procedures are the two main categories under which UC methods fall. There are two types of preparative ultracentrifugation: density gradient ultracentrifugation and differential ultracentrifugation. Ultracentrifugation usually entails many centrifugation cycles with different forces and durations. To recover extracellular vesicles from cell culture media or clinical samples and distinguish exosomes from co-vesicles according to their size.^[48]

Cellular debris was eliminated from the sample using ultracentrifugation. The medium underwent centrifugation for 30 minutes at 2000 g, followed by an additional centrifugation at 10,000 g. The supernatant underwent centrifugation for 70 minutes at 100,000 g to purify the exosomes. Following PBS washing, the pellet was subjected to ultracentrifugation for 70 minutes at 100,000 g. The pellet was subsequently resuspended in PBS and stored. The exosomes were separated using ExoQuick-TC and Total Exosome Isolation kits. The supernatant was then cultured overnight at 4°C. The sample was subsequently centrifuged at 10,000 g for 60 minutes for total exosome isolation and at 1500 g for 30 minutes for ExoQuick-TC. The bicinchoninic acid (BCA) protein assay kit was employed to measure the protein concentration of the exosomes.

Except for the initial equipment expense, ultracentrifugation is affordable and does not need complex sample preparation. Nevertheless, it takes a lot of time and only produces somewhat pure exosomes.^[49]

7.2. Size isolation methods

7.2.1. Ultrafiltration

Ultrafiltration is a popular size-based method for isolating exosomes, using the size and molecular weight cut-off of the membrane to separate larger particles from smaller ones.^[50] Ultrafiltration is a rapid and efficient method of small-volume fluid separation, but has drawbacks such as potential exosome deformation, contamination by smaller fluid components, and loss of exosomes through clogging of filter pores by proteins and biopolymer molecules.^[51]

7.2.2. Size exclusion chromatography

SEC is a high-resolution separation method used for large molecules like proteins, polymers, and liposome particles, based on their size, after passing through a porous stationary phase.^[48]

Chromatography-based techniques, such as size-exclusion chromatography (SEC), offer a quick and accurate method for isolating exosomes, making them suitable for proteomic research.^[52]

The method of size-exclusion chromatography is effective for isolated exosome purity, but its initial volume and recovery rate limit its application. Combining this with immunocapture techniques improves exosome function and purity.^[53]

7.3. Precipitation method

Precipitation methods attempt to lower the solubility and volume of input for exosomes separation with a hydrophilic polymer like Polyethylene glycol (PEG). Extra PEG is a technique for exosome purification, exosome concentration, and isolation of sufficient content for analysis. Commercial kits for isolation yield varying quality and purity, but precipitation methods are attractive for clinical research due to simplicity, rapidity, and minimal equipment requirements. However, they co-isolate contaminants that restrict their application in proteomic analysis.^[54]

7.4. Immunoaffinity capture method

This technique utilises ligand and antibody binding for the collection of target material from diverse mixtures. Biomarkers are low-abundance proteins on the exosome surface membranes, e.g., endosomal sorting complex required for transport (ESCRT) complex and four-transmembrane protein superfamily. Institutional animal care (IAC) can give outcomes comparable to ultracentrifugation with small sample volumes but of high specificity, sensitivity, purity, and yield.^[55]

8. EXOSOMES IN THE TREATMENT OF LIVER CANCER

High biocompatibility, minimal immunogenicity, and high transport efficiency are characteristics of exosomes, which contain a variety of bioactive compounds. Exosomes have materialized as a focus of research and have great potential for use as drug carriers, therapeutic agents, therapy targets, biotherapeutics, and biomarkers for cancer diagnostics.^[56]

Mesenchymal stem cell-derived Exosomes are essential for the early detection of HCC, angiogenesis, and the clarification of signal transduction pathways between hepatoma cells. These compounds found in exosomes have been implicated in liver cancer growth, metastasis, and angiogenesis. They have also been demonstrated to suppress the formation of liver cancer by disrupting the signalling pathway of liver cancer cells. Furthermore, the exosome compounds may serve as indicators for early liver cancer detection.^[57]

8.1. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and a major cause of cancer-related deaths worldwide. It ranks as the ninth most common cause of cancer-related fatalities in the United States.^[58] An oncogenic agent is any drug that induces chronic liver damage, ultimately leading to cirrhosis. Alcohol, together with the hepatitis B (HBV) and hepatitis C (HCV) viruses, is of paramount relevance. Risk factors also encompass non-alcoholic steatohepatitis, primary biliary cirrhosis, and deposition of iron or copper, which contribute to hepatocyte death.^[59] Clinical attributes, Weight loss, and pain in the right upper quadrant are two principal clinical manifestations of HCC. An acute abdominal crisis resulting from the rupture of a hepatic neoplasm with intra-abdominal haemorrhage, diminished hepatic function in a patient with established cirrhosis, and several atypical extrahepatic manifestations are additional clinical situations indicative of this diagnosis. However, this diagnosis is becoming increasingly common. Approximately 23% of 461 Italian patients with HCC were asymptomatic at initial presentation; 32% experienced abdominal discomfort, 9% reported malaise, 8% exhibited fever, 8% had ascites, 8% presented with jaundice, 6% suffered from anorexia, 4% experienced weight loss, 4% had bleeding, and 2% displayed encephalopathy.^[60] Imaging modalities, including computed tomography and magnetic resonance imaging, reveal lesions that exhibit a distinct classical pattern of early arterial enhancement followed by contrast media "washout" in the late venous phase, forming the primary basis for diagnosis. A biopsy of the lesion is occasionally necessary to verify the diagnosis when imaging studies yield equivocal results. The predominant staging method for liver

cancer globally is the Barcelona Clinic strategy, which is also recommended by international recommendations for HCC management. Tumour excision, liver transplantation, sorafenib, and loco-regional therapies such as radiofrequency ablation, aldolization, and chemoembolization constitute the existing therapeutic modalities.^[61]

8.2. Therapeutic applications of exosomes

Researchers are exploring the use of exosomes in medicine as immunomodulators, drug delivery systems, therapeutic agents, and biomarkers for disease diagnosis. Exosomes regulate intracellular communication and pathways and are thus susceptible to managing various diseases. Benefits include stability, enrichment of biomarkers, and non-invasive sampling. Exosomes are attractive due to their intrinsic targeting capability, stability, low toxicity, safety, modifiability, and tolerance by the immune system.^[62] Delivery of drugs and cellular uptake. As previously indicated, exosomes offer the advantages of a diverse cargo-loading capacity and specificity due to their intrinsic cellular messenger status. Exosomes are known to have homing capabilities that allow them to transport cargo to targets that are far away and across cells that are biocompatible, as well as to control the activities of the targeted cells temporarily. According to reports, there are two ways that exosomes communicate with target cells: either they fuse with the target cell's plasma membrane to transfer bioactive cargo, or they directly attach to the recipient cell's membrane receptors for content internalisation. Researchers aim to enhance the ability of exosomes to deliver therapeutic agents directly to tumour cells while minimising off-target effects through modifications to their surface. One approach involves utilising ligand-receptor interactions; for example, exosomes can be engineered to display ligands or antibodies on their surface that specifically bind to receptors that are overexpressed on HCC cells. Incorporating aptamers or peptides into the exosome membrane enhances binding affinity to target cells, representing a supplementary strategy [Figure 5].^[63]

Tumour cells are destroyed by the immune system, but some are dishonest. Exosomes from tumours contain immunosuppressive chemicals that impair immune cell function, hastening tumour growth. Exosome PD-L1 helps tumour cells avoid the immune system's onslaught by attaching to T cell receptors. High exosome PD-L1 levels can predict immunotherapy effectiveness. Experimental investigations show that preventing exosome production in cancer and stromal cells can slow cancer growth and metastasis. Blocking macrophage phagocytic activity via CD73 could enhance tumour therapeutic effect.^[63]

Genome editing, including methods like zinc finger nuclease (ZFNs), transcription activator-like effector nuclease

(TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9, can target genetic mutations in cancerous cells. These mutations can be repaired using high-throughput radiation treatment (HDR). For HCC, CRISPR/Cas9 targets the breakpoint MAN2A1-FER fusions, while non-homologous end joining (NHEJ) can target specific genetic alterations through genetic knockout.

Compared to protein small-molecule inhibitors, the expenses and dangers of genome editing are still unknown.

9. MODULATION OF TUMOUR MICROENVIRONMENT

The TME is the complex environment around the tumour, consisting of endothelial cells, immune cells, stromal cells, extracellular matrix, growth factors, and chemokines. The TME is crucial for tumour proliferation. Mesenchymal Stem Cells Derived Exosomes (MSCs-Exo) can help in tumour progression by carrying regulatory proteins and miRNA to various types of recipient cells through dynamic interactions, altering the phenotypes of recipient tumour/stromal cells.^[64] According to the type of MSCs source, it could either promote or inhibit the tumour. All studies on TA-MSCs-derived exosomes show a promoting effect on tumour development.^[65] MSCs-Exosomes can promote cancer by accelerating processes like epithelial-mesenchymal transition (EMT), activating signalling pathways such as the ERK/c-Fos pathway, which is triggered by factors like increased adenosine triphosphate (ATP) levels in TME, and delivering pro-tumourigenic proteins, lipids, and non-coding RNAs (e.g., lncRNAs, miRNAs) that suppress tumour suppressor genes or activate oncogenic pathways. Examples include X-inactive specific transcript (XIST), HCP5, DN3M3OS, miR-301b-3p, miR-19b-3p, miR-21-5p.^[66] MSCs-exosomes can impede tumour growth by downregulating Vascular Endothelial Growth Factor (VEGF) production in tumour cells, hence inhibiting tumour angiogenesis. Activation of multiple tumour suppressor pathways, including miR-142-3p, miR-381, miR-3182, miR-424, miR-320a, miR-30c-5p, miR-222-3p, miR-199a, miR-302a, miR-512-5p, miR-145-5p, and miR-375, could limit tumour growth. All these pathways are initiated by administering their activating miRNA.^[66] MSCs-Exosomes replicate stem cell features and demonstrate potential in tissue repair, anti-fibrosis, and cancer treatment via processes such as immunomodulation, angiogenesis, and regulation of signalling pathways. Exosomes are thought to be a promising therapeutic target.^[67] Exosomes are believed to promote apoptosis during cell progression and could induce adverse mechanisms, for example, tumour cell proliferation, migration, invasion, angiogenesis, chemotherapy resistance, immune exhaustion, and EMT.^[68] MSCs-Exosomes can regain

homeostasis and tend to regenerate cells through modulation of specific pathways.^[69]

10. IMMUNOSUPPRESSIVE EFFECT (IMMUNE MODULATION)

Exosomes formed from mesenchymal stem cells (MSCs-exosomes) convey biological substances such as RNA, proteins, and cytokines, influencing the immune system by either inhibiting or enhancing immunological responses.^[70] One of the most crucial functions is immunological suppression. Augmenting PD-L1 expression in myeloid cells and diminishing PD-1 expression in T cells limits their activity.^[71] Exosomes derived from MSCs may facilitate the polarization of macrophages toward the M2 phenotype, diminishing their anti-inflammatory properties and establishing an immunosuppressive milieu. Reduced levels of pro-inflammatory cytokines, including IFN- γ , IL-6, and TNF- α , along with the suppression of CD4+ and CD8+ T cell proliferation, diminish the immune system's anti-tumour efficacy. This investigation yields identical results to research conducted by Liu *et al.* In addition to their immunosuppressive effects, these exosomes promote angiogenesis in tumour cells, thereby enhancing the delivery of oxygen and nutrients essential for tumour proliferation.^[72]

Exosomes derived from MSCs exhibit multiple mechanisms that augment anti-tumour immunity. One mechanism involves the inhibition of M2 macrophage polarization. This procedure diverts the immune system towards anti-tumour activity by transferring microRNA-1827 (miR-1827) and downregulating the expression of the SUCNR1 receptor. Besides M2, these exosomes can modulate cytokines and convey certain miRNAs, thereby limiting tumour invasion, growth, and metastasis. Furthermore, these modified exosomes may facilitate the delivery of RNAs and chemotherapeutic agents, counteracting the immunosuppressive effects inside the TME.^[73]

Tumour-derived exosomes (TEXs) can convey substances with either immunostimulatory or immunosuppressive properties, but MSC-derived exosomes do not influence immunological responses, impacting immune cell formation, development, and antitumor efficacy. Experiments on mice indicate that TEXs possess greater amounts of immune-stimulating chemicals compared to tumour lysates, suggesting that TEXs may serve as a source of antigens for cancer vaccines, as they can more efficiently activate cytotoxic T lymphocytes (CTLs) and enhance anti-tumour immunity.^[74]

Exosomes possess the capacity to modulate the pre-metastatic immunological milieu, mostly through the regulation of immune cells. Exosomes are abundant in immunosuppressive proteins, including PD-L1, FasL, TGF- β , and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), which

impair the anti-tumour immune response.^[75] Exosomes can transport tumour antigens, co-stimulatory chemicals, and MHC molecules, thus activating the immune system. This dual function enables these exosomes to facilitate both immunological repression and immune activation.^[76]

11. ANTI-ANGIOGENIC PROPERTIES

Angiogenesis refers to the development of new blood capillaries from existing ones. This process encompasses multiple stages: the stimulation of endothelial cells (ECs) by vascular endothelial growth factor (VEGF), the degradation of the vascular basement membrane by enzymes, the proliferation of vascular endothelial cells, branching, and the formation of tubes.^[77] In normal conditions, the proangiogenic factors and antiangiogenic factors are in balance. Tumours break through this balance, secreting various substances resulting in uncontrolled angiogenesis, creating a complex vascular system surrounding cancer, providing the supply of oxygen and nutrients, promoting tumour growth and migration. Tumour angiogenesis is a sign of tumour growth, and exosomes can regulate this process.^[78] Recent studies show antiangiogenic and antitumorigenic effects of MSCs-exosomes by releasing ncRNAs.^[79] Previous studies show that exosome-derived miR-451a targets LPIN1, resulting in an inhibition of tumour angiogenesis and apoptosis in HCC cells. There is a study that showed that miR-125b-enriched MSC-EVs show an antiangiogenic effect in Triple-negative breast cancer (TNBC) through reducing endothelial VEGF levels, limiting the tumour's blood supply, lowering angiogenesis, and limiting tumour growth and metastasis. MSC-exosomes promote angiogenesis by delivering key proteins like HGF and SDF-1 to endothelial cells (ECs), enhancing their migration, proliferation, and activation.^[80]

Overall, the angiogenic potential of exosomes is not only linked to their bioactive cargo but could also be affected by environmental conditions, such as hypoxia, which triggers their pro-angiogenic effects, showing the adaptability of exosomes in supporting vascular repair and tissue regeneration.^[81]

12. DRUG DELIVERY POTENTIAL OF MSC-EXO

Due to exosomes' ability to transfer biological cargo like RNA, proteins, and lipids between cells. They show promising solutions as drug delivery systems because of their ability to overcome natural barriers.^[82] Exosome loading mechanisms can be done in two ways. One way is by loading exosomes with drugs in the donor cell before secretion into the extracellular environment.^[83] Another way is loading exosomes with drugs after the secretion into the extracellular environment.^[84]

Due to the large potential of drug-loaded exosomes and their signal-carrying capacity, researchers started working on it. There is a study carried out by Sun *et al.* that prepared

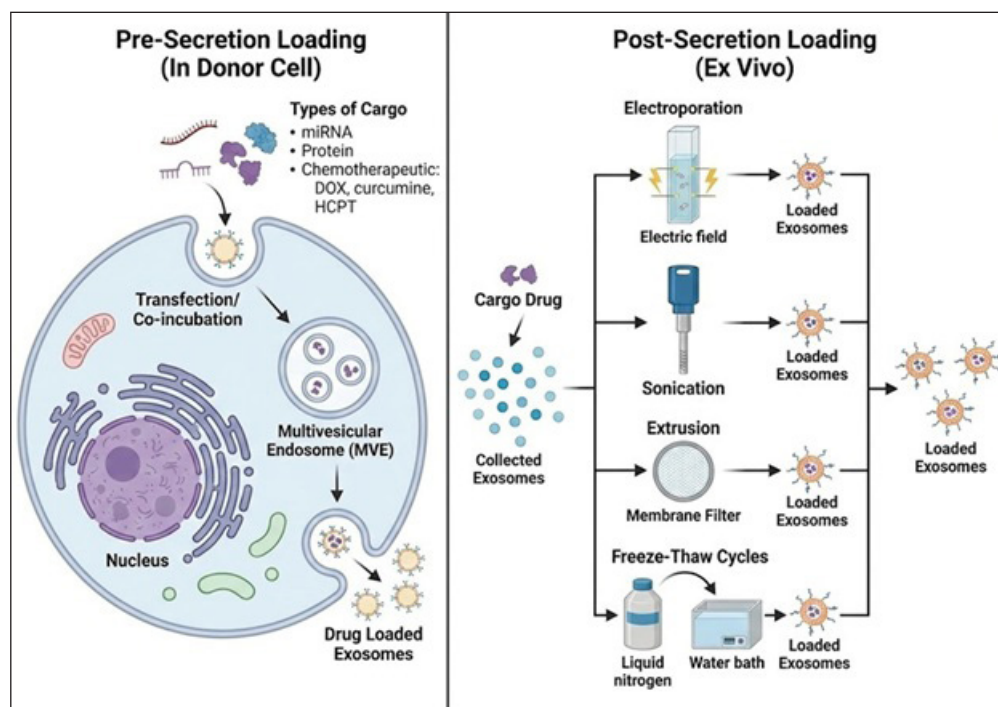


Figure 5: Overview of exosome-based drug loading strategies and therapeutic applications in liver cancer. The upper panel illustrates pre- and post-secretion loading techniques. The lower panel summarizes targeted exosome therapies including genetic cargo delivery, chemotherapeutic loading, anti-angiogenic effects, and modulation of tumour microenvironment. DOX: Doxorubicin, HCPT: Hydroxycamptothecin.

curcumin-loaded exosomes derived from various types of stem cells, showing better results than regular curcumin methods. Exosomes can be a drug-delivery system or a therapeutic agent.^[85]

In exosome-based drug delivery, exosomes are very special with their loading varieties.^[86] Exosomes can deliver genetic substances like miRNA, spherical nucleic acid (SNA), and siRNA.^[11] Naturally, exosomes deliver miRNA, which can be modified to provide specific miRNA.^[87] Just like miRNA, proteins were carried naturally by exosomes, which were used by researchers to deliver special proteins such as enzymes, cytoskeletal proteins, and transmembrane proteins. Leading to tumour inhibition and phagocytosis of tumour cells by macrophages. And there are many studies on providing chemotherapeutic drugs such as curcumin, paclitaxel (PTX), dopamine, and doxorubicin (DOX). All show promising results when loaded by exosomes, either by increasing efficiency or enhancing cytotoxicity.^[85]

Some research highlighted the role of cancer-cell-derived exosomes in tumour growth and resistance to chemotherapy. For example, a study on the management of HCC cells with sorafenib (Sora) showed an increase in the expression of lncRNA retinoic acid receptor-related orphan receptor (ROR) and linc-very low-density lipoprotein receptor (VLDLR), increasing cytotoxicity and apoptosis caused by treatment

of HCC.^[88,89] Target delivery exosomes with SP94 peptide loaded with hydroxycamptothecin (HCPT) show great results by achieving 60% higher drug accumulation in tumour cells and reducing tumour volume by 50%, also lowered systemic toxicity, reducing nephrotoxicity by 35% and enhancing tumour tissue drug absorption by 45%, these findings shows the potential of engineered exosomes in improving the efficiency and safety of HCC treatment through exosomes targeted-delivery systems.^[90]

13. CONCLUSION AND FUTURE PERSPECTIVES

Mesenchymal stem cells (MSCs) and their exosome derivatives have proved to be extremely promising next-generation therapeutic entities in regenerative medicine, particularly in the treatment of liver pathology and cancer. Their ability to modulate immune responses, promote tissue regeneration, and deliver bioactive molecules to specific sites makes them the frontrunners among next-generation cell-based and cell-free therapies. In addition, the special biological properties of MSC-derived exosomes, including low immunogenicity, high biocompatibility, and effective cargo delivery, render them particularly promising for clinical use. Despite with encouraging preclinical and early clinical results, there are several obstacles to be addressed. Among these are standardisation of MSCs and exosome

manufacturing, increasing purity and yield of exosomes, gaining knowledge about their biodistribution and safety profile, and identification of the precise molecular process whereby they have their therapeutic effects. Also, the two-way potential of MSCs toward cancer, tumour-promoting or tumour-suppressing, should be considered when designing MSC-based strategies for oncology.

Technological advancements will play a fundamental role in overcoming current limitations in the future. Advanced technologies such as CRISPR-Cas9 for genome editing, 3D bioprinting for tissue modelling, and microfluidic systems for exosome isolation at high-throughput rates. Integration of nanotechnology can also enable the development of smart exosome-based delivery systems with controlled release and targeted delivery capabilities. In addition, combining MSC-derived exosomes with conventional therapies such as chemotherapy, immunotherapy, or targeted therapy may provide synergistic effect and pave the way for personalized and precision medicine.

In short, MSCs and their exosomes represent a dynamic, constantly evolving field with the potential to revolutionize the therapeutic approach to chronic and complicated diseases. Continuous interdisciplinary communication between cell biology, bioengineering, materials science, and computational modelling will be essential to maximise their therapeutic potential and overcome the bench-to-bedside gap.

14. TECHNOLOGICAL IMPLICATIONS

This review's findings underscore the significant promise of mesenchymal stem cell-derived exosomes (MSC-Exos) as a novel technology platform in regenerative medicine, drug delivery, and cancer. Their nanoscale dimensions, stability, and capacity to traverse biological barriers render them as advanced therapeutic vectors for precision and personalized treatment. MSC-Exosomes serve as a natural medium for the precise distribution of proteins, RNAs, and small molecules, reducing immunogenicity and systemic toxicity in comparison to manufactured nanoparticles. Additionally, engineered exosomes can be altered to improve tissue selectivity and therapeutic delivery, facilitating the advancement of bioinspired nanocarrier systems and intelligent exosome-based therapies. These advancements have the potential to transform the therapeutic management of liver disorders and cancer by facilitating non-invasive, biocompatible, and highly effective treatment options.

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