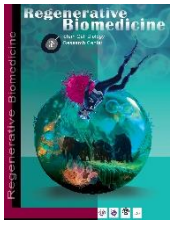

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Mini-Review Article

Exosome Therapy Using Mesenchymal Stromal/Stem Cells

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Abstract

Exosome therapy using mesenchymal stromal/stem cell (MSC)-derived exosomes is a rapidly evolving field with significant implications for regenerative medicine and immunomodulation. Exosomes are small extracellular vesicles secreted by various cell types, including MSCs, and are known to contain a diverse range of bioactive molecules, such as proteins, lipids, and nucleic acids. MSC-derived exosomes have emerged as promising therapeutic agents due to their regenerative and immunomodulatory properties. The biogenesis and composition of MSC-derived exosomes are key factors in their therapeutic potential. These exosomes are formed through the endocytic pathway, where multivesicular bodies containing intraluminal vesicles fuse with the plasma membrane, releasing exosomes into the extracellular space. MSC-derived exosomes are enriched in specific proteins, such as CD9, CD63, and CD81, and contain various bioactive molecules, including growth factors, cytokines, and microRNAs, which play important roles in mediating their therapeutic effects. MSC-derived exosomes exert their therapeutic effects through various mechanisms, including immune modulation, anti-fibrotic effects, and tissue regeneration. Preclinical studies have demonstrated the efficacy of MSC-derived exosomes in various disease models, including myocardial infarction, stroke, and osteoarthritis. These studies have shown that MSC-derived exosomes can improve tissue repair and regeneration, reduce inflammation and fibrosis, and promote functional recovery in animal models. Overall, MSC-derived exosomes represent a promising new approach for regenerative medicine and immunomodulation, with the potential to address unmet medical needs in a wide range of conditions. Further research is needed to optimize their isolation and delivery methods, elucidate their mechanisms of action, and evaluate their safety and efficacy in clinical trials.

Keywords: Exosomes, Mesenchymal Stem Cells, Regenerative Medicine, Immunomodulation, Biogenesis

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Introduction

Exosome therapy has garnered considerable interest in recent years as a promising avenue for regenerative medicine (1). Exosomes, small extracellular vesicles secreted by various cell types, including mesenchymal stromal/stem cells (MSCs), are known to carry a diverse array of bioactive molecules such as proteins, lipids, and nucleic acids (2). MSC-derived exosomes, in particular, have emerged as a compelling therapeutic option due to their unique regenerative and immunomodulatory properties (3).

The regenerative potential of MSC-derived exosomes lies in their ability to promote tissue repair and regeneration (4). These exosomes contain a variety of growth factors, cytokines, and extracellular matrix components that can stimulate cell proliferation, migration, and differentiation (5). Studies have shown that MSC-derived exosomes can enhance the regeneration of damaged tissues, such as cardiac muscle after a heart attack, by promoting the growth of new blood vessels and reducing scar formation (6).

In addition to their regenerative effects, MSC-derived exosomes also exhibit potent immunomodulatory properties (7). These exosomes can modulate the activity of immune cells, such as T cells, B cells, and macrophages, to dampen excessive inflammation and promote tissue healing (8). By regulating the immune response, MSC-derived exosomes have the potential to treat inflammatory and autoimmune diseases (9).

The unique properties of MSC-derived exosomes, coupled with their ability to be easily isolated and manipulated in vitro, make them an attractive candidate for therapeutic applications (5). Unlike MSCs themselves, which can be limited by issues such as immunogenicity and tumorigenicity, MSC-derived exosomes offer a safer and more targeted approach to regenerative therapy (10).

In this minireview, we aim to provide a comprehensive overview of exosome therapy using MSCs, focusing on their biogenesis, composition, mechanisms of action, preclinical studies, clinical trials, challenges, and future directions. Understanding the therapeutic potential of MSC-derived exosomes is crucial for advancing regenerative therapies and improving patient outcomes.

Biogenesis and Composition of MSC-derived Exosomes

Exosomes are small membrane vesicles with a size range of 30-150 nm that are secreted by cells as a means of intercellular communication (11). They are formed through the endocytic pathway, which begins with the invagination of the plasma membrane to form early endosomes (12). These early endosomes mature into late endosomes, also known as multivesicular bodies (MVBs), which contain intraluminal vesicles (ILVs) formed by the inward budding of the endosomal membrane (13). The MVBs can either fuse with lysosomes for degradation or with the plasma membrane for exosome release (14). When MVBs fuse with the plasma membrane, the ILVs are released into the extracellular space as exosomes (15).

MSC-derived exosomes are characterized by their specific protein and nucleic acid contents (10). Commonly used markers for identifying exosomes include tetraspanins (CD9, CD63, CD81), heat shock proteins (HSP70, HSP90), and membrane transport and fusion proteins

(Alix, TSG101) (16). These proteins are involved in the biogenesis, cargo sorting, and secretion of exosomes (12).

The cargo of MSC-derived exosomes is composed of a variety of bioactive molecules, including proteins, lipids, and nucleic acids (2). These molecules play important roles in mediating the therapeutic effects of MSC-derived exosomes (17). For example, the proteins contained in exosomes can include growth factors (e.g., VEGF, FGF, HGF), cytokines (e.g., TGF-β, IL-10), and enzymes (e.g., MMPs) (2). The lipids in exosomes are involved in membrane structure and signaling, while the nucleic acids, especially microRNAs (miRNAs), can regulate gene expression in recipient cells (18). Exosomes has the potential to be manipulated an act as a cargo for drug delivery (19, 20).

Mechanisms of Action

MSC-derived exosomes mediate their therapeutic effects through a variety of mechanisms, making them promising candidates for regenerative medicine and immunomodulation (21). One key mechanism is their ability to modulate the immune response (10). MSC-derived exosomes can suppress the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while promoting the secretion of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) (22). This immunomodulatory effect can help to dampen excessive inflammation and reduce tissue damage in inflammatory conditions (23). Another important mechanism of action of MSC-derived exosomes is their anti-fibrotic effects (24). Excessive fibrosis, characterized by the accumulation of extracellular matrix components, can lead to tissue scarring and dysfunction (25). MSC-derived exosomes have been shown to inhibit fibrosis by reducing the expression of fibrotic markers, such as collagen and alpha-smooth muscle actin (α-SMA), and promoting the expression of anti-fibrotic factors, such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) (26). This anti-fibrotic effect can help to prevent tissue scarring and promote tissue repair (27). Additionally, MSC-derived exosomes play a role in tissue regeneration (28). They can stimulate the proliferation, migration, and differentiation of various cell types, including stem cells and progenitor cells, which are involved in tissue repair and regeneration (29). MSC-derived exosomes can also enhance angiogenesis, the process of new blood vessel formation, which is crucial for supplying oxygen and nutrients to regenerating tissues (30).

Preclinical Studies

Preclinical studies have provided compelling evidence for the therapeutic efficacy of MSC-derived exosomes in a variety of disease models (31). In myocardial infarction (MI), for instance, animal studies have shown that intramyocardial injection of MSC-derived exosomes can improve cardiac function and reduce scar formation (6). This is thought to be due to the ability of exosomes to stimulate angiogenesis, reduce inflammation, and promote the survival of cardiomyocytes (32). In a porcine model of MI, treatment with MSC-derived exosomes resulted in increased capillary density in the infarcted area,

improved left ventricular function, and reduced infarct size compared to controls (33).

In addition to MI, preclinical studies have also demonstrated the potential of MSC-derived exosomes in stroke (34). In a mouse model of ischemic stroke, intravenous administration of MSC-derived exosomes improved neurological function and reduced infarct size (35). This was associated with increased angiogenesis and neurogenesis in the peri-infarct area, suggesting that MSC-derived exosomes can promote brain repair and functional recovery following stroke (36).

Furthermore, MSC-derived exosomes have shown promise in the treatment of osteoarthritis (OA) (37). In a rat model of OA, intra-articular injection of MSC-derived exosomes reduced cartilage degeneration and synovial inflammation, and improved joint function (37). These effects were attributed to the ability of exosomes to modulate inflammation and promote the regeneration of damaged cartilage tissue (38).

Overall, preclinical studies have provided strong evidence for the therapeutic potential of MSC-derived exosomes in a range of disease models (9, 39, 40). These studies have laid the foundation for clinical trials investigating the safety and efficacy of MSC-derived exosome therapy in human patients, with the aim of translating these promising preclinical findings into clinical practice (41).

Conclusion

In conclusion, exosome therapy using mesenchymal stem cell (MSC)-derived exosomes holds great promise for regenerative medicine and immunomodulation. MSC-derived exosomes are small extracellular vesicles that contain a diverse array of bioactive molecules, including proteins, lipids, and nucleic acids. These exosomes exert their therapeutic effects through various mechanisms, including immune modulation, anti-fibrotic effects, and tissue regeneration.

Numerous preclinical studies have demonstrated the therapeutic potential of MSC-derived exosomes in a variety of disease models, including myocardial infarction, stroke, and osteoarthritis. These studies have shown that MSC-derived exosomes can improve tissue repair and regeneration, reduce inflammation and fibrosis, and promote functional recovery in animal models.

Overall, the preclinical evidence suggests that MSC-derived exosomes have the potential to be effective therapeutic agents for a wide range of conditions. However, further research is needed to fully understand their mechanisms of action, optimize their isolation and delivery methods, and assess their safety and efficacy in clinical trials.

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