REVIEW

Research progress of mesenchymal stem cell exosomes in multiple organ inflammatory diseases

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ABSTRACT

Inflammation is generally considered as a pathological process, and the occurrence of multi-organ inflammatory diseases is usually accompanied by an inflammatory response. Persistent inflammation can eventually lead to organ dysfunction. In recent years, the study of mesenchymal stem cell-derived exosomes has found its unique anti-inflammatory effect, which provides a new idea for the treatment of multi-organ inflammatory diseases. This article reviews the effect of mesenchymal stem cell exosomes on multi-organ inflammatory diseases.

Key Words: Inflammation, Exosomes, Mesenchymal stem cells

1. INTRODUCTION

Mesenchymal stem cells (MSC) are a class of adult pluripotent stem cells originating from the mesoderm, which can not only play anti-inflammatory, anti-apoptosis and angiogenesis roles, but also regulate cell proliferation, differentiation, and migration. Small biologically active vesicles secreted by various tissue cells enter the extracellular environment, i.e., the extracellular vesicles. Broadly speaking, the extracellular vesicles include microvesicles, apoptosis bodies and exosomes. Exosomes, as an important part of parocrine, with a diameter of 50-200 nm, are secreted by cells through endocytosis. The cell membrane first spits inward to form intracellular polyvesicles, then the polyvesicles gradually migrate to the cell marginal zone and fuse with the cell membrane, and then concave inward again to form granular vesicles, i.e., exosomes, which mediate the transfer of intercellular active substances and participate in intercellular information exchange.[1]

Inflammation is the common pathological basis of multi-organ inflammatory diseases, and the inflammatory response plays an important role in tissue homeostasis. On the one hand, the inflammatory response can sense changes in the tissue environment, induce tissue homeostasis imbalance and cause tissue damage. On the other hand, the inflammatory response can also allow damaged tissues to repair and heal through the regeneration of parenchymal and mesenchymal cells. The inflammatory response is characterized by redness, swelling, fever, pain, and immune cell infiltration in the short term, and the tissue can be restored to its normal structure after the control of acute inflammation. When acute inflammation develops into chronic or unresolved inflammation, it can lead to tissue and organ dysfunction. Therefore, the early control of the development of the inflammatory response pro-

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cess is an effective measure for the treatment of multi-organ inflammatory diseases.[2] Studies have shown that MSC-derived exosomes are closely related to the polarization of M2-type macrophages with anti-inflammatory effects in the treatment of multi-organ inflammatory diseases.[3] Other studies have shown that bioactive molecules (e.g., miRNA) contained in MSC-derived exosomes also have the function of regulating multi-organ inflammatory diseases.[4] In addition, exosomes have become excellent carriers for drug delivery due to their small size, low immunogenicity and strong biocompatibility.[5,6] This article reviews the role of MSC-derived exosomes in inflammatory diseases in the brain, heart, lungs, liver, kidneys, and intestines.

2. The role of MSC-derived exosomes in cerebral inflammatory diseases

Cerebrovascular disease is, which is a type of acute neurological disease, is a common systemic disease, of which ischemic cerebral infarction is the most common, occurring after the obstruction of blood flow to the cervical spine or the brain. Inflammatory response is one of the important mechanisms of dysfunction caused by cerebral infarction.[7] Microglia activation is of great significance in the process of brain inflammatory response, activated microglia can be polarized into M1 and M2 types, M1 microglia can promote the inflammatory response, and M2 microglia can relieve inflammatory response.[8] It has been found that MSC-derived exosomes can inhibit the activation of microglia after cerebral ischemic injury.[9] Animal experiments by Zhang et al.[10] showed that, through the injection of human umbilical cord MSC-derived exosomes into a mouse model of ischemic stroke, it was found that the amount of M1 microglia was decreased while the amount of M2 microglia was increased, and the expressions of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and IL-1β were also significantly decreased in the experimental group; it was also found in the study that human umbilical cord MSC-derived exosomes could reduce the pro-inflammatory activity of microglia in vitro. In the rat unilateral midbrain artery occlusion model, the injection of adipose MSC-derived exosomes overexpressing miR-126 through the tail vein could significantly inhibit the activation of ischemic cortical microglia and reduce the generation of pro-inflammatory cytokines such as TNF-α and IL-1β, thereby promoting the recovery of neurological function after cerebral ischemia in rats.[11] Other studies have shown that in a model study of pigs with traumatic brain injury, animals treated with bone marrow MSC-derived exosomes had lower levels of nuclear factor kB and inflammatory markers (IL-1, IL-6, IL-8 and IL-18) in comparison to the control group; in the treatment of subarachnoid hemorrhage in rats, bone marrow MSC-derived exosomes significantly reduced the levels of inflammatory proteins, such as high-mobility group protein B1, toll-like receptor-4 and TNF-α,[12] in addition, miRNAs in MSC-derived exosomes, such as miRNA-21, miRNA-23a, miRNA-125b, and miRNA145, can also inhibit M1-type microglial polarization, thereby attenuating inflammatory injury after cerebral ischemia in model mice.[13]

3. The role of MSC-derived exosomes in cardiac inflammatory diseases

Acute myocardial infarction is an extremely common and critical disease, and the degree of inflammation is closely related to the degree of myocardial infarction, and continuous inflammatory response may lead to poor left ventricular remodeling after myocardial infarction. Therefore, reducing the inflammatory response after myocardial infarction is an effective way to improve the prognosis.[14] SC-derived exosomes attenuate myocardial inflammation by regulating miRNA-182 targeting the toll-like receptor-4/phosphatidylinositol-3 kinase/protein kinase B signaling pathway to promote the polarization of M2-type macrophages,[15] studies have shown that the inflammatory response of cardiomyocytes is induced after myocardial infarction, a large amount of inflammatory cells accumulate and infiltrate, and after administration of MSC-derived exosomes, hematoxylin-eosin staining shows a significant reduction in inflammatory cell infiltration.[16] It has been found that bone marrow MSC-derived exosomes can regulate local inflammatory cytokines in infarct myocardium, and the injection of bone marrow MSC-derived exosomes can greatly inhibit acute myocardial infarction-induced inflammatory cytokines, including IL-1β, IL-6 and TNF-α, as well as targeting pro-apoptotic proteins such as apoptosis-related factor ligands and tensin homolog genes. In addition, bone marrow MSC-derived exosomes can promote the polarization of M1 macrophages to M2 macrophages in vitro and in vivo, thereby alleviating the inflammatory response.[17] Animal experiments by Fu et al.[18] also demonstrated that the treatment of myocardial infarction model mice with bone marrow MSC-derived exosomes significantly reduced the release of inflammatory cytokines TNF-α, IL-6, IL-1β, and transforming growth factor-β. In addition, miRNA-125b in bone marrow MSC-derived exosomes down-regulated the expression of B-cell lymphoma-2-associated X protein and cysteine protease-3 in a rat model of myocardial ischemia-reperfusion injury, up-regulated the expression of B-cell lymphoma-2, and reduced the levels of inflammatory factors such as IL-1β, IL-6 and TNF-α.[19] In addition, the use of adipose MSC-derived exosomes overexpressing miRNA-126 significantly reduced the levels of M1-type macrophages and pro-

inflammatory cytokines (including IL-6, IL-1β, interferon-γ, TNF-α) that predominate in infarcted myocardium and relieved cardiac fibrosis.[17]

4. The role of MSC-derived exosomes in pulmonary inflammatory diseases

Acute lung injury is the most common acute critical illness in clinical practice, which is induced by various internal and external risk factors. The imbalance between pro-inflammatory and anti-inflammatory mediators is the main pathogenesis, and the damage to pulmonary capillary endothelial cells and alveolar epithelial cells is the main pathological manifestation.[20] Recent studies have shown that MSC-derived exosomes can modulate immune cells, reduce neutrophil influx in bronchoalveolar lavage fluid, and attenuate macrophage-mediated inflammation. At the same time, MSC-derived exosomes can enhance bacterial monocyte phagocytosis and reduce alveolar macrophage activation and influx in acute lung injury, thereby relieving the inflammatory response.[21] It has also been found that MSC-derived exosomes with a high expression of miRNA-233-5p can induce the polarization of alveolar M2 macrophages, while MSC-derived exosomes with low expressions of miRNA-125b-5p and miRNA-127-3p can increase the polarization of M1 macrophages.[3] Some scholars have found that bone marrow MSC-derived exosomes can reduce airway inflammation in asthma by up-regulating the expression of inhibitory cytokines IL-10 and transforming growth factor-β1 in peripheral blood mononuclear cells from asthma patients, and promoting regulatory T cell proliferation and immunosuppressive ability.[22] Adipose MSC-derived exosomes exhibit immunomodulatory and lung protective effects in endotoxin-infected mouse models, which are achieved by transferring mitochondrial components (particularly mitochondrial DNA) from stressed macrophages in the lungs from MSCs; The research group found that exosomes containing mitochondrial DNA showed a stronger effect on cellular inflammatory responses than free mitochondrial DNA.[23] In addition, Lian Xihua et al.[24] found that the levels of TNF-α, IL-6 and serum chemokine-1 were significantly reduced, and the degree of inflammatory response was significantly reduced after administration of adipose MSC-derived exosomes in a mouse model of chronic obstructive pulmonary disease with smoke-induced hyperinflammatory response.

5. The role of MSC-derived exosomes in hepatic inflammatory diseases

Chronic liver inflammation damages hepatic epithelial cells and induces reactive oxygen species and DNA damage, increasing the frequency of genomic DNA mutations. In addition, chronic inflammation causes changes in the hepatic immune system, allowing cancer cells to evade immune surveillance and proliferate rapidly.[25] The mechanism of continuous inflammation and abnormal tissue regeneration is not well understood. However, the inflammatory response is always an important reason for promoting liver tissue damage and leading to the occurrence and development of liver malignant diseases.[26] Studies have shown that the hepatoprotective effect of MSC-derived exosomes relies on the inhibition of nucleotide-binding oligomerization domain-like receptor protein 3-dependent activation of caspase-1 and caspase-1-driven apoptosis, which is characterized by plasma membrane rupture, cytoplasmic swelling, osmotic cleavage, DNA lysis and massive release of inflammatory cytokines (IL-1β and IL-18). Thus, MSC-derived exosomes exert their hepatoprotective effects by inhibiting apoptosis and hepatocyte death, as well as attenuating IL-1β and IL-18-driven inflammatory responses.[4] It was found that bone marrow MSC-derived exosomes could significantly reduce the levels of interferon-γ, IL-1β and IL-6 in the serum of mice with acute liver failure, and significantly up-regulate the levels of IL-10; Human umbilical cord MSC-derived exosomes significantly down-regulated the levels of TNF-α, IL-6 and IL-1β in the liver tissues of mice with acetaminophen-induced acute liver failure; adipose MSC-derived exosomes can be taken up by hepatic macrophages and downregulate the levels of TNF-α, interferon-γ, IL-6, IL-1β and IL-18 in the serum.[27] Through in vivo and in vitro studies by Shao et al.,[28] they verified that exosome secretion from human umbilical cord MSCs can promote the secretion of miRNA-455-3p, inhibit liver Kupffer cells, and downregulate the levels of various inflammatory cytokines. In addition, Zhao et al.[5] constructed a drug-carrying exosome called exosome@dexamethasone for the treatment of inflammatory liver disease by loading the potent anti-inflammatory drug dexamethasone into MSC-derived exosomes.

6. The role of MSC-derived exosomes in renal inflammatory diseases

Glomerulonephritis represents a family of kidney diseases characterized by an inflammatory response within the glomeruli and small blood vessels, with high morbidity and mortality, often difficult to treat, sometimes incurable, and potentially capable of chronic kidney disease and end-stage renal disease of the kidneys.[29,30] Studies have shown that MSCs can increase the activity of regulatory T cells and the expression of anti-inflammatory cytokines such as IL-10, thereby attenuating the inflammatory response, and in animal models of membranoproliferative glomerulonephritis,

intravenous infusion of MSCs can reduce the glomerular expression of pro-inflammatory cytokines, reduce monocyte infiltration, mesangial hyperplasia, connective tissue matrix synthesis and proteinuria; in a rat model of focal segmental glomerulosclerosis (doxorubicin-induced nephropathy), several intravenous infusions of bone marrow-derived MSCs increased the synthesis of glomerular vascular endothelial growth factors while attenuating glomerular monocyte infiltration, podocyte apoptosis and podocyte-parietal epithelial bridging.[31] Other studies have shown that MSC-derived exosomes can reduce the inflammatory response of lupus nephritis by regulating innate and adaptive immune responses, reducing B cell proliferation and activation, mediating T cell apoptosis and reducing lymph node and spleen weight, while inhibiting macrophage polarization to M1 and correcting the imbalance between M2/M1 macrophages; the research group also found that exosomes, as excellent carriers for drug delivery, can not only effectively avoid drug degradation, but also easily penetrate through a variety of barriers to reach the target organs, and at the same time, different routes of administration can be selected according to the location of the lesion.[6]

7. The role of MSC-derived exosomes in intestinal inflammatory diseases

Inflammatory bowel disease is a chronic autoimmune disease of the gastrointestinal tract, including Crohn's disease and ulcerative colitis, with symptoms characterized by intermittent relapse and resting inflammation.[32] In intestinal inflammatory diseases, pro-inflammatory factors (TNF-α, IL-6, IL-1β, etc.) secreted by macrophages and T cells can induce inflammatory responses in colon tissues, destroy the structure and physiological function of intestinal mucosal tissues, and these pro-inflammatory factors directly act on intestinal mucosal cells to cause increased cell permeability and further aggravate inflammatory responses.[33] In animal experiments, it has been found that the expression of anti-inflammatory factor IL-10 and the expression of pro-inflammatory factors TNF-α, IL-1β and IL-6 decreased in the treatment of intestinal inflammation response model mice treated with human umbilical cord MSC-derived exosomes; The research group found that MSC-derived exosomes can not only downregulate the intestinal inflammatory response, but also maintain the integrity of the intestinal mucosal barrier and polarize macrophages to the M2 phenotype without causing intestinal fibrosis.[34] In addition, human umbilical cord MSC-derived exosomes inhibit macrophage function by downregulating nitric oxide synthase and IL-7, thereby reducing intestinal inflammatory responses. Bone marrow MSC-derived exosomes promote M2 macrophage polarization and exert anti-inflammatory protective effects in colitis mice by regulating protein tyrosine kinase 1/signal transduction and transcription activator factor 1/signal transduction and transcription activator factor 6 signaling pathway.[35]

8. Summary and prospect

MSC-derived exosomes have powerful immunomodulatory and inflammatory inhibitory effects, which can act by regulating inflammatory cells or inflammatory cytokines on the one hand, and can exert anti-inflammatory effects as drug-carrying vehicles on the other hand. Therefore, MSC-derived exosomes are a potential therapeutic means to alleviate the inflammatory response in multi-organ inflammatory diseases, and it is worthy of further research to improve the prognosis in patients. However, the inability to produce MSC-derived exosomes in large quantities is the biggest obstacle to current exosome research; in addition, the specific mechanism and specific components of exosomes exerting anti-inflammatory effects in multi-organ inflammatory diseases need to be further studied.

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Authors contributions

Te Ba and Lingfeng Wang are responsible for the overall idea and review of the article, Biao Zhou and Yangyang Li are responsible for data collection and writing, all authors read and approved the final manuscript.

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