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MESENCHYMAL STEM CELLS HAVE THE POTENTIAL TO MODULATE THE IMMUNE RESPONSE DURING INFECTIONS

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ABSTRACT

Mesenchymal stem cells (MSCs) can differentiate into various cell types and may play an important role in infections. Myeloid cells are a group of blood cells that derive from the myeloid lineage of hematopoietic stem cells, present in the bone marrow. These cells play a fundamental role in both the innate and adaptive immune systems. MSCs are a type of adult stem cell with immunomodulatory and regenerative properties. Their ability to influence the immune system makes them a potential therapeutic tool for many inflammatory diseases and their use in infections is still being developed. MSCs can induce macrophage polarization toward an M2 anti-inflammatory phenotype and can enhance macrophage phagocytic activity and modulate cytokine production by inhibiting pro-inflammatory cytokines such as TNF and IL-1β. Moreover, MSCs enhance antimicrobial activity, modulate the immune response against infections, and can secrete antimicrobial peptides that inhibit bacterial growth. MSCs are useful in sepsis processes where they modulate both inflammation and immune cell responses against infectious agents. They may provide new and promising applications for the treatment of various infectious diseases.

KEYWORDS: *Mesenchymal stem cell, immune response, infection, immunomodulation, inflammation*

INTRODUCTION

Mesenchymal stem cells (MSCs) can differentiate into various cell types and can be immunomodulatory (1). They interact with myeloid cells and may also play an important role in infections, a topic of considerable interest (2). Myeloid cells are important immune system elements which include dendritic cells (DCs), neutrophils, monocytes, and macrophages (3). MSCs influence myeloid cells through direct cell-to-cell contact and secretion of various soluble factors (4). MSCs can inhibit the maturation of DCs, resulting in a reduction in their ability to present antigens and stimulate T cells (5). These reactions are mediated by several important cytokines (5). MSCs can modulate DC secretion by inducing an anti-inflammatory state (5).

DISCUSSION

MSCs are multipotent cells useful in tissue regeneration and repair after a sepsis process (6). Their reparative effect in inflammatory processes is exerted partly by secreted exosomes which are extracellular vesicles with a diameter of about 50-150 nm (7). Exosomes can polarize macrophages to M1 (producing pro-inflammatory cytokines) or M2 (secreting anti-inflammatory molecules) (8). Therefore, MSCs can induce the polarization of macrophages towards an anti-inflammatory M2 phenotype which is involved in tissue repair and regeneration (9). These phenomena are mediated

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by cytokines such as IL-10 and TGF-β (10). In addition, MSCs can enhance the phagocytic activity of macrophages and modulate cytokine production, reducing pro-inflammatory cytokines such as TNF and IL-1β and increasing anti-inflammatory cytokines such as IL-10 and IL-37 (11). IL-37 is a new anti-inflammatory cytokine belonging to the IL-1 family that is known for its immunosuppressive and anti-inflammatory properties. IL-37 plays a crucial role in modulating immune responses during infections by suppressing pro-inflammatory cytokines such as IL-1β, IL-6, and TNF, and by reducing the severity of infection-induced inflammation. In addition, IL-37 inhibits the NF-κB and MAPK signaling pathways, thereby limiting immune hyperactivation. It also enhances regulatory T cell (Treg) function, inhibits excessive neutrophil infiltration, and is protective in sepsis by reducing tissue and organ damage. MSCs can enhance neutrophil survival by inhibiting apoptosis and modulating neutrophil functions, including chemotaxis and release of reactive oxygen species (ROS) (12).

MSCs enhance the antimicrobial activity of neutrophils against pathogenic microorganisms and monocytes can influence their differentiation into macrophages or DCs (13). In addition, MSCs are implicated in the migration of macrophages in inflammatory reactions (14). Therefore, MSCs can modulate the immune response during infections, regulating the immune reaction towards microorganisms and reducing tissue damage caused by an exaggerated inflammatory response (15).

In bacterial infections, MSCs can enhance infectious clearance by modulating macrophage activity and promoting phagocytosis (16). Recently, MSCs have been reported to secrete antimicrobial peptides, such as IL-37, which directly kill bacteria (17). In viral infections, MSCs act in a complex manner depending on the type of virus. In some cases, MSCs can enhance antiviral responses, while in others, they may promote inflammation that results in increased tissue damage (18). Moreover, MSCs can modulate the activity of various immune cells, including T cells and natural killer (NK) cells, which are critical for controlling viral infections.

In experimental models of sepsis, MSCs have shown promising results by showing a modulatory action in the inflammatory response, improving microbial clearance, and increasing survival in laboratory animals (19). The action of MSCs on infectious processes occurs in immune cells, which are reprogrammed to obtain a better response without worsening the inflammatory reaction.

The immunomodulation exerted by these cells occurs through different mechanisms: a) MSCs secrete various cytokines, chemokines, and growth factors such as IL-10, TGF-β, and PGE2, which influence the pathophysiology of immune cells; b) MSC-derived extracellular vesicles, including exosomes, carry bioactive molecules such as proteins, lipids, and miRNAs that can modulate the functions of immune cells; and c) they can act on cell-to-cell contact and therefore direct interactions between MSCs and immune cells through surface molecules including PD-L1 and ICAM-1, which are important for immunomodulatory effects (20).

ICAM-1 plays a significant role in the pathophysiology of sepsis. It is an adhesion molecule expressed on endothelial cells and immune cells which facilitates leukocyte adhesion and transmigration during inflammation. In sepsis, pro-inflammatory cytokines such as TNF and IL-1β increase ICAM-1 expression on endothelial cells, leading to excessive leukocyte recruitment and vascular inflammation. Increased ICAM-1 expression contributes to endothelial permeability, tissue edema, and organ dysfunction, all hallmarks of sepsis. Dysregulation of ICAM-1 has been linked to worsened outcomes in sepsis, including progression to septic shock and multiorgan failure.

MSCs can potentially be used in all infectious and inflammatory diseases, including autoimmune, bacterial, viral and fungal diseases that can affect various organs (21). In particular, in regard to infectious diseases, MSCs could be used when conventional treatments are insufficient or no longer effective. Another potential way of using MSCs is in tissue repair, promoting a regenerative environment through the modulation of immune cells and repairing tissues damaged by infectious and inflammatory processes (22).

CONCLUSIONS

MSCs are cells that may be useful in the processes of sepsis due to their capability of modulating both inflammation and immune cell responses against infectious agents. MSCs may play a crucial role in promoting the anti-inflammatory response and enhancing pathogen clearance. These cells can be considered new and promising applications for the treatment of various infectious and inflammatory diseases, especially in those cases where conventional therapies are not satisfactory.

Conflict of interest

The author declares that they have no conflict of interest.

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