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Review

Role of the regulation of mesenchymal stem cells on macrophages in sepsis

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Abstract

Sepsis is a common clinical critical disease with high mortality. The excessive release of cytokines from macrophages is the main cause of out-of-control immune response in sepsis. Mesenchymal stem cells (MSCs) are thought to be useful in adjunctive therapy of sepsis and related diseases, due to their function in immune regulation, anti-inflammatory, antibacterial, and tissue regeneration. Also there have been several successful cases in clinical treatment. Some previous studies have shown that MSCs regulate the function of macrophages through secreting cytokines and extracellular vesicles, or transferring mitochondria directly to target cells, which affects the progress of sepsis. Here, we review the regulation of MSCs on macrophages in sepsis, mainly focus on the regulation ways. We hope that will help to understand the immunological mechanism and also provide some clues for the clinical application of MSCs in the biotherapy of sepsis.

Keywords

Macrophage, mesenchymal stem cell, sepsis, immune dysfunction, paracrine

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Introduction

Sepsis is a common severe disease in clinic, which is characterized as a life-threatening organ dysfunction caused by the host's maladjusted response to infection. About eight million people die of sepsis every year around the world, with a mortality rate of 25–50%, and the prevalence rate is still increasing year by year.[1] Also the high mortality rate of severe patients with COVID-19 is also mainly caused by septic shock.[2]

The impaired immune function and out-of-control immune response are the main pathological mechanism for sepsis, and the excessive release of "waterfall" cytokines from activated macrophage is the main cause of immune dysfunction, which also is the key point for the treatment of sepsis.[3] However simply inhibiting macrophages is not a good treatment for sepsis because the over inhibition of immune response will lead to secondary infection and the high mortality.[4,5] Therefore, cell therapy is considered to be an effective adjunctive treatment to inhibit the overactivation of immune cells and block the release of cytokines.[6]

Mesenchymal stem cell (MSC) is a kind of adult stem cells with self-renewal ability, multi differentiation

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potential, and immune regulation ability.[7] MSCs are thought hopeful in sepsis treatment for the abilities of immune regulation, anti-inflammatory, anti-bacterial, and tissue regeneration.[8] Among them, the regulation of MSCs on macrophages is thought to be one of the key points.[9]

Here, we searched the publications from the databases such as Web of Science, Elsevier Science Direct, SpringerLink, Wiley Online Library, MDPI, and Pubmed, mostly in past 10 years, in the field of regulation ways of MSCs on macrophages in the progress of sepsis. The keywords were mainly sepsis & MSC & macrophage. We hope to promote the study on septic immunological mechanism and provide some clues for the clinical application of MSCs for sepsis therapy.

Role of MSCs in the progress of sepsis

Because of these functions of immune regulation, anti-inflammatory, anti-bacterial, and tissue regeneration, MSCs are thought to be good candidate in treating sepsis and septic shock related diseases with immune and inflammatory dysfunction.[8] MSCs can regulate inflammatory response through paracrine cytokines and intercellular interaction, which can enhance bacterial clearance, reduce the level of pro-inflammatory factors, strengthen tissue repair ability, improve multiple organ dysfunction,[10,11] and reduce mortality in sepsis.[3,4] Clinical trials have shown that MSCs reduce the Sequential Organ Failure Assessment (SOFA) score and improve the survival rate of sepsis patients.[12]

Role of macrophages in sepsis

As the central cells in innate and adaptive immunity, macrophages play important roles in all stages of sepsis. In the early stage of bacterial infection, macrophages are activated by pattern recognition receptor (PRR), showing a pro-inflammatory state and releasing a large number of inflammatory factors and cytokines.[13] While in the late stage of sepsis, the bactericidal activity of macrophages is reduced, that causes immunosuppression and increases secondary infection of sepsis.[4]

The mitochondrial autophagy of macrophages also plays a role in the progress of sepsis. Inhibiting autophagy of macrophages increases the release of reactive oxygen species (ROS) and affects the polarization and inflammatory bodies activation, and then influencing the prognosis of sepsis.[14,15] In addition, some studies have shown that in the sepsis mouse models induced by cecal ligation and puncture (CLP), bacteria exposed to the peritoneal cavity increases the expression of Cx43 and extracellular ATP release in macrophages. Through binding with purinergic receptors in macrophages themselves, ATP induces the release of pro-inflammatory factors, resulting in further deterioration of sepsis.[5,16,17] In addition, the activation of purinergic receptors can also damage the activation of NLRP3 inflammatory bodies, which is positively correlated with the high mortality of sepsis patients.[18] Inhibiting the secretion of pro-inflammatory factors decreases the myocardial dysfunction and mortality in sepsis.[19]

MSCs regulate macrophages in sepsis

MSC transplantation regulate macrophages in the progress of sepsis mainly in several ways: secreting paracrine cytokines or extracellular vesicles or directly forming nanotubes/gap junctions between cells to transfer messages.[9,20–23] Below, we review how these ways play roles and summarize them in Figure 1.

MSCs regulate macrophages through paracrine factors to affect sepsis

Macrophages are the main target cells of MSCs in treating sepsis.[24] MSCs secrete cytokines to regulate the production of inflammatory factors and polarization of macrophages, affect phagocytosis and other related functions, inhibit macrophage infiltration in tissues, and reduce pathological damage of organs, all of those effectively improve the survival rate of sepsis.

In sepsis, macrophages are mainly composed by pro-inflammatory M1 type, and the number of macrophages is related to the prognosis of sepsis.[25] MSCs secrete cytokines to induce the transformation of macrophage polarization from M1 to anti-inflammatory M2 type, which regulates the out-of-control inflammatory response in sepsis.[13,26,27] Also, MSCs enhance the phagocytosis and bacterial killing ability of macrophages through heme oxygenase-1 and improve the survival rate of septic animals.[28]

MSCs also produce prostaglandin E2 (PGE2) that binds with the receptors EP2 and EP4 on the surface of macrophages, which induces polarization to M2 type and increases the secretion of anti-inflammatory cytokine IL-10,[24] in turn activates STAT6 and mTOR signaling,[29] induces the production of PI3K and ROS,[30] affects the activation of inflammatory body NLRP3,[31] decreases the inflammation and improves acute liver failure, and finally relieves symptoms of sepsis.

Qiu et al. have found that MSCs secrete TGF-β1 to induce LPS stimulated-macrophage polarization to M2 type through Akt/FoxO1 signaling pathway, which enhances phagocytosis, inhibits excessive inflammatory response in sepsis.[32]

MSCs also secrete CCL2 and CXCL12 as heterodimers, which bind with receptor CCR2 on the surface of macrophages, upregulate the expression of IL-10 and induce polarization to M2 type, and reduce intestinal injury.[33]

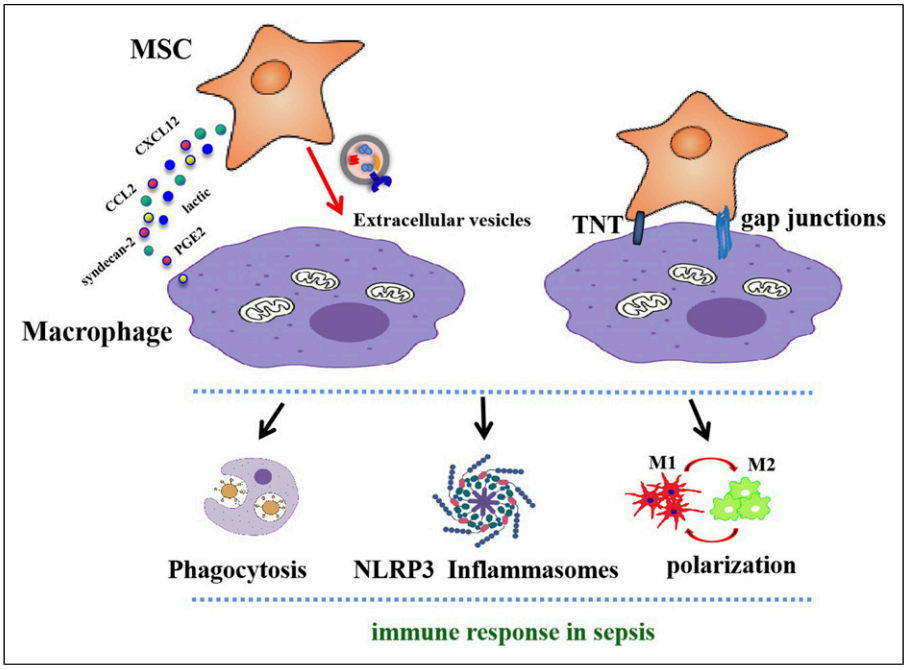

Figure 1. The regulation ways of MSCs on macrophages in sepsis.

MSCs also affect the inflammatory phenotype of sepsis by secreting lactic acid[26] to induce M2 polarization and secreting syndecan-2 to regulate the bacterial clearance ability of macrophages[34]

In conclusion, MSCs can secrete cytokines to regulate macrophages and play roles in the progress of sepsis.

MSCs regulate macrophages through extracellular vesicles to affect sepsis

Extracellular vesicles (EVs) include exosomes, micro vesicles (MVs), micro particles (MPs), and apoptotic bodies. MSCs can secrete EVs to regulate macrophages and affect the progress of sepsis.[20]

Exosomes are vesicles formed by fusion of multivesicular bodies (MVBs) and plasma membrane, which can mediate signal transfer and affect the function of target cells. Many studies have investigated the role of exosomes from MSCs in regulating macrophages in sepsis, especially miRNA among exosomes. For example, mir-146a[35] and mir-21[36] in exosomes increase the efficacy of MSCs pretreated by IL-1β in septic mice. MiR-17 in exosomes mediates the activation of NLRP3 inflammasomes in macrophages and reduces LPS induced acute lung injury.[37] The exosomes enriched with exogenous mir-223 reduce the inflammatory response in septic mice and protect from heart injury.[38] Exosomes from MSCs can also regulate macrophage polarization by inhibiting glycolysis[39] or affect the production of IL-27 to improve LPS induced lung injury.[40] Vesicles similar to exosomes from MSCs decrease the expression of TNF-α and IL-6 in macrophages and alleviate inflammatory response in sepsis mouse models.[41]

The mitochondria transfer mediated by EVs from MSCs to macrophages increases oxidative phosphorylation and ATP production, promotes polarization to M2 type, increases bacteria clearance, and reduces lung injury in LPS induced septic mice.[20,42] The transplantation of exosomes from apoptotic and healthy MSCs both significantly improve the survival rate of septic rats and reduce pulmonary inflammation.[43]

In conclusion, both of cytokines and extracellular vesicles secreted from MSCs play roles in the progress of sepsis by regulating macrophages. Also some studies have shown that conditioned medium (CM) from MSCs also induces macrophage M2 polarization[27] and improves lung injury and inflammation in mice treated by LPS.[44] MSC-CM demonstrates a potent anti-inflammatory effect on LPS-activated macrophages, and the IL4 stimulation improves this effect.[45] These results further identify the role of MSC paracrineon macrophages in sepsis, including factors and extracellular vesicles in conditioned medium.

MSCs regulate macrophages through direct intercellular transfer to affect sepsis

MSCs can transfer mitochondria and other substances by forming tunneling nanotubes (TNT)[22] or gap junctions[46,47]

with target cells. In sepsis, several studies have investigated on the transfer from MSCs to macrophages.

MSCs transfer mitochondria through nanotubes to macrophages, which can enhance oxidative phosphorylation and bioenergy, and increase phagocytosis under inflammation[48] and bacterial clearance ability,[22] while Cx43-formed-gap junctions are not involved in this progress.[22] Though M2 polarization of macrophages can be induced only through paracrine of MSCs in sepsis, which is further promoted with the presence of intercellular contact, suggesting that direct contact between cells is also necessary for the regulation of MSCs on macrophages.[49] However, some other studies have shown that direct intercellular contact between MSCs and macrophages is not necessary for the treatment of LPS induced sepsis.[50]

In addition to the aforementioned, some studies have shown that MSCs also regulate the progress of sepsis by affecting the production of ROS, bacterial killing ability,[28,30] or the activation of NLRP3 inflammatory bodies[51] in macrophages, without illustrating the regulation ways of MSCs on macrophages.

Precondition improves the curative effect of MSCs on sepsis via regulating macrophages

The regulation effect of MSC is related to the inflammatory state of the body. The inflammatory level is high, the better.[52] Therefore, pretreating MSCs with inflammatory factors before injection can improve the curative effect. TGF-β1 overexpression in MSCs inhibits macrophage infiltration in tissues, reduces the level of pro-inflammatory cytokines and organ damage in septic mice.[53] Pretreating MSCs with IL-1β significantly inhibits M1 phenotype of macrophages, while promotes M2 phenotype, which enhances immunosuppression, accordingly alleviates liver and lung injury and increases the survival rate of sepsis model mice,[35] maybe via the abundantly upregulation of miR-21 and package in exosomes from MSCs upon IL-1β stimulation.[36] Iron oxide–based synthetic nanoparticles (SPION) pretreated MSCs promote macrophages to polarize towards the M2 phenotype under sepsis-induced liver injury in mice.[54] Similarly, IL-4 stimulated MSCs improve the anti-inflammatory effect on LPS-activated macrophages.[55] From all of these results, MSCs precondition may be a promising therapeutic approach to improve outcome in septic patients.

At present, infection control and supportive therapy are still the main therapeutic methods on sepsis. However, adjunctive therapy is considered a promising direction to improve the survival rate. Some phase I/II clinical and preclinical trials[56] have been processed via MSCs intravenous injection.[57–61] These trials proved that MSCs were safe[62] in treating sepsis without obvious side effects. But the sample size was still not large enough to identify the effectiveness.

The limitations of clinical application include the variance of activity and quality of MSCs cultured in vitro. Also, the functional heterogeneity of MSCs may play its part. In addition, the mode and timing of MSC transplantation should be considered. The answers of these questions will help to develop more effective MSCs for clinical treatment of sepsis.

The limitation of the review is only focus on the regulation ways of MSCs on macrophages in sepsis. Maybe the cellular mechanism behind the ways is more significant for the clinical application of MSCs in sepsis. Also, in sepsis the damages of tissues and organs affect the cellular microenvironment, for example, in intestinal tract.[63] Then how the microenvironment affects the function of MSCs, which is not well investigated. Now only some in vitro data show that septic serum or LPS precondition affect the function of MSCs.[64–66] These questions need more investigation to summarize and illustrate in future.

Conclusion

Here, we review the regulation ways of MSCs on macrophages in the progress of sepsis mainly through secreting cytokines and extracellular vesicles or transferring mitochondria directly between cells by forming nanotubes/gap junctions.

Author contributions

Jie Xing, Rui Wang, Fengqi Cui, and Linlin Song were mainly involved in reference collection, Quanlin Ma and Huiyun Xu wrote and made final checks on the manuscript.

Declaration of conflicting interests

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