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EDITORIAL

Mesenchymal stem/stromal cells (MSCs): origin, immune regulation, and clinical applications

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Dr. Yufang Shi

Dr. Jun Zhou

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The associations between inflammation and tissue regeneration are highly conserved during the evolution of multicellular organisms [1]. Appropriate activation of immune cells is vital for the repair of damaged tissues and the maintenance of tissue homeostasis [2]. Mesenchymal stem/stromal cells (MSCs) are of the most responsive cell populations to inflammation in tissues. MSCs are a kind of tissue stem cells that were initially identified in the bone marrow stroma in the late 1960s by Friedenstein [3] and further characterized and renamed by Arnold Caplan [4]. MSCs possess stemness, as defined by their ability to differentiate into osteoblasts, adipocytes, and chondrocytes [5]. These cells are present in almost all tissues and are highly mobile in response to tissue damage signals [6]. In this special issue, experts took different perspectives and analyzed MSCs based on immune regulation, pathogenesis, infection, mechanisms of action, and clinical applications. It is anticipated that this special issue will provide valuable information to improve understanding of the critical pathophysiological roles and appropriate clinical applications of this unique cell population.

Although most tissues possess MSCs, it is still unclear whether these cells are developmentally determined tissue-resident cells or are continuously replenished by the bone marrow. As the name "mesenchymal stem/stromal cell" indicates, MSCs are often believed to be derived from mesoderm. However, ectoderm-derived dental stem cells (DSCs) are also called MSCs. In this issue, Li et al. [7] compared the immunoregulatory properties and the underlying mechanisms of mesodermal MSCs and dental MSCs. Both cell types can be isolated and robustly expanded in vitro for therapeutic applications, and these cells have remarkable immunomodulatory properties. MSCs and DSCs have been shown to exert therapeutic effects on several inflammatory diseases. Li et al. [7] also discussed the molecular mechanisms, extrinsic inflammatory cues, and intrinsic metabolic pathways that govern the immunoregulatory functions of these two cell types. Overall, the basic properties of MSCs and DSCs are largely similar, although the degree of their responsiveness to inflammation may differ.

It is widely acknowledged that MSCs are highly immunomodulatory. Giacomini et al. [8] analyzed the literature and pointed out that the mechanism of MSCs is that their secretome, which is largely responsible for their immunomodulatory activity, is inflammation dependent. This finding suggests that inflammation plays a crucial role in mediating the functions of MSCs and that tissue stroma sense damage and initiate tissue repair by reprogramming the inflammatory environment. Based on their own discoveries, Giacomini et al. [8] also proposed another mechanism by which MSCs can undergo rapid apoptosis after injection, and these apoptotic cells are phagocytosed by monocytes/macrophages, which then become anti-inflammatory cells. This finding suggests that the activation state of T or NK cytotoxic cells may be exploited as a biomarker to predict clinical responses to MSC treatment. Interestingly, these different mechanisms of action may coexist and be instructed by two different types of MSC "licensing": one that is contact-dependent

and one that is mediated by inflammatory cytokines. The complex and varied mechanisms by which MSCs can orchestrate inflammatory responses highlight their potential for tissue repair and homeostasis. Overall, while the therapeutic potential of MSCs remains promising, further research is needed to better understand their mechanisms of action and how they can be used effectively in clinical practice.

MSCs are essential for tissue regeneration and reparation. Paradoxically, these cells can also promote pathogenic processes. Yang et al. [9] discussed the pivotal roles of endogenous MSCs in the development of liver fibrosis/cirrhosis. Surprisingly, exogenous MSCs have also been shown to treat liver fibrosis. The complex pathogenesis of liver fibrosis/cirrhosis involves various cell types and inflammatory pathways, which permit MSCs to differentiate into myofibroblasts, which are the main producers of extracellular matrix (ECM) components in fibrotic livers. Additionally, MSCs can secrete various cytokines, chemokines, and growth factors that promote inflammation, angiogenesis, and fibrogenesis. Therefore, targeting MSCs has been proposed as a therapeutic strategy for hepatic fibrosis/cirrhosis. Several clinical trials have used expanded exogenous MSCs to treat liver cirrhosis. Efficacy has been observed in some completed clinical trials; however, controversies remain. On the one hand, preclinical studies have shown that the administration of MSCs can reduce liver fibrosis by inhibiting the activation of hepatic stellate cells (HSCs) by promoting HSC apoptosis and enhancing hepatocyte regeneration. On the other hand, some studies have suggested that MSCs can promote liver fibrosis by differentiating into myofibroblasts and contributing to ECM deposition. Moreover, the optimal dose, route, and timing of MSC administration for liver fibrosis/cirrhosis have not been established, and the long-term safety of MSC therapy remains uncertain. Nonetheless, MSCs play both beneficial and harmful roles in the pathogenesis and treatment of hepatic fibrosis/cirrhosis.

In addition to liver and lung fibrosis, MSCs are also involved in infections, especially those that promote the formation of cysts or nodules. One of the best examples is the pathogenic process of tuberculosis. Kumari et al. [10] discussed the potential role of MSCs in modulating and shaping immune responses through the expression of unique signaling molecules and the secretion of various soluble factors during *Mycobacterium tuberculosis* infection. The authors used the term "Janus" to describe the dual functions of MSCs in balancing host protective immune responses with the ability to harbor the pathogen. At the site of *M. tuberculosis* infection, tissue damage signals recruit MSCs, which are known to exert their immunomodulatory effects through the expression of immunomodulatory factors such as iNOS (rodents)/IDO (nonrodent mammalian species) and immunosuppressive cytokines. In this manner, *M. tuberculosis* uses MSCs as a niche to evade host protective immune surveillance mechanisms. Importantly, *M. tuberculosis* can also reside in MSCs and establish dormancy. Coupled with the expression of ABC efflux pumps on MSCs, this dormancy contributes to drug resistance and prolonged *M. tuberculosis* infection. These novel roles of MSCs in *M. tuberculosis* infection could be used for potential therapeutic applications of MSCs to treat infections.

The properties and identities MSCs have been established mainly based on exogenously expanded cells. These cells were first identified by Alexander Friedenstein [3] and almost 30 years later, MSCs were shown to regulate inflammatory responses. The Le Banc team was the first to apply MSCs to humans and successfully treated a boy suffering from steroid and cyclosporine double-resistant GvHD [11]. This exciting discovery ignited active investigation of the applications of MSCs for systemic inflammation and restricted tissue inflammation. In this special issue, the Le Blanc team [12] discussed the use of bone marrow-derived mesenchymal stromal cells (MSCs) to treat systemic inflammation associated with GvHD. The safety profile of MSCs has been

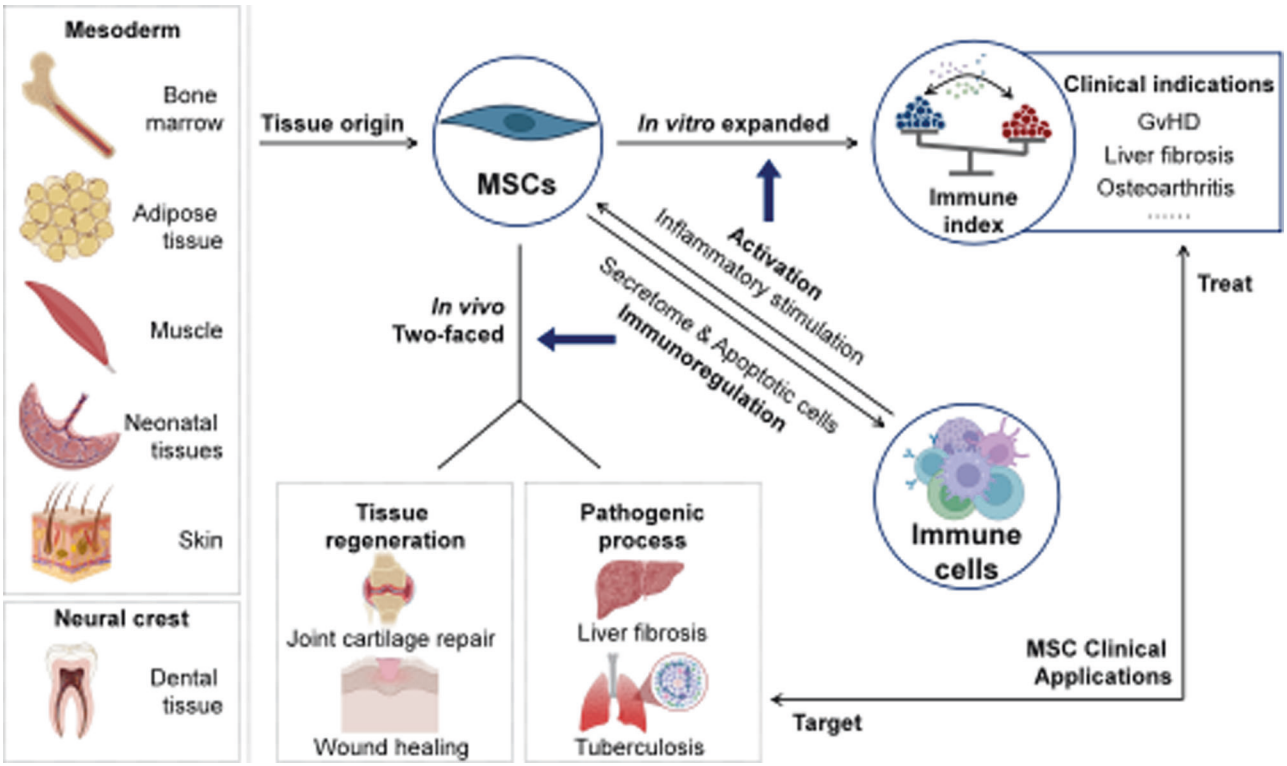

Fig. 1 The origin, immune regulation, and clinical applications of MSCs. MSCs exist in almost all tissues. These cells play critical roles in not only tissue regeneration but also the pathogenic process by interacting with various immune cells in different activation stages. MSCs can also be robustly expanded in vitro and applied to patients to control inflammatory diseases and promote tissue regeneration

established, but finding potency assays and biomarkers that predict the capacity of a specific MSC batch to alleviate GvHD has been challenging. This may be due to the variability in the underlying biology of patients recruited for clinical trials, as GvHD diagnosis and staging are based solely on clinical criteria. The review suggests that patient-specific biomarkers or immune characteristics may be necessary to determine MSC responsiveness. On the other hand, accumulating evidence suggests that MSC efficacy may be dependent on a permissive inflammatory environment. To address these challenges, the authors recommend a combined approach that correlates clinical recovery with the analysis of disease biomarkers and MSC potency assays. This approach may help identify patients with GvHD who are likely to benefit from MSC therapy.

Along with the modernization of lifestyle, our society is seeing more cases of autoimmune diseases, which often cause inflammation in restricted tissues rather than systemic inflammation, as seen in GvHD patients. One of the most active clinical trials involves the use of MSCs to treat knee osteoarthritis (OA). This disease is complex and involves multiple tissues with structural, inflammatory, and metabolic changes. Copp et al. [13], evaluated 15 randomized controlled clinical trials (RCTs) and 11 nonrandomized RCTs using culture-expanded MSCs in knee OA and found a net positive effect on mitigating pain, improving function, and protecting or repairing cartilage in most studies. The authors also highlighted the importance of several parameters, such as MSC dose, tissue of origin, autologous vs. allogeneic, patient clinical phenotype, endotype, age, sex, and level of OA severity, in determining the clinical effectiveness of MSCs. However, the sample size of 610 patients limits definitive conclusions. Further investigations are required to understand the immunomodulatory, chondroprotective, and other clinical mechanisms of MSCs in OA, and the relevance of MSC basal "fitness" to treatment efficacy. The need to match a subset of OA patients defined by molecular endotyping and clinical phenotyping with basally "fit" or engineered-to-be-fit-for-OA MSCs in well-designed, data-intensive clinical trials is important to advance the field.

The investigations on MSCs in the last two decades have provided critical information to understand of the pathophysiological role of these cells and attracted the attention of experts in different fields. The available data strongly suggest that endogenous MSCs play fundamental roles in processes such as hematopoiesis, tissue and organ homeostasis, aging, fibrosis, and infection (Fig. 1). However, most of the information has been derived from exogenously expanded MSCs. These cells are promising therapeutic tools for various clinical conditions due to their immunomodulatory properties and ability to promote tissue regeneration and homeostasis. The application of in vitro expanded exogenous MSCs in tissue regeneration not only relies on their limited differentiation ("cell replacement") but also on their ability to immunologically modulate the immune microenvironment and release growth factors to activate endogenous cells to repair tissues ("cell empowerment") [14]. A better understanding of the mechanisms governing the crosstalk between MSCs and immune cells should provide insights into how to apply these cells in clinical settings.

Jun Zhou[1] and Yufang Shi[1]✉
[1]*The Third Affiliated Hospital of Soochow University, State Key Laboratory of Radiation Medicine and Protection, Institutes for Translational Medicine, Suzhou Medical College of Soochow University, Suzhou 215123 Jiangsu, China.* ✉*email: yfshi@suda.edu.cn*

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AUTHOR CONTRIBUTIONS

ZJ outlined the structure, performed literature review and wrote part of the manuscript. YF designed the whole project and finalized the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Yufang Shi.

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