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Editorial

Mesenchymal Stem Cells vs. Mesenchymal Stem Cell Secretome for Rheumatoid Arthritis Treatment

Kim HS*

Department of Biomedical Sciences and Institute for Bio Medical Convergence, Catholic Kwandong University College of Medicine, Republic of Korea

***Corresponding author**

Kim HS, Department of Biomedical Sciences, Catholic Kwandong University, 24 Beomil-ro 579beon-gil, Gangneung-si, Gangwon-do 210-701, Republic of Korea, Tel: +82-33-649-7237; E-mail: hankim63@gmail.com

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EDITORIAL

Rheumatoid arthritis is a systemic autoimmune disease that affects joint tissues in the wrists, hands, and feet. The severe chronic inflammation and immune responses cause not only destruction of tissue integrity in joint tissues leading to bone erosion and joint deformation, but also lead to other serious complications such as osteoporosis, heart failure, pulmonary disorders and lymphomas [1]. Although several medical options including steroids, cyclosporin and recent biologics (targeting the key elements of inflammation, TNF-TNR-receptor axis) to suppress immune system/inflammation and prevent disease progression are available, they only improve symptoms temporally and possess long-term adverse effects associated with non-specific immune suppression. Currently, there is no known therapeutic that can repair and regenerate damage tissue for this chronic disorder.

One of the most promising treatments for the disease is stem cell therapy that uses stem cells to repair and/or regenerate the damaged or diseased joint tissues. Stem cells are undifferentiated cells with the ability to self-renew and differentiate into a number of tissue cells under physiological or experimental conditions. While stem cells can be derived from a number of different tissue sources and developmental stages, one of the most common and best studied cells for the rheumatoid arthritis treatment are mesenchymal stem or stromalcells (MSCs). MSCs are ubiquitous residents in postnatal tissues and organs, possess capacity to differentiate to other mesodermal lineage cells (such as chondrogenicosteogenic, adipogenic and myogenic) [2]. Under appropriate conditions, these cells are known to display characteristics of cells of ectodermal (epithelial or neuronal) or endodermal origins.The main function of tissue resident MSCs is to maintain structural homeostatsis and this can be achieved by modulating local inflammation and immune cell activity upon injury or infection. They exert immunomodulatory effects on cells of both innate and adaptive immune systems, including inhibition of macrophage function, dendritic cell maturation and activation, cytotoxic capacity of NK cells, effector T lymphocyte function (helper T cells and cytotoxic T cells) and B lymphocyte function with activation of regulatory T cells [3]. How does single cell do all these actions? A number of different mechanisms have been suggested including direct cell-cell interaction and paracrine factors (such as soluble cytokines, chemokines, chemical messengers, and enzymes and extracellular vesicles) [4]. Because of these features, they are one of the best therapeutic modality of immune-mediated disorders, such as graft-vs-host diseases, autoimmune diseases, neurodegenerative disorders and others. Yet, only a small fraction of MSCs is retained and engrafted in the target tissuesimplying that paracrine action could be the key mechanism of tissue repair.

Several studies have demonstrated the therapeutic efficacy of MSCs in animal model of rheumatoid arthritis (collagen-induced arthritis) by suppressing inflammation, immune cell function against joint tissues and reversing tissue deformation without affecting systemic immune suppression [5,6]. Others reported that MSCs displayed no benefits or even harmful effects [7-9]. These conflicting results can be explained on the basis of different experimental models and/or conditions applied. Alternatively, MSCs may have a narrow therapeutic window; only effective at an early phase of disease, but not in advanced stages. Indeed, a recent study showed that the chronic inflammatory environment associated with autoimmune diseases transforms administered MSCs from immunosuppressive to immunostimulatory one [10]. Furthermore, MSCs and fibroblast-like synoviocytes, one of the key cell contributing to the damage of cartilage and bone in rheumatoid arthritis, may represent different functional stages of same lineage implying that administered MSCs may have potential to worsen the disease under overwhelming inflammatory environment. Although clinical application of MSCs in a number of autoimmune diseases including rheumatoid arthritis, osteoarthritis and systemic lupus erythematosusrevealed the beneficial effects [11], more clinical trials are needed to resolve the issue of controversial outcomes of MSCs in preclinical and clinical studies with these chronic autoimmune diseases.

Accumulating evidence indicates that the most, if not all, of the beneficial effects of MSCs in tissue repair and regeneration are mediated by secretome (i.e., sum of secreted molecules and

elements by biological cells and tissues).Unlike cell therapy, the components and function of MSC secretome are not modulated by local and systemic environment. Thus, secretome from MSCs can be an alternative therapeutic option for autoimmune diseases, including rheumatoid arthritis, where cell therapy is likely to be ineffective at advanced stages. Repeated administration of secretome may also extend the action of therapeutic components with inherent short half-life. Furthermore, ease of standardized production, storage and transportation/delivery with little concerns of cell-mediated toxicity, tumorigenicity and immunogenicity (donor matching with HLA-typing) makesecretome of MSC an ideal 'off-the-shelf' drug for the autoimmune diseases.While the recognition of secretome as a therapeutic value prompted intensive studies in a various animal disease models, only a few clinical studies were reported, i.e., treatment of female hair loss [12], skin wound healing [13] and alveolar bone regeneration with MSC conditioned medium [14], indicating that further studies are essential to translate the findings of *in vitro* and animal experiments to bedside.

There are issues to be resolved prior to the clinical translation of secretome. First, the identification of active ingredients with underlying mechanisms of action is essential. Second, cell type and culture condition for a given disease must be standardized for mass production. Third, drug formulation, optimal dosage, route of delivery and frequency should be determined. Fourth, long-term safety of secretome in clinical settings remains unsolved. Lastly, the use of stem cells in combination with secretome is highly anticipated for the successful regeneration of lost tissues. While current guidelines for the manufacturing process and quality control of stem cell-based therapeutics can provide guidance for the GMP grade secretome manufacture, solid experimental evidence as well as regulatory/safety issues will be the key challenges for future clinical translation.

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