Treatment of Rheumatoid Arthritis (RA) Using Mesenchymal Stem Cells (MSC)

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Abstract. Rheumatoid arthritis (RA), as an persistent autoimmune condition, it is known for causing persistent synovitis, gradual deterioration of cartilage and bone, ultimately resulting in disability and widespread inflammation. Until now, the onset and development mechanisms of RA remain elusive, although the new technology and drugs can certainly help patients to certain degree. However, about 30% RA patients is not responsible for targeting treatment or serious side effects, such as bone marrow inhibition, organs dysfunction, and inflection due to immune inhibition. Research data showed that therapeutic mesenchymal stem cells (MSCs), is a novel therapeutic strategy with safety and effective to inhibit inflammation and promote regeneration of bone and cartilage, especially for refractory RA. Here, the author summarized the development MSC-based treatment for RA models and patients, analysis the optimistic outlook and possible difficulties for clinical applications in future.

Keywords: Rheumatoid arthritis (RA), Mesenchymal stem cells (MSCs), MSC-derived exosomes, Therapeutic strategy.

1. Introduction

Rheumatoid arthritis (RA), as a chronic disease with autoimmune abnormality, which typical features are joints synovitis, erosion and destruction in local cartilage and bone, leading to joints swollen, painful and disable. In the decades of preclinical or early phrase, this disease mainly influence synovial joints, then spread to systemic abnormality, such as osteoporosis, interstitial lung disease, and vasculitis. Meanwhile, RA, as high incidence autoimmune disorders, which has an estimated prevalence of 0.5–1.0% in worldwide, which incidence apparently increasing year by year because of changing in environment. As the pathogenisis of RA becomes better understood, more and more effective therapies have been developed, including corticosteroids, NSAIDs and DMARDs, also known as “targeted biologics” [1]. There are roughly 30% of RA patients experience ineffective treatment or serious side effects including inhibition of bone marrow, dysfunction of solid organs or blood system, as well as immune inhibited-infection [2]. Because the current treatments still have many potential issues and challenges, it is really important to alternative new methods improvement the effectivity and tolerability for long-term treatment or lower rate in side effects of specific drugs. Under a large amount of reference and researches, new type of therapy can be guaranteed, especially the mesenchymal stem cells (MSCs). These novel therapeutic methods aim to resolve difficulties in current treatment strategies and focus on to induce tissue regeneration and modulate immune functions, eventually commit to high-quality and long-term remission for RA patients. In this review, the author summarizes the current status of MSC-based treatment in clinical research, analysis the optimistic outlook and possible difficulties for clinical applications for RA treatment in future.

2. Classification of Therapeutic MSC

The main marker of MSCs include CD105+, CD90+ or CD73+, sometimes added CD45+, CD34+ or HLA-DR+. Recently, increased data in preclinical studies as a result of its multipotent properties have indicated optimistic outcomes for some regenerative diseases, such as refractory RA. The therapeutic MSC often used ESCs and induced iPSCs [3].

In contrast to ESCs and iPSCs, treatment using MSCs are more easier, without obvious ethical issues for personalized therapy, although not be superior in aspects of accessibility, expandability and

pluripotency [3]. What's more, MSCs can differentiate into multiple cell types and be benefit for RA bone regeneration and immune regulation, such as osteocytes and chondrocytes. Meanwhile, other optimistic characteristics for treatment RA patients using therapeutic MSC include paracrine therapeutic EVs and other inhibitory inflammation molecular, or modulation the interaction between immune cells through cell-cell contact. Firstly, immunosuppressive factors of IL-10 and TGF-β from MSCs to inhibit activation of dendrtic cells and Th cells. Meanwhile, these cytokines and surface molecular are both capable of upregulation of Treg cells function and inducing production of tolerogenic dendritic cells (tDCs) from monocyte, further suppression of inflammation. In addition, the production of immunosuppressive molecular, like IL-10, TGF-β, and PGE2 from therapeutic MSCs can also reduce the pathogenesis of B cells in RA, such as inhibition of autoimmune B cell production and proliferation, downregulation of autoantibodies secretion and chemokine receptor expression [4]. The therapeutic MSCs are directly divided into two types according to its phenotype, which characteristic and treatment effects associated with modulation of immune cells functions following as Table 1.

Table 1. The phenotype of MSCs and their therapeutic effects for RA

MSCs phenotype	Characteristics	Expressed molecules	Effects for RA subtypes
Proinflammatory MSC1	Activation by TLRs Migration to inflammatory sites Lower expression of immunosuppressive factors Promotion M1 polarization from macrophage	TLRs (TLR2 and TLR4), MIPs, MIP-1α/β, and low levels of IDO and NO	Mainly treated in the early phase of RA Suitable for low inflammatory microenvirnment Induce differention of osteogenesis Decrease differentiation chondrogenesis Enhance physiological healing
Antiinflammatory MSC2	Upregulation of immunosuppressive factors expression Influence of immune homeostasis Inhibition of T cell proliferation Enhancement of Treg production	TGF-β, IL-10, PGE2, IDO, HLA-G5, IFN-γ, HGF, heme oxygenase, and galectins	Suitable for pre-inflammatory microenvironment Decreasing synovitis Immune inhibition

3. Different tissue sources of MSC for treating RA

Actually, the bone marrow, umbilical cord, synovial membrane and adipose tissue are mainly tissue sourses of therapeutic MSCs. The MSCs derived from different tissue sources have certain advantages and limitations using for RA treatment, which depend on their differentiation potentials (Table 2) [5].

Table 2. The therapeutic-MSCs from different tissues for RA treatment

Tissue sourse	Advantages	Limitations
BM-MSCs (bone marrow)	Higher differentiation capacities Lower immunogenicity Effective repairment of bone and cartilage	Depends on donor's health situation and age Limited yield and infected risk Therapeutic mechanisms underexplored
UC-MSCs (umbilical cord)	Superior differentiation and self-renewal potentials Easily and painlessly harvested Greater proliferation rate Regulate Th17/Treg balance No ethical issue	Easily phenotypical changes Lower proliferated capacities Lower adherence efficiency
UCB-MSCs (umbilical cord blood)	Distinct differentiation capacities Low risk of transmitting infections Lower immunogenities Higher immunomodulation	Heterogeneity Limited yield
SM-MSCs (synovial membrane)	Higher proliferation rates Higher expansion Multilineage differentiation potentials Low immunogenicity Higher chondrogenic potential Effective cartilage repairment and ostegenesis	Relatively low-density expansion
AD-MSCs (adipose tissue)	Abundant yields Strong immunosuppressive effects Effective cartilage and bone regeneration	Expression of HLA-ABC and HLA-DR Requires donor-matching for allogenic application

4. Experimental data from MSC-based treatment for RA

The clinical and preclinical trials using MSCs increased obviously due to bio-techniques development quickly in recent years. Here, we just described two groups research data exosomes of MSC from bone marrow and human umbilical cord, and then using one data of MSC sources from umbilical cord to compare the therapeutic effects and side reactions,

The releasing MSCs-derived exosomes are capable of rebuild an novel milieu suppression of inflammation, enhancement of tissue healing and modulation of immune balance. One study from Li X et al showed that the exosomes of MSC from human umbilical cord are capability to inhibit apoptosis of primary aritcular chondrocytes in vitro through suppression of ROS production, indicating its regeneration potentials for RA patients with serious bone erosion in clinical application. The mechanisms analysis showed that the therapeutic effects of hucMSCs-derived exosomal mainly associated with miR-100-5p, which downregulated the expression of NOX4 through bioinformatic analysis. Transfection experiments using shRNA and overexpression further showed that exosomes derived miR-100-5p from human umbilical cord MSC play a key roles in targeting NOX4, suggesting miR-100-5p/NOS4 axis as a optimistic candidate therapeutic strategy for bone regeneration in RA patients [6].

Another group researches the effective and mechanisms of extracellular vesicles from bone marrow MSCs found numerous of apoptotic vesicles (apoVs) production to influence immune immune cell activation through inducing inflammatory Th17 cells apoptosis and regulation of of Th17/Treg cells balance, as well as suppression of IL-2 secretion and CD25 expression. Meanwhile,

the cytokines from effector T subsets, such as IFN-γ, IL-10 and IL17A, were also decreased in a dose-dependent manner while Treg cells were maintained. The mice of apoV deficiency rescued proliferation of pathological lymphocytes. Importantly, administration of apoVs reduced synovitis and cartilage destruction in arthritic mice model through preventing Th17 differentiation and memory formation, suggesting its potential effects for RA treatment [7].

Compared to using exosomes, Álvaro-Gracia JM et al chose 53 refractory activated RA patients treatment with adipose-derived stem cells (Cx611), evaluated the therapeutic effects and its safety. It is a phase Ib/IIa clinical trial using multicentre, randomised, double-blind experiment to evaluate its efficacy and single-blind placebo-controlled to record its safety. The adverse events include lacunar infarction, diarrhoea, tendon rupture, which were very common for adverse drug reactions. The responses of American College of Rheumatology 20 in all group were 29-45% at one month and decreased to 0-25% at three months, respectively. The clinical efficacy of intravenous injection of Cx611 is encouraging and the general tolerance was good without in general well tolerated, without more serious toxicity as increment of dose and time through dose- and time-dependent studies [8].

5. Mechanisms of MSCs treatment for RA

The potential mechanisms of MSC-based therapy include secretion of soluble molecular and interaction between cells through cell–cell contact, while the main type is pro-inlammatory MSC1 and opposite of MSC2 (Figure 1).

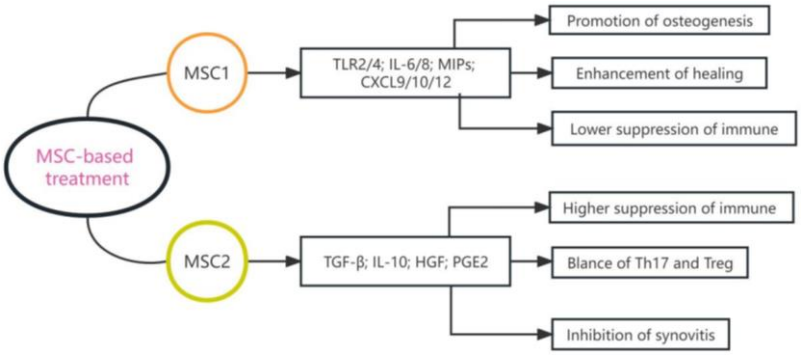

Figure 1. Mechanisms of therapeutic MSCs for RA

Exosomes from MSCs, as a communication substances between cells, affect cellular functions through an numbers of bioactive chemicals. In addition, new therapeutic mechanisms continue to be discovered, such as inducing apoptosis of certain cells. As a creation and novel therapeutic method, it's necessary to further understand the fundamental mechanisms of inflammation ablation, tissue regeneration and immune homeostasis through influencing target gene expression by transferring lncRNA or miRNAs [9], and compare the side affection with MSCs to supply a guideline for refractory RA in the future.

6. Challenges of MSCs Treatment for RA

MSC-based treatment represent a optimistic and promising option for RA patients. Meanwhile, to optimize effects and reduced the risks, several difficulties need to be resolved including the tissue resources, basic condition of donors including age, gender, and history of diseases and medicine, and administration routes, et al. Actually, the risks of MSC treatment decreased by low immunogenicity. However, a standard procedure for isolating, culturing and maintaining of MSC cells needs to be proceeded for gaining sufficient numbers in clinical application, as well as decrement of inflammatory phenotypes changing after culture in vitro. In comparison with other stem cell therapy, MSC therapy is much cost-effective because they can be isolated from some kinds of tissues. Some tissue sources of MSC are preferred for autoimmune and chronic inflammatory diseases treatment because of their immunomodulatory and anti-inflammatory capacities, such as RA. In addition, the

isolation procedure of cell-free MSC products is much easier and safer than MSC, such as MSC-derived exosomes (MSC-Exos) [10]. Recently, the mechanisms of MSCs declined the pathogenesis of RA have been gradually unraveled through the immunomodulatory and anti-inflammatory capacity. These factors have significant impacts on the effects of therapeutic MSC and needed to be taken measures to improvement. From numerous data, it is obviously that people are struggling with focusing on therapeutic MSC against RA all over the world, which is challenging and also show the fast development of biological science.

7. Conclusion

The large number of studies gained in the last decade has demonstrated that therapeutic MSC using for RA patients is optimistic and encouraging both on the effectiveness and risks. Besides the anti-inflammatory effects and immune regulations, the MSCs-based therapy have been shown to benefit for osteogenesis and cartilage repairment, which potentially improves joint tissue regeneration. However, it still has some challenges to limit its clinical application, such as variable yields, transmitting infection, heterogeneity, ethic issues, and underexplored mechanisms. Therefore, it's important to advance the techniques to improve the production progresses and explore its mechanisms with the development of related theoretical basis in future.

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