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Research Article

Immune Response to Rheumatoid Arthritis Inflammation and Mesenchymal Stem Cell Influence on Inflammatory Response

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Abstract

Rheumatoid arthritis (RA) is triggered by a series of immune responses to an acute inflammation. The failure of the initial immune response to control the inflammation leads to a chronic inflammatory condition. In which case the loop of positive feedback of immune cells is triggered. This abnormal immune response leads to its classification as an autoimmune disease. Mesenchymal stem cells (MSC) are a self-regenerative, multilineage stem cells that have an immunosuppressive nature. These qualities make them a great candidate for the treatment of autoimmune disorders, specifically RA. RA is a genetically inherited marker that cannot be changed. However, studying the immune response to this inflammatory condition along with the influence of MSC on immune cells can direct us towards a new regenerative drug that can reverse or antagonize the damage caused in advanced cases of RA.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory and degenerative disease triggered by defects in the body's immune system. This abnormal immune response leads to its classification as an autoimmune disease. According to a recent study the global prevalence of rheumatoid arthritis is 1,996,5115 cases. While North American and Eastern Mediterranean population contribute substantially to the global prevalence, several studies have shown that prevalence is higher in females than in males amongst different age groups (Safiri et al., 2019). Although there is no current cure for rheumatoid arthritis, treatments exist that aid with pain management, preventing diseases progression and further joint destruction. Some of the more common pharmacological treatments include nonsteroidal anti-inflammatory drugs (NSAIDs) that reduce inflammation by blocking prostaglandin production, but they do not stop joint deterioration. Glucocorticoids, like NSAIDs, reduce inflammation without effecting disease progression but through the reduction of pro-inflammatory cytokines. Disease-modifying antirheumatic drugs (DMARDs) prevent further disease progression and inflammation while contributing to joint repair but they have aggressive side effects. Tumor necrosis factor (TNF)-α inhibitors are used in the form of injections to manage the chronic inflammation that results from RA (Lv et al., 2021). Non-pharmacological approaches include leech therapy, exercise, massage therapy, and acupuncture. Additionally, surgical interventions such as arthroscopy (Pas et al., 2017) also exist to help patients with pain relief and to alleviate dysfunctions in their joints. In the recent years, mesenchymal stem cells (MSCs) have piqued interests as the potential treatment of RA. While other more traditional methods (medications) demonstrated severe side effects, especially with long term use, MSC's proved to be safe. Because mesenchymal stem cells are multipotent, meaning they can develop into multiple distinct types of cells, and have regenerative qualities; they are useful for treatment of autoinflammatory conditions.

There is sufficient literature that hypothesizes the causes of inflammation – defects in immunological pathways related to B-and T-cells as well as their checkpoints. Enough research has also been conducted on the cascade effect these inflammatory markers can have and how progression of rheumatoid arthritis can be prevented. It has been shown that taking proper medication in the initial stages of the disease slows the progression of rheumatoid arthritis (Koliaraki et al., 2020). Numerous studies have found that cell-to-cell contact is of the utmost importance. It should also be noted that mesenchymal stem cells can be found in bone marrow, adipose tissue, and in the umbilical cord. Depending on the location of origin of mesenchymal stem cells, they will have differing qualities that make them fit for specific use. For example, one study claims that mesenchymal stem cells derived from adipose tissue have higher immunomodulatory success, while those derived from the umbilical cord have shown to lower the risk of an allogenic immune response (Cattaneo et al., 2018).

This study will focus mostly on the immunomodulatory effects of mesenchymal stem cells derived from bone marrow, umbilical cord, and adipose tissues. The different types of arthritic diseases will be given a brief review, but the focus will remain on the inflammatory qualities of the condition by providing a detailed review on the immunological response to inflammation. Additional focus will be given to the specific immune cells (cytokines, chemokines, and growth factors) that contribute to the progression of inflammatory diseases, more specifically of rheumatoid arthritis. We will elaborate on the relationship of chronic inflammation and immunosenescent cells. The effects of mesenchymal stem cells on the innate and adaptive immune responses will be explored by going into detail about the reaction of each immune cell to mesenchymal stem cell therapy. This will allow us to conclude whether the benefits in pursuing mesenchymal stem cell therapy will outweigh the risks.

Contribution of Phagocytes and Lymphocytes to Inflammatory Response

In a healthy individual, neutrophils circulate within the blood until they are phagocytosed by macrophages within a period of 24-48 hours. Pro-inflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α) cause a defect in the maturation of neutrophils at the site of inflammation (Wang L, 2022). This dysregulation, along with pro-inflammatory cytokines, leads to delayed apoptosis of neutrophils (Fresneda Alarcon et al., 2021); (Wright et al., 2017). In healthy individuals, there is a homeostatic balance between osteoclasts and osteoblasts, ensuring that there is not too much bone formed or destroyed. In individuals with rheumatoid arthritis, however, the increased release of TNF-α leads to higher levels of osteoclasts, which then causes a cascade of inflammatory responses (Kucuksezer et al., 2021); (Hassani et al., 2020).

There are three types of macrophages, two of which are of significance to this study. The two relevant macrophages are M1 and M2. M1 macrophages are pro-inflammatory, whereas M2 are anti-inflammatory (Kemble et al., 2021). The pro-inflammatory M1 macrophages are recruited to the site of inflammation and either release more inflammatory cytokines or phagocytose the invading cells, and additionally activate M2 macrophages. M2 macrophages have regenerative qualities that aid in the repair of damaged tissues (Pajarinen et al., 2019). In the case of chronic inflammation, however, we are confronted with more inflammatory cytokines, chemokines, and growth factors that impair the proper immune response to the inflammation. Chronic inflammation and factors such as IL-1β, TNF-α, IL-12, and IL-18 (Chávez-Galán et al., 2015) stimulate the production of enzymes that are degenerative to cartilage, thus causing damage to the inflamed tissues.

The release of Natural Killer (NK) cells is initiated by certain receptors and cytokines such as the interleukins IL-12, 15, 18, and 23. Some of the functions of NK cells as a part of the innate immune system is their cytotoxic ability to remove infected cells while controlling the adaptive immune response to inflammation to prevent autoimmunity (Zitti et al., 2018). NK cells are pro-inflammatory in nature, which explains the increase in synovial NK levels in patients with RA. This gives rise to the production of more pro-inflammatory factors by the synovial NK cells. IL-15 is up-regulated in patients, which causes NKp46 to decrease. It should be noted that NKp46 plays an important role in the cytotoxic functions of NK cells (Lin, 2020) hence a decrease can result in the failure of NK cells to carry out their innate function, resulting in an uncontrolled inflammatory condition. The overexpression of IL-15 leads to a resistance against IL-15 and apoptosis of osteoclasts that is triggered by IL-15 stimulating the production of receptor activator of nuclear factor kappa-B ligand (RANKL); (Fessler et al., 2018). It is demonstrated that peripheral NK cell count in patients with RA also increases,

however, those NK cells prove to be defective or dysfunctional. IFN-γ, a cytotoxic cytokine released by NK cells, inhibits the production of Th-17 cells. This is the leading factor of arthritic diseases, as it causes a defect in NK cytotoxicity (Yang, 2021). Another study by Kucuksezer provides contradictory results, claiming that NK cell levels decreased in peripheral blood (2021). TNF-α secreted by NK cells promotes osteoclastogenesis, while also inducing the secretion of other pro-inflammatory cytokines. This then activates and recruits other innate and adaptive immune cells to the synovium. Both peripheral and synovial NK cells prove to be defective in patients with RA. This contributes to the progression and worsening of the disease, as well as their symptoms. Results, however, are inconclusive, and more research needs to be conducted.

Active Immune Cell Contribution to Inflammation

The innate immune response to inflammation triggers the activation and recruitment of T-lymphocytes to the inflammatory region. Dendritic cells are antigen-presenting cells (APCs) that produce various inflammatory cytokines (e.g. IL-1β, IL-6, IL-23, and IL-12) that are necessary for the differentiation and proliferation of T-lymphocytes (Moro-García, 2018). In a 2019 study by Luque-Campos et al. briefly mentions that although CD4+ naïve T-cells differentiate into Th1, Th2 Th17 and T Follicular helper (Tfh), cytotoxic T lymphocytes (CTL) are a result of CD8+ evolution. Pro-inflammatory cytokines enhance the differentiation of CD4+ type 1 T-helper cells and of Th17 cells. Th17 cells also contribute to the progression of inflammation by producing a critical cytokine (which at the same time is also produced by macrophages and mast cells), IL-17. IL-17 in turn promotes neutrophils, activates B-cells, and enhances osteoclastogenesis. Under healthy conditions, regulatory T-cells (T-regs) are what maintain the immune homeostasis between the release of IFN-γ and IL-10 (Wehr et al., 2018). Patients with RA show a downregulation in T-regs, causing an imbalance and higher levels of pro-inflammatory cytokines. T-cells contribute to chronic inflammation by resisting apoptosis, which continues the positive feedback loop of immune cell production.

Macrophages induce the release of APCs (dendritic cells and B-cells) that prompt the activation of T-cells alongside macrophages. In patients with RA, checkpoints that are crucial to the successful development of B-cells are dysregulated. This dysregulation leads to the development of defective T-regs, which function to control autoreactive lymphocyte production. This leads to an accumulation of autoreactive B-cells, triggering T-cells. T-cells differentiate into Th1, Th2, and Th17, thus triggering macrophages and B-cell activation, as well as increasing osteoclastogenesis. All of these factors act to further disease progression (Yap, 2018). B-lymphocytes secrete cytokines such as TNF-α, IFN-γ, IL-6, IL-1β, IL-17, and IL-10. This increase in TNF-α production in RA patients enhances the expression of Receptor Activator of Nuclear Factor KB ligand (RANKL). RANKL plays a major role in osteoclast differentiation, further contributing to the osteoclast-osteoblast balance in the synovium. Patients with RA have presented with a decrease in regulatory B-cells (B-regs). B-regs produce IL-35, which acts as an antagonist to the progression of RA (Wu et al. 2021). With the accumulation of pro inflammatory cytokines and the damage to the regulatory checkpoints of the immune response, we are confronted with autoimmunity.

Immunosenescent cells

Patients with RA show evidence of accelerated aging or premature immunosenescence. Immunosenescence is the change (a decline) that occurs in the immune system and response due to ageing. This dysregulation results in immune malfunction and an increase in the risk of developing autoimmune disorders which makes this an important topic to discuss for this study. An aging immune system is characterized by an increase in pro-inflammatory factors, giving rise to the term "inflammaging". Along with telomeric shortening, there are biomarkers that are the key determinants of whether the immunity of the subject being studied is aging: CD28, IL-6, IL-10 and CD4; all which are pro-inflammatory cytokines that typically increase in older adults (Pawlec, 2018). Immunosenescence is a result of the accumulation of senescent cells that don't proliferate or go through apoptosis and remain active by acquiring cytotoxic qualities. It is suspected that the loss of cytotoxicity in NK and T-cells in RA patients is compensated by CD28- developing NK cell receptors. CD28 cell plays a crucial role in the proliferation and activation of T-cells which are extremely significant in inflammatory response. While CD4+ T cell contributes to the worsening of RA, CD28- is measured to determine the severity of the disease. As mentioned previously, with inflammation, an increase in TNF-a triggers IL-17 and heightens RANKL expression. Senescent Tregs prove to have less of a suppressive quality which results in the rapid advancement of RA. According to Fessler et al., RANKL is directly related

to the activation of osteoclastogenesis and is expressed at higher levels by CD4+CD28- T cells and more efficiently than CD28+ (Fessler et al., 2018). In patients with RA, senescent cells are accumulated and premature immunosenescence is induced because of impaired defense mechanisms. In his paper, Bauer explores the psychological influence of chronic RA on the patient. As suspected, RA has a negative effect on cognitive health and emotional wellbeing. The expansion of peripheral senescent immune cells that are communicating with the brain through several pathways result in depressive behavior and tendencies. As confirmed by Pawlec, IL-6 expression showed impairment in cognitive function while Bauer confirmed the correlation between CD4+ expression and observing anxiety in patients with RA (Bauer, 2020).

Interaction of Mesenchymal Stem Cells with Immune Cells

Overaccumulation of immune cells in response to inflammation, improper development/maturation, and their failure to go through natural apoptosis are the main causes of rheumatoid arthritis and chronic inflammation. In vitro, when primed or conditioned with IFN-γ and TNF, MSCs have been shown to suppress the inflammatory cytokines produced by T-cells while upregulating T-regs and IL-10 (an anti-inflammatory cytokine). More specifically, according to Liu et al., the differentiation of CD4+ T-cells into Th17 (and IL-17) is disrupted by MSCs while regulatory and anti-inflammatory T-cells are enhanced (2020). In a study by Li et al., Li demonstrates that the inhibitory effects of MSCs are accomplished only at certain inflammatory stages (2017). In other words, the stronger the pro-inflammatory signals, the more powerful the inhibitory effects of MSCs will be. MSCs have also been demonstrated to induce T-cell apoptosis, which is resisted in RA patients (Li et al., 2017) (Malemud, 2018).

When B-regs and IL-10 are promoted, B-cell production is in return suppressed. The inhibitory response of B-cells to MSCs also depends on the strength of inflammation (specifically levels of IFN-γ) (Li, 2017). Earlier it was mentioned that IL-1 is a pro-inflammatory cytokine that further induces inflammatory responses. A study by Luz-Crawford et al. shines a light on the anti-inflammatory qualities of the IL-1 Receptor Antagonist (IL1RA) that is induced by MSCs. IL1RA has shown to contribute to the polarization of the anti-inflammatory M2 macrophages (2016). Treatment of macrophage cells with MSCs lead to generation of M2 macrophages. MSC-treated macrophages tended to polarize toward the M2 phenotype due to enhanced anti-inflammatory factors and discouraging pro-inflammatory effectors. MSCs also showed to have immunosuppressive effects on dendritic cells in vitro. MSC treated dendritic cells showed a decrease in IL-12 levels and lowered T-cell production (Song, 2020). There is, however, contradictory evidence about the influence of MSCs on NK cells. The stimulation or downregulation of NK cells is seen to depend on the conditioning of MSCs, such as the MSC:NK ratio, or the duration of incubation. For example, in high MSC:NK ratios, MSC can inhibit NK cells (Moloudizargari et al, 2021). Because of this flexibility and dependency on the condition of MSC, NK cells seem to be a good target for MSC RA therapy. It will be easier to manipulate immune outcomes and help to influence and realign the immunological cascade of reactions – thus breaking the positive feedback loop.

According to Lopez-Santalla et al., there have been more preclinical RA studies done using bone marrow mesenchymal stem cells (BM-MSCs), but umbilical cord MSCs (UC-MSCs) have been the source for clinical RA trials. While discussing the benefits of allogenic and xenogeneic MSCs, the opportunity provided by allogenic cells to institute cell banks for convenient use is brought to light. The time period, dosage and even the route of administration makes a difference in the level of success of the MSCs therapy. More research must be conducted to find the optimum protocol for MSC therapy. For example, while it is believed that long term use will result in better therapeutic outcome, there is no optimal route of administration when studying the systemic effect of MSCs. Although intravenous (IV) administration of MSCs is the preferred method of administration in clinical RA trials, there has not been conclusive evidence regarding its contribution to the success of biodistribution. The best results for MSC treatment were seen when infused during the early phases of RA. Several approaches have also proved to improve MSC efficacy: pre-treatment of MSCs, combination of MSC with alternative therapies, MSC-derived vesicles, scaffolding methods, and genetic modification of MSCs. The pre-treatment technique consists of exposing MSCs to pro-inflammatory cytokines that essentially activate the anti-inflammatory and immunosuppressive qualities of MSCs prior to administration, hence improving the efficacy of the treatment. MSC-derived vesicles (MV) lower the potential risks of negative immune reactions to MSC. A risk associated with intravenous administration is a pulmonary embolism that can be eliminated by using the MV technique (2021).

Contribution of Mesenchymal Stem Cells to Tissue Repair

Due to the multipotent quality of bone marrow-derived mesenchymal stem cells (BMSCs), they can differentiate into any of the following three cell types: adipocytes, chondrocytes, and osteoblasts (Hu et al, 2018). They are attracted to sites where they are needed to enhance tissue repair and regeneration. Transcription factors and signaling pathways have crucial roles in the MSC differentiation and cell fate. Factors such as Osterix and run-related transcription factor 2 (runx2) promote osteoblast differentiation (Hu et al., 2018). Enhancement of these transcription factors can be beneficial for patients with advanced RA who have also shown evidence of bone resorption (Liu et al., 2018). Chemical and mechanical factors affect the migration of bone marrow derived mesenchymal stem cells. These factors include cytokines, chemokines, and growth factors such as stromal derived factor-1 (SDF-1), osteopontin (OPN), platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β). When treated in vitro with BMSC, all proved to have a positive impact on BMSC migration towards damaged tissue. However, BMSC migration was inversely related to basic fibroblast growth factor (bFGF) concentration; as the concentration decreased, migration increased. The results of mechanical influence, however, varied. For example, mechanical stretch and matrix stiffness promote cell migration from bone marrow to site of injury while microgravity inhibits homing. Increase in shear stress, like bFGF, lead to a decrease in BMSC migration (Fu et al, 2019). This research can be useful in maximizing the benefits of MSC treatment by preconditioning BMSCs.

Risks Associated with Mesenchymal Stem Cell Treatment

The age of the donor could have an inverse effect on the productivity of the MSCs. This is coupled with an ethical dilemma – how young is okay for the age of a donor? MSCs can also potentially be used in mediating allogenic immune responses, such as to prevent Graft versus Host Disease (GVHD). Another risk to consider is occlusion of MSCs in microvessels when they are administered through venous or arterial injection. Although arterial injections seemed to be more effective, they are not completely safe. BMSCs were found to promote tumorigenesis into certain cancers when they were injected with tumor cells. Studies reviewed by Musial-Wysocka et al. confirmed some associated risks with adipose-derived MSCs. For example, patients treated with Adipose Tissue-Derived Mesenchymal Stem Cells (AT-MSCs) presented with thrombosis (2019) and nephrotoxicity – specifically in cases where they were used in patients with chronic kidney disease (Kim et al., 2017); (Chen et al. 2017). It is important to mention that many of the above risks mentioned can be avoided. For instance, the use of umbilical cord MSC's can resolve the ethical dilemmas associated with MSC use. According to Lv et al., UCMSC's are not only ethical but they present lower evidence of major histocompatibility complex I and no evidence of major histocompatibility complex II which lowers the risks of rejection (2021). Sarsenova and colleagues explore preclinical studies that demonstrate the different ways of administrating MSC treatment that could reduce risks and optimize results. Other than biological risk factors, MSC treatment has proved to be an expensive procedure that there is no proper protocol for (2021). However, many studies claim that MSC treatment is overall safer than traditional methods of treatment for RA.

Discussion

The overall role of the immune cells in inflammation demonstrates a dependency and closed loop of positive feedback that leads to the formation of senescent cells and worsening of RA. The chronic inflammation leads to immunosenescence and eventual cognitive and mental damages by circulating senescent cells. To prevent further progression of inflammation and damage to joints and bones, it will be helpful to start reviewing the defects in checkpoints that control cell maturation and apoptosis. When compared to traditional treatments for RA, MSC have less adverse risk and are more beneficial with long-term use. Research should be conducted to show the effect of MSC on all immune cells simultaneously. MSC treatment as mentioned in multiple studies, RA and various other autoimmune diseases develop due to the defect in T-and B-cells. This makes it worthwhile to study immunological checkpoints and pathways that are implicated by RA, as it may be possible to develop a drug that regulates the defective checkpoints and either lowers the chances of developing RA or prevent progression of the disease.

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