World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

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A review on mesenchymal stem cell-based therapies for autoimmune disorders

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World Journal of Biology Pharmacy and Health Sciences, 2023, 15(02), 170–175

Publication history: Received on 11 July 2023; revised on 18 August 2023; accepted on 21 August 2023

Article DOI: https://doi.org/10.30574/wjbphs.2023.15.2.0363

Abstract

Mesenchymal stem cells (MSCs) or adult multipotent progenitor cells with the ability to self- renew and differentiate, are extracted from a variety of tissues, including bone marrow, adipose tissue, umbilical cord blood, Wharton's jelly, tooth pulp, menstrual blood, and others. Since they are multipotent, cultured MSCs can differentiate into the adipogenic, chondrogenic, and osteogenic lineages after being isolated. Due to their immunomodulatory, immunosuppressive, and regenerative potentials, multipotent mesenchymal stem cells (MSCs) have received extensive scrutiny as an efficient tool for cell-based therapy of inflammatory, immune- mediated, and degenerative illnesses. The clinical applications and therapeutic potential of this cell type, the therapeutic mechanisms of MSCs, techniques to increase their therapeutic potentials, such as manipulation and preconditioning, and potential/unexpected risks that should be taken into account as a preliminary step before they are put to clinical use. In large part, due to their distinct immunomodulatory capabilities, MSCs have been touted as an ideal choice for the treatment of immune-related illnesses throughout the past few decades. In this review study we are mainly focusing on the MSC based treatments currently being developed for autoimmune diseases, type 1 diabetes and rheumatoid arthritis.

Keywords: MSC; Autoimmune disorders; Type 1 diabetes; Rheumatoid arthritis

1. Introduction

Over the past few years, stem cell therapy has been the subject of considerable research. Although there are a lot of things about MSC therapy that need to be well defined, translational medicine has tremendous expectations for mesenchymal stem cell (MSC) therapy [1]. Clinical trials focus on MSCs because of their regenerative, immunosuppressive and immunomodulatory abilities. Potential consequences of stem cell therapy remain murky because numerous methods are being researched and the majority of in vivo MSC administration results, on the other hand, have demonstrated favourable outcomes and established their safety [2]. Although clinical trials focus on MSCs because of their regenerative and immunomodulatory abilities, from a clinical research perspective, there are a few potential risks of MSC therapeutics that have to be taken into account: (i) immunogenicity of the cells, (ii) biosafety of culture/medium components, (iii) potential risk of ectopic tissue formation, and (iv) potential in vitro transformation of the cells during cultural expansion that could lead to malignancy [3].

In more recent years, the discipline of regenerative medicine has gradually given way to the study of autoimmunity as a result of the finding of MSC immunomodulatory capabilities as traditional immunosuppressants may be hazardous in this category of illnesses caused by immune system activation that is out of control and results in loss of self-tolerance and auto-reactivity [4]. The immunological flexibility of MSCs, which leads to immunosuppression that is only temporary and limited in space, might be one benefit of MSC-based therapy. Additionally, these progenitor cells exhibit the stem cell markers CD73, CD90, CD44, and CD105 while staining negative for the hematopoietic lineage markers CD34, CD45, CD11b, HLA-DR, and CD3. According to flow cytometer analysis of cell surface molecular pattern MSCs tend to demonstrate little immunogenicity [5]. The exosomes derived from MSCs also through numerous studies have

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demonstrated their capacity to control the proliferation of PBMCs [6]. Due to their unique ability of being able to detect damage or inflammation followed by switching to the necessary response, MSCs have a dynamic immunomodulatory profile [7]. MSCs possess distinctive characteristics such as; ease of isolation and cultivation, plasticity, intrinsic tropism towards injured area (homing) which is of two types, namely systemic homing and non-systemic homing [8].

MSCs show little to no expression of MHCII antigens and co-stimulatory components, while they only show intermediate expression levels of MHCI [9]. MSC transplantation or therapy can be of allogenic or autologous nature depending on the type of therapy, the nature of ailment to be treated and health of the patient among others factors as the two transplantation types have their own specific advantages and disadvantages [10]. As we discussed previously, MSCs show moderate expression of MHCI, this however is enough to cause immunologic response upon allorecognition that can lead to failure of treatment in the patient [11]–[13]. MSC mortality and local inflammation, resulting from humoral and cell-mediated rejection of MSCs by the immune system, can happen suddenly or over time [14]–[16]. Major histocompatibility complex (MHC) class I antigens present on the surface of MSCs aid the allorecognition of these stem cells in the patient/recipient after transplantation [13], [17], [18]. Severe immune response after allorecognition may be eliminated or reduced significantly by matching the MHC antigens of the patient to the donor as closely as possible [14], [18]. In this review, we specifically discuss the use of MSCs in the treatment of autoimmune disorders like Rheumatoid Arthritis and Type 1 Diabetes.

2. MSC-based therapy

2.1. MSC-based therapy for Type 1 Diabetes

Although most of the tumours are eradicated by our immune system at immune surveillance checkpoint, there are some that sue the very checkpoints to evade the immune action. These tumours cause the upregulation of programmed death ligand 1 (PD-L1) which then go and bind to their counterpart receptors called programmed death protein 1 (PD-1) present on the surface of T cells. This ultimately leads to the suppression of an appropriate immune action, as the function of PD-1 is that it helps keep the immune responses in check, immune responses that could have otherwise eliminated the tumour. Using immunomodulators to block cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) have improved the treatment of a broad spectrum of cancers [19]. However, as mentioned before it can also trigger immunogenic side effects. We see so in the case of treatments associated with immune checkpoint inhibitors (ICIs) which ultimately leads to the manifestation of autoimmune disorders, one of which is type 1 diabetes, the prevalence of which varies between 0.2% to 1.3% [20]–[24]. Type 1 diabetes may vary from being fulminant type to being acute onset type [25]. This progression may be slow where it leads to complete loss of beta cells over a span of months or it can be immediate in a span of just a few days as in case of fulminant type [26].

This paper sheds light on how immune checkpoint inhibitors (ICIs) reactivate the immune system against tumour cells but can also trigger autoimmune side effects, including type 1 diabetes. The goal of this study was specifically to demonstrate whether systemic MSC treatment could in any way prevent or even curb the development of type 1 diabetes in a NOD mouse model. Expression of PD-1 occurs in T cells that have been activated by signalling pathway of the T-cell receptors [27]–[29]. PD-L1, however, are expressed by islet cells and antigen presenting cells [30], [31]. It was documented that NOD, non-obese diabetic male mice, that are susceptible to diabetes developed type 1 diabetes after being administered with purified PD-L1 monoclonal antibodies [32]. The deficiency of PD-1 in mice causes the onset of type 1 diabetes among other autoimmune diseases [33]. MSCs derived from human adipose tissue were injected into tail veins after which immunofluorescence was used to investigate T cells, macrophages, and monocyte-derived macrophages that expressed C-X-C motif chemokine ligand 9 (CXCL9) in pancreatic sections from NOD mice and a cancer patient who had developed diabetes after receiving ICI therapy. Analyses were also conducted on plasma exosome levels, plasma cytokine profiles, and tissue localization of the injected MSCs [34].

In addition to directing fibrosis and tissue regeneration, mesenchymal stem cells (MSCs) have drawn interest for their role in immunomodulation [35]. Apart from regeneration, which repairs damaged tissues, the secretions of MSCs, which includes cytokines and exosomes, is believed to be important in therapeutics which has been successfully demonstrated in a pressure overload induced heart failure model [36], [37]. In NOD mice that were administered with anti-PD-L1 monoclonal antibodies (mAb) without hMSCs [MSC(-)], PD-1/PD-L1 inhibition caused diabetes in 16 of 25 (64%) of the mice model, however, MSC delivery reduced the incidence to 4 of 21 (19%) in NOD mice who got anti-PD-L1 mAb with hMSCs [MSC(+)]. Diabetes incidence, T cell and CXCL9-positive macrophage accumulation in the islets were dramatically decreased after treatment with MSCs (45% and 67%, respectively) which was coupled with the observation of a boost in islet beta cell area (2.7-fold) and insulin content (1.9-fold) [34].

2.2. MSC-based therapy for Rheumatoid Arthritis

Rheumatoid Arthritis affects the joints while the disrupted macrophage and monocyte ratio is the root cause of RA pathogenesis and inflammation [38]. Peripheral tolerance abnormalities and the resulting aberrant infiltration and activation of various immune cells into the synovial membrane have been extensively discussed as being crucial for the development and progression of RA [39]. It is also notable that the inflammatory M1 macrophage expression shows an abnormal increase in case of RA[40]. There have been numerous attempts at treating RA, nonetheless more often than not these treatments either fail to give the desired results or show limited alleviation of symptoms [41]. In this study, to be specific, we look into the potential effects of interleukin-1β stimulated human umbilical cord derived MSCs (IL-1β-hUCMSCs) on the immunoregulation of macrophages, especially on M1/M2 ratio, both in vitro as well as in the RA mouse model.

Macrophage are known to show polarization which means that they develop specific functional phenotype in response to stimuli from their immediate surrounding environment [42]. M1 macrophage polarization can be induced with the aid of lipopolysaccharide (LPS) whereas M2 macrophage polarization can be achieved with the help of interleukin 4 (IL-4) [43]. In this study, both LPS and IL-4 were used to achieve M1 and M2 polarization. This was done specifically to understand the effect of administered IL-1β-hUCMSCs on the polarization of the macrophages and on their apoptosis, in case of rheumatoid arthritis. This specific study is focused on the use of TRAIL to control the proliferation rate of M1 and M2 macrophages. TRAIL is protein that induces apoptosis of malignant cells [44, p. 8]. TRAILS, or TNF-related apoptosis-inducing ligand, as we already discussed before, gives way to apoptotic pathway by binding to death receptors, DR4 and DR5, however their effects may differ from cell to cell [45]. From a study done previously, it has been observed that treatment with IL-1β lead to an upregulation in the expression of both membrane bound and soluble TRAILS [46]. Cytokines and other relevant drugs can be used to upregulate the expressions of DR4 and DR5, the death receptors, to induce apoptosis. So, in this specific study, cleaved capase-3,8 and 9 were used to achieve the same. Hence, what we see in the result is an induced apoptosis of M1 macrophage. This happens because of an upregulated expression of TRAIL in IL-1β-hUCMSCs as well as DR4 and DR5 in M1 macrophages which ultimately leads to the induced cell death of M1 macrophage via both extrinsic and intrinsic pathways.

As discussed previously, the ratio of M1 to M2 macrophages plays a crucial role into the pathogenesis of RA. We know from already existing studies that M1 macrophages produce factors that are anti-inflammatory and which tend to worsen the signs and symptoms of RA [47]. However, M2 macrophages function differently, the anti-inflammatory factors that are released by these macrophages relieve the symptoms of RA and work towards repairing the damage [48]. In case of this study, for both in vitro and in vivo results depicted that interaction between IL-1β-hUCMSCs and TRAIL/DR4 or TRAIL/DR5 induced programmed cell death or apoptosis of M1 macrophages while promoting M2 polarization [49]. Hence, as we can see from the results, MSCs have a lot of promise as well as potential for the treatment of immune disorders as more research and study continues to garner extensive data and information to further clinically establish this kind of treatment [50], [51].

3. Conclusion

Although there are many different types of experimental treatments that make use of MSCs, few render successful results and even fewer make it to clinical level of implementation. From this review we have come to a discernment that there is still a lot of research that needs to be done to fully understand the machinations of MSCs which means that we know little about the molecular mechanisms of stem cells in general and so to implement the same for regenerative therapy is a double-edged sword. We need to invest more time and money to resolve these issues so that we are able to use stem cells to their fullest potential and revolutionize the field of regenerative medicine.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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