European Journal of Cell Biology 98 (2019) 151041

Contents lists available at ScienceDirect

European Journal of Cell Biology

journal homepage: www.elsevier.com/locate/ejcb

Review

Mesenchymal stem cell therapy for the treatment of inflammatory diseases: Challenges, opportunities, and future perspectives

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ARTICLE INFO

Keywords:
Mesenchymal stem cells
Inflammatory diseases
Immunomodulation

ABSTRACT

Mesenchymal stem cells (MSCs) are promising alternative agents for the treatment of inflammatory disorders due to their immunomodulatory functions, and several clinical trials on MSC-based products are currently being conducted. In this review, we discuss recent progress made on the use of MSCs as immunomodulatory agents, developmental challenges posed by MSC-based therapy, and the strategies being used to overcome these challenges. In this context, current understanding of the mechanisms responsible for MSC interactions with the immune system and the molecular responses of MSCs to inflammatory signals are discussed. The immunosuppressive activities of MSCs are initiated by cell-to-cell contact and the release of immuno-regulatory molecules. By doing so, MSCs can inhibit the proliferation and function of T cells, natural killer cells, B cells, and dendritic cells, and can also increase the proliferation of regulatory T cells. However, various problems, such as low transplanted cell viability, poor homing and engraftment into injured tissues, MSC heterogeneity, and lack of adequate information on optimum MSC doses impede clinical applications. On the other hand, it has been shown that the immunomodulatory activities and viabilities of MSCs might be enhanced by 3D-cultured systems, genetic modifications, preconditioning, and targeted-delivery.

1. Introduction

Inflammation is a protective response to harmful external stimuli and aids tissue repair and remodeling, but when dysregulated can have detrimental effects (Okin and Medzhitov, 2012). In fact, excessive prolonged dysregulation of the immune system can lead to a vast array of inflammatory and autoimmune disorders, which include allergic responses, asthma, coeliac diseases, inflammatory bowel diseases (IBD), glomerulonephritis, hepatitis, graft-*versus*-host disease (GVHD), type I diabetic, and arthritis (Davidson and Diamond, 2001; Okin and Medzhitov, 2012). Furthermore, regulatory immune cell loss, infectious agents, and other environmental triggers predispose autoimmune and inflammatory diseases (Davidson and Diamond, 2001). Corticosteroids, immunosuppressants, and monoclonal antibodies are used to treat immune disorders (Davidson and Diamond, 2001; Tabas and Glass, 2013), but drug resistance, non-responsiveness, and adverse reactions limit their usages (Lightner, 2017; Tabas and Glass, 2013). Thus, alternative methods are needed to treat inflammatory and autoimmune diseases. Recently, regulatory T cell (Treg) -based therapies and T-cell vaccination were introduced (Trzonkowski et al., 2015), but economic burden due to technical difficulties in generating high number of Tregs and safety concerning T cell therapy remain major hurdles to their clinical applications for the treatment of auto-immune and inflammatory diseases (Bluestone, 2005; Theil et al., 2015; Trzonkowski et al., 2015). In this context, mesenchymal stem cells (MSCs) offer a promising alternative cell therapy for the treatment of several immune disorders (Figueroa et al., 2012).

Stem cells are defined as unspecialized cells with self-renewal and differentiation potentials that cells have the abilities to maintain stemness or differentiate into more specialized cells. Due to less ethical concerns, ease of isolation, and abundance MSC-based cell therapy have been attractive to the researchers (Shen et al., 2015; Zuk et al., 2002). In 2006, the International Society of Cellular Therapy (ISCT) defined the following minimum criteria for MSCs (also referred to multipotent/mesenchymal stromal cells); fibroblastic adherent cells that express CD73, CD90, and CD105 surface markers, are devoid of CD14, CD34, CD45, CD19, CD11b, CD79a, and HLA-DR, and can differentiate into adipocytes, osteoblasts, or chondroblasts *in vitro* (Dominici et al., 2006; Duscher et al., 2015; Hocking and Gibran, 2010). However, cytokine-primed MSCs exhibit a robust upregulations of MHC-I, MHC-II, CD112, CD155, CD54, CD106, CD200, PDL-1, and Jagged-1 but no upregulation of costimulatory molecules such as CD80 and CD86 suggests resting and primed-MSCs exhibit different immune-phenotype (Galipeau et al., 2016; Krampera et al., 2013). Thus, a precise definition

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https://doi.org/10.1016/j.ejcb.2019.04.002
Received 15 February 2019; Received in revised form 1 April 2019; Accepted 9 April 2019

of MSCs remains obscure because their characteristics are dependent on the microenvironment and the stimuli encountered.

MSCs have also been reported to exhibit anti-inflammatory and immunomodulatory activities *in vitro* and *in vivo*. The profound immunosuppressive effects of MSCs are due to their abilities to inhibit T-cell proliferation and attenuate the T-cells functionality (Nauta and Fibbe, 2007; Uccelli et al., 2008), and to reprogram M1 macrophages to the M2 phenotype (Kim and Hematti, 2009). Although the molecular mechanism responsible for T-cell suppression by MSCs is not clearly understood, some reported findings indicate that various cytokines/chemokines and other soluble factors govern their T cell suppressing effects (Nauta and Fibbe, 2007; Sato et al., 2007a). The therapeutic effects of MSCs on various inflammatory and autoimmune diseases have been extensively studied (Uccelli et al., 2008), and interactions between MSCs and immune cells have been shown to contribute to tissue remodeling and healing (Kim and Hematti, 2009; Maggini et al., 2010; Zhang et al., 2010). Under these circumstances, the definition of MSCs should include criteria regarding the functional markers related to their immunomodulatory effects. For this reason, ISCT introduced guidelines for the immunological characterization of MSCs for clinical use that require assessments of the regulatory properties of MSCs based on immune plasticity assay, functional analysis of secretomes derived from MSCs, investigations of culture modalities and cellular biochemistry of MSCs, and use of appropriate animal model for preclinical evaluation (Galipeau et al., 2016).

Multiple studies have focused on the differentiation potentials of MSCs and their abilities to regenerate of different tissue types (Heino and Hentunen, 2008; Kalinina, 2011; Scott et al., 2011; Shen et al., 2017; Solchaga et al., 2011), In addition, studies other have focused on the immunomodulatory effects of MSCs for the treatment of inflammatory and autoimmune diseases (Gao et al., 2016; Lu et al., 2017; Wang et al., 2016b; Zhao et al., 2016), and this switch in research emphasis has created new a direction for the use of MSCs. Several authors have proposed MSCs can interact with immune cells, including monocytes and T cells, to regulate cytokine secretion and immune responses (Ma and Chan, 2016; Wang et al., 2018b), and this is considered to be the rationale behind the use of MSCs for the treatment of immune-mediated disorders (Bernardo and Fibbe, 2013).

MSCs responses to immune cells depend on inflammatory signals in the microenvironment. As they adopt an anti-inflammatory phenotype during inflammatory conditions but maintain a pro-inflammatory phenotype in the absence of inflammation. Furthermore, balance between contrasting functional states prevents excessive tissue damage and promotes tissue repair (Bernardo and Fibbe, 2013). Thus, MSC therapy offers an attractive substitute for the treatment of immune disorders, especially those of the relapsing/refractory type (de Girolamo et al., 2013). However, despite its potential for the treatment of immune disorders, reductions in cell quality during *in vitro* expansion, poor cell survival after *in vivo* transplantation, and inefficient migration to targeted sites limit the effectiveness of MSC therapy.

2. Interactions between MSCs and immune cells and their immunomodulatory effects

The immunomodulatory effects of MSCs provide the basis for the treatment of inflammatory and immune disorders. *In vitro* and *in vivo* studies have demonstrated the immunomodulatory effects of MSCs (Sala et al., 2015; Soler et al., 2016; Uccelli et al., 2011). Significant reductions in the incidence and severity of GVHD after allogenic MSC transplantation in a clinical trial encouraged the use of MSCs as immunomodulatory agents (Amorin et al., 2014). Although the mechanism responsible for immunomodulation by MSCs has not been fully elucidated, it has been established to be primarily orchestrated by paracrine or direct interactions with immune cells of the innate and adaptive systems (Fig. 1).

2.1. Interaction of MSC with NK cells

NK cells are vital players in the immune system and act as a bridge between the adaptive and innate immune systems (Gianchecchi et al., 2018). Although the effects of MSC-NK cell interactions are poorly understood, MSCs have been reported to suppress NK cell proliferation, cytotoxicity, and cytokine secretion. The mechanism of MSC-mediated NK cell suppression is attributed not only by the secretion of soluble factors such as TGF-β1, PGE2, IDO, and HLA-G5 but also by the contact-mediated communication of MSCs and NK cells (Aggarwal and Pittenger, 2005; Selmani et al., 2008). Although MSC have limited expression of MHC-I, INF-γ primed MSCs showed dramatic upregulation of MHC-I and MHC-II (Krampera et al., 2013), which might explain MSC escape from NK cell-mediated lysis. However, MSCs could not affect the NK cell-mediated lysis of target cells (Rasmusson et al., 2003). In another study, MSCs inhibited the proliferation of non-activated NK cells but only marginally inhibited that of activated NK cells (Spaggiari et al., 2006). In contrast, it was suggested in a recent study, NK killed foreskin-derived MSCs in cytokine-dependent manner by secreting abnormally large degranulation enzymes (Najar et al., 2018). Study performed by Galleu et al. suggested the apoptosis of MSCs by NK cells might be beneficial for providing an immunosuppressive effect (Galleu et al., 2017). Due to these opposing findings, further studies are required to reveal the consequences of MSC-NK cell interactions.

2.2. Interaction between MSCs and dendritic cells

Dendritic cells (DCs) are a major component of the innate immune system that process antigens and present them to T cells. MSCs have shown to inhibit the maturation of monocytes to DCs *via* the secretion of various soluble factors (Jiang et al., 2005). Co-culture of MSCs with DCs reduced the cell-surface expressions of MHC-II molecules, CD11c, and CD83. This impaired the antigen-presenting abilities of the DCs (Jiang et al., 2005; Nauta et al., 2006a). Furthermore, when cultured *in vitro* with MSCs, DCs secreted less TNF-α and more IL-10 (Jung et al., 2007), indicating MSCs can inhibit the differentiation, maturation, and migration of DCs (Fig. 1). These observations suggest that MSC-mediated T cell response might be partly DC dependent because DC differentiation, maturation, and migration are known to play crucial roles in adaptive immune response (Aggarwal and Pittenger, 2005). Furthermore, the effects of MSCs on DCs has also been shown to be mediated by soluble factors, such as PGE2 (Spaggiari et al., 2009), IL-6 (Djouad et al., 2007b), IL-10 (Allavena et al., 1998), and galectin-3 (GAL-3) (Nikolic et al., 2018) (Fig. 2).

2.3. Interaction between MSCs and macrophages

Macrophages play a vital role in the innate immune system and an importantly contribute to tissue repair and regulation of inflammation. Furthermore, the interaction between MSCs and macrophages reprograms macrophages to adopt the anti-inflammatory phenotype. This cross-talk between macrophages and MSCs increases IL-10 production by macrophages through a NO/COX-2/PGE2 dependent pathway (Nemeth et al., 2009). In addition, MSCs are activated in the presence of elevated levels of IFN-γ, TNF-α, and/or LPS. This results in the up-regulation of cyclooxygenase 2 (COX2) and IDO which augments homeostatic response to urge M2 polarization (Francois et al., 2012; Nemeth et al., 2009). In addition, IL-6, PGE2, and IDO, which are constitutively produced by activated MSCs, polarize monocytes (M0) toward IL-10 production and the anti-inflammatory M2 phenotype (Eggenhofer and Hoogduijn, 2012), and this polarizing effect has been reported to be closely associated with the abilities of MSCs to generate Treg cells and the chemokine CCL18 from MSC-induced M2 macrophages (Melief et al., 2013). In contrast, when IFN-γ and TNF-α levels are low, MSCs polarize M0 toward pro-inflammatory M1 macrophages, which topically express costimulatory molecules and secrete IFN-γ and

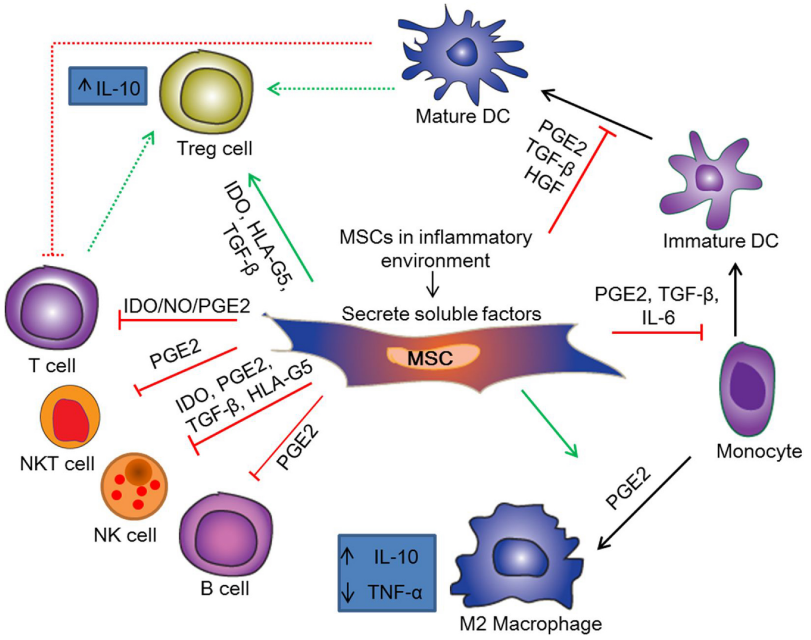

Fig. 1. MSCs exert their immunosuppressive effects by regulating different cell types in the innate and adaptive immune systems by secreting various soluble factors.

TNF-α to stimulate T cell activation. However, high levels of pro-inflammatory signals trigger a feedback mechanism that provokes the anti-inflammatory pathway (Fig. 3) (Le Blanc and Mougiakakos, 2012). Accordingly, the ability of MSCs to switch between pro- and anti-inflammatory states is determined by molecular signals in the surrounding microenvironment (Ren et al., 2008a).

2.4. Interactions between MSCs and lymphocytes

Lymphocytes are major players in the adaptive immune system. Lymphocytes are mainly composed of T and B lymphocytes, and MSCs have been shown to interact with both cell types. T cell responses are mainly mediated by T cell proliferation and increased cytokine secretion (Budd and Fortner, 2017). MSCs have a suppressive effect on the proliferation of activated helper T cells, caused by cell cycle arrest in the G0/G1 phase rather than by the induction of T cell apoptosis (Di Nicola et al., 2002; Rasmusson, 2006). This inhibition of T cell proliferation reduces IFN-γ secretion by Th1 cells and IL-17 secretion from Th17 cells and increases IL-4 secretion by Th2 cells (Aggarwal and Pittenger, 2005; Batten et al., 2006; Zappia et al., 2005), indicating a change in T cell polarization from the inflammatory to the anti-inflammatory phenotype (Aggarwal and Pittenger, 2005).

Cytotoxic T lymphocytes (CTL) are T lymphocytes that are capable of killing virus infected cells or cancer cells through CD8-mediated recognition of MHC-I. However, despite surface expression of MHC-I, MSCs escape CTL-mediate lysis. In addition, during the initial activation phase, MSCs inhibit cytotoxic T cells and substantially reduce CTL-mediated cytotoxic effect. Interestingly, no significant effect of MSCs was observed after the CTL activation (Rasmusson et al., 2003). Plessers et al. found clinical grade bone marrow derived progenitor cells significantly decreased perforin expression and impaired function in CTL predominantly *via* contact dependent mechanism (Plessers et al., 2016). In a mouse model of GVHD, activated $CD8^+$ T cells in recipients caused MSC apoptosis. The phagocytosis of these apoptotic cells induced the production of IDO by phagocyte which is crucial for immunosuppression (Galleu et al., 2017).

NKT cells are T lymphocytes that possess some of the markers of NK cells. The proliferation of NKT cells was significantly inhibited when co-

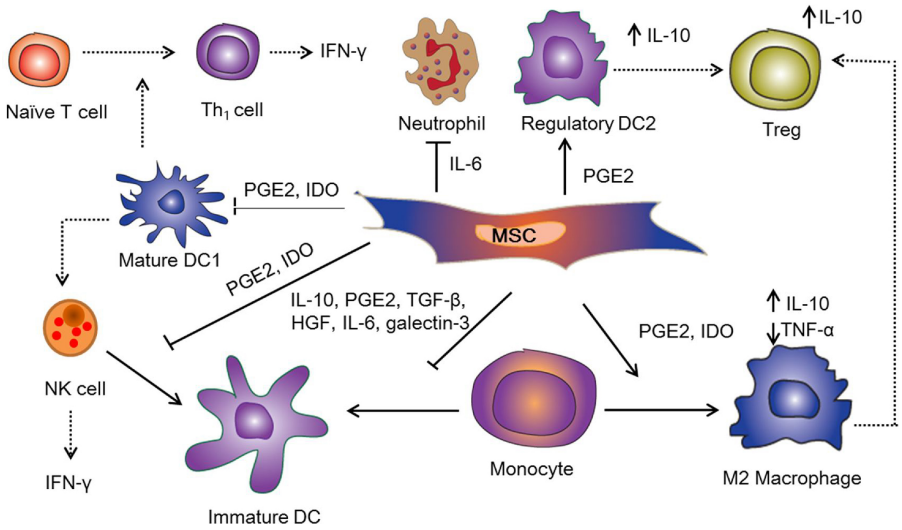

Fig. 2. Possible effects of interactions between MSCs and cells of the innate system on immune modulation. MSCs interact with different types of immune cells in the innate immune system, including NK cells, neutrophils, DCs, and macrophages. Furthermore, MSC-DC interactions indirectly but crucially regulate the adaptive immune system and NK cells to inhibit inflammation.

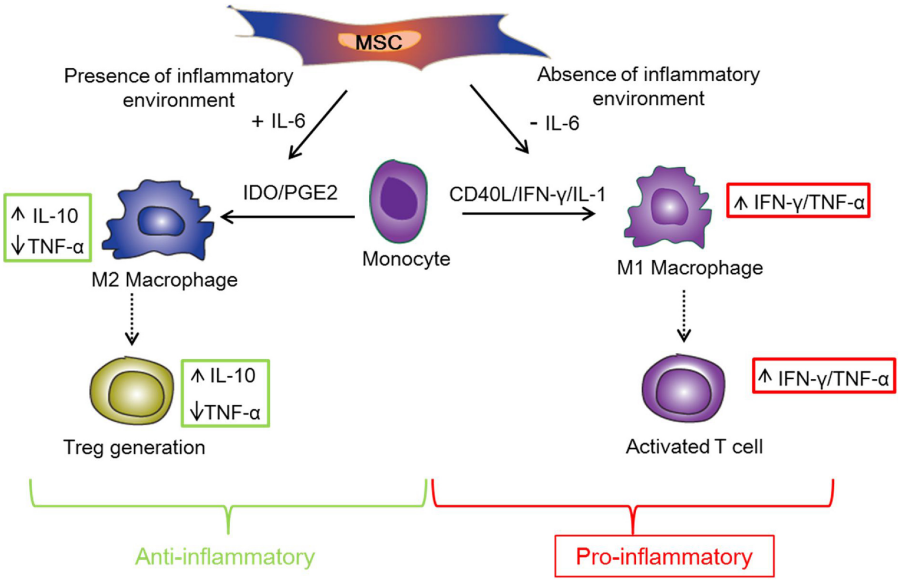

Fig. 3. Pro- and anti-inflammatory effects of MSCs. MSC exhibit anti-inflammatory properties in the presence of high levels of inflammatory cytokines *via* Treg generation and pro-inflammatory properties in the presence of low levels of inflammatory cytokines *via* T cell activation. MSCs interplay with pro- and anti-inflammatory factors creating balance between immune activation and immune suppression.

cultured with MSCs in PGE2-dependent mechanism. However, the MSCs could not inhibit the NKT-mediated cell lysis (Prigione et al., 2009). In the model of concanavalin and α-galactosylceramide-induced liver injury, MSCs exhibited a disease inhibitory effect by reducing expressions of FasL, TRAIL, and CD107 on liver derived NKT cells, and also attenuated the infiltration of TNF-α, IFN-γ, and IL-4 producing NKT cells (Gazdic et al., 2018b).

B lymphocytes participate in the maintenance of adaptive and humoral immunity by presenting antigen and acting as antibody producing cells. Corcione et al. suggested that MSCs can inhibit B cell function, proliferation, differentiation to plasma cells, and chemotaxis. Notably, the productions of IgM, IgG, and IgA by B cells was significantly impaired by MSCs, and the inhibition of B cell differentiation and the down-regulations of CXCR4, CXCR5, and CCR7 expressions reduced the chemotactic properties of B cells (Corcione et al., 2006). However, in some cases, MSCs support the proliferation and terminal differentiation of B cells (Ji et al., 2012), and because B cell responses are T cell dependent, the effects of MSCs on B cells might also be influenced by MSC-mediated T cell inhibition.

MSCs have also been reported to facilitate the de-novo generation of induced Tregs, which were as effective as natural Treg cells in terms of their immune suppressive functions (Engela et al., 2013). Furthermore, MSC-induced production of IL-10 by regulatory DCs was found to inhibit allogenic lymphocyte proliferation and to trigger Treg generation, and thus, helped to maintain immune homeostasis and self-tolerance (Zhang et al., 2009). Similarly, Tregs co-cultured with MSCs exhibit more pronounced immune-suppressive effects, which might have been caused by IL-10 secretion (Yan et al., 2014) (Fig. 4).

The induction of MSC-mediated immune suppression might be mediated by contact-dependent or soluble factor-dependent mechanisms. In the case of contact-dependent mechanisms, studies have shown the inhibition of T-cell proliferation and the transductions of various cytokines require binding between inhibitory molecule PD1 and its ligand PDL1 (Augello et al., 2005). As regards to soluble factor-dependent mechanism, soluble immune suppressive factors either produced or released by MSCs after cross-talk with targeted cells might participate in MSC-mediated immune suppression. Soluble factors like transforming growth factor-ß (TGF-β) (Xu et al., 2014), hepatocyte growth factor (HGF) (Yen et al., 2013), IL-6, hemeoxygenase-1 (HO-1) (Chabannes et al., 2007), soluble human leukocyte antigen-G5 (HLA-G5), nitric oxide (NO) (Ren et al., 2008a; Sato et al., 2007a), IDO (Meisel et al., 2004b), and prostaglandin E2 (PGE2) (Chen et al., 2010) also play crucial roles in immune suppression by MSCs. When exposed to high levels of IFN-γ, MSCs produce IDO, which depletes tryptophan, an essential amino acid for lymphocyte proliferation (Krampera et al., 2006). Furthermore, IDO and PGE2 has been reported to block NK cell activity (Fig. 2). Similarly, HLA-G5 production by MSCs has been reported to suppress T cell proliferation and promote Treg generation (Morandi et al., 2008; Selmani et al., 2008).

In inflammatory environments, MSCs are actively converted to immunosuppressive phenotype (MSC2), which expresses high levels of Toll-like receptors (TLR3) and results in the secretions of high levels of soluble factors, such as, IDO, NO, PGE2, HGF, HO-1, and TGF-β. Moreover, the transformation of MSCs to the MSC2 suppresses T cell proliferation/activation and promotes Treg generation (Waterman et al., 2010). Collectively, the ability of MSCs to maintain balance between anti-inflammatory Tregs and inflammatory effector T cell facilitates proper tissue repair and healing.

2.5. MSCs can exert pro-and anti-inflammatory effects

The immunomodulatory effects of MSCs vary with microenvironment immune status. Immunomodulatory activity of MSCs is triggered by activation of TLR receptor in MSCs by pathogen-associated molecules like LPS or double-stranded RNA from viruses. MSCs may be also be primed to TLR3 or TLR4 stimulation resulting two distinctly opposite roles in immune system, that is, TLR3-primed MSCs exhibited anti-inflammatory effects whereas TLR4-primed MSCs are pro-inflammatory (Waterman et al., 2010). The recognition of a microbial molecule by MSCs results in increased secretions of IL-6, IL-8, macrophage migration inhibitory factor (MIF), granulocyte stimulating factor (GM-CSF), and chemokines, which promote the recruitments of neutrophils and monocytes. The recruited monocytes are then programmed to adopt the pro-inflammatory M1 phenotype and secrete inflammatory cytokines and express costimulatory molecules to stimulate T cells (Brandau et al., 2010). Moreover, TLR4-primed MSCs after microbial molecules recognition secrete chemokines such as MIP-1α and MIP-1β, RANTES, CXCL9, CXCL10, and CXCL11, which aid the recruitment of lymphocytes at sites of infection. At low levels of inflammatory cytokines, MSCs secrete insufficient level of NO or IDO which causes T cell activation and further enhances immune-stimulating effects of MSCs. However, when inflammation is severe and inflammatory cytokines levels are high due to excessive immune activation, MSCs switch to TLR3-primed anti-inflammatory type MSCs to weakens immune activation (Li et al., 2012b). When the MSCs were co-cultured with freshly-isolated spleenocytes at low density in presence anti-CD3 stimulation,

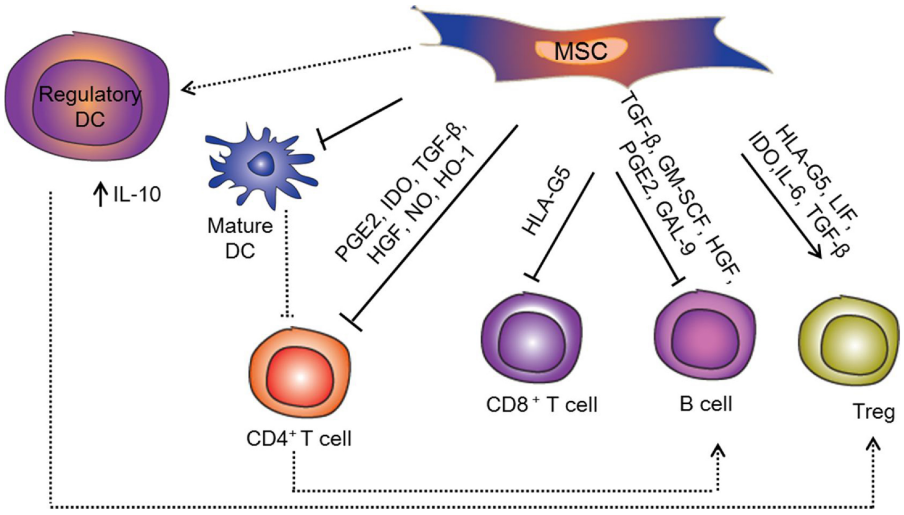

Fig. 4. Interactions between MSCs and lymphocytes. MSCs directly suppress the activations of helper T and cytotoxic T cells through cell-cell interactions or by secreting soluble factors. MSCs inhibit $CD4^+$ T cells directly *via* the secretion of insoluble factors or inhibition of maturation of DC to mature DC. B lymphocytes are directly suppressed by MSCs or influenced by MSC-mediated T cell inhibition. Similarly, MSCs promote the proliferation of Tregs directly using soluble factors or *via* regulatory DC-mediated stimulation of Treg generation.

the spleenocytes proliferated. However, when co-cultured at high density, the spleenocyte proliferation was inhibited indicating MSCs adopt pro- and anti-inflammatory roles depending on immune status of local microenvironment (Fig. 3). The pro-inflammatory effect of MSCs is beneficial during early phases of inflammation and microbial infections whereas their anti-inflammatory effects are useful during later phases when excessive immune activation would cause tissue damage or acute injury. These unique dual properties of MSCs make them attractive tools for immune activation and suppression.

3. Mechanism of MSC-mediated immunomodulation

Immunomodulation by MSCs is regulated *via* various molecular mechanisms that involve interactions between inflammatory factors and MSCs. These interactions activate MSCs to release various secretory factors or chemokines that have immunosuppressive effects. The treatment of MSCs with inflammatory factors like TNF-α, IFN-γ, or IL-1 causes rapid inflation in the expressions of chemokines, inducible nitric oxide synthase (iNOS), and IDO leading to inhibition of T cell proliferation (Su et al., 2014). The chemokines like CXCR3 and CCR4 ligands act as chemoattractants and are responsible for T cell recruitment, and these recruited T cells are suppressed *via* iNOS or IDO (Ren et al., 2008a). Several studies have suggested a crucial role of iNOS and IDO in mediating immunomodulatory effects of MSCs (Ling et al., 2014; Sato et al., 2007b). For example, abolition of iNOS in MSCs blocked the therapeutic effectiveness of the MSCs in experimental model of acute liver injury and fibrosis (Chen et al., 2015b). In another study, deletion of IDO obliterated the immunosuppressive effect of MSCs (Ling et al., 2014). Sato et al. reported that iNOS-induced immunosuppression was mediated *via* NO production subsequent cell cycle arrest in T cells (Sato et al., 2007). Qian et al. found IDO-induced depletion of tryptophan and immune cell apoptosis (Qian et al., 2009).

Various factors secreted by MSCs such as cytokines, growth factors, anti-inflammatory factors, and extracellular vesicles (EV) are responsible for immunomodulatory effects of MSCs. TGF-β secreted by MSCs play pivotal role in inducing Treg generation and restricting lymphocyte activation (English et al., 2009). MSCs also produce growth factors such as HGF and leukemia inhibitory factor (LIF) in the presence of inflammatory signals, that act by inhibiting the differentiation of Th1 and Th17 cells (Bai et al., 2012; Cao et al., 2011). In addition, anti-inflammatory factors like PGE2, TSG6, HO-1, IL-10 and GAL are secreted by MSCs (Volarevic et al., 2017). PGE2 is an extensively studied anti-inflammatory factor that causes IL-10 secretion by macrophages (Vasandan et al., 2016), Treg generation (Tatara et al., 2011), inhibition of DC migration (Aggarwal and Pittenger, 2005), and NK cell suppression (Galland et al., 2017). On the other hand, LPS signaling in MSCs induced PGE2 secretion and elimination of PGE2 compromised the therapeutic potential of MSCs (Németh et al., 2009). TSG6 is another important immune regulator produced by cytokine-stimulated MSCs that attenuates inflammatory responses and aids tissue repair after acute lung injury (Wang et al., 2017b), peritonitis (Choi et al., 2011), myocardial infraction (Lee et al., 2009), arthritis (Mindrescu et al., 2002), and IBD (Song et al., 2018) by inhibiting the migrations of innate immune cells (*e.g.*, neutrophils, monocytes, and macrophages) (Dyer et al., 2016). Furthermore, EV derived from MSCs are enriched with micro RNAs (miRNAs) that are responsible for therapeutic effects in hepatic injury (Li et al., 2012a), acute kidney injury (AKI) (Aghajani Nargesi et al., 2017), and myocardial ischemic injury (Yu et al., 2015). miR-15a, miR-15b, and miR-16 suppress pro-inflammatory macrophage accumulation in infected regions *via* inhibition of macrophage chemoattractant (CX3 C chemokine ligand) (Du et al., 2014). Similarly, GATA-4 overexpressing MSCs-derived exosomes enriched in miR-19a have been reported to be cardioprotective (Yu et al., 2015). In addition, oxidatively-stressed MSCs secrete EV that promote the transfer of their depolarized mitochondria to neighboring macrophages for mitophagy. These EV, in turn, shed miRNA that suppress TLR signaling and causes macrophage desensitization (Phinney et al., 2015).

Cellular interactions are also important to maintain immunomodulatory effect of MSCs. MSCs, by interacting directly with cell surface receptors affect production of effector molecules, proliferation, and survival through the modulation of downstream pathways in immune cells. FASL and PDL1 are responsible for direct interactions between MSCs and immune cells. Upregulation of PDL1 and its binding to PD1 receptors on immune cells trigger inhibitory signaling pathways in immune cells (Ni et al., 2018; Sheng et al., 2008). In addition, FAS-FASL binding facilitates the immunosuppressive effects of MSCs by enhancing lymphocyte apoptosis (Akiyama et al., 2012).

Interestingly, apoptotic MSCs have also been found to exert immunomodulatory effects (de Witte et al., 2017). Studies have reported the immunosuppressive effects of apoptotic MSCs occurs as the result of their engulfment by phagocytes, release of IDO from MSCs in the cytoplasm of phagocytes, and the secretion of IDO by the phagocytes, which has been reported to inhibit and kill T cells (de Witte et al., 2018; Galleu et al., 2017; Laing et al., 2018; Mancuso et al., 2017; Williams et al., 2008). Galleu et al. proposed the possibility of the application of apoptotic MSC in the treatment of GVHD. They showed alleviation of GVHD in mice after intraperitoneal injection of apoptotic MSC. Although this finding shows a new insight in the use of MSC for inflammatory diseases, a number of concerns regarding the use of MSC remain unexplained in this study. First, the authors have shown that the intraperitoneal injection of apoptotic MSC were beneficial for treating GVHD while the intravenous injection of the same MSC remain

Table 1
Soluble factors governing MSC-mediated immune suppression.

Immunomodulatory factors	MSC type	Effects	Reference
PGE2	Human Bone marrow stromal cell (hBMSC)	• Inhibition of NK cells	Spaggiari et al. (2008)
	Mouse B	• Reprogramming of the host macrophages to promote their IL-10 production	Nemeth et al. (2009)
	MSC: Mouse BMSC	• Inhibition of T-helper 17 cell differentiation by PGE2 through EP4 receptor	Duffy et al. (2011)
		• Inhibition of DC maturation	Spaggiari et al. (2009)
	hBMSC	• Induction of Tregs	English et al. (2009)
	hBMSC	• Polarization of macrophage to anti-inflammatory M2 phenotype	Németh et al. (2009)
IDO	hBMSCs	• Inhibition of T cell responses	Meisel et al. (2004a)
		• Suppression of third-party T-cell proliferation	Guan et al. (2018)
		• Inhibition of proliferation, cytokine secretion and cytotoxicity of NK cells	
TGF-β	MSCs	• Inhibition of NK proliferation, differentiation and cytotoxicity	Ye et al. (2018)
TSG-6	MSCs	• Immunomodulation mediated by TSG6 inhibit the inflammation and injury	Li et al. (2018), Yang et al. (2018b)
	Canine adipose derived MSCs (ADMSCs)	• Induction of M2 macrophage polarization	Song et al. (2018)
miRNA-26a	MSCs	• Reduction of IR injury by suppressing GSK3β expression	Ribault et al. (2018)
LIF	BMSCs	• Inhibition of proliferation, cytokine secretion and cytotoxicity of T cells	Nasef et al. (2008)
		• Generation of Tregs	
HLA-G5	BMSCs	• Suppression of T lymphocytes and induction of Tregs	[59]
miRNA-147	hUCMSCs	• Attenuation of macrophage activation and aortic inflammation	Spinosa et al. (2018)
IL-6	hBMSCs	• Inhibition of differentiation of dendritic cells	Djouad et al. (2007a)
	Mouse BMSCs	• Promotion of survival of and production of antibody by Plasma cells	Kayaba et al. (2018)
	MSCs	• Reduction of proliferation of reactive astrocytes	He et al. (2019)
TGF-β, HGF	hBMSCs	• Inhibition of T-cell proliferation	Di Nicola et al. (2002)
NO	hBMSCs	• Suppression of T cells	Sato et al. (2007a)
HO-1	hBMSCs	• Inhibition of T cell proliferation	Chabannes et al. (2007)
		• Protection against ischemic liver injury *via* autophagy regulation	Wang et al. (2018c)
		• Enhancement of anti-apoptotic and paracrine functions of MSCs	Chen et al. (2018b)
GAL-3	Mouse BMSCs	• Down regulation of inflammatory cytokines in DC and attenuation of MHC-II expression on their surface	Nikolic et al. (2018)
GAL-9	MSCs	• Significant reduction in IgG production by B cells	Christopher et al. (2014)

Table 2
Signaling pathways governing MSC-mediated immune suppression.

Signaling pathway	Cell type	Effects	Reference
mTOR	BMSCs	Inhibition of mTOR signaling by rapamycin improve the immunosuppressive effect of MSCs with upregulation of COX-2 and PGE2	Wang et al. (2017a)
MAPK	MSCs	Attenuation of inflammation during sepsis by inhibition of MAPK pathway	Pedrazza et al. (2017)
TLR4/NF-κB	BMSCs	Activation of TLR4 with inflammatory signals activate NF-κB and COX-2, subsequently resulting in upregulated synthesis of PGE2	Németh et al. (2009)
MAPK, IFN-γ, NF-κB	BMSCs	Attenuation of macrophage inflammatory response	Wang et al. (2016a)
PDL-1/PD-1 and GAL-9/TIM-3	ADMSCs	Inhibition of NF-κB in T cells through PD-L1/PD-1 and GAL-9/TIM-3 pathways partially mediate immunoregulatory function	Zhou et al. (2018)
iNOS/COX-2/PGE2	MSCs	Reduction of inflammatory markers and pro-inflammatory cytokines in activated macrophage because of COX-2/PGE2 upregulation	Nemeth et al. (2009), Yang et al. (2018a)
JAK/STAT3	MSCs	HO-1 overexpression in MSCs improved cell survival, alleviated inflammatory responses in sepsis associated acute kidney injury (AKI) through JAK/STAT3	Yan et al. (2018a)

ineffective. These contradictory findings do not provide a satisfactory explanation about the real advantage of apoptotic MSC in GVHD. Therefore further studies should reveal the therapeutic benefit of the apoptotic MSC after injection with various other routes of injection. Second, the therapeutic effectiveness of the apoptotic MSC was evaluated only with intraperitoneal injection of the MSC in GVHD. Whether the apoptotic MSC remain functional in other inflammatory diseases remains to be elucidated. Third, the effect of MSC after viability-improving interventions was not evaluated in the above study. In contrast to this several other studies focused on strengthening the MSC viability. Therefore, studies comparing the effectiveness of apoptotic MSC and viability-strengthened MSC should be performed. Fourth, long-term

functioning of MSC is desirable in chronic types of inflammatory disorders. The use of apoptotic cells cannot fulfill this criteria as they are rapidly cleared-off by the innate immune system of the host. Therefore, further studies on the safety and efficacy of apoptotic are required. Tables 1 and 2 provide summary of factors secreted by MSCs and the pathways that govern MSC-mediated immune suppression, respectively.

4. Application of MSC in inflammatory diseases: preclinical and clinical studies

The remarkable therapeutic effects of MSCs on a broad range of diseases have been established by preclinical and clinical studies. Due to their abilities to differentiate, home to inflamed areas, and exert immunomodulatory effects, MSCs have been widely used to treat autoimmune, neurodegenerative, cardiovascular, bone and cartilage, liver, lung, and kidney diseases. In addition, MSCs have been used in organ transplantation, diabetes, as well as other chronic and acute tissue injuries. Till date, 906 clinical trials with MSCs have been registered in ClinicalTrials.gov.

4.1. IBD

IBD is characterized by chronic and uncontrolled inflammation of intestinal mucosa. It primarily composed of two disorders, namely, ulcerative colitis (UC) and Crohn's disease (CD). In many patients, IBD often relapses and is refractory to conventional therapy (Peyrin-Biroulet et al., 2012). In this context, MSC therapy a promising alternative treatment (de Girolamo et al., 2013). Transplanted MSCs exert their therapeutic effects in IBD *via* immunomodulation, angiogenesis, and epithelialization (Markovic et al., 2018). Immortalized MSC transplantation enhances colonic VEGF secretion and promotes epithelial regeneration. In addition, MSCs trans-differentiate into colonic epithelial-like cells and promote repair process (Khalil et al., 2007). MSCs attenuate Th1 and Th17 immune responses, inhibit inflammatory cytokines and chemokines, and the promote infiltration of regulatory and anti-inflammatory macrophage to colon (Duijvestein et al., 2011; González et al., 2009). In murine model, umbilical cord derived MSCs (UC-MSCs) ameliorated colitis by the regulating of inflammation in a PGE2-dependent mechanism, and suppressing Th1 and Th17 immune responses (Liang et al., 2011). In addition to their immunomodulatory effects, UC-MSCs transplantation reduced intestinal permeability and enhanced colonic tight junction restoration (Lin et al., 2015). Similarly, pharmacological inhibition of GAL-3 in bone marrow-derived MSCs (BMSCs) promoted M2 polarization of macrophages and attenuated DSS-induced colitis. In another study, adipose-derived MSCs (ADMSCs) were found to ameliorate TNBS-induced colitis *via* secretion of miR-1236 that directs the weakening of Th1 immune response (Zhang et al., 2015b). In addition, IFN-γ priming of MSCs improved their therapeutic effects in colonic inflammation (Duijvestein et al., 2011). In human studies, MSCs have been administered either locally to lesions or systemically (intravenously) for inhibition of intestinal inflammation. Administration of autologous or allogenic MSCs to CD patients with fistula significantly improved clinical outcomes in patients. More specifically, four doses of intra-fistular injection of autologous BMSCs in patients with refractory CD reduced disease activity, promoted rectal mucosal healing, and closed the fistula in 70% of the patients without any side effects (Ciccocioppo et al., 2011). Allogenic BMSC therapy in refractory cases of perianal fistula achieved complete healing of fistula in 50% of the patients after 12 weeks in a phase II clinical trial (Molendijk et al., 2015). Randomized phase III trial using ADMSCs conducted in 200 patients with complex cryptoglandular perianal fistula showed moderate healing rate within 12 weeks. However, long-term healing rates were not noteworthy than with the placebo group. (Herreros et al., 2012). In another double-blind phase III clinical trial, the local intralesional injection of allogenic ADMSCs (12×10^7 cells) into tissue adjacent to fistula effectively healed the fistula without significant side effects (Panés et al., 2016). In contrast, systemic infusion of autologous and allogenic MSCs produced mixed results in patients (Dhere et al., 2016; Duijvestein et al., 2010; Turse et al., 2018). Interestingly, the use of endogenous circulating MSCs has also been proved beneficial for the treatment of CD without any adverse effects (Marlicz et al., 2012). Till date, most of the countries across the globe have not been approved clinical use of MSCs in humans. Recently, Alofisel is near approval in Europe and when approved will be first allogenic MSC treatment for complex perianal fistulas in Crohn's disease (Sheridan, 2018).

4.2. Multiple sclerosis (MS)

MS is a common autoimmune disease of the central nervous system (CNS) characterized by multifocal CNS lesions, perivenular accumulation of inflammatory cells, demyelination, and neuronal degeneration. In an early study, intrathecal injection of MSCs in 10 MS patients did not cause any adverse effects, which suggested MSC transplantation is feasible, safe, and well-tolerated in MS (Mohyeddin Bonab et al., 2007). In addition, recent studies reported intravenous administration of culture-expanded MSCs was safe, feasible, and was well-tolerated in MS patients (Cohen et al., 2018; Planchon et al., 2018). In the study performed by Yamount et al., autologous BMSC transplantation in advanced MS patients revealed disability score improvements in 5/7, stabilization in 1/7, and worsening in 1/7 patients, with visual improvement in5/6 and worsening in 1/6 patients (Yamout et al., 2010). Another study also concluded the safety and effectiveness of MSC transplantation in MS, and immunological analysis after 24 h of MSC transplantation exhibited increased proportion of Tregs and reduced inflammatory immune cell proliferation (Karussis et al., 2010). Constantinescu et al. found MSCs derived from MS patients showed higher proportions of Th17 cells in peripheral blood as compared with healthy donors, and suggested this may have been due to deficient IL-10 production (Constantinescu et al., 2018). In experimental autoimmune encephalomyelitis (EAE), autologous MSCs failed but systemic infusion of allogenic MSCs remarkably improved clinical symptoms (Sargent et al., 2017). In combination with steroids, MSCs effectively ameliorated EAE (Kim et al., 2018). Although MSCs are well tolerated, the requirement of immunological monitoring and the use of autologous MSCs need to be reevaluated. Preclinical studies have demonstrated remarkable results in the treatment of MS. Nevertheless, further large scale, randomized, and well-control studies are required for clinical translation of MSCs in MS.

4.3. Systemic lupus erythematosus (SLE)

In SLE, there is activation of T and B lymphocytes that leads to an imbalance between Th1 and Th2 cells and between Tregs and Th17 cells (Yang et al., 2009). Studies have reported that MSC treatment is well-tolerated and is found to improve the disease conditions (Kamen et al., 2018; Liang et al., 2010b). MSC transplantation effectively treated SLE patients by upregulating Tregs and downregulating Th17 in TGF-β and PGE2 dependent manners (Wang et al., 2015). In patients with refractory SLE, MSC transplantation achieved clinical improvement without any severe side effects (Liang et al., 2010a,b). In another study, MSC transplantation displayed low immunogenicity, dramatically improved the proteinuria levels, reduced medication doses, and improved renal functions without clinical signs of acute immune rejection (Barbado et al., 2018). However, *in vitro* culture of MSCs with B cells derived from SLE patients and healthy donor exhibited enhanced proliferation and differentiation of B cells arising special concerned while using MSCs in treatment of SLE (Traggiai et al., 2008). Similar to other autoimmune diseases MSCs showed mixed and contradictory results in SLE. Nevertheless, the potential of MSC therapy for the treatment of SLE could not be underestimated. However, large double-blind

and multi-centered clinical trials with close monitoring of immune system are required before clinical translation.

4.4. Graft-versus-host diseases (GVHD)

GVHD is a major complication of allogenic hematopoietic stem cell transplantation where symptoms usually resemble those of autoimmune and other immunological disorders (Sullivan, 2003). The immunomodulatory effect of MSCs was first evaluated in a patient with GVHD, and authors reported MSCs as a safe and feasible alternative for the treatment of gastrointestinal steroid refractory GVHD (Le Blanc et al., 2004). More recently, allogenic MSC treatment improved the survival rate and ameliorated skin, oral mucosa, and liver inflammation in GVHD patients (Le Blanc et al., 2008; Peng et al., 2015). MSCs also promoted survival and proliferation of IL-10 secreting regulatory B cells (Peng et al., 2015). However, in a phase III trial of MSCs for the treatment of steroid-refractory GVHD, no significant increase in clinical symptoms remission was observed compared to placebo (Martin et al., 2010). In another study, children responded better than adults to MSC therapy (Kurtzberg et al., 2010), and response to early treatment was better than delayed treatment (Ball et al., 2013). Recently, Good manufacturing practice (GMP)-quality MSC were reported to be highly effective in children and adults with refractory advanced GVHD, and early treatment was found to be associated with better and faster responses (Bader et al., 2018). A recent multicenter non-randomized phase I/II study in steroid-refractory acute GVHD demonstrated the safety of umbilical cord-derived MSCs and claimed improvements in overall survival and response rate (Algarotti et al., 2018). Disparities between studies are probably due to manufacture-associated heterogeneity, MSC sources, and the conditions of MSCs used. Prochyma (approved in Canada) and TEMCELL (approved in Japan) are now commercially available for the treatment of GVHD (Galipeau and Sensébé, 2018).

4.5. Liver injury

Although liver transplantation is the major treatment strategy used to treat end-stage liver diseases, donor shortages have led to a search for alternative MSC-based therapies (Iansante et al., 2018). MSCs rescued D-Galactosamine (D-GalN)-induced hepatotoxicity in mice (Ramanathan et al., 2017). Furthermore, MSCs significantly protected mice from concanavalin A and α-galactosylceramide-induced hepatotoxicity by inhibiting inflammatory influx and up-regulating anti-inflammatory IL-10, and reduced NK cell induced liver toxicity in an IDO or iNOS-dependent manner (Gazdic et al., 2018b; Markovic et al., 2017). Moreover, animal studies showed MSC-derived exosomes were responsible for its hepatoprotective effects (Jiang et al., 2018; Mardpour et al., 2018; Alzahrani et al., 2018; Damania et al., 2018). Gazdic et al. concluded crosstalk between MSCs and Treg cells is crucial for the attenuation of acute liver injury (Gazdic et al., 2018a), and Liu et al. noted PGE2 secretion from MSCs aids hepatocyte proliferation and protects against acute liver injury (Liu et al., 2018b). Wang et al. reported MSCs enhanced hepatocyte autophagy (Wang et al., 2018c) and inhibits hepatic pyroptosis (Wang et al., 2018a). Kharaziha et al. in a phase I/II trial on liver cirrhosis found liver function was improved after autologous MSC injection (Kharaziha et al., 2009). Furthermore, in a phase II trial on alcoholic cirrhosis patients, MSC transplantation reduced liver fibrosis and improved liver functions (Suk et al., 2016). In addition, allogenic MSC therapy was compared with standard medical therapy where MSC therapy significantly improved the survival rate and decreased the incidence of severe infections in patients with hepatitis (Lin et al., 2017). In another study, MSC adjunctive therapy improved the liver functions of Chinese patients with liver cirrhosis compared to routine supportive therapy alone (Tao et al., 2018). Meta-analysis of clinical efficacy of MSCs suggests promising and satisfactory results in liver failure patients and multi-centered studies are required for further clinical translation.

4.6. Kidney injury

Acute kidney injury (AKI) is a commonly encountered emergency case in the clinic with high incidence and mortality. The major causes of AKI are renal ischemia, use of nephrotoxins and sepsis. Dialysis and renal transplantation are the only choices for AKI treatment. However, developments in stem cell therapy field suggest MSCs may provide an alternative therapy (Zhao et al., 2018b). Many clinical and preclinical studies have been conducted to evaluate the efficacy and safety of MSCs in kidney injuries. Preclinical studies have confirmed the abilities of MSCs to protect renal cells, suppress kidney fibrosis and renal epithelial apoptosis, and to improve renal functions (Cho et al., 2018; Crigna et al., 2018; Havakhah et al., 2018). These encouraging pre-clinical results led to the initiation of many clinical trials using MSCs for the treatment of renal diseases. Clinical studies reported safety and feasibility of MSCs in the treatment of kidney diseases (Thomspon et al., 2018). In contrast, allogenic MSC transplantation in AKI could not recover the kidney functions (Swaminathan et al., 2018). Miller et al. designed a new delivery approach using extracorporeal MSCs therapy and evaluated it phase Ib/IIa clinical trial in dialysis-dependent AKI patients to determine whether it overcame the pharmacokinetic barrier of MSCs transplantation. The delivered MSCs responded to the soluble inflammatory signals without direct physical contact, and authors hypothesized this could be used to enable viable MSCs to secret anti-inflammatory proteins, cytokines, growth factors and EV efficiently and exert cytoprotective and regenerative effect on injured renal tissue (Swaminathan et al., 2018). Local delivery of MSCs into kidney provides an alternative means of maximizing MSC densities in inflamed tissues and enhancing contact-dependent immune inhibition. However, further studies are required to evaluate the effectiveness of local renal delivery. Table 3 summarizes some of the clinical trials conducted on different diseases.

5. Major challenges and opportunities of MSC-based cell therapy

Variabilities in cell sources, doses and dosing intervals, isolation, culture, and expansion protocols present problems that have yet to be resolved and have resulted in disparities between studies that are difficult to rationalize (Gao et al., 2017). In addition, inadequate cell survival, impaired paracrine effects, and poor homing capacity have limited the therapeutic benefits of MSC therapy (Silva et al., 2018b).

Despite the compatibility of autologous MSCs and the immune system, application are limited by inadequate cell source, loss of therapeutic potential obtained from elderly donors, and the risk of obtaining defective MSCs from unhealthy donors. In addition, it is often difficult to treat acute diseases because the preparation of autologous MSCs is time-consuming. To overcome these limitations, allogenic MSC transplantation has been proposed. Although many reports have described the immune-privileged or hypo-immunogenic nature of MSCs, recent studies indicate allogenic MSCs trigger antibody production and are prone to rejection (Eliopoulos et al., 2005; Nauta et al., 2006b; Zangi et al., 2009a). Thus, the immune system appears to recognize transplanted MSCs as foreign bodies, triggers immune rejection, and rapid clearance. Although allogenic MSCs may be immunogenicity due to expression of MHC-I and other co-stimulatory molecules, their potent immunosuppressive effects have fascinated researchers working on treatment of various inflammatory diseases. The study performed to evaluate the safety and efficacy of allogenic *versus* autologous MSCs transplantation showed a non-significant difference in immunogenicity with two types of MSCs (Hare et al., 2017). In addition, multiple studies support the effectiveness and safety of allogenic MSC transplantation (Noriega et al., 2017; Vega et al., 2015; Yuka et al., 2016). In another study, Ryan et al. showed the non-immunogenic nature of allogenic MSCs (Ryan et al., 2005). In contrast to the above findings, some studies

Table 3
Clinical trials on MSCs for the treatment of immune disorders.

SN	Disease	Source	Dose and route	Findings	Reference
1	Active luminal CD Phase II	Autologous BMSCs	$2 \times 10^6\,kg^{-1}$ body weight, (intravenous infusion per week for 4 weeks)	Reduction in CDAI and CDEIS scores in patients and improvement in mean quality of life score	Forbes et al. (2014)
2	CD Phase	Autologous ADMSCs	$3–30 \times 10^6$ (intrafistular injection)	Fistula healing was observed in 71 percent of patient	Garcia-Olmo et al. (2009)
3	Complex perianal fistula Phase II	Autologous ADMSCs	20×10^6 cell with or without fibrin glue, the repeated dose of 20×10^6 cells in case of incomplete closure at 8 week (intralesion)	CDAI, HBI, and corticosteroid dosage had decreased by 62.5 ± 23.2, 3.4 ± 1.2, and 4.2 ± 0.84 mg/day, respectively, in the UC-MSC group and by 23.6 ± 12.4, 1.2 ± 0.58, and 1.2 ± 0.35 mg/day	Zhang et al. (2018)
4	Refractory Crohn's fistula	Autologous BMSCs Fistula	$15–30 \times 10^6$ cells, (intrafistular injections 2–5 monthly)	Safe and tolerable Improved healing and closure of fistula	Molendijk et al. (2015)
5	Complex Perianal Fistula	Allogenic ADMSCs	120×10^6 cell (Single intralesional injection)	Effective and safe	Panés et al. (2016)
6	Steroid-resistant, severe, acute GVHD: a phase II study	Allogenic BMSCs	$0.4–9 \times 10^6$ cells per kg bodyweight (1–5 doses of BMSCs i.v.)	Infusion of MSC, irrespective of the donor, might be effective for the treatment of steroid-resistant acute GVHD.	Le Blanc et al. (2008)
7	Acute steroid refractory GVDH	Allogenic BMSCs	$2 \times 10^6\,kg^{-1}$ on day 173, 201 and 270 *via* i.v. infusion	Two patient exhibited complete remission whereas in one patient partial remission was achieved.	Česen Mazič et al. (2018)
8	Multiple Sclerosis	Autologous MSC	$1–2 \times 10^6$ MSCs/kg i.v.	Feasible, safe, and well tolerated	Cohen et al. (2018)
9	Rheumatoid arthritis Phase I/II	Autologous BMSCs	40×10^6 cell/joint (intra-articular implantation)	Safe and well tolerated Improvement in standing time and reduction in methotrexate and prednisolone doses	Shadmanfar et al. (2018)
10	Rheumatoid arthritis Phase Ia	Allogenic UC-MSCs	2.5×10^7, 5×10^7, or 1×10^8 cells (single i.v. infusion)	Reduction of inflammatory cytokines at 24 h of cell infusion	Park et al. (2018)
11	Osteoarthritis Phase I/II	Autologous BMSCs	40×10^6 cells intra-articular implantation	Great improvement in physical function and painless walking	Emadedin et al. (2018)
12	Chronic kidney diseaes	Autologous BMSCs	$1–2 \times 10^6$ cells/kg i.v. single dose	Safe and tolerable Nonsignificant reduction in the rate of eGFR decrease	Makhlough et al. (2018)
13	Autosomal dominant polycystic kidney disease (ADPKD)	Autologous BMMSCs	$1–2 \times 10^6\,kg^{-1}$ BW	Safe and tolerable Significant reduction in the rate of serum creatinine decrease	Makhlough et al. (2017)
14	SLE	Autologous UC-MSCs	2×10^8 two doses once a week *via* i.v.	75% remission in UC-MSCs group *versus* 83% remission in control Similar improvement in serum albumin and other renal functions	Deng et al. (2017)
15	Hepatitis B virus related acute-on-chronic liver failure	Allogenic BMSCs	$1.0–10 \times 10^5$ cells/kg i.v. infusion weekly for 4 weeks	Improvement in the survival rate, liver functions in MSCs treated group than standard medical therapy goup	Lin et al. (2017)

have shown the rejection of allogenic MSCs and failure of MSC-based therapy (Eliopoulos et al., 2005; Zangi et al., 2009b). Others have reported allogenic MSCs enhanced inflammation and donor-specific antibody levels, and suggested these up-regulations might the responsible for allogenic MSC-based therapy failure (Gu et al., 2014; Seifert et al., 2012). Cho et al. reported multiple injections of allogenic MSCs enhanced alloantibody production (Cho et al., 2008). Interestingly, Huang et al. showed that the immunogenicity of MSCs depends on the condition of MSC. They found undifferentiated MSCs had low immunogenicity, whereas differentiated MSCs were strongly immunogenic (Huang et al., 2010). Hence, the stimulation of transplanted MSC immunity appears to depend on several factors, which include cell condition, site of transplantation, and nature of the local microenvironment.

When allogenic MSCs were transplanted to treat hematopoietic stem cell-induced GVHD, their effects were short-lived, and invasive mold infections were observed in some patients (Blennow et al., 2016; Remberger and Ringdén, 2012; Uhlin et al., 2011). Although transplantation of allogenic MSCs has been reported to reduce incidence of GVHD, Brown et al. found it increased the risk of viral and fungal infection and suggested this might be due to inhibitory effect of MSCs on thymic reconstitution and subsequent immune recognition impairment (Brown et al., 2010). Many clinical trials have determined the safety of allogenic MSCs, but others have suggested increased infection risk, and thus, close monitoring is required after MSCs transplantation.

Cell survival and sufficient engraftment after transplantation are crucial to the success of MSC therapy (Zhang et al., 2008). Excessive oxidative stress, acute immune response, or highly inflammatory or hypoxic microenvironments at sites of injury are probably the major factors that limit stem cell survival and engraftment (Chang et al., 2013b). The elevation in production of reactive oxygen species (ROS) impaired cell adhesion and engraftment at the injured site (Song et al., 2010). PI3K/AKT/PTEN, p53, and p39/JNK signaling pathways are involved in ROS-mediated apoptosis of MSCs (Matsuda et al., 2018; Wei et al., 2010a). The bioenergy challenge by harsh ischemic and inflammatory microenvironment is another cause of MSC apoptosis *in vivo*. During *in vitro* expansion, MSCs are cultured in 20% oxygen and 10% serum concentration. However, after *in vivo* implantation, they encounter harsh hypoxic or nearly anoxic microenvironment and are nutrient deprived. Under these circumstances, MSCs rely exclusively on anaerobic glycolysis or autophagy activation for energy. MSCs are more likely to undergo apoptosis due to exogenous nutrient deficiency at the transplantation site, limited stock of intracellular glucose, and rapid depletion of energy reserves (Deschepper et al., 2013; Moya et al., 2018). p38/caspase-12 signaling pathway has been investigated as an important signaling mechanism causing apoptosis in MSCs induced by hypoxia and nutrient deprivation (Chen et al., 2018a). Furthermore, an enzyme treatment is used to detach MSCs from culture plate before transplantation, and this process leads to significant loss of extracellular matrix and may cause anoikis and trigger apoptotic signals.

In addition, systemic MSC infusion often results in poor homing and compromises desirable effects on target organs (Barbash et al., 2003). Also, the injection process may cause mechanically disrupt cells, and immediately after transplantation, hypoxic microenvironments and acute immune responses may reduce cell survival before cells become functional (Bliss et al., 2006; Li et al., 2007b; Seif-Naraghi et al., 2010).

5.1. Use of 3D-cultured cells

MSCs have been used to treat immune- and inflammation-mediated diseases, including GVHD (Ringdén et al., 2006), Crohn's disease (González et al., 2009), and rheumatoid arthritis (Gonzalez-Rey et al., 2010). To enhance the viability and immunomodulatory effects of MSCs, various approaches such as 3D culture have been developed. 3D culture increases the intracellular levels of pro-inflammatory cytokines, such as, TNF-α, IL-1α, IL-1β and IL-8, which creates an early inflammatory microenvironment that activates MSCs to produce various soluble factors that regulate immune cells, attenuate inflammation, and facilitate tissue repair (González et al., 2009; Shi et al., 2012). Self-activated spheroids trigger PGE2 secretion, which subsequently converts macrophages of the M1 phenotype (pro-inflammatory) to the M2 phenotype, and consequently reduces the secretion of pro-inflammatory cytokines like TNF-α, CXCL-2, and IL-6, and augments the secretion of anti-inflammatory cytokines like IL-10 and IL-1RA (Ylöstalo et al., 2012). Stem cell spheroids have higher engraftment efficiency and survival at transplantation sites than monolayer-cultured cells, and exhibit elevated Bcl-2 levels (anti-apoptotic) and diminished Bax levels (pro-apoptotic) (Cesarz and Tamama, 2016; Petrenko et al., 2017). Similarly, levels of angiogenic growth factors, such as, VEGF, FGF, and HGF, are higher in spheroids than in monolayer-cultured cells. Furthermore, spheroids secrete more extracellular matrix proteins and exhibit greater survival pathway (AKT) activation (Bhang et al., 2011), both of which support stem cell survival. In our recent study, we observed better therapeutic effect of 3D spheroids of MSCs when they were transplanted into portal vein in mouse model of acute liver injury. 3D spheroids of MSCs showed strong antioxidant effects and protected cell viability during oxidative stress. In another study, we found an attenuation of DSS-induced experimental colitis when MSCs spheroids were delivered intraperitoneally, where the MSC spheroids were found to exert enhanced immunomodulatory action compared to that of the 2D-cultured MSCs (our unpublished data). Furthermore, we also observed enhanced differentiation of MSCs when 3D hybrid clusters prepared by using MSCs and NO-releasing microspheres (Regmi et al., 2017). Thus, it seems that the 3D hybrid clusters containing drug-loaded microspheres and MSCs offer means of improving MSC-based therapy through improvement therapeutic effects of MSCs. In addition, we successfully prepared ECM-modified beads that enhance MSC proliferation *in vitro* culture (our unpublished data). Several studies have indicated that 3D culture of MSCs enhances their anti- inflammatory and immunomodulatory properties (Table 4).

5.2. Genetic modification of stem cells

Transplantation of billions of MSCs at inflammatory sites has yielded marginal outcomes, which is explained at least in part by the limited *in vivo* viability of MSCs (Shake et al., 2002); for example, in one study, only 1% of MSCs remained viable after 4 days of transplantation into inflamed hearts (Toma et al., 2002). Despite the immune

Table 4
Effect of 3D culture on the immunomodulatory activities of MSCs.

Method of preparation of 3D	Animal model	Therapeutic effect	Reference
Hanging drop technique	Endotoxin induced inflammation	Enhancement of their anti-inflammatory phenotype in macrophages and debilitation of inflammatory cytokines	Ylöstalo et al. (2012)
Hanging drop technique	Zymosan-induced peritonitis	Amelioration of their anti-inflammatory properties	Bartosh et al. (2010)
Bioreactor	CCL_4 induced acute liver failure (ALF)	Augmentation of effect of MSC to rescue ALF with spheroid derived cells	Zhang et al. (2015a)
Hanging drop technique	Acute kidney injury	Enhancement of survival and paracrine effect of spheroid derived cells	Xu et al. (2016)
Hanging drop technique	GalN/LPS-induced ALF	Improvement of survival and anti-inflammatory effect of stem cell spheroid	Our unpublished data

suppressive property of MSCs, many clinical trials have failed during later phases due to poor cell engraftment efficiencies. These observations adequately demonstrate that MSC survival and engraftment are crucial aspects of MSC-based therapies. Attempts have been made to improve MSC therapy using cells overexpressing AKT (a serine threonine kinase), Bcl-2 (an anti-apoptotic protein) (Li et al., 2007a; Mangi et al., 2003), or HO-1, to enhance the anti-inflammatory and anti-apoptotic effects (Tang et al., 2005; Yoon et al., 2017). *Liao et al.* engineered IL-10 expressing MSCs to inhibit immune cells by attenuating inflammation (Liao et al., 2016). Another recent study showed that the immune suppressive effects of MSCs depend on the surface expression of FasL (Akiyama et al., 2012). Interestingly, a micro-RNA based strategy involving knockdown of mRNA Let-7a using a specific inhibitor, effectively suppressed inflammation in experimental colitis and GVHD (Yu et al., 2017). Similarly, injection of TGF-β-transduced MSCs suppressed the progression of joint inflammation and autoimmune arthritis (Park et al., 2011), and more recently, MSCs expressing IL-35 were found to protect intestinal mucosa by suppressing mucosal immune response (Yan et al., 2018b). In another study, decorin-modified MSCs enhanced the immunomodulatory effect of MSCs in a mouse model of radiation-induced lung injury (Liu et al., 2018a), and G-CSF (granulocyte colony stimulating factor) over expression in MSCs also enhanced the paracrine effects of MSCs in experimental cardiomyopathy (Silva et al., 2018a). Despite observed improvements in therapeutic outcomes in various disease models, use of viral vectors raise safety issue, and thus, the long-term safeties of genetically-modified MSCs need to be investigated in preclinical models.

5.3. Preconditioning of stem cells

The immunomodulatory effect of MSCs appears as a consequence of inflammatory cytokines at the engraftment site. When MSCs were treated with inflammatory cytokines, they were activated and their immunosuppression effect was enhanced *via* upregulated expression of iNOS and chemokines (Ren et al., 2008b). Similarly, upregulation of ICAM-1 and VCAM-1 was observed in MSCs treated with inflammatory cytokines, and these facilitated T cell accumulation around MSCs and suppressed T cell proliferation (Shi et al., 2010). The major objective of MSC priming with inflammatory cytokines is to boost their immunosuppressive effects. MSC survival and engraftment are another issues, and they encounter high level of oxidative stress (Jaeschke, 2011; Wei et al., 2010b), severe hypoxia, and nutrient deficiency (Deschepper et al., 2013; Moya et al., 2018), are thus, more likely to undergo apoptosis during early days post-transplantation. Interestingly, pretreatment of MSCs with antioxidants upregulates enzymes that defend against oxidative stress after *in vivo* injection (Drowley et al., 2010; Valle-Prieto and Conget, 2010), and similarly, pre-exposure of MSCs to hypoxia upregulated various pro-survival and pro-angiogenic proteins involved in cell survival pathways (Chacko et al., 2010; Hu et al., 2008; Oh et al., 2010; Rosova et al., 2008). In addition, pretreatment with serum-deprived media was found to enhance autophagy activation and helped to combat nutrient deficiency and oxidative stress after transplantation (Hou et al., 2013). Activation of NOD2 by its ligand muramyl dipeptide (MDP) induced the production of PGE2 in MSCs *via* the NOD2-RIP2 pathway, and this induction suppressed the proliferation of mononuclear cells derived from human umbilical cord blood. In addition, the PGE2 produced by MDP-treated cells increased the production of IL-10, which further increased the population of Treg cells and reduced the severity of DSS (dextran sulfate sodium)-induced colitis (Kim et al., 2013). Moreover, pre-treating MSCs with IL-1ß and/or IFN-γ was found to enhance the therapeutic effectiveness of MSCs in DSS-induced colitis (Fan et al., 2012). In summary, priming of MSCs with cytokines, hypoxia, nutrient-deficient media, heat-shock, oxidative stress, or chemicals have been shown to boost MSC survival or function after transplantation. The primary objective of MSC priming or preconditioning is to acclimatize the MSCs to the harsh environments encountered after transplantation or to facilitate required effects. Table 5. summarizes some of the pretreatment strategies used to boost MSC function and viability.

5.4. Targeted or local-delivery of stem cells

Many studies have described the efficiency of MSC homing, whereby CXCR4 surface expression on MSCS acts as a homing receptor specific for stromal-derived-factor-1 (SDF-1), which is primarily secreted during inflammation (Shi et al., 2007). However, *in vitro* expansion of MSCs causes loss of CXCR4 expression and results in poor homing (Rombouts and Ploemacher, 2003). In addition, most MSCs administered intravenously are trapped in lungs and only a small percentage reach their intended targets (Gao et al., 2001; Schrepfer et al., 2007). Thus, the effectiveness of local or targeted delivery to sites of massive tissue damage have been investigated. When CXCR4, being a homing receptor, is overexpressed in the MSCs, homing of MSCs to the area of disease and effectiveness of treatment are improved (Nan et al., 2018; Zheng et al., 2018). In one study, coating MSC with antibody against addressins (Ab_{VCAM-1}-MSC) facilitated delivery to colon and enhanced therapeutic effectiveness (Ko et al., 2010). In another study, mRNA transfection of MSCs with P-selectin glycoprotein ligand-1 and Sialyl-Lewisx enhanced their homing efficiencies to inflamed tissues (Sridharan et al., 2014). Furthermore, intraperitoneal stem cell delivery was reported to treat colitis and chronic peritonitis more effectively than intravenous injection (Baştuğ et al., 2014). In contrast, Costa et al. reported intravenous route as the superior to intraperitoneal in treatment of experimental colitis (Gonçalves Fda et al., 2014). Thus, these contradictory results suggest the need of further investigation regarding choice of delivery route. Nevertheless, intrafistular or intralesional administration of MSCs was more effective at treating of CD than systemic infusion (Markovic et al., 2018), and intra-mesenteric delivery of MSCs significantly reduced the clinical symptoms of experimental colitis (Fu et al., 2018). MSCs secrete various cytokines and growth factors, and thus, local delivery improves the microenvironments in damaged tissues (Kinnaird et al., 2004), and is more effective therapy than systemic delivery (Ciccocioppo et al., 2011; Dhere et al., 2016). Recently, we observed that intraportally administered MSC spheroids engrafted better than monolayer-cultured MSCs when transplanted into a GalN/LPS-induced mouse model of acute liver disease (unpublished results). These observations indicate MSCs have the ability to modulate immune cells locally and promote tissue healing.

Many other studies have been conducted with the aim of promoting migration of MSCs to the injured sites. In one study, genetic modification of MSCs with CXCR2 enhanced the migration of MSCs to the inflamed sites showing CXCL2 upregulation, in an animal model of radiation-induced oral mucositis (Shen et al., 2018). In another study, Angiotensin-II receptor shRNA transfection in MSCs enhanced the migration of MSCs to injured lungs, which showed angiotensin upregulation, and resulted in better therapeutic outcomes (Xu et al., 2018). The targeting of MSCs to the sites of inflammation or local delivery provide means of overcoming non-specific distribution and the fates of MSCs.

5.5. Autophagy induction

Autophagy is fundamental cellular process that eliminates cellular wastes and damaged organelles but also serves as a source of cellular energy (Denton et al., 2015). Thus, autophagy plays an important role in maintenance of stemness and differentiation capacity of MSCs. In addition, autophagy helps in survival and engraftment of transplanted MSCs (Nuschke et al., 2014; Sbrana et al., 2016; Zhang et al., 2017). Autophagy activation in MSCs attenuated the ROS production and promoted survival of MSCs against oxidative stress (Hou et al., 2013; Liu et al., 2015; Song et al., 2014), and the induction of HIF-1α in MSCs protects them from oxidative stress through autophagy activation (Lv

Table 5
Regulation of the immunomodulatory function of MSCs by preconditioning.

Cell source	Preconditioning approach	Outcomes/results	Reference
Mouse BMSC	TGF-α	Improvement of MSC-mediated post-ischemic myocardial functional recovery and reduction of inflammatory cytokine production and apoptotic signaling	Herrmann et al. (2010)
BMSC	Hypoxia	Induction of pro-survival genes, chemoattractant, and growth factors	Chang et al. (2013a), Cruz and Rocco (2015), Jaussaud et al. (2012), Lan et al. (2015), Rosova et al. (2008)
mBMSC	IFN-γ	Enhancement of immunosuppression properties of MSC	Polchert et al. (2008)
hUC-MSC	Polyribocytidylic acid (a ligand of TLR3)	Suppression of proliferation of activated immune cells *via* the overproduction of PGE2 and increment in the production of anti-inflammatory cytokines	Qiu et al. (2016)
BMSC	TNF-α, IL-1β, and Nitric oxide	Augmentation of paracrine effects *via* HO-1 dependent mechanism	Chen et al. (2015a)
rBMSC	TNF-α	Amelioration of immunomodulation by delivery of TNF-α primed MSC with 3D PLGA scaffold	Aktas et al. (2017)
UC-MSC	LPS	Improvement of anti-inflammatory effect through secretion of extracellular vesicles	Ti et al. (2015)
Human embryonic stem cell derived MSC	Trimetazidine and Diazoxide	Enrichment of immunomodulatory effect of MSC *via* increased secretion of IL-10, TNF-α, and IL-1β from LPS-induced peripheral blood mononuclear cells.	Jahandideh et al. (2017)
hBMSC	IL-17A	Suppression of T cells along with Th1 cytokines, IFN-γ, TNF-α, and IL-2	Sivanathan et al. (2015)
hBMSC	Nutrient deprivation	Development in the potential of MSC to withstand encountered metabolic stress after transplantation	Moya et al. (2017)
hUCMSC	MDP	Enhancement of immunomodulatory effect of MSC mediated by COX-2/PGE2 upregulation	Kim et al. (2013)

et al., 2017). Thus, modulation of autophagy in MSCs is likely to promote long-term survival of engrafted MSCs. Recently, we have also observed improved viability of MSC when treated with rapamycin as an autophagy inducer (our unpublished data). Therefore, autophagy induction prior to transplantation might also be an alternative way to increase the survival and immunomodulatory effects of MSCs *in vivo*.

5.6. Cell-free MSC-based therapy

Cell-free MSC-based therapy has been proposed to resolve problems of allogenic MSC transplantation. In particular, MSC-derived EV have been introduced as new functional moieties in MSC-based therapy. EV are membrane-enclosed droplets that contain growth factors, cytokines, mRNA, regulatory miRNA, and signaling lipids (Phinney and Pittenger, 2017). They are heterogeneous in terms of release mechanism from donor cells or their size. Mainly, EV are composed of microvesicles (MV) and exosomes. MV are released *via* outward budding of cell membrane with size ranging from 50–1000 nm. Exosomes are smaller EV ranging from 30–150 nm and the fusion of multivesicular bodies with the plasma membrane results in the release of exosomes by exocytosis (Abels and Breakefield, 2016). MSC-derived EV promote tissue repair and have immunomodulatory effects in various inflammatory diseases. Furthermore, MSC-derived EV treatment has been reported to stimulate angiogenesis (Bian et al., 2014), activate pro-survival signaling, and reduce oxidative stress (Zhou et al., 2013), and ameliorate kidney disease (Ebrahim et al., 2018; Eirin et al., 2018), liver disease (Borrelli et al., 2018; Mardpour et al., 2018; Xu et al., 2019), and lung disease (Fujita et al., 2018). MSC-derived exosomes also reduced apoptosis of cardiomyocytes through autophagy induction *via* MPK/mTOR and Akt/mTOR pathways (Liu et al., 2017) and induced miRNA-132-assisted angiogenesis in myocardia infraction (Ma et al., 2018). Moreover, MSC-derived exosomes exhibited outstanding therapeutic effects in inflammatory brain diseases by inhibiting neuronal cell death (Mitsialis et al., 2018; Williams et al., 2018). Exosomes exert their anti-inflammatory effects by causing macrophage polarization to anti-phenotype by increasing the transactivation of arginase-1 (Zhao et al., 2018a) and decreasing the expression of NLRP3 inflammasome (Jiang et al., 2019). Moreover, MV potentially inhibit lymphocyte proliferation, induce activated T cell apoptosis, and promote the regulatory T cells to secrete IL-10 and TGF-β (Mokarizadeh et al., 2012). In addition, they are also responsible for inhibition of Th1/Th17 differentiation of T cells (Favaro et al., 2014). Furthermore, MSC-derived MV exert inhibitory effect on proliferation and differentiation of B-cells (Budoni et al., 2013).

EV contents and their effects are highly dependent on MSCs microenvironment and tissue of origin (Baglio et al., 2015). For example, EV content of BMSCs isolated from acute myeloid leukemia patients and healthy donor were different (Muntión et al., 2016). The ADMSC-derived exosomes were found to be more effective than BMSCs for treatment of Alzheimer's disease (Katsuda et al., 2013). Since culture conditions, media compositions, microenvironment, cell passage, and cell density influence the contents of secreted EVs, the bio-manufacture of these therapeutic EV should be designed based on consideration of these factors (Patel et al., 2018; Serejo et al., 2019). Under these circumstances, heterogeneous EV compositions, limited yields under routine culture conditions, and lack of proper isolation techniques, and purification methods present challenges to the application of MSC-derived EVs in regenerative medicine. To overcome these challenges, a GMP-complying method was developed for large-scale production of EV (Bari et al., 2018), and large scale 3D-culture methods and extracellular matrix-based scaffolds have been devised for the large-scale production of functional EV (Phan et al., 2018). Therefore, techniques that enable the production of functionally-uniform MSC-derived EV might provide therapeutic agents in various inflammatory conditions.

6. Conclusion and future directions

Stem cells have been extensively used in many fields of tissue engineering and regenerative medicine. This fascinating area of research has resulted in breakthroughs and potential means of effectively treating various inflammatory disorders. In particular, the finding that the immunomodulatory effects of stem cells are mediated by anti-inflammatory cytokine release indicates a promise regarding the treatment of inflammatory diseases. Despite the preclinical success of MSC-based therapy for the treatment of different diseases, clinical studies have produced mixed and often contradictory results. Optimal selection criteria for MSC doses, donors, culture conditions, routes of administration, and patients and clinical evaluation criteria have yet to be

established. The optimal selection and harmonization of these factors would provide concrete conclusions regarding the potential of MSC-based therapy. Moreover, we hold that further research on MSC biology and the mechanisms responsible for the therapeutic effects of MSCs under various pathological conditions will provide directions for future applications.

Declarations

The authors declare no competing financial interest.

Funding

This study was supported by grants from the Basic Science Research Program through the National Research Foundation (NRF) of Korea funded by the Korean Ministry of Science, ICT, and Future Planning (grant no. 2015R1A5A2009124 and no. 2017R1D1A1B03027831), the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health and Welfare, Republic of Korea (Grant HI18C0453), and from the Creative Economy Leading Technology Development Program of the Gyeongsangbuk-do and Gyeongbuk Science & Technology Promotion Center (grant no. SF316001A).

Availability of data and materials

Not applicable.

Author contributions

Conceptualizations: S.R., S.P., and J.H.J. Writing review: S.R. and S.P. Editing: S.R., S.P., C.Y., J.H.J., J.O.K. Supervision: C.Y. and J.H.J.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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