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Review Article

Bioactive Mediators Associated with Mesenchymal Stem Cells-Mediated Immunomodulation

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Abstract

Human mesenchymal stem cells (MSCs) have gained the attention in the field of regenerative medicine and cell therapy due to the low immunogenicity, distinctive immunomodulatory properties and also for the large potential to differentiate into many cell lines with not only mesenchymal origin. Our knowledge of the reparative, regenerative and immunomodulatory properties of MSCs is advancing. At the present we have a very comprehensible understanding how the MSCs affects the immune system. The MSCs are able to influence both the innate and adaptive immune responses via wide range of effector mechanisms. In particular, these mechanisms include secretion of soluble bioactive agents, induction of regulatory T cells, modulation of tolerogenic dendritic cells, and induction of anergy and apoptosis. In order to exert the immunomodulatory properties the MSCs require priming by inflammatory factors released into the local microenvironment. Subsequently, in order to perform tissue repair functions, the MSCs influence the microenvironment by modulation of inflammatory processes and release of various bioactive factors. Based on these unique features we can state that the MSCs can be successfully used as the powerful tools in the therapies of tissue damage on the immunological basis. In conjunction with gene manipulation techniques these cells can serve as carriers for therapeutic agents. Additionally, the MSCs may be used in anticancer therapies and as the cells that positively influence the survival of transplanted tissues and organs.

Keywords: Mesenchymal Stem Cells; Immunomodulation; Soluble Bioactive Factors; Homing; Inflammatory Environment.

Introduction

Mesenchymal stem cells (MSCs) are the subset of non-hematopoietic stem cells that can be found in almost all tissues capable of regeneration [1]. They play a key role in the maintenance of a homeostasis and the regulation of maturation of hematopoietic cells in the bone marrow [2]. The MSCs are located typically in the perivascular niches as a pericytes expressing CD146 [3]. However, not all MSCs can be considered as equivalent to the pericytes, nor all pericytes have characteristic MSCs properties [4, 5].

Mesenchymal stem cells were identified for the first time as an adherent population of fibroblast-like cells located in the bone marrow capable of osteogenic differentiation [6]. It has been shown that the MSCs can also be routinely isolated from tissues such as adipose tissue, peripheral blood, umbilical cord, placental membranes and many others [1,7,8]. Additionally, the MSCs can be expanded more than 10^4-times in *in vitro* conditions without the loss of differential potential [9].

Even with the absence of the exlusive marker, the MSCs can be identified by positive expression of CD44, CD71, CD73, CD90, CD105 and CD271^{bright} surface markers and by lacking the expression of CD11b, CD14, CD19, CD34, CD45, CD79α and co-stimulatory molecules CD80, CD86 [10,11,12]. The MSCs should also exhibit low expression levels of major histocompatibility complex (MHC) class I molecules and under standard tissue culture conditions have to be able to adhere on culture plastic.

After the appropriate stimulation the MSCs can differentiate into many cell types with not only of mesenchymal origin, such as osteocytes, chondrocytes, adipocytes, myocytes and astrocytes [2]. Besides the action of specific growth factors and chemical mediators [2] differentiation process can be affected by many other factors. These include the tissue origin from which the MSCs are isolated [1], donor age [13], density of cells and their arrangement [14-16], the stage of the culture and passage [9], variety of electrical and mechanical forces involved [17-19] and the physical properties of a carrier or substrate [15,20,21].

Mesenchymal stem cells are characteristic with their migratory abilities. After the administration to the recipient the MSCs specifically migrate to the sites of inflammation or other tissue damage. This is typically associated with cytokine outburst [22,23].

A large number of previously conducted *in vitro* studies described the effects of MSCs on innate and adaptive immune responses. The authors pointed out that the MSCs have ability to affect various components of the innate immune system what include complement [24,25], Toll-like receptors signaling (TLRs) [26], monocyte/macrophages [27,28], dendritic cells (DCs) [29,30], NK cells [31,32], neutrophils and mast cells [33,34]. In relation to the adaptive immune responses the MSCs are able to inhibit directly T cell functions, skew the balance between T helper (Th) subsets and modulate regulatory T cells (Treg) [35-37]. Several findings also indicate that the MSCs are capable to modulate B cells proliferation and functions [38,39].

One of the key characteristics in the process of immunomodulation is ability to release many different growth factors, cytokines and adhesion molecules by which the MSCs affect the microenvironment of the inflamed or degenerating target tissue, thus having a positive paracrine effect on the tissue repair [40-42].

MSCs mediate immunomodulatory activity in a number of *in vivo* models, such as graft versus host disease (GvHD) [43,44], experimental autoimmune encephalomyelitis (EAE) [45], inflammatory bowel disease [46], allergic respiratory diseases [47] and many others [48]. It has been shown that MSCs are able to escape the immune system recognition mechanisms and modulates the host's defense mechanisms [40-42]. Therefore, the MSCs may modulate peripheral tolerance, transplantation tolerance, tolerance between mother and fetus, and also play an important role in autoimmune response [2,44,48]. The MSCs may act as primary matrices in the tissue repair processes during inflammation and injury [49,50]. Due to high affinity to the tumor tissue, as part of tumor stroma, the MSCs can also serve as targeted carriers for therapeutic agents used in anti-cancer therapy [51,52].

Immunosuppressive bioactive factors produced by mesenchymal stem cells

Opinions about the role and function of the MSCs in inflammatory environment had gradually changed in recent years. Novel experimental data triggered significant shifts in hypotheses or firm beliefs on these mechanisms [53].

MSCs have been initially investigated as feeder layers (1) providing an adequate environment for cultivation of hematopoietic cells. Later they have been examined as cells capable of repair (2) which can be transplanted into damaged tissue and after that differentiate into functional cells thus replacing damaged cells. Recently, experimental data show that activated MSCs in most cases appear only temporarily in the damaged tissue (3). In order to limit the destruction and increase the intensity of reparative and regenerative mechanisms the MSCs briefly interact with other immune cells as well as with the cells of damaged tissue. These modulatory mechanisms include an increase of gene expression and modulation of the excessive inflammatory and immune responses. These short term interactions provide a protective niche for increase of the proliferation and differentiation of endogenous progenitor cells [53]. The MSCs activities are thus able to modulate many immune cells types *in vitro* and *in vivo*. This action is largely associated with release of soluble immunomodulatory factors [40,42,54]. Most of these factors are constitutively expressed by MSCs, but as described above, their production is managed under specific microenvironmental conditions.

Based on these findings it is likely that the importance and function of specific mediators varies according to the characteristics of the local microenvironment. Therefore, we propose that the actual priming process of MSCs is a complex procedure and resulting therapeutic effect of the MSCs is often carried out through the synergistic action of several factors.

Prostaglandin E2

Prostaglandin E2 (PGE-2) is a small short-acting lipid mediator which plays an essential role in immunomodulation processes. The MSCs constitutively express PGE-2 and its expression is increased through action of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and TLR 3 ligands. However, the PGE-2 expression does not increase via the action of TLR4 ligands [55,56].

Prostaglandin E2 is able to affect various T cell functions but its action is concentration dependent. At a higher concentration the T cell proliferation is inhibited due to lower interleukin-2 (IL-2) production and inhibition of IL-2 receptor expression [57,58]. It is believed that these processes inhibit a signaling through the Janus kinase 3 (JAK3) which weakens the binding of signal transducer and activator of transcription-5 protein (STAT-5) to the DNA. The lower concentrations of PGE-2 have preferable modulatory functions via skewing the Th1 type of responses towards a Th2/Th17 of response [59]. The shift of the Th1 immune responses towards a Th2 is mediated by blocking of the pro-inflammatory cytokines production (IL-12 and IFN-γ) and by stimulation of Th2 cytokines (IL-4 and IL-5). The important feature of the PGE-2 pathway is induction of functional Foxp3+ Treg via activation of PGE receptor subtypes 2 and 4 (EP2/EP 4) possibly through activation of nuclear fac-

tor-κB (NF-κB) pathways [60].

In addition to the specific effects against T cells [61] PGE-2 produced by MSCs plays an important role in the process of re-programming of macrophages and DCs [30,62,64]. It also has been shown that MSCs have the ability to inhibit the functions of mast cells through the cyclooxygenase-2 (COX-2)-dependent mechanism [33]. However, in the process of MSCs mediated immunoregulation PGE-2 acts in combination with other immunomodulatory molecules. It was found out that PGE-2 produced by human MSCs acts together with the indoleamine 2,3-dioxygenase (IDO). Simultaneously they modulate the NK cells functions, T cell proliferation and alter the cell cytotoxicity or cytokine production [30,64,61].

Indoleamine 2,3-dioxygenase

Indoleamine 2,3-dioxygenase (IDO) is an enzyme that along kynurenine pathway catalyzes the rate limiting step in the catabolic pathway of tryptophan what is an essential amino acid necessary for the T cell proliferation [65]. Reduction in local tryptophan concentration and its pathway metabolites contributes to the immunomodulatory effect of IDO expressing cells by blockade of T cells cell cycle [66] through the induction of apoptosis via activation of caspase 8 and cytochrome c mitochondrial release [67].

Indoleamine 2,3-dioxygenase expression is induced in MSCs upon the IFN-γ stimulation [68,69], or through the TLR3 and TLR4 ligands [26]. The expression of IDO is further bolstered by the other pro-inflammatory cytokines such as TNF-α and IL-1 [70]. It was shown that stimulation via TLR3 induced the IDO production but the TLR4 did not [56]. Other findings suggest that the MSCs activation through TLR3 and TLR4 abolished the immunosuppressive effect of the MSCs [71]. Effect of IDO produced by MSCs was also associated with the process of immune cells re-education what also includes polarization of macrophages towards anti-inflammatory M2 phenotype [39], the induction of tolerogenic DCs [30] and Treg *in vivo* as well as the skewing of Th1→Th2 response [72]. In addition to these effects the IDO produced by MSCs is able to directly affect T cells differentiation [73] and proliferation of T and NK cells [31,32]. Studies using the IDO inhibitor (1-methyl-L-tryptophan) or $IDO^{-/-}$ MSCs have shown that IDO plays an essential role in the control of immune responses mediated by MSCs [10,34,74].

However, based on comparison of the MSCs isolated from different species, some species variations in MSCs-mediated immunosuppression have been identified. During the immunomodulation process mouse MSCs primarily uses the nitric oxide (NO) pathway, while human and monkey MSCs requires action of IDO [71]. Since the total amount of tryptophan in the body is not significantly affected by these processes it should be pointed out that tryptophan depletion or production of its metabolites through the action of IDO acts only locally [28,72]. Additionally, mouse and human MSCs produce a number of specific chemokines which allow them to attract the immune cells within their vicinity [71].

Nitric oxide

Nitric oxide (NO) is a highly labile oxidative compound active only in close proximity to the cells that produce it. Its biological activity is already greatly reduced by distance of a few cells from the production site [75]. This explains the observation why immunosuppression mediated by the MSCs was restricted if the cells were separated with semipermeable membrane [76]. NO is a product of the enzymatic reaction catalyzed by inducible NO synthase (iNOS) and is capable to inhibit the proliferation of T cells and induce apoptosis by suppression of the STAT-5 phosphorylation [76,77]. It was also found out that stimulation of MSCs via IFN-γ, and TNF-α or IL-1 increased the iNOS expression in mice [76].

NO is also able to influence the primary and secondary immune response. In addition to its effects on T cells it is also able to inhibit TNF-α and prevent maturation of DCs in humans through the action of cyclic guanylate monophosphate (cGMP) [78]. Since the characteristic ability of mature DCs is antigen presentation this ability is inhibited in a NO sufficiently enriched environment and the resulting immune responses are suppressed [30,79]. The experimental use of cGMP inhibitors such as methylene blue and LY-83583 showed that the cGMP function as a T cells suppressor. Reversing the suppression of T cells indicates that cGMP plays an essential role in the inactivation of T cells [80].

Through the synergistic action of chemokines and adhesion molecules produced by MSCs the immune cells accumulate within the MSCs vicinity. The cells are then affected by the action of high NO concentrations. It was found out that inhibition of iNOS activity in *in vivo* studies largely reverses the therapeutic effect of MSCs in the animal models [76,81].

TNF-stimulated gene 6 protein

TNF-stimulated gene 6 protein (TSG-6) is a protein with anti-inflammatory properties, induced by IL-1/TNF and is highly expressed by variety of cells in patients with inflammatory or autoimmune diseases [82]. It has been shown that the TSG-6 produced by MSCs mediate the protective-modulating effects in different models of tissue injury [83-85]. In all these models the TSG-6 has been able to inhibit the early inflammatory response. In particular, the function of inflammatory cytokines and neutrophil infiltration was affected. The anti-inflammatory effect of TSG-6 in the model of corneal injury was dose-dependent and the inhibition of early immune response significantly decreased neovascularization and further development of the opacity [85]. In another injury model an increased survival of allogeneic corneal graft was associated with reduced activation of the antigen presenting cells (APC) presented in the graft and draining lymph nodes [89]. TSG-6 produced by human MSCs was also able to mitigate the zymosan-induced peritonitis through the reduction of TLR2/NF-κB signaling in resident macrophages [83]. Exactly how the TSG-6 mediates its effect at different stages of inflammation or how it cooperates with other mediators, such as IDO, NO or PGE-2 needs to be further elucidated.

Transforming growth factor β1

Transforming growth factor β is a pleiotropic growth factor that consists of three separate isoforms (TGF-β 1-3) and has demonstrated to have immunosuppressive properties. It is able to inhibit T cell proliferation by modulating IL-2-induced activation of signal transducers and activators of JAK transcriptional pathways in T cells [86]. In addition to its direct immunosuppressive function TGF-β is able to induce Treg lymphocytes by increasing the expression of Foxp3 [86-88] It is believed that activation of Foxp3 subsequently strengthens the TGF-β signaling in induced Treg cells through the reduction of Smad-7 inhibitor protein [88,89]. Several authors associated the TGF-β secretion by the MSCs with activation and expansion of Treg cells [59,87,90]. Experimental findings show that the neutralization of TGF-β1 in co-culture of MSC/CD4+ T cells leads to the reduction of Foxp3 expression to background level [87]. Since it was observed that TGF-β1 and hepatocyte growth factor (HGF) produced by MSCs, isolated from bone marrow and placenta, were able to modulate T cell proliferation it is likely that TGF-β coordinates its modulatory actions in association with HGF [91,92]. This observation was confirmed in study where the proliferation of T cells was fully restored by antibodies blocking the TGF-β1 and HGF [91]. Similarly, the addition of antibodies against TGF-β and IL-10 partially reversed the immunosuppressive effect of human MSCs derived from a placenta [92].

Hepatocyte growth factor

Mesenchyme-derived hepatocyte growth factor (HGF) is a multifunctional cytokine involved in the cells growth, morphogenesis, angiogenesis and cell motility [93,94]. HGF in combination with receptor tyrosine kinase regulates signal transduction through the transmembrane receptor encoded by c-Met proto-oncogene [93,94]. There are two major effector signaling pathways for the c-Met/HGF signal transduction: mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K) signaling pathway. However, the effects of HGF depend mostly on the state of the target cell, and therefore is described as pro-apoptotic and anti-apoptotic [93,94]. Since the transduction of survival signal via MAPK, PI3K-Akt and NF-κB is responsible for anti-apoptotic nature of c-Met [95,96] it was found out that activation of c-Met in the cells with DNA damage prevents their apoptosis. Moreover, the c-Met may also bind to Fas receptor and thus block the Fas/FasL interaction, and thus prevent cell death [94,97]. In addition to the immunomodulatory effects of HGF on T cells, the ability to affect the different functions of DCs was also observed [98].

Interleukin-10

Although the IL-10 activity is associated with MSCs-mediated immunomodulation its direct production by MSCs has not yet been definitely demonstrated. Some studies point out that the MSCs alone or stimulated with LPS/IL-3 do not express IL-10 whereas other studies suggest that MSCs could express high levels of IL-10 while co-cultured with activated lymphocytes [99-101]. Meanwhile, it was found out that direct MSCs contact with APCs, such as DCs and monocytes induced IL-10 production [49,102].

Even though that the IL-10 is acting as strong immunosuppressive interleukin it also possesses some immunostimulatory properties [103,104]. Through the inhibition of the NF-κB activity IL-10 diminishes the production of Th1 cytokines. On macrophages modulates the expression of MHC class II antigens and co-stimulatory molecules [105]. IL-10 also reduces the expression of MHC class I molecules [106] and its activity is associated with induction of the other immunomodulatory agents such as HLA-G what is representative of non-classical HLA class molecules [107]. IL-10 retains distinctive effects against T cells, monocytes, macrophages and DCs what ultimately leads to the inhibition of inflammatory response outcome. It also mediates the regulation of growth and differentiation of T cells, B cells, NK cells and other cells involved in inflammatory response. Moreover, IL-10 is able to stimulate the formation of Treg cells what is characterized by modification of their suppressory functions, necessary in the prevention or management of autoimmune and inflammatory processes [103,108]. However, it has been shown that IL-10 blocking did not affect the MSCs-mediated immunosuppression of lymphocytes [109].

HLA-G5

HLA-G is an atypical member of the HLA class I family and unlike most other HLA class I molecules has a low polymorphism. Under physiological conditions its expression is limited to a small number of cell types, such as placental trophoblast cells, thymic medullary epithelium, pancreas, cornea, nail matrix, monocytes, erythroid and endothelial precursors, and different immune cell populations [110-112]. However, its expression can be increased during certain inflammatory conditions [113]. It is known that HLA-G has immunosuppressive properties and is able to influence the CD4+ and CD8+ T cells, NK cells and DCs functions [108,110,113]. There have been identified three HLA-G receptors so far. The NK cells express KIR2DL4/CD158d receptor. Myeloid cells express LILRB2/ILT-4/CD85d receptor and a number of other immune system cells, including B cells, T cells, NK cells, monocytes and DCs express the LILRB1/ILT-2/CD85j receptor [114]. The interaction between HLA-G/LILRB is capable to inhibit leukocyte activation and LILRB2/HLA-G interaction plays a key role in DCs inactivation. This process can be also affected by LILBR1 [110]. It has been found that the interaction of HLA-G/LILRB2 follows the IL-6/STAT-3 pathway of DCs inactivation [115]. As a result of the MEK/ERK activation pathway blockage the NK cell cytotoxicity is reduced [116].

There are seven known isoforms of HLA-G. The MSCs secretion of HLA-G was identified for the first time in fetal MSCs. Since then, it also has been isolated from the adult human bone marrow-derived MSCs [117]. The immunosuppressive effects of HLA-G5 produced by MSCs have been documented after finding that neutralization of this protein partially restored the T cell proliferation in response to allogeneic stimuli. The secretion of HLA-G5 is increased during allogeneic stimulation what

has been essential for the expansion of functional Foxp3+ Treg cells. However, the molecular basis of these processes remains unclear [107].

Heme oxygenase 1

Heme oxygenase 1 (HO-1) is one of the heme oxygenase isomers; an enzyme that mediate the degradation of heme to biliverdine which together with the other metabolic products show potent anti-apoptotic, anti-oxidative and anti-inflammatory effects [118-121]. Until now there have been described three isomers of this enzyme (HO-1, 2, 3) from which only the HO-1 is not expressed constitutively. HO-1 can be induced through a variety of stress factors, pro-oxidative stimuli, inflammatory cytokines, heavy metals, lipopolysaccharide (LPS) and many other factors [119]. It was observed that HO-1 executes its modulatory function in the pathogenesis of various diseases and different injury models [119,121,122], positively affects a graft survival [123,124], it is capable of inhibiting the APC activity [125], and also acts protectively in GvHD *in vitro* [126]. HO-1 is able to suppress cytokine production and proliferation of T and NK cells [120,127,128]. The induction of Treg via IL-10 is one of the mechanisms by which the HO-1 cytoprotective function is provided. On model of ovalbumin-induced airway inflammation was found out that IL-10-deficient Treg cells were capable of suppressing T cell activation [122]. Based on these these findings HO-1 has been identified as an important mediator of the MSCs immunosuppressive action including the induction of Treg [120,128].

Monocyte chemotactic protein 1

The role of the CCL2 chemokine, also known as monocyte chemotactic protein 1 (MCP-1), that acts as an antagonist of related CCR2 receptor, was described during the MSCs-mediated immunosuppression in EAE model [129,130]. CCL2-deficient MSCs showed a much lower potential to inhibit the IL-17 secretion by activated T cells what subsequently caused the loss of protective action against the EAE [130]. Though, the effects of CCL2 were not limited only to the maintenance of IL-17 production by T cells. This chemokine was also capable of suppressing the production of immunoglobulins by plasma cells via the inactivation of STAT-3 and induction of paired box protein 5 (PAX5) [130]. After TLRs stimulation, during bacterial infection, the MSCs were capable of CCL2 production what subsequently induced the emigration of monocytes from bone marrow to the periphery [129,131].

Besides the above mentioned mediators, there are also other possible factors involved in the MSCs-mediated modulation of immune cells. These include leukemia inhibitory factor (LIF) [132], IL-6 [133], IL-27 [134], galectins [135,136], programmed death-ligand 1 (PD-L1) [137,138], intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) [139]. The amount of mediators identified so far suggests that the MSCs are able to use a wide range of immunomodulatory mechanisms in context of their therapeutic potential over various pathological conditions. Therapies utilizing the MSCs has been successful in a number of disease models and clinical conditions associated either with pathological responses of effector T cells or failure of disease control provided by Treg [74,72,81,140,141]. Therefore, we can state that the MSCs are able to convey effectively modulatory effects against the immune cells most of which are suppressive by nature.

Conclusion

Typical feature of mesenchymal stem cells is their well known potential to differentiate into various tissue-specific cell populations and the ability to create immunomodulatory microenvironment in order to help to minimize organ damage caused by the inflammation or cells activated by the immune system. The MSCs are currently part of well-established pharmaceuticals and therapeutic procedures for the treatment of many disorders related to the cartilage or bone repair and cardiovascular related tissues injuries. However, the spectrum of applications gradually extends to the other conditions such as diabetes, stroke, diseases on the immunological basis and some types of cancer. At the present time there are numbers of clinical studies focused on the stem cells utilization in the treatment of the above mentioned disorders. The MSCs are susceptible to the action of microenvironment and after appropriate activation they have potential to modulate and re-programme immune cells functions. Thus the MSCs are able to support the host immune defense or inhibit the inflammatory processes preferably by releasing a variety of bioactive soluble factors. It appears that even long-term implantation of MSCs within lesion is not necessary to exert immunomodulatory and pro-reparatory properties. A detailed knowledge of the inflammatory microenvironment suggests that the precise characterization of the microenvironment in relation to a particular disease or injury is important condition for a successful therapeutic application. Understanding the functions of key molecules and mechanisms of action is essential. Therefore the objectives of future research will have to result in an effort to define in better detail the stem cells niche characteristics *in vitro* and *in vivo*. The detailed knowledge of key molecules that regulate and determine the fate of MSCs will lead to the improvement of the cell therapy efficiency.

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