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REVIEW

Secretion of immunoregulatory cytokines by mesenchymal stem cells

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Abstract

According to the minimal criteria of the International Society of Cellular Therapy, mesenchymal stem cells (MSCs) are a population of undifferentiated cells defined by their ability to adhere to plastic surfaces when cultured under standard conditions, express a certain panel of phenotypic markers and can differentiate into osteogenic, chondrogenic and adipogenic lineages when cultured in specific inducing media. In parallel with their major role as undifferentiated cell reserves, MSCs have immunomodulatory functions which are exerted by direct cell-to-cell contacts, secretion of cytokines and/or by a combination of both mechanisms. There are no convincing data about a principal difference in the profile of cytokines secreted by MSCs isolated from different tissue sources, although some papers report some quantitative but not qualitative differences in cytokine secretion. The present review focuses on the basic cytokines secreted by MSCs as described in the literature by which the MSCs exert immunodulatory effects. It should be pointed out that MSCs themselves are objects of cytokine regulation. Hypothetical mechanisms by which the MSCs exert their immunoregulatory effects are also discussed in this review. These mechanisms may either influence the target immune cells directly or indirectly by affecting the activities of predominantly dendritic cells. Chemokines are also discussed as participants in this process by recruiting cells of the immune systems and thus making them targets of immunosuppression. This review aims to present and discuss the published data and the personal experience of the authors regarding cytokines secreted by MSCs and their effects on the cells of the immune system.

Key words: Mesenchymal stem cells; Immunomodulation; Cytokines; Chemokines; Dendritic cells

Core tip: Autoimmune diseases affect approximately 5% of the human population, leading to serious disability and effective methods to treat these diseases are still not perfect. Mesenchymal stem cells (MSCs) are assumed to be promising agents, both for regenerative medicine and cell therapy for autoimmune disorders. Under the influence of some factors, mesenchymal stem cells secrete cytokines which induce suppression of the immune response. Studies on the secreted cytokines and the precise mechanisms involved in these suppressive mechanisms would create possibilities for efficient application of MSCs as a therapeutic means for treatment of autoimmune diseases.

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INTRODUCTION

Maintenance of immunological self-tolerance and immune homeostasis in the organism is under the control of a complex and sophisticated process of immunoregulation and its dysfunction could be a critical factor in the development of autoreactive and potentially life-threatening conditions. Profound understanding of the precise mechanisms underlying this immunoregulatory process could lay the ground to develop a more suitable and efficient therapy for autoimmune diseases. Regulation of the immune response by mesenchymal stem cells (MSCs) is mediated by a number of cell subtypes and secreted factors and recently new cell-based therapeutic approaches have emerged as successful strategies for treatment of various inflammatory and autoimmune conditions. In the last decades, mesenchymal stem cells, one type of adult stem cells, have gained considerable interest as extremely promising cell therapeutic agents[1,2] due to their unique combination of immunomodulatory properties and self-renewal and multilineage differentiation capacity[3,4]. MSCs have been shown to exert profound anti-inflammatory and immunomodulatory effects on almost all the cells of the innate and adaptive immune systems *via* a variety of mechanisms, notably cytokine and chemokine secretion[5].

Mesenchymal stem cells are a population of undifferentiated multipotent adult stem cells that naturally reside within the human body and are generally defined as plastic-adherent, fibroblast-like cells possessing extensive self-renewal properties and potential to differentiate *in vitro* and *in vivo* into a variety of mesenchymal lineage cells[4,6]. MSCs were initially described in the bone marrow by Friedenstein *et al*[7,8] as a small subpopulation of colony-forming unit fibroblasts which could be distinguished from the rest of the bone marrow cells on the basis of their plastic adherence, spindle-shaped appearance and rapid expansion[7].

After their initial discovery in bone marrow (BM-MSCs), MSCs were isolated and characterized from a wide variety of other adult and fetal tissues, including adipose tissue (AT-MSCs), umbilical cord, dental pulp, skin, tendon, skeleton, muscle, spleen, brain, liver, periosteum, placenta, synovial and amniotic fluids[9,10]. MSCs from different sources may display some differences in the expression of surface markers. However, in general, the phenotypes of these cells are very similar and in the absence of an individual specific marker, MSCs are commonly defined by a panel of cell surface markers that include CD73, CD90 (Thy-1), CD105 (endoglin) and MHC class I , as well as the adhesion molecules CD44, CD29, CD54 (ICAM-1; intercellular adhesion molecule 1), CD106 (VCAM-1; vascular cell adhesion molecule) and CD166[11]. MSCs do not express hematopoietic markers such as CD34, CD45, CD14 and CD11 or co-stimulatory molecules like CD80, CD86 and CD40[11].

According to the minimal criteria of the International Society of Cellular Therapy (ISCT, 2006), the required functional and phenotypic features for defining MSCs include: (1) plastic adherence of the isolated cells under standard culture conditions; (2) positive expression of CD105, CD90 and CD73 markers in at least 95% of a cell population and lack of expression of CD34, CD45, CD11b, CD14, CD19 or CD79a and HLA-DR markers in greater than 95% of the culture, as measured by flow cytometry; and (3) trilineage differentiation potential into osteoblasts, adipocytes and chondroblasts in *in vitro* culture with specific stimuli[12].

Besides this, trilineage multipotency experimental data have demonstrated that MSCs can also differentiate into other mesodermal lineages, such as skeletal myocytes[13,14], cardiomyocytes[15], tenocytes[16,17] and endothelial cells[18,19]. Moreover, it has been reported that under appropriate conditions, MSCs have the capacity to differentiate into types of cells of endodermal and ectodermal lineages, including hepatocytes[20,21], neuronal cells with neuron-like functions[22-24], insulin-producing cells[25,26], photoreceptor cells[27], renal tubular epithelial cells[28], epidermal and sebaceous duct cells[29]. In addition to their comprehensive differentiation potential, MSCs have the ability to migrate and engraft at sites of inflammation and injury in response to cytokines, chemokines and growth factors[30,31]. At a wound site, they can exert local reparative effects through transdifferentiation into tissue-specific cell types or *via* the paracrine secretion of soluble factors with anti-inflammatory and wound healing activities[32-34].

Another aspect that makes MSCs of particular clinical interest is the finding that they exert a wide range of immunomodulatory activities affecting both cell-mediated and humoral immune response. A search in the PubMed data base reveals 149 papers, while the ScienceDirect data base contains 495 papers in peer-reviewed journals describing animal models developed to study various aspects of the immunomodulatory effects of MSCs in the period of 2001-2014. The promising results obtained prompt clinical trials in humans using MSCs as a biological agent for immunomodulation. According to the web site of Clinical Trials.gov (a service of the United States National Institutes of Health), more than 418 clinical trials are currently under way to assess the clinical effects of mesenchymal stem cells isolated from various sources, with the greater part of the trials studying the immunomodulatory effect of autologous or allogeneic MSCs in autoimmune diseases such as ulcerative colitis, multiple sclerosis, primary Sjogren's syndrom, systemic scleroderma, Crohn's disease *etc*. Similarly, numerous trials are devoted to the effect of MSCs on modulating the reactions after allogeneic transplantation, such as chronic graft-versus-host disease (GVHD), poor graft function, *etc*.

Table 1 Cytokines secreted by mesenchymal stem cells and the corresponding target cells

Cytokines secreted by MSCs	Target cells
IL-10	Mph, Neu, DCs, Th1, Tregs, Tr1, tumor cells
IL-6	Neu, Mo, DCs, B, Th2, Tregs, Th17, CD8+FoxP3+
TGFβ	Mph, NK, DCs, B, T, Tregs
Chemokines	Neu, Mo, NK, Eo, Baso, DCs, Ly
CCL-2/MCP-1	Mph, EC, PL, Th2, Th17
CCL-5/RANTES	Neu, Mo, DCs, Th1, Tregs, CD8+FoxP3+
IDO	Mo, DCs, B, T, Tregs
VEGF	DCs, EC, Th1, Th17, Tregs
ICAM	T, MSCs
PGE2	Mph, Mo, NK, DCs, T, Tr1

MSCs: Mesenchymal stem cells; TGFβ: Transforming growth factor β; CCL: CC chemokine ligand; MCP-1: Monocyte chemotactic protein 1; RANTES: Regulated on activation, normal T cell expressed and secreted; IDO: Indoleamine-2,3-dioxygenase; VEGF: Vascular endothelial growth factor; ICAM: Intercellular adhesion molecule; PGE2: Prostaglandin E2; Mph: Macrophages; Neu: Neutrophils; DCs: Dendritic cells; Th: T helpers; Tregs: T regulatory cells; Tr1: T regulatory 1; Mo: Monocytes; B: B cells; NK: Natural killers; T: T cells; Eo: Eosinophils; Baso: Basophils; Ly: Lymphocytes; EC: Endothelial cells; PL: Plasma cells.

In general, the data from these studies have shown that MSCs exert immunomodulatory effects by both cell-to-cell contacts and by secreting biologically active substances, growth factors, cytokines and chemokines.

MSCs have been shown to inhibit T-cell activation and proliferation triggered by mitogenic or antigenic stimulation with allogeneic cells (mixed lymphocyte cultures) or nominal antigens[35,36]. MSCs can also influence T-cell responses indirectly through suppression of CD34+ progenitor cell and monocyte-derived dendritic cell differentiation, as well as through inhibition of their antigen-presenting functions[37-40]. A number of studies have demonstrated that MSCs have the capacity to inhibit B-cell proliferation, differentiation and immunoglobulin production *in vitro*[41,42] as well as to down-regulate the proliferation, cytokine production and cytotoxicity of NK cells[43,44]. Their ability to promote the generation and to maintain the activity of different subtypes of regulatory T cells (Tr1, CD4+FoxP3+, CD8+FoxP3+) is well documented, especially CD4+FoxP3+, also known as Tregs[45-48]. In addition, MSCs are considered as not being inherently immunogenic as they express low-intermediate levels of HLA class I antigens and either do not express or express negligibly low levels of HLA class II antigens and co-stimulatory molecules, such as CD80, CD86 and CD40[49,50]. Therefore, they should be able to escape not only from the recognition by alloreactive T cells[49,51], but also the cell-specific lysis by cytotoxic T lymphocytes (CTLs)[52] and freshly isolated alloreactive NK cells[53]. Some of these *in vitro* properties have already been successfully clinically exploited for the treatment of disorders such as acute graft-versus-host disease[54,55], multiple sclerosis[56] and systemic lupus erythematosus[57].

Although the precise mechanisms underlying MSCs immunomodulation are still not completely understood, a number of soluble factors involved in the process have already been identified.

The present review discusses some MSC secreted cytokines which are involved in regulation of the immune response. For the purposes of this review, the term "immunoregulation" is used in a very strict sense as an influence on immunocompetent cells. It should be pointed out that the immunomodulatory effects of MSCs are jointly executed by both secretory factors and direct cell-to-cell contacts. In that case, cytokines most commonly do not directly affect the target cells but interact with other biologically active factors to achieve the effect of immunosuppression. There are some papers describing fine differences in MSC secreted cytokine profiles with immunoregulatory effects but in this review the generally accepted cytokines most often cited in the literature are discussed. The mechanisms of immunomodulation by direct cellular contacts will not be discussed in this review.

MSCs isolated from different tissues are different in some fine specifics as mentioned above. However, no data have been published describing significant differences in the profiles of secreted cytokines by different types of MSCs. Most authors report either a lack of differences or find some quantitative differences in the levels of cytokines secreted by AT-MSCs or BM-MSCs[58-60]. Our experimental data also show some quantitative differences in the cytokine secretion[37]. Similar findings are reported when embryonic, fetal and adult MSCs have been compared[61].

MSCs secrete cytokines either "spontaneously" or after induction by other cytokines, the most important being IFNγ, TNFα and IL-1β[62-64], and it should be underlined that MSCs are not always immunosuppressive. It is assumed that their effects are determined by the local conditions of the microenvironment and sometimes the pro-inflammatory IFNγ, TNFα and IL-1β cytokines may induce secretion of anti-inflammatory immunosuppressive factors. Engagement of certain Toll-like receptors (TLR) expressed by MSCs can determine their pro or anti-inflammatory effects[65-67]. The definition of cytokines as pro or anti-inflammatory is quite far from their real effects because it seems that there is not a single cytokine which is not engaged in both types of reactions. Nev-

ertheless, that definition is quite convenient and will be used further in the present review. The most important immunoregulatory cytokines described in the literature are presented in Table 1.

INTERLEUKIN 10

Interleukin 10 (IL-10) is pleiotropic cytokine identified in the 1980s and characterized by its anti-inflammatory effect related to the induction of immune tolerance[68-71]. It has been established that IL-10 suppresses the functions of macrophages and neutrophils[70,72], inhibits the Th1 immune response[70,73-76], influences NF-kB synthesis[77] and causes expression of anti-inflammatory molecules, such as protease inhibitors[78] and IL-1 and TNFα antagonists[79].

The major function of IL-10 in induction of immune tolerance is its effect on the antigen presenting cells and particularly on the dendritic cells (DCs). IL-10 suppresses the secretion of pro-inflammatory cytokines (TNFα, IL-1, IL-6, IL-8, IL-12) by DCs and the expression of MHC Ⅱ molecules, as well as co-stimulatory complex B7 on their surface[75-77]. In parallel to that, IL-10 is capable of inducing anergy of T lymphocytes by directly inhibiting the phosphorylation of CD28. In that way, one of the basic immunosuppressive mechanisms is executed by IL-10 by inducing a tolerogenic type of dendritic cells with reduced HLA-Ⅱ and B7 expression and by suppression of CD28 (the partner of B7) expression on the surface of the T lymphocytes. This "two sided" suppression of the second signal which is unconditionally needed for activation of the T lymphocytes induces a deep anergy in this cell population[37,69-71,76].

Further on, IL-10 is directly engaged in the induction of immune tolerance by two types of T regulatory lymphocytes: Tregs and Tr1[76]. IL-10 is one of the cytokines related to the generation of Tregs[73] which secretes IL-10 by itself and this process has been described both for "natural" FoxP3+ Tregs and for FoxP3+ Tregs generated after response to a specific antigen[70,73,80].

A specific feature of IL-10 and some other cytokines is that the producing cells are both the source and target of the cytokine effect and this predominantly affects the dendritic and T regulatory cells. A good example is that tolerogenic DCs secrete IL-10 and thus induce the generation of regulatory T helpers (FoxP3 and Tr1) which secrete IL-10 inducing tolerogenic phenotype of DCs[70,71,76]. Likewise, many other cytokines IL-10 can also act in an autocrine loop.

The effect of IL-10 is mediated *via* its binding to its specific receptor (IL-10R) and subsequent interaction between JAK1 and STAT-3[73,77], a mechanism which is common for many other cytokines. Besides the antigen-presenting cells and particularly tolerogenic DCs, Tregs and Tr1, other immune cells secrete IL-10 and these include T and B lymphocytes, NK cells, neutrophils and macrophages[76,80]. The role of IL-10 secreted by Th2 helpers is well known[76,80] but some recently published data show that this cytokine in a somewhat paradoxical manner is secreted by both Th1 and Th17 cells. Quite often these "double secreting" cells (IL-10 simultaneously with IFNγ or IL-17) use IL-10 to suppress their own pro-inflammatory effect, both directly and/or with the help of tolerogenic antigen-presenting cells[71,74].

IL-10 is considered to be a classical cytokine inducing immune tolerance but there are data which show that, similarly to most cytokines, IL-10 acts in more than one way. Its pro-immune effect has been described in tumorigenesis[70,72] and IL-10 is detected in a tumor environment and shown to have an anti-tumor effect. It is assumed that this effect is due to inhibition of the tumor angiogenesis and enhancement of the nitric oxide secretion. IL-10 is also connected to the inhibition of the expression of MHC by the tumor cells which makes them an easier target for the NK cells. Some pro-inflammatory effects of IL-10 have been demonstrated which seem to lead to enhanced apoptosis of Tregs and stimulation of the antigen up-take by the antigen-presenting cells[70].

IL-10 is the cytokine most commonly discussed in relation to the immunoregulatory effects of MSCs. Nevertheless, the published data demonstrating the secretion of IL-10 by MSCs are quite contradictory. Almost half of the papers discussed in the present review report positive secretion of IL-10 by MSCs[62,66,81-84], while the other half and our own experimental results reject such a possibility[60,64,69,78,85-88]. It is quite logical to support the concept proposed by some authors claiming that MSCs secrete IL-10 under specific conditions with the inflammatory environment and presence of cytokines (IFNγ, IL-1b and TNFα) which activate certain Toll-like receptors on MSCs[63,65,67]. Although there is no definite opinion about the conditions under which MSCs secrete IL-10, their role is indisputable as a factor which causes indirect stimulation of IL-10 secretion by other cells. It has been shown that MSCs secrete factors which up-regulate the secretion of IL-10 by peripheral blood mononuclear cells (PBMCs)[59], as well as by tolerogenic macrophages[89] and tolerogenic DCs[37,69,90]. It is also assumed although not undoubtedly proven that MSCs induce generation of Tregs[59,62,90] and our results show that when cultured in MSC conditioned medium, the fraction of CD4+FoxP3+ lymphocytes is increased and this effect is directly induced by MSCs without any involvement of DCs[69].

IL-6

IL-6 was identified in 1986 as a factor stimulating B lymphocytes[91]. It is now known that it is a pleiotropic cytokine with a key role in a multitude of processes such as regulation of the immune response, hematopoiesis, inflammation, cell survival, apoptosis, cell proliferation and oncogenesis[91,92]. The action of IL-6 is mediated by its binding with a membrane IL-6 receptor (mIL-6R) and gp130 as gp130 interacts with the JAK-STAT system[91]. A small fraction of cells show expression of mIL-6R but almost all cell types express gp130. Cells express-

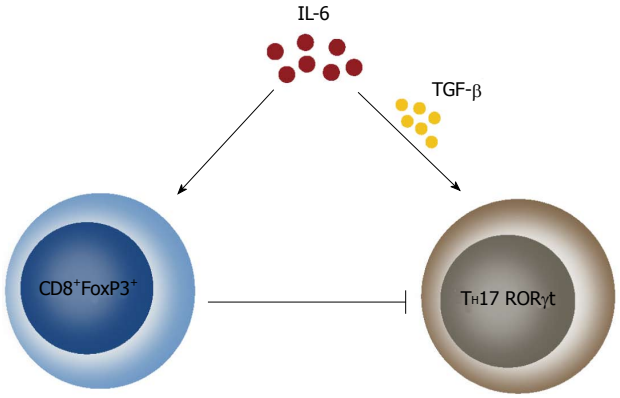

Figure 1 Effect of Interleukin 6 on Th17 formation. IL-6 exerts a dual effect on the generation of Th17 cells. On one side, IL-6 in concert with TGFβ facilitates the generation of this cell population and on the other side, IL-6 inhibits the Th17 cells by inducing the generation of $CD8^+FoxP3^+$ T lymphocytes. TGFβ: Transforming growth factor β.

ing only gp130 can bind the complex IL-6/soluble IL-6R (sIL-6R), a process known as trans-signaling, which makes a lot of cell populations susceptible to the effects of IL-6[93,94]. Some authors believe that the effect of IL-6 mediated by trans-signaling (IL-6/sIL-6R) is related to a pro-inflammatory effect, while the "classical" pathway (IL-6/mIL-6R) of activation is connected to the anti-inflammatory action of the cytokine[94]. Such an assumption sounds quite logical, keeping in mind the dual nature of IL-6 because of its pro-inflammatory and/or anti-inflammatory effects[75,82]. IL-6 is routinely described as a classical pro-inflammatory cytokine based on well proven effects of this cytokine. In concert with IL-1 and TNFα, this cytokine induces secretion of acute phase proteins, causes neutrophil recruitment, expression of cell adhesive molecules and a switch from neutrophil to macrophage induced inflammation[72,75,94]. IL-6 stimulates T cell proliferation[64,72] and together with IL-4 participates in the generation of the Th2 immune response[94]. IL-6 has a significant role in the triggering of humoral immune response by stimulating the B cell differentiation and secretion of antibodies[95]. Some recent data demonstrate that IL-6 together with TGFβ is engaged in regulation of the balance between the pro-inflammatory Th17 and immunosuppressive response mediated by Tregs as both cytokines acting together induce expression of RORγt which is the major transcription factor defining the Th17 cells[94,95].

Recently, simultaneously to the proven pro-inflammatory function of IL-6, quite convincing data have piled up about its function as an anti-inflammatory cytokine. It has been established that IL-6 suppresses the secretion of many pro-inflammatory cytokines, such as IL-1, TNFα, GM-CSF, IFNγ, but on the other hand, it induces the synthesis of glucocorticoids, IL-10, IL-1 receptor antagonist and soluble receptor for TNFα[72,75,79,96]. It has been demonstrated that IL-6 exerts its anti-inflammatory effect both locally and systemically because mice deficient to IL-6 gene have increased production of pro-inflammatory TNFα, GM-CSF and MIP-2[72]. Moreover, some new results show that IL-6 is a key factor in the formation and functions of the CD8+FoxP3+ cell population, which is related to suppression of the Th17 immune response[97]. Altogether, these data show that IL-6 has a "two sided" engagement in the modulation of the immune response by regulatory and Th17 cells. On one hand, IL-6 together with TGFβ induces formation of Th17 cells and on the other hand, IL-6 directly inhibits this response by its effect on CD8+FoxP3+ (Figure 1).

Contrary to IL-10, there is no doubt that IL-6 is secreted by MSCs and almost all authors agree with this statement[69,78,82,84,86,87]. Its secretion by MSCs has been demonstrated both in mice and in humans[62,66] and is detected either after induction with TNFα, IL-1b and IFNγ or spontaneously[37,61-63,72,95]. When MSCs were tested for 120 cytokines at mRNA and protein levels, it was established that IL-6 has the highest expression and the conclusion was made that IL-6 was the basic cytokine responsible for the immunoregulatory effects of MSCs[60]. After the secretion of IL-6 by MSCs, a suppression of the apoptosis of neutrophils is observed[64,68,81] and this effect could be very important for the connection between defects of apoptosis and triggering of autoimmune reactions. However, it is still not truly clarified whether IL-6 causes generation of classical Treg cells (CD4+FoxP3+), although there is no doubt about its direct effect on the generation of CD8+FoxP3+ cells. The fact that MSCs secrete active factors, increasing the numbers of Tregs, has been proven in a number of experiments[59,62,69] but there are no sure data that this effect is mediated *via* IL-6. It should be stated that such a mechanism is quite probable, keeping in mind the effect of IL-6 on the generation of CD8+FoxP3+.

MSCs can be both a source and a target of the effects of IL-6. It has been established that under the influence of IL-6, MSCs can transform malignant cells and have tumorogenic properties and this effect is mediated through the mechanism of trans-signaling[98]. These facts raise questions about the interactions between MSCs and the tumor microenvironment which is most commonly very rich in IL-6.

INTERACTIONS BETWEEN IL-6 AND IL-10

IL-6 stimulates the secretion of IL-10 by different types of cells and this effect has been proved without any doubt but the reverse interaction has not been demonstrated so far[96]. The effect of IL-6 on monocytes and dendritic cells is of particular importance for the complex process of immunoregulation. Some publications describe a pathway in which MSCs secrete IL-6 which directly or *via* induction of autocrine secretion of IL-10 influences the monocyte activity inhibiting their differentiation as dendritic cells[37,81]. Both IL-6 and the autocrine reacting IL-10 also suppress the capacity of DCs to present antigens and thus a population of immature tolerogenic dendritic cells is formed which secrete

IL-10[37,38,59,64,69,99,100]. Its effect stimulates the generation of T regulatory cells secreting IL-10 by themselves and potentiating further formation of tolerogenic DCs[62,85]. However, it should be noted that IL-6 and IL-10 are not the only cytokines involved in these complex interactions, for example, prostaglandin E2 (PGE2) which is another immunosuppressive factor secreted by MSCs interacting with IL-6 in suppression of the DCs differentiation[68].

TRANSFORMING GROWTH FACTOR BETA

One of the most prominent immunomodulatory cytokines produced and constitutively secreted by MSCs is transforming growth factor beta (TGFβ). As a pleiotropic cytokine, TGFβ regulates multiple fundamental cellular functions, including proliferation, differentiation, migration, adhesion and apoptosis, that affect numerous biological processes such as development, wound healing, carcinogenesis, angiogenesis and immune responses[101]. TGFβ is a member of a superfamily of dimeric polypeptide growth factors that consists of about 40 members in vertebrates, also including bone morphogenetic proteins (BMPs), activins, inhibins, growth differentiation factors (GDFs) and glial cell line-derived neurotrophic factor (GDNF)[102]. In mammals, three homologous TGFβ isoforms have been identified (TGFβ1, TGFβ2 and TGFβ3) that are controlled by specific genes[103]. Each isoform may exert a distinct role which depends on the target cell type, its state of differentiation and growth conditions[103].

TGFβ is now established as a principal mediator of immune regulation which plays an essential role in orchestrating the initiation and resolution of inflammatory responses, as well as in induction and maintenance of immune tolerance by influencing leukocyte proliferation, differentiation, activation and survival[104,105]. The diversity of modulatory activities that TGFβ exerts on the immune cell functions is quite extensive and includes effects such as inhibition of effector T-cell proliferation and function, generation of regulatory T cells from naïve T lymphocytes, attenuation of cytokine production and cytolytic activity of NK cells, suppression of B cells, dendritic cells and macrophages[105].

As TGFβ is constitutively produced by MSCs and most of its effects on immune cells mentioned above have also been demonstrated to be intrinsic features to MSCs, it is reasonable to assume the putative involvement of TGFβ as a mediator of their broad immunoregulatory properties.

It has been reported that MSCs isolated from human bone marrow were able to suppress CD4+ and CD8+ T-cell proliferation induced by cellular or nonspecific mitogenic stimuli and that this effect could be reversed by the addition of monoclonal anti-TGFβ1 neutralizing antibodies[35]. Later, it was shown that human bone marrow-derived MSCs, activated by blood CD14+ monocytes, secreted TGFβ1 which is responsible for inhibition of T-lymphocyte responses[106]. It has also been observed that TGFβ1 was involved in a cell contact-dependent inhibition of T-cell proliferation by MSCs[107]. Furthermore, MSCs obtained from dental pulp were found to produce TGFβ and to suppress the proliferation of PBMCs, which could be neutralized with anti-TGFβ antibodies[108]. In contrast, the addition of TLR-3 agonist augmented the suppressive potential of dental pulp-derived MSCs and potentiated TGFβ secretions by these cells[108].

Numerous mechanisms have been suggested to be involved in TGFβ-mediated inhibition of T-cell proliferation, differentiation and effector functions. One pathway by which TGFβ exerts its anti-proliferative effect on T lymphocytes is through blockade of the production of the T-cell mitogenic cytokine IL-2[109]. Functional analysis revealed that this is most likely due to impaired IL-2 gene transcription as a result of inhibition of IL-2 promoter/enhancer activity[109]. In another study[110], the transcription factor Smad3 was also shown to be critical for TGFβ1-mediated inhibition of IL-2 expression. Moreover, it has been demonstrated that the addition of exogenous IL-2 partially but not completely reversed the antiproliferative effects of TGFβ, indicating the suppressive activity of TGFβ on both production and intracellular signaling of IL-2[111].

TGFβ also inhibits cell proliferation through controlling the expression of cell cycle regulators, including up-regulation of cyclin-dependent kinase inhibitors (CKIs) p15, p21 and p27 and down-regulation of cell cycle-promoting factors, such as c-myc, cyclin D2 and cyclin E[112-115]. However, it has been reported that TGFβ is able to suppress the proliferation of T cells from mice deficient for all three CKIs mentioned above, demonstrating their dispensable role in this process[116]. In addition, a Smad3-dependent down-regulation of CDK4 has been described, suggesting a potential mechanism underlying resistance of Smad3-/- T cells to the induction of growth arrest by TGFβ[116].

TGFβ is a strong suppressor of T-cell differentiation and effector functions. In the presence of TGFβ, CD8+ T cells fail to acquire CTL function and CD4+ T lymphocytes do not become Th1 or Th2 cells[117]. The inhibition of T-cell differentiation occurs even in the presence of added IL-2, while at the same time T-cell proliferation remains unaffected[118].

One of the possible mechanisms of inhibition of T-cell differentiation by TGFβ is associated with decreased expression of IL-12 receptor β2-chain (IL-12Rβ2) and therefore with possible blockade of IL-12 signaling, which is required for Th1-cell development[119]. However, a more recent study has demonstrated that inhibition of T-bet (T-box expressed in T cells), a transcriptional activator of Th1 development, was critical for TGFβ-induced suppression of Th1-cell differentiation and that down-regulation of IL-12Rβ2 expression appeared not to be important for the TGFβ-mediated effect but rather was an event secondary to T-bet inhibition[120]. It has also been shown that restoration of T-bet expression through retroviral transduction of T-bet into

developing Th1 cells abrogated the inhibitory effect of TGFβ[120] which indicated that T-bet was the most critical and primary target for the inhibition of Th1 differentiation by TGFβ. In addition, TGFβ can also function indirectly to suppress Th1-cell differentiation by inhibiting IFNγ production by NK cells[121]. In this regard, it has been found that bone marrow-derived MSCs were able to suppress NK cell proliferation and IFNγ production through the secretion of TGFβ1 and prostaglandin E2[43].

TGFβ has also been found to potently down-regulate Th2-cell differentiation. A few studies[122,123] have shown that TGFβ-mediated prevention of Th2-cell development is due to suppressed expression of the transcription factor GATA-3, a key transcriptional activator of Th2-cell differentiation[124]. Moreover, TGFβ is able to induce the transcription factor Sox-4 and therefore negatively regulate GATA-3 function indirectly by two distinct mechanisms[125]. First, Sox-4 binds directly to GATA-3, preventing its transcriptional activity, and second, Sox-4 binds to the promoter of IL-5, a Th2 cytokine, and prevents GATA-3-mediated induction of gene expression[125].

In addition to suppressing proliferation, TGFβ has also been demonstrated to inhibit CD8+ T-cell effector functions through down-regulation of the expression of several essential CTL effector molecules such as perforin[126], Fas ligand (FasL)[127] and IFNγ[128,129]. Furthermore, the release of cytolytic granules by CTLs can be selectively suppressed by Tregs in a TGFβ-dependent manner[130].

Another important immunosuppressive activity of TGFβ could be its implication in the development of regulatory T cells. TGFβ promotes the conversion of naive CD4+T cells to Treg cells by induction of transcription factor FoxP3[131-133]. Several reports have indicated an essential role for both Smad2 and Smad3 transcription factors in TGFβ-mediated induction and maintenance of Foxp3 expression[134-137]. For instance, it was demonstrated that Smad2 and Smad3 double deficiency lead to complete ablation of FoxP3 upregulation by TGFβ, suggesting a functional redundancy between these two transcription factors in the induction of Tregs[137].

A recent paper has shown that both TGFβ1 and prostaglandin E2 derived from MSCs contributed to allogeneic MSCs induction of CD4+CD25+ FoxP3+ regulatory T cells that possess the ability to suppress alloantigen-driven proliferative responses in a mixed lymphocyte reaction[46]. Later, MSC-derived TGFβ1 was reported to be largely responsible for the increase in Treg frequency based on knockdown studies, thereby protecting breast cancer cells from immune clearance[138].

Recently, a mouse model of ragweed-induced asthma was described in which iv injected MSCs were capable of suppressing Th2-driven allergic responses *via* secretion of TGFβ[139]. The results suggested that IL-4 and/or IL-13 were able to activate the STAT6 pathway in MSCs which resulted in an increase of their TGFβ production. It seemed that TGFβ secreted by MSCs could mediate its beneficial effects (*i.e.*, inhibition of eosinophil infiltration and excess mucus production in the lung, decreased levels of Th2 cytokines (IL-4, IL-5 and IL-13) in bronchial lavage and lowered serum levels of Th2 immunoglobulins (IgG1 and IgE), either alone or together with recruited Treg cells[139].

CHEMOKINES

Chemokines are a family of structurally related peptides with comparatively small molecules (7,5-12,5 kDa) with chemoattractive properties[140]. Their physiological role is participation in processes like regulation of inflammation, cell differentiation and migration of immune cells, as well as angiogenesis[141]. Chemokines are produced and secreted by various cell types as a response to pro-inflammatory stimuli with the aim to attract and activate neutrophils, monocytes, lymphocytes and other effector cells to sites of infection[140].

It has been established that *in vitro* cultured MSCs constitutively secrete a multitude of different members of the chemokine family, such as CCL2 (MCP-1), CCL3 (MIP-1α), CCL4 (MIP-1β), CCL5 (RANTES), CCL7 (MCP-3), CCL20 (MIP-3α), CCL26 (eotaxin-3), CXCL1 (GROα), CXCL2 (GROβ), CXCL5 (ENA-78), CXCL8 (IL-8), CXCL10 (IP-10), CXCL11 (i-TAC), CXCL12 (SDF-1) and CX3CL1 (fractalkine)[142]. Our own data have shown that MSCs isolated from human bone marrow or adipose tissue secrete IL-8, GROα, MCP-1, RANTES and SDF-1 and these chemokines can be demonstrated to be present in MSC conditioned medium[59,69].

It is quite reasonable to assume that the types and the combinations of chemokines expressed by MSCs could vary depending on the specific microenvironment and contacts with surrounding cells, especially as the latter are immune cells. The target cells attracted by the cited group of chemokines are neutrophils, monocytes, eosinophils, basophils, T and B lymphocytes, DCs, NK cells, hematopoietic and endothelial progenitors[142].

These data might suggest that the MSC secreted chemokines just have a chemoattractive effect which does not seem to be related to immunoregulation. Nevertheless, chemokines could be considered a crucial element in exerting the immunomodulatory activity of MSCs *in vivo* because it is assumed that the chemokines mediate the interactions between MSCs and other types of immunocompetent cells. By attracting immune cells in close proximity with MSCs, the secreted chemokines provide direct cell-to-cell contact as well as a possible paracrine immunoregulatory effect of other effector molecules also secreted by the MSCs. Thus, Ren *et al*[143] established that the chemokines CXCL9, CXCL10 and CXCL11 stimulate the migration of T cells in the proximity of MSCs and that these cells are targets of the local suppressive effect of nitrogen oxide secreted by the stem cells. Nevertheless, MSC secreted chemokines predominantly exert chemotactic activity and many data point to their direct role in the process of immunomodulation.

Monocyte chemoattractant protein-1 (CCL2/MCP-1)

CCL2 is a key chemokine regulating the recruitment and migration of cells of the monocyte-macrophage system.

It is secreted from monocytes and other types of cells, including endothelial cells, microglial cells, NK cells *etc*[144]. CCL2 is related to multiple disorders associated with accumulation of activated monocytes, including atherosclerosis, bronchial asthma, inflammatory processes of the intestines *etc*[144]. CCL2 plays a role of direct mediator for angiogenesis and its effect is manifested by formation of new blood vessels, as proven in animal models[145]. Much data shows that CCL2 modulates the T cell immune response, causing a switch from Th0 to Th2 with predominant secretion of IL-4[146,147]. The role of CCL2 in immune regulation has been proven by the fact that it induces secretion of MCPIP1 (MCP-1 induced protein-1) which acts as RNAse and stimulates mRNA degradation for some cytokines such as IL-6 and IL-1[148]. MCPIP1 acts as a negative regulator of CCL2 and inhibits macrophage activation[149]. It has also been established that CCL2, CCL5 and some other chemokines induce proliferation and activation of specific CD56+ cytolytic cells designated as CHAK (CC chemokine-activated killer) which act similarly to the IL-2 activated cells (LAK)[150].

Some recent studies report that CCL2 is one of the factors associated with the immune modulation caused by MSCs. Secretion of this chemokine by the MSCs causes enhanced FasL dependent apoptosis of T lymphocytes. The apoptotic T cells stimulate secretion of higher levels of TGFβ by macrophages and the latter cytokine is associated with generation of CD4+FoxP3+ Tregs[151]. Other authors comment about the anti-apoptotic effect of CCL2 and describe inhibition of caspase 3 in the cell line of embryonic cardiomyoblasts cultured in the presence of MSC conditioned medium[152]. So it seems that there are data suggesting a dual function of CCL2, either pro-apoptotic or anti-apoptotic depending on the microenvironment and the general cytokine profile. It has been shown that CCL2 mediated in an autocrine manner the migration of MSCs towards the site of inflammation, ischemic damage, trauma or a developing malignant process and there the MSCs exert their immunomodulating effect[152].

Some data have been reported demonstrating that the inhibiting effect of MSCs on the immunoglobulin production by plasma cells is the result of the effector effect of CCL2 and CCL7 chemokines secreted by the MSCs[153]. It has been established that this effect is due to inhibition of the phosphorylation of STAT3 which causes activation of the transcription factor PAX5 and suppression of the immunoglobulin synthesis[153]. This assumption is substantiated by the fact that neutralizing the CCL2 neutralizes the suppressive effect of MSCs on plasma cells[153]. A possible participation of CCL2 in the inhibition of the pro-inflammatory CD4+ Th17 cells caused by MSCs has been hypothesized as an alleviation of clinical symptoms observed in EAE (experimental autoimmune encephalomyelitis)[154]. Furthermore, it has been established that MSC conditioned medium exerts an inhibitory effect on the activation of CD4 T cells obtained from EAE mice. This effect is mediated *via* CCL2-dependent suppression of STAT3 phosphorylation[154]. In addition, the key role of CCL2 produced by MSCs has been supported by the fact that MSCs isolated from CCL2 knock-out mice and injected in EAE mice do not demonstrate any therapeutic effect[154].

Regulated on activation, normal T-cell expressed and secreted (RANTES/CCL5)

RANTES/CCL5 was initially identified as a product secreted by activated T lymphocytes[155] which mediates the chemotactic activity of some cell types, including monocytes, lymphocytes and dendritic cells. It is engaged in regulation of leucocyte migration, angiogenesis[156,157] and some processes of wound healing[158]. CCL5 is a mighty activator of leucocytes and neutrophils, the effect of which is similar to that of mitogenic stimuli[159]. Besides its functions as a chemokine, CCL5 participates in the anti-viral immune response by blocking HIV replication *in vitro* and the disease progress[160,161]. CCL5 inhibits the T cell response and maybe functions as a blocking factor (suppressor of alloantigen specific T cells) by inducing cell apoptosis by modulating Bcl-2 levels and by a caspase independent mechanism[162]. There are data that CCL5 is involved in blocking the development of monocytes and memory Th1 cells[163]. CCL5 secreted by NKT cells leads to formation of CD8+ FoxP3+ cells which is the probable mechanism to induce tolerance in alloreactive T cells[164]. CCL5, similarly to CCL2, stimulates the migration of MSCs to sites of tissue damage in an autocrine manner and there are data that some tumors stimulate de novo secretion of CCL5 by MSCs with the aim to support metastases, the invasiveness and the mobility of tumor cells[165,166].

Data reported by different authors show that the effects of the chemokines should not be interpreted in one way. Most probably, chemokines secreted by MSCs do not only recruit various types of immune cells in order to exert immunomodulation but on the other hand, they act in an autocrine manner leading to migration of stem cells to the sites of tissue damage and at a later stage, support the immunomodulatory properties of the MSCs.

INDOLEAMINE-2,3-DIOXYGENASE

Indoleamine-2,3-dioxygenase (IDO) is the tryptophan-catabolizing enzyme that possesses immunosuppressive and antimicrobial effects. IDO is one of the key immunoregulators secreted by MSCs, tumors and during pregnancy. IDO is expressed by a wide range of MSCs, like decidual MSCs[167], amnionic fluid MSC[168], multipotent adult progenitor cells (MAPCs)[169], umbilical cord MSCs[170], AT-MSCs[171] *etc*. IDO expression is species specific. Murine MSCs possess very little IDO[172], while human MSCs do just the opposite - express an abundant amount of IDO. MSCs from monkey, pig and humans utilize IDO, whereas mouse, rat, rabbit, hamster[173] and equine[174] MSCs do not produce IDO. This variation should be considered when mouse MSCs are used as a

model for studying immunoregulation properties since differences in expression of molecules involved in the process by murine and human MSCs are unquestionable.

Not activated MSCs normally express low levels of IDO, but on stimulation with inflammatory cytokines, mainly IFNγ, the IDO mRNA levels are found to be elevated[175]. IDO is not an exclusive mechanism for MSCs immunomodulation in basal states but is essential for MSC suppression in the presence of IFNγ[176]. Glucocorticoids, budesonide or dexamethasone treatment of MSCs also lead to enhanced IDO expression and is able to regenerate IDO synthesis in over-passaged MSCs[177]. Damage associated molecular patterns (DAMPs) are also involved in the IDO expression regulated by MSCs[178]. IDO is expressed after stimuli generated by the crosstalk of MSCs and cells co-cultured with them[168,179].

The cross-talk of MSCs and PBMCs causes increased IL-10 and IDO expression from MSCs that seems to be the mechanism responsible for the immunosuppressive action of the human amnionic fluid stem cells[168]. After IFNγ priming of MSCs, the IDO expression leads to B-cell growth arrest and apoptosis[180], in contrast to not activated MSCs that are IDO negative and support B-cell proliferation and survival. The addition of 1-methyl-DL-tryptophan (1-MT), an IDO inhibitor, also restored the proliferative capacity of both naive and pre-activated T cells[181]. The feedback regulation between MSCs and activated T cells may limit the immunosuppressive effects of MSCs only to sites containing ongoing inflammatory responses where the activated T cells induce the up-regulation of IDO from MSCs[179].

Direct and indirect pathways are engaged in MSC meditated immunosuppression. The catabolic activity of IDO, secreted by MSCs, can directly suppress T-cell proliferation as a result of rapid tryptophan degradation.

In addition to the direct mechanism, an indirect pathway is described and is provided through the MSC mediated differentiation of monocytes into IL-10 secreting, CD206+ immunosuppressive M2 macrophages which contribute to T-cell suppression[182].

Induction of regulatory T cells is another indirect mechanism for immunoregulation explored by MSCs. IDO expression is responsible for induction of IL-10+IFNγ+CD4+ regulatory T type 1 [T(R)1]-like cells by MSCs[183]. Neutralization of IDO is also a reason for Treg reduction[184]. Feedback regulation between Tregs and MSCs exist since Tregs do not alter the secretion of IFNγ by immune cells and hence contribute to MSC activation. MSCs by themselves secrete IDO and are able to induce the production of IL-10 from Tregs[185].

As described above, MSCs can suppress dendritic cell maturation and function, mediated by soluble factors which also include IDO. It was demonstrated that MSCs inhibit the maturation of DCs through the stimulation of IL-10 secretion and by activating the JAK1 and STAT3 signaling pathway[186].

VASCULAR ENDOTHELIAL GROWTH FACTOR

The VEGF family are the key mediators of angiogenesis and it is largely known that this process plays a critical role in tumor progression as well as in acute and chronic inflammation. The main mechanism of action of VEGF is as endothelial cell mitogen that stimulates angiogenesis by promoting endothelial cell survival, proliferation, migration and differentiation.

Six proteins of the vascular endothelial growth factor (VEGF) family are described (VEGF-A,-B,-C,-D,-E and PlGF). VEGF-A interacts with two receptors, VEGF-R1 and -R2, which are expressed on endothelial cells and on some immune cells. In addition to its best known function in angiogenesis, VEGF has a role in immunity and inflammation. VEFG is responsible for recruitment of inflammatory cells and expression of co-stimulatory molecules on recruited and resident mononuclear cells. As a result, pro-inflammatory Th1 and Th17 cytokines are up-regulated[187]. Vascular endothelial growth factor is a key mediator in the development of T cell priming and in the polarization to type 1 and type 17 T helper cells in the airways. Affecting functions of memory T cells in pro-inflammatory responses has also been described after VEGF stimulation[188]. VEGF also have an indirect immunosuppressive function on lymphocyte activation and proliferation by increasing IDO secretion from dendritic cells[189].

VEGF-A secreted by tumor cells is involved in immunosuppression *via* down regulation of the transcription factor NF-κB and as a result, there is an inhibition of dendritic cell maturation, trafficking and antigen presentation[190-192]. An increased VEGF plasma level in cancer patients correlated to the presence of immature DCs and immature myeloid cells in the peripheral blood[193,194]. These findings are substantiated by results from mouse model studies showing that treatment with anti-VEGF antibody increases the numbers and enhances the functions of DCs[195-197]. VEGF-A administration decreases splenic T cells and suppresses their function[198]. Placental growth factor (PlGF), a VEGF-R1 ligand, also impedes DC differentiation[190]. *In vitro* experiments have demonstrated that PlGF could block the capacity of human myeloid-derived DCs to stimulate a Th1 response[199].

MSCs are a potent source of VEGF. It has been shown that high expression levels of VEGF were maintained during prolonged culture periods and that *in vivo* hMSCs engrafted into immunodeficient mice could survive and secreted human VEGF[200]. MSCs from decidua were also found to secrete VEGF[167]. Measurement of secreted VEGF-A by ELISA in serum-free medium from cultured MSCs showed a reproducible concentration of 4.1 ± 0.9 ng[201]. Wang *et al*[202] hypothesized that hypoxia or TNFα activates MSCs which are able to release VEGF by STAT3 and p38 MAPK dependent mechanisms. Human MSCs that released VEGF in response to TLR-2

and NOD-1 ligands were also described[203].

INTERCELLULAR ADHESION MOLECULE

Intercellular adhesion molecule-1 (ICAM-1) is a membrane glycoprotein belonging to the immunoglobulin superfamily. Expressed on endothelial cells, leukocytes (lymphocytes and monocytes) and MSCs[204,205], ICAM-1 (CD54) is a ligand that binds primarily the heterodimeric, leukocyte-restricted β2-integrin receptors-αLβ2 (LFA-1), αMβ2 (MAC-1). ICAM-1 plays important functions in leukocyte transmigration through vessels, cell to cell adhesion impacting immune responsiveness during infections and disease pathogenesis. The level of membrane expression of ICAM on endothelia and MSCs is up-regulated by pro-inflammatory cytokines (IL-1, IL-6, TNFα) and IFNγ from activated T cells[204,206,207] and does not depend on intercellular adhesion. Generally, MSCs are renowned for their immune-suppressive function which is crucially dependent on membrane expression of ICAM-1, as demonstrated in a mouse experimental model. It was unambiguously shown that blocking antibodies against ICAM-1 receptors or ICAM-1 deficiency of MSCs abrogated the suppressive effect of MSCs on activated T cells. Strengthening the adhesion of MSCs to T cells *via* ICAM-1 proportionally potentiates the function of MSCs represented by lagging of T cells proliferation[204]. Besides the direct role of ICAM-1 in MSCs interaction with immune cells, the importance of membrane expression of ICAM-1 spans MSCs migration[208], proliferation and differentiation capacity[209]. Seemingly indirectly related, the essence of the processes like migration, proliferation and differentiation of MSCs is also regulated by the inflammatory environment[66]. Therefore, specifically attracted to the sites of inflammation, like tissue damage, carcinogenesis and infection, MSCs participate in immune modulation, tissue repair and cell differentiation processes.

Apart from the membrane form of ICAM, a soluble ICAM (sICAM) also exists which is formed after shedding by proteolytic cleavage from the cell membrane[210,211] or by coding of specific mRNA transcripts in cells[212]. Elevated amounts of a biologically active form of sICAM is detected in serum, cerebrospinal fluid, synovial fluid, urine and sputum in pathologies with an underlying inflammatory status, like autoimmune and degenerative diseases[213-215] and tumor pathogenesis[216,217]. Different reports point to various cell sources of sICAM in health and pathologies, including endothelial cells[218], peripheral blood mononuclear cells, keratinocytes, epidermoid carcinoma cell lines, melanoma cells[219] and tumors[216,217,220]. sICAM can be secreted spontaneously or after specific inductions[220]. Limited data demonstrate that some but not all MSCs are a source of sICAM. Profiles of cytokine arrays revealed high expression of sICAM from human MSCs derived from umbilical cord and deciduas[221,222] and null expression from bone marrow-derived MSCs[221]. The exact physiological role of sICAM in health and pathology is still not completely revealed but reports demonstrate its potential to stimulate endothelial cell differentiation in conditions with angiogenic growth in tumorigenesis[223]. In relation to this finding, a speculation imposes that the process of massive angiogenesis which takes place during placentation might be related to the secretion of sICAM from umbilical cord-derived and decidua-derived MSCs. Hypothetically, the lack of such a requirement for bone marrow-derived MSCs suggests acquisition of varying functions of MSCs according to the tissue localization. Furthermore, the importance of sICAM secreted from human umbilical cord-derived MSCs for microglia functioning and neuronal survival is depicted in a model of Alzheimer's disease[222].

Insufficiently explored, the paracrine function of sICAM seems to counteract the classical biological function of membrane ICAM by preventing leukocyte interactions. sICAM affects trafficking of immune cells *via* hampering attachment to endothelial cells[224] and blocks immune response development due to deteriorated immune cell contacts. In addition, the increased sICAM during inflammation probably affects MSC migration, proliferation and differentiation and detailed exploration of their biology can help understand and modulate the regulatory properties of MSCs in different pathologies.

PROSTAGLANDIN E2

Prostaglandins (PGs) are products of cyclooxygenases (COX) synthesis from arachidonic acid. COX1 is constitutively expressed from virtually all tissues, while COX2 is induced under inflammatory conditions (by LPS, IL-1, TNFα for example)[225]. COX2 is shown to preferentially metabolize prostaglandin E2 (PGE2)[226] that acts as a messenger molecule through a paracrine and autocrine manner on surrounding cells.

Together with IDO, PGE2 is another major effector molecule responsible for immunoregulatory competence of MSCs[183]. MSCs constitutively produce detectable levels of PGE2[44,227,228]. Under inflammatory conditions of the environment, PGE2 is induced, substantially increasing secreted amounts from MSCs. LPS as well as cytokines like IFNγ, TNFα, IL-1β are mediators directly regulating PGE2 production from MSCs[227,229,230]. Multiple studies show that direct contact of PBMCs, monocytes and NK cells with MSCs induces PGE2 augmentation *via* the mentioned cytokines[44,227-229]. Activated by environmental signals, PGE2 from MSCs exert regulatory influence on the activation status, proliferation, differentiation and function of immune cells from adaptive and innate immunity. Acting by a contact or paracrine manner[229,231], PGE2 has a systemic anti-inflammatory effect of reducing TNFα, IL-6 and vascular permeability in an experimental model of sepsis[230]. Particularly, the cellular targets of PGE2 are PBMCs, NK cells, monocytes, macrophages and the transitional processes of differentiation of monocytes into immature DCs[228,230,232]. PGE2 indirectly affects polyclonally or allogenically activated PBMCs by substantial suppression of

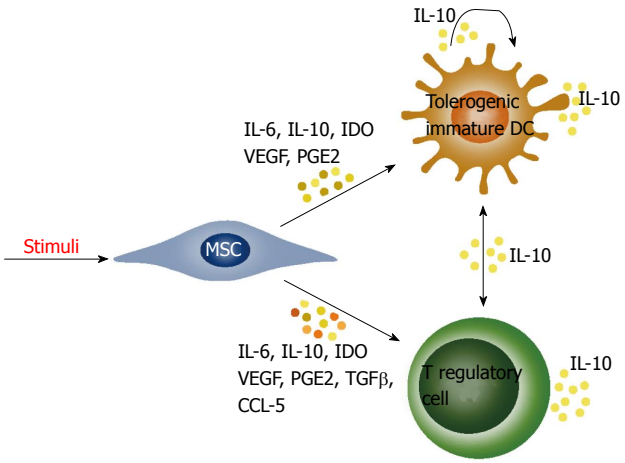

Figure 2 Mesenchymal stem cells provide an immunoregulatory effect by interactions with dendritic cells and T regulatory cells. Under the influence of cytokines secreted by MSCs and autocrine secreted interleukin-10 (IL-10), the dendritic cells acquire an immature tolerogenic phenotype characterized by a low expression of MHC II and B7 molecules, as well as a higher secretion of IL-10. The secretion of IL-10 induces generation of different subtypes of regulatory T cells which further secrete IL-10 and induce tolerogenic phenotype in dendritic cells. Cytokines secreted from MSCs also lead directly to formation of regulatory T cells. VEGF: Vascular endothelial growth factor; PGE2: Prostaglandin E2; MSCs: Mesenchymal stem cells; IDO: Indoleamine-2, 3-dioxygenase; TGFβ: Transforming growth factor β; DCs: Dendritic cells; IL: Interleukin; CCL: CC chemokine ligand.

proliferation and IFNγ secretion[227,229,231]. Simultaneously, the effect on T cells is accompanied by a prevailing bias towards IL-4 production[227] and induction of regulatory IL-10 secreting T cells[183,233]. The influence of MSCs on T cells that represent the effector arm of adaptive immunity is shown to be mediated *via* the antigen presenting cells (APCs). They are subjected to the direct effect of PGE2, resulting in reduced effectiveness of reaching the stage of immature DCs from monocytes showing an affected phenotype as a low number of CD1a cells and decreased expression of co-stimulatory CD80, CD86[228] and antigen-presenting molecules MHC Ⅱ[231]. Furthermore, when co-cultured with MSCs, the production of IL-12 from APCs (especially DCs) is low[228,231,232], while IL-10 (from DCs and macrophages) is increased[227,230]. In total, when differentiating in the presence of MSCs, DCs stay immature in a tolerogenic state and unable to elicit a Th1 immune response. On the other hand, MSCs do not affect the differentiation of immature into mature DCs. The latter demonstrates normal expression of CD80, CD86, CD83 receptors, normal capacity for T cell activation and even increased IL-12 secretion[228]. Retained in an undifferentiated state, DCs when in co-culture with MSCs largely deteriorate/aggravate the cytotoxicity properties of NK cells as well. Investigations show that due to changed chemokine profile and reduced IL-12 secretion from DCs, NK cells do not properly recruit to DCs[232]. Under these circumstances, NK cells have low activation, diminished IFNγ secretion and cytotoxicity against their targets[232], including the reactivity against MSCs[234]. Summarizing the influence of PGE2 on immune cells with regulatory function endows MSCs a central place in controlling of inflammatory responses. Extremely sensitive to activation signals from the environment, MSCs seem to link the crossroads between innate and adaptive immunity. By suppressing inflammatory mediators, they participate in the activation of feed-back processes, counteracting non-self[55,183] and autoimmune reactivity[233,235,236], leading the immune system to a steady homeostatic state.

CONCLUSION

A general conclusion can be drawn that MSCs can realize their immunoregulatory functions even when they are an object of different stimuli. One of the mechanisms to exert these functions is secretion of cytokines which can directly influence the effector immune cells. In addition to that, when secreting cytokines MSCs are involved in complex multi-directional interactions, including predominantly dendritic cells and different subtypes of T regulatory cells (Figure 2). Detailed elucidation of these interactions might be of key importance for the effective application of mesenchymal stem cells in therapy for autoimmune diseases.

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