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Immunosenescence of mesenchymal stem cells and autoimmune diseases; the dark side of immune system

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Our understating of the mechanisms underlying the immunomodulatory properties of mesenchymal stem cells (MSCs) has greatly advanced during previous decades.Considering their unique regulatory effects, numerous applications have been establishedfor treating autoimmune diseases. However, cellular senescence and inefficient functions were found in MSCs isolated from autoimmune patients when they were particularly utilized in autologous settings. Several attempts have beenconducted to provide an in-depth understanding of mechanisms involved in MSC senescence andits negative impacts on autoimmune disease onset/ progression.Accordingly, indirect evidence of the role of immunosenescent MSCs hasbeen reported during the immunopathogenesis of systemic sclerosis, osteoarthritis, systemic lupus erythematosus, diabetes, psoriasis, and immune thrombocytopenia. This connection is mediated primarilythroughthe reduced self-renewability of MSCs and their abnormal immunoregulatory functions in the polarization of immune cells.Such knowledge is critical for developing therapeutic interventions to re-induce autoimmune patients' immune balance.To further explore the basic and clinical characteristics of MSC senescence in autoimmune disorders, this review comprehends the available information regarding molecular mechanisms and cellular interactions that finally perturb immuno-homeostasis of MSCs.

Keywords: Mesenchymal stem cell; Cellular senescence; Autoimmune disease; Immunoaging

Introduction

Mesenchymal stem cells (MSCs) aremultipotent and adult stem cellsfound in blood, bone marrow, umbilical cord, and many other tissues [1]. It is believed that MSCs originate from a group of cells called pericytes [1, 2]. Pericytesare vascularsurrounding cells that activate and differentiate into MSCs under inflammatory conditions or injuries. These cells can potentially modulate their environment by releasing various cytokines and growth factors [3]. In other words, it has been demonstrated that MSCs bear immuno-modulatory and regenerative properties,also termed medical signaling cells [4]. Therefore, MSC deficiency may negatively influence numerous biological processes which can potentially lead to autoimmune diseases.

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Autoimmune diseasesare pathological conditions in which the immune system mistakenly targets self-antigens [5]. The immune system normally protects the body against foreign antigens from ingerms and cancer cells. Still, autoimmune disease happens when the immune system tense part of the body as foreign and misfires healthy cells [6]. To avoid autoimmunity, a complex network of special cells must appropriately moderate the immune response to most body parts. To this end, immunomodulatory mechanisms are constitutively dedicated to subsets of T cells, dendritic cells, macrophages, and MSCs to induce tolerogenic response against self-antigens [7]. Immune responses are generally modulated in their function by MSCs in a cell-cell contact-dependent orcontact-independent manner. Cell contact-mediated signals, like MHC-T cell receptor (TCR) interaction or tunneling nano-tubes, are necessary for functions and self-renewability of MSCs together with the polarization of other immune cells. It has been shown that the underlying mechanism behind their immunomodulatory function also depends on the release of cytokines and extracellular vesicles (contact-independent) [8]. Both mechanisms proceed after the MSCs detect an exogenous signal. To do this, MSCs express a various level of toll-like receptors (TLRs) and cytokine receptors, including TLR2, TLR3, TLR4, TLR7, TLR9, IL-6 receptor, interferon (IFN)-γ receptor, transforming growth factor (TGF)-β receptor, according to their tissue origin [9-11]. In response to inflammation or injury, they can migrate or home to an inflammatory tissue and act as a double-edged sword. For example, MSCs express immuno-suppressive phenotype upon stimulation by TLR3 ligands or a robust amount of inflammatory cytokines (IFN-γ and TNF-α). These MSCs are characterized by high secretion of IL-10, TGF-β, hepatocyte growth factor (HGF), nitric oxide (NO), and prostaglandin E2 (PGE2), which result in polarization of regulatory T cells (Treg) and M2 macrophages. The possible involved signaling mediators include phosphatidyl inositol 3-kinase (PI3K) and a Signal transducer and activator of transcription 1 (STAT1) [12, 13]. But in the presence of TLR4 agonists or low levels of inflammatory cytokines (IFN-γ and TNF-α) MSCs, in turn, release various proinflammatory cytokines (such as chemokine ligand (CCL)3, CCL4, CCL5, CXCL9, and CXCL10) that recruit T cell responses to sites of inflammation [14, 15]. Another important feature of pro-inflammatory MSCs is a decline in NO and indoleamine 2,3-dioxygenase (IDO) production that is mediated by numerous signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) [16]. These dynamic regulatory phenotypes of MSCs are necessary to balance anti- and pro-inflammatory immune responses. Prominent changes generally termed ‘immuno-aging’ or ‘immunosenescence’ dysregulate MSCs' activities and may then attenuate them to inhibit self-reactive immune responses, thereby contributing to the pathogenesis ofcancers and inflammatory diseases.

A clear knowledge of the phenotype and potential of mesenchymal stem cells, particularly their immune properties, should be obtained when considering any autologous MSC therapy, as their beneficial effects may be impaired.We thus sought to review and compare the first basic features of MSCs isolated from autoimmune patients and healthy individuals, which can involve their disease onset and/or progression. If MSCs adopt an immunoreactive phenotype, they would be worthless for autologous therapy in autoimmune patients.

Immunoaging, the Interplay between the Immune System and Autoimmune Diseases

Several studies believe that aging is associated with reduced renewability of stem cells and impaired differentiation capacity to immune cells [17, 18]. These changes in the immune system can cause highly susceptible peopleto spontaneous activation of inflammatory responses and compromised immune protection from infections [19]. Natively, inflammation is an immune defense mechanism against injury and microbial invasion. Still, long-term and low-grade inflammationcan cause harmful effects, especially concerningimmune senescence and autoimmune diseaseinitiation [20]. This process has been recognized particularlyduring aging and therefore is called immunoaging. It is of note that immunosenescencecan develop at early ages and only manifest its clinical symptoms at more advanced ages.Early immunosenescence is mostly caused in genetically susceptible or environmentally sensitive individuals. For example, telomer shortening is facilitated in immune cells (granulocytes, T cells, etc.)

of rheumatoid arthritis (RA) patients [21]. Surprisingly, it has been noticed that healthy and youngadults genotyped for HLA-DRB1*04, an allele associated with RA, also demonstrate an accelerated telomer erosion similar to RA patients [22]. X-linked lymphoproliferative syndrome is a rare genetic immunodeficiency characterized by excessive proliferation of T cells [23]. The research found that young patients show a fast telomereloss similar to healthy old individuals, indicating that proliferation, not necessarily aging, stimulates telomere shortening [21]. These data suggest that age-related inflammation may not be the principal cause of early immunosenescence in immune diseases.

The etiology of immune senescence development refers to endo- and exogenous reasons. Endogenous factors are events thathave originated internally. For instance, duringimmunoaging, cellular debris (so-called damage-associated molecular patterns (DAMPs)) is released due to cell injury and/or tissue repair dysfunction in multiple organs. Then, DAMP-sensing receptors (particularly Nlrp3 inflammasome) detect the danger signal and promote the secretion of proinflammatory cytokines (IL-1β and IL-18), contributing to the onset of chronic inflammation [24, 25]. In search of other endogenous reasons, Gallenga*et al.*noticed that age-related macular degeneration may derive from inappropriate activation of the complement system in patients older than 60 [26]. Endogenous immunoaging may also be due to increased activation of the coagulation system. A hypercoagulable state observed in aged subjects can increase the risk of thrombosis. In this state, vascular walls become damaged and release proinflammatory mediators that recruit leukocytes [27]. Thus, thrombosis and inflammation have a reciprocal association in which one can trigger the other. As far as is known, immunoaging with an exogenous origin is mostly linked to environmental factors that disrupt the central tolerance of the immune system. The exactmechanism is not fully clarified, but it has been proposed that exposure to viral and bacterial components, categorized as pathogen-associated molecular patterns (PAMPs), activate innate immune receptors like TLRs and NOD-like receptors (NLRs), facilitating proinflammatory cytokine production. In this case, the gut microbiota is the main source of PAMPs that can penetrate the underlying tissues andcirculatory system [28]. Besides, high-fat feeding appears to inducethe production of numerous inflammatory cytokines [29]. This diet is associated with reduced regulatory T cells in obese individuals [30]. A similar process occurs in age-related metabolic dysfunction and fat tissue dysregulation, where inflammatory cytokines with systemic effects (especially TNF-α, IL-1β, and IL-6) further promote adipogenesis and induce lipid cell lipolysis, releasing fatty acids (like arachidonic acid) that exacerbate the inflammation [31].

Senescent MSCsas a Key Regulator of Immunoaging

The balance in the regulatory function of MSCs declines with immunoaging, as MSCs undergo subtle changes that fuel immune-associated disorders. In other words, various beneficial properties of MSCs gradually turn into harmful aspectsas they age.In this regard, most available information was obtained via in vitrostudies that we will briefly reviewhere. Senescent MSCs morphologically appears large (flattered shape) with high cell membrane extensions (cellular processes) andgranular cytoplasm [32]. The mean telomere length, proliferation rate, and diff-erentiation capacity of senescent MSCs decrease understandingof culture conditions [32, 33]. Some metabolic markers are also associated with the aging of MSCs and other cell types. Since 1995, senescence-associated β-galactosidase (SA-β-gal) expression has been widely used to detect senescent MSCs. Moreover, senescence-associated lysosomal α-L-fucosidase (SA-α-Fuc) was later recognized as a novel marker of DNA damage-induced senescence in MSCs [34]. **Oxidative stress** is another hallmark of aging in MSCs. In this respect, nuclear factor erythroid 2-related factor 2 (NRF2) (a critical transcription factor of antioxidant genes) and ataxia telangiectasia mutated (ATM) serine threonine-protein kinase (a master regulator of stress response to DNA damage) have been identified to beartranscription defects, leading to the reactive oxygen species (ROS) production and ROS-induced MSC senescence [35, 36]. Oxidative stress makes senescent MSCs produce higher amounts of NO, exacerbating inflammation [37]. It is true that under normal physiological conditions, there are NO presentation-

inflammatory effects, but its over production in abnormal situations is considered a pro-inflammatory mediator in the immune system [38]. The proliferation rate and immunosuppressive features of MSCs substantially decrease during extensive subculturing in vitro [32]. After about 20-30 times doubling, cell cycle arrest occurs in MSCs, and the exhausted cells demonstrate a significant change in the expression of cell cycle checkpoint regulators [33]. For instance, the upregulation of checkpoint protein p16INK4a is now well known in many studies as a key molecule that induces early senescence of many cells, including MSCs isolated from autoimmune patients or MSCs extensively cultured in-vitro [39,40]. p16INK4a or cyclin-dependent kinase inhibitor 2A (CDKN2A), as well as p21, are multi-functional proteins that decelerate the cell cycle progression from the G1 to S phase [41]. When cell cycling is stopped and MSCs no longer proliferate, their chromatin becomes condensed, and the chromosomes are transcriptionally inactive, which is against their immunoregulatory properties [42]. In this state, senescent MSCs also tend to spout out **cell debris** that stimulates innate immune receptors mentioned earlier [33].

Senescent MSCs also release numerous **pro-inflammatory** cytokines (called senescence-associated secretory phenotype (SASP)) that alter the microenvironment and affect the nearby cells [43]. Among SASPs, abnormal production of TNF-alpha and, most importantly, IL-6 was found more pivotal for immunoaging events [44]. These cells exhibit lower anti-inflammatory and higher pro-inflammatory behaviors during senescence, makingelderly persons vulnerable toautoimmunity initiation. So far, we have only explained senescence originated because of stressors (extrinsic factors) and activation of the p16-pRB signaling pathway thatresult in premature or early senescence of MSCs. On the other hand, there is another mechanism of senescence induction accomplishedvia the shortening of telomeres or the P53 signaling pathway (telomer-induced cellular senescence) [43]. A combination of the two mechanisms of cellular senescence has been under investigation in autoimmune studies. These attributes will be separately explained in the context of each autoimmune disease. Figure 1 comparatively provides an overview of MSC immunosenescence's main molecular and cellular characteristics.

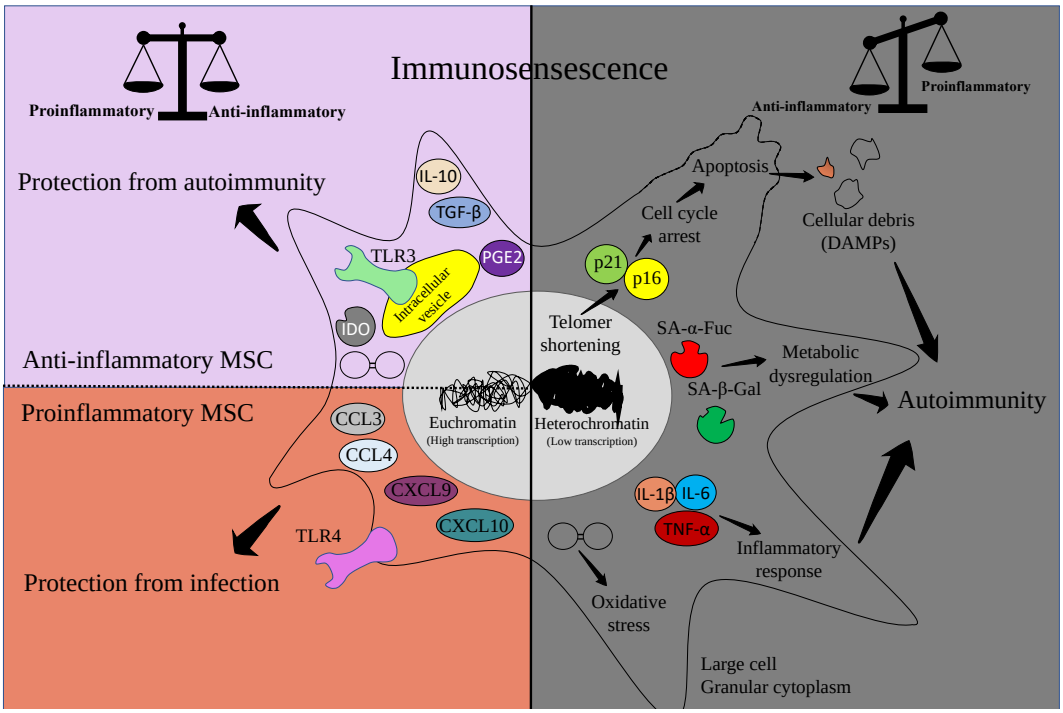

Figure 1. Comparative alterations of MSCs during immunosenescence.

Figure 1 shows the main characteristics of MSCs in normal condition when proinflammatory and anti-inflammatory phenotype of MSC is balanced. During immunosenescence, MSCs undergo numerous changes toward proinflammatory phenotype.These alterations can potentially result in autoreactive immune responses.

Systemic Sclerosis

Systemic sclerosis (SSc or Scleroderma) is a rare and progressive autoimmune disease characterized by multi-organ involvement and various clinical symptoms [45]. As stated by the following studies, there seems to be a minor footprint of senescence in MSCs isolated from SSc patients.

For the first time, Ciprianietal.found that MSCs isolated from SSc patients have normal morphology, clonogenicity, and differentiation potential. However, early senescence was identified during culture (based on analysis of the cell cycle, SA β-Gal activity, p21, and p53 expression) [46]. Compared to healthy MSCs, SSc-MSCs display almost the same immuno-suppressionon the proliferation of activated syngeneic and allogeneic peripheral blood mononuclear cells (PBMCs) [47]. However, the patient'sserum negatively affected the immuno-suppressive potential of healthy MSCs on PBMC proliferation [48]. So far, none of these studies hasassessed the possible effects of SSc-MSCs on T cell subsets. Recently, Ciprianiet al. deeply analyzed the SSc-MSCs once more and reported upregulation of IL-6, lower proliferation ability, andhigher sensitivity to genotoxic stress caused by adding doxorubicin to the culture.MSCs from SSc patients were comparable to the normalcells regarding TGF-β expression, Treg induction, and suppression of activated PBMCs proliferation [49].

Osteoarthritis

Osteoarthritis (OA) is an age-induced joint disease characterized by inflammation, hypertrophy, osteophytosis, and cartilage degeneration. The disease onset is independent of self-reactivity, but the immune response is involved in its progression [50]. As MSCs contribute to rehabilitating damaged joints [51], scientists have investigated these cells' immunological and regenerative role in osteoarthritis. Recent data indicated that accumulating p16INK4a-positive senescent MSCs is a marker of OA in murine synovial tissue [52]. Next, some authors aimed to assess whether the senescence of MSCs can contribute to OA development. Thus a senescence-promoting DNA damage inducer was added to the cell culture to overexpress $p16^{INK4a}$ in human MSCs. Senescent MSCs significantly lost their proliferative rate and self-renewability *in vitro*. Then MSCs co-cultured with OA chondrocytes or injected into the healthy mice synovium. The Proteome profile of senescent MSCs comprised of proteins including DKK1 (an OA inducer when overexpressed in mice), two disease markers (chitinase-3-like protein 1 (CHI3L1), and insulin-like growth factor-binding protein 3 (IGFBP-3)) and inflammatory cytokines (IL-8 and CCL2). Also, various SASPs like IL1-β, IL-6, and matrix metalloproteinase 13 (MMP13) were detected in senescent MSC-treated synovium. Concomitantly, it was shown that senescent MSCs also have impaired suppressive influence on OA chondrocytes *in vitro* and can develop early osteoarthritis in healthy mice [53].

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a polymorphic and progressive autoimmune disorder typically recognized by autoantibody production and dysregulated immune response [54]. The primary culture of MSCs isolated from SLE patients implied numerous abnormalities, including reduced proliferation rate and defects in differentiation capacity and migration properties [55, 56]. These cells are also more susceptible toapoptosis due to downregulation of the antiapoptotic Bcl-2 level and upregulation of Fas and TNF-α receptor1 [57]. In addition, the cytokine profile of SLE-MSCs is distinct from normal cells, as they have reducedtran scription of *TGF-β*, *IL-6*, and *IL-7*genes [56, 58]. Moreover, SLE-MSCs have an impaired potential to induce Tregs *in vitro* [56] possibly due to TGF-β downregulation [59]. Another study showed that SLE-MSCs have significantly lost their capacity to inhibit the proliferation and differentiation of activated B cells due to decreased production of CCL2 in MSCs. Further analysis clarified that MSC-mediated B lymphocyte suppression is associated with matrix metalloproteinase1 (MMP1) cleavage of CCL2when MMP1 expression was found to be decreased in SLE-MSCs [60].

There are several genetic imbalances in mediators of signaling pathways that contribute to the MSC dysfunctions in SLE patients. (1) Olfactory 1/early B cell factor-associated zinc-finger protein (OAZ) is a transcription factor upregulated in SLE-MSCs and involves bone morphogenic protein (BMP) signal transduction. OZA is believed to suppress CCL2 production in MSCs, and knockdown of OZA restores MSC capability to inhibit B cell proliferation and differentiation [61].

(2) Upregulation of $p16^{INK4a}$ is also confirmed in SLE-MSCs, and knockdown of $p16^{INK4a}$ were was seen to retrieve the immune properties of SLE-MSCs in vitro, especially TGF-β production and Treg induction. In addition, scientists have noticed that $p16^{INK4a}$ promotes the immunosenescence of MSCs by suppressingthe extracellular signal-regulated kinase 1/2 (ERK1/2) pathway [40, 56]. Differently, another study hasconducted cDNA microarray for SLE-MSCs, and their gene ontology analysis revealed the overactivation ofmitogen-activated protein kinase (MAPK) signaling pathway in SLE-MSCs through phosphorylation and activation of ERK1/2 [58]. MAPK signaling gives rise to apoptosis and pro-inflammatory cytokine productionin favor of SLE pathogenesis [55].

(3) Lately, the mTOR pathway has been recognized to induce senescence of SLE-MSCs. After rapamycin therapy, mTOR overactivity was suppressed, and immunoaging attributes of MSCs significantly improvedi n a mouse model of lupus nephritis in human patients. But the exact mechanism is not well explained yet [62].

(4) Another study found that neutrophil-activating peptide2 and leptin elevate SLE serum and promote MSC aging through PI3K/Akt signaling pathway. A specific inhibitor reversed the senescence properties of SLE-MSCs [63]. Overall, the PI3K/AKT/mTOR pathway contributes cell to cell regulation,particularly when oxidative stress isinduced in malignant and non-malignantcells [64]. (5) In 2017, Gaoet al. reported the upregulation of interferon-β (IFNβ) as another SASP for SLE-MSCs. It is well known that mitochondrial antiviral signaling protein (MAVS) does induce IFNβ production. Therefore, the authors hypothesized that there must be a positive feedback loop between MAVS and IFNβ.As anticipated, MAVS silencing essentially reduced both IFNβ production and immunosenescence features of SLE-MSCs [65].

According to available data, SLE-MSCs display senescence features, and somewhat unexpectedly, higher telomerase activity has been reported for MSCs isolated from SLE patients with high clinical scores. It means MSCs aging is a result of early induction of senescence via molecular stressors [66]. However,some reports of p53 overexpression in SLE-MSCs refer to low telomerase function [65, 67]. The study participants probably do not have an active disease with high clinical scores.

Type 2 Diabetes

Type 2 diabetes (T2D) is an immuno-metabolic complication distinguished by insulin resistance and sugar intake impairments. Hyperglycemia in T2D patients is believed to dysregulate the immune response, leading to inflammation which unable fat and pancreatic tissues to well respond to energy sources in the blood[68].T2D-MSCs demonstrated senescence markers, including high accumulation of intracellular SA-β-gal, impaired self-renewal abilities, decreased multipotency, and susceptibility to apoptosis [37, 69, 70]. Regarding their cell death, upregulation of $p16^{INK4a}$, p53, p21, andproapoptotic protein BAX has been reported for these cells. A diabetic state influencesoxidative stressvia the Nox4-dependent generation of ROS, which can consequently enhance apoptosis and senescence of MSCs [71]. Additionally, it has been noticed that a high glucose milieu pushes MSCs toward premature senescence through theAkt/mTOR signaling pathway [69]. Natural antioxidant coenzyme Q10 has also been shown to inhibit hyperglycemia-induced senescence of MSCs via the Akt/mTOR pathway [72].

T2D-derived MSCs also display an inappropriate immune response in case of overactivity of NLRP3 inflammasome and, accordingly, pro-inflammatory cytokine production (IL-1β, IL-6, TNF-α, and MCP-1). Downregulation of TGF-β1 and PGE2 plus ineffective inhibition of T and B cell proliferation demonstrate a more blunted immunomodulatory response indiabetic MSCs. MSCs are not only unable to suppress lymphocyte proliferation and surprisingly increase lymphocytes' multiplication rate after co-culture.

Versus normal MSCs, T2D-MSCs express major histocompatibility complex (MHC) type II and co-stimulatory molecules (CD40, CD80) [73, 74]. As a result, they can induceautoreactive $CD4^+$ T cells during the immunopathogenesis of diabetes.

Psoriasis

Psoriasis is a chronic autoimmune disease characterized by skin inflammation and keratinocyte hyperproliferation, which cause skin scalps, nail changes, and tiny pits [75]. Dermal MSCs isolated from psoriatic skinlesions are large, with a low proliferation rateand impaired differentiation capacity [76]. They are also hypofunctionalfor oxyradialperoxynitrite scavenging, leading to NO concentration in the culture media [77]. Lesional and non-lesional dermis MSCs from psoriasis patients show higher HLA-I expression than healthy cells [76]. In addition, these cells demonstrate attenuated suppressive effects on T cell proliferation [76, 78]. Several researchers also investigated the immunological transcriptome of psoriasis MSCs, and both pro- or anti-inflammatory MSCs were found in different tissues. These mediators involve in cell migration as well as inflammatory responses of psoriasis. It has been demonstrated that psoriatic dermal MSCs express a high level of IL-6, IL-8, IL-17, IL-21, IL-23A, INF-γ, TNF-α, CCL2, CCL20, CXCL2, CXCL5, CXCl9, CXCL10, chemokine receptor (CCR) 5, TLR2, and IL-17RA. On the contrary, no significant changes were noticed for the expression of IL-2, IL-3, IL-4, IL-13, IL-22, IL-27, TGF-β1, CCL1, CCL22, and CXCL12 on mRNA level.These data reflect a pathologicalimbalance of cytokine profile toward Th1 and Th17 polarization in the patients [79]. Interestingly, TNF-α inhibitors can restore the abnormal cytokine milieu (Th1 -Th17 vs. Th2 axis) provided by pro-inflammatoryMSCs of thepatients [80]. Oppositely, the psoriasis MSCs isolated from bone marrow clearly show an anti-inflammatory phenotype with low expression of IL-1, IL-3, TNF-α, CCL8, CCL16, CXCL12, CCR1, CCR5, HGF, and leukemia inhibitory factor (LIF) [81].

Some controversial reports also indicate an aberrant gene expression profile in dermal MSCs isolated from psoriasis legions that do not fit the previous findings [82, 83]. For instance, a group found that skin MSCs isolated from healthy volunteers and psoriatic patients indicate comparable TGF-β1 production, a high potential of IL-11 secretion, and reduced production of IL- 6 and HGF [78]. By the way, other markers of MSC senescence havenot been investigatedyet.

Immune Thrombocytopenia

Immune thrombocytopenia (ITP), or idiopathic thrombocytopenic purpura, is a common hematological autoimmune disease characterized bymegakaryocyte dysfunction and platelet degeneration [84]. Accumulating data point to a dysregulated function of senescent MSCs in the pathogenesis of ITP. ITP-MSCs appear large and do not show conventional proliferation ability. The intrinsic and extrinsic pathways of apoptosis induction (p53 and p21 expression) are increased in these cells. In this concern, MSCs were also found to indicatea decrease in Bcl2/BAX ratio and increased activation of caspase-3, 8, and 9, indicating mitochondrial impairments' role in cell apoptosis. At the same time, the expression of the death receptor pathway, Fas and Fas ligand, was significantly elevated in ITP-MSCs compared to normal cells [85].

Regarding their immune function, senescent ITP-MSCs derived from bone marrow exhibit a lower capacity of suppression on the anti-platelet antibody synthesis (anti-glycoprotein IIb-IIIa, as one of the main pathogenic antibodies in ITP development) and proliferation of T cells. Furthermore, an impaired capability of Treg induction was also detected for ITP-MSCs *in vitro* [85, 86]. Dendritic cells (DCs) differentiated with ITP-MSCs also reveal numerous impairments, including an increased expression of pro-inflammatory IL-12 and CD80/CD86 co-stimulatory molecules. These DCsbear an inefficient potential to suppress T cell proliferation and Th1 polarization along with impaired ability to induce anergic and regulatory T lymphocytes. Further evaluations clarified that the underpinning mechanism involved in the compromised function of ITP-MSCs in stimulating regulatory DCs is associated with low expression of Notch-1/Jagged-1 signaling mediators, as induction of this pathway in ITP-

MSCs distinctly increased immunomodulatory effects of DCs co-cultured with ITP-MSCs [86]. Some more genetic studies refer to the MSC deficiencies that contribute to ITP immunopathogenesis.

NF-κBis a transcription factor involved in pro-inflammatory immune responses, and its signaling termination is regulated by TNF-α-induced protein 3 (TNFAIP3). Yun He *et al.* have recently noticed a significant decrease inTNFAIP3 expression in ITP-MSCs. They also found that amplifying TNFAIP3 expression in ITP-MSCs rescuedthe beneficial impact of MSCs to induce megakaryocyte differentiation and thrombopoiesis of $CD34^+$ hematopoietic stem cells *in vitro* [87]. Given that $nestin^+$MSCs are present in bone marrow I sthe main source of CXCL12 responsible for $CXCR4^+$ megakaryocyte expansion [88]. Accordingly, a group of researchers has found that apoptosis of these MSCs is essentially elevated in ITP patients. They indicate a reduced expression of CXCL12 at mRNA level and protein concentration. Their findings demonstrated that MSC-mediated CXCL12/CXCR4 axis impairment is responsible for the abnormal distribution of megakaryocytes in ITP patients [89].

Another group performed microarray analysis to compare the RNA profile of ITP-MSCs and normal cells. They noticed that miR-98-5p is upregulatedin ITP-MSCs and targets the insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1), which subsequently down-regulates the expression ofinsulin-like growth factor 2 (IGF-2) expression and leads to inhibition of PI3K/Akt signaling pathway and MSC deficiency. Moreover, miR-98-5pwas found to inhibit the p53 ubiquitination mediator and cause p53 elevation in ITP-MSCs. It has also been shown that overexpression of miR-98-5p in MSCs and then administration of miR-98-5p-modified MSCs to a mouse model of ITP diminish the immuno-therapeutic effects of MSCs in ITP micethrough down-regulation of IL-10 and TGF-β plus upregulation of IFN-γ [90, 91].

The main characteristics of immunosenescent MSCs, isolated from mentioned immune diseases, are summarized in Table 1.

Table 1. A brief summary of immunosenescent MSCs characteristics in various inflammatory diseases

Characteristics\ disease	Systemic sclerosis	Osteoarthritis	Systemic lupus erythematosus	Type 2 diabetes	Psoriasis	Immune thrombocytopenia
Phenotype (large & flattered shape)					✓	✓
Attenuated stemness (proliferation and or differentiation capacity)		✓	✓	✓	✓	
Impaired immunosuppressive effect		✓	✓	✓	✓	✓
Metabolic dysregulation (SA-β-gal & SA-α-Fuc expression)	✓			✓		
Oxidative stress (ROS production)				✓	✓	
Cell cycle arrest and apoptosis	✓ (↑p16, p53)	✓ (↑p16)	✓ (↓Bcl2) (↑ p16, Fas, TNF-α receptor1)	✓ (↑p16, p53, p21, Bax)		✓ (↑p53, p21,Bax/Bcl2)
SASP cytokine	↑IL-6	↑IL-1β, IL-6, MMP13	↑IFNβ	↑IL-1β, IL-6, TNF-α, and MCP-1	↑IL-6, IL-8, IL-17, IL-21, IL-23A, INF-γ, TNF-α, CCL2, CCL20, CXCL2, CXCL5, CXCl9, CXCL10	

Conclusion

The studies conducted in the last two decades have demonstrated that MSCs can protect the body against autoimmune diseases, cancer, and infection by regulating the balance of immune response. In this regard, allogeneic MSCs yielded promising results. Numerous studies have supported the hypothesis that resident MSCs might beimpaired and even give rise to disease progression. The senescence of MSCs is of important defects recognized in these cells and refers to a particular phenotype with inefficient immune-modulation features. Thus, a part of the failure in MSC therapy for autoimmune diseases may result from the patients' senescence-inducing micro-environment, suggesting the importance of furtheranalyzing the basic properties of these cells when considering any autologous MSC-based therapy.

Conflict of Interest and Financial Statements

All the authors declare no conflict of interest in this study.

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