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REVIEW

- 281 Dysfunctional stem and progenitor cells impair fracture healing with age
Wagner DR, Karnik S, Gunderson ZJ, Nielsen JJ, Fennimore A, Promer HJ, Lowery JW, Loghmani MT, Low PS, McKinley TO, Kacena MA, Clauss M, Li J
- 297 Physical energies to the rescue of damaged tissues
Facchin F, Canaider S, Tassinari R, Zannini C, Bianconi E, Taglioli V, Olivi E, Cavallini C, Tausel M, Ventura C
- 322 Effects of various antimicrobial agents on multi-directional differentiation potential of bone marrow-derived mesenchymal stem cells
Li H, Yue B

MINIREVIEWS

- 337 Effect of aging on behaviour of mesenchymal stem cells
Fafián-Labora JA, Morente-López M, Arufe MC

ORIGINAL ARTICLE**Basic Study**

- 347 Similarities and differences between mesenchymal stem/progenitor cells derived from various human tissues
Kozłowska U, Krawczyński A, Futoma K, Jurek T, Rorat M, Patrzalek D, Klimczak A

ABOUT COVER

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Effect of aging on behaviour of mesenchymal stem cells

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Abstract

Organs whose source is the mesoderm lineage contain a subpopulation of stem cells that are able to differentiate among mesodermal derivatives (chondrocytes, osteocytes, adipocytes). This subpopulation of adult stem cells, called “mesenchymal stem cells” or “mesenchymal stromal cells (MSCs)”, contributes directly to the homeostatic maintenance of their organs; hence, their senescence could be very deleterious for human bodily functions. MSCs are easily isolated and amenable their expansion *in vitro* because of the research demanding to test them in many diverse clinical indications. All of these works are shown by the rapidly expanding literature that includes many *in vivo* animal models. We do not have an in-depth understanding of mechanisms that induce cellular senescence, and to further clarify the consequences of the senescence process in MSCs, some hints may be derived from the study of cellular behaviour *in vivo* and *in vitro*, autophagy, mitochondrial stress and exosomal activity. In this particular work, we decided to review these biological features in the literature on MSC senescence over the last three years.

Key words: Mesenchymal stem cells; Aging; Autophagy; Mitochondrial stress; Extracellular vesicles

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Core tip: The point of interest of this work is the behaviour of the mesenchymal stromal cell (MSC) through aging, which can occur over time in the culture (*in vitro*) or in its own physiological niche (*in vivo*). This review defines the current knowledge published in the MSC field that focuses mainly on the mechanisms that influence its senescence *in vivo* and *in vitro* in the last three years. Three cellular mechanisms are of special importance in this review, since they can decisively influence the behaviour of MSC in aging, such as autophagy, oxidative stress and the production of extracellular vesicles.

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INTRODUCTION

Mesenchymal stem cells (MSCs) are located in specific areas of tissues, called “niches”, and are characterized as being in a state of relative quietness, from which they can exit under the proper conditions to obtain the proliferative potential necessary for tissue regeneration^[1]. MSCs have sustained interest among researchers by contributing to tissue homeostasis and modulating inflammatory response, all activities accomplished primarily by the secretion of cytokines and growth factors, because their paracrine action is the main mechanism explaining their effects, regardless of source.

Senescence is defined as a mechanism for limiting the regenerative potential of stem cells which is involved with metabolic changes in the oxidative state of the cell, this process that has been also linked to mitochondrial fission and fusion events could indicate association between mitochondrial dynamics and senescence^[2]. Furthermore, senescence-associated phenotypes are characterized by increased activity of SA- β -gal, altered autophagy, and increased G1 cell cycle arrest, reactive oxygen species (ROS) production and expression of p53 and p21^[3]. It is now evident that senescent cells secrete dozens of molecules, for which the terms “senescence-associated secretory phenotype (SASP)” and “senescence-messaging secretome (SMS) factors” have been proposed. Premature aging produced by overexpression of mutant *LMNA* called progerin in the rare disease Hutchinson-Gilford Progeria Syndrome is linked to upregulation of SASP by GATA4-dependent regulation *via* MCP-1 in human MSC aging^[4]. The secreted factors contribute to cellular proliferative arrest through autocrine/paracrine pathways as well as *in vivo* and *in vitro*^[5-8]. SMS factors released by senescent cells play a key role in cellular senescence and physiological aging by activation of cytoplasmic signalling circuitry, so SMS factors secreted in conditioned medium of senescent MSCs induce a paracrine mechanism of premature senescence in young cells^[9].

The milestone in MSC investigation will be discovering senescence markers to determine the quality of the *in vitro* cells for cell-based therapies. Madsen *et al*^[10] have proposed TRAIL receptor CD264 as the first cellular senescence mesenchymal marker in bone marrow-derived MSCs, because it has the same expression profile of p21 during culture passage and it is not linked to sex^[10]. On the other hand, it is a good approach to identify immunogenic markers from age tissue sources, and the first study was developed by Amati *et al*^[11], who proposed the angiotensin-converting enzyme CD143 as a marker expressed in adult tissue sources from the screening using bone marrow- and cord blood-derived MSCs (Figure 1B).

MSCs' BEHAVIOUR IN VITRO

After long-term expansion, the phenotype of MSCs keeps stable and cells present similar immunogenic properties to lower passage cells. However, their immunosuppressive properties are reduced^[12]. One of the drawbacks of MSCs is the decline in their self-renewal capacity with increased donor age (Figure 1A) and *in vitro* expansion^[13-18] (Figure 1B). However, by increasing the number of umbilical cord vein-MSC passages, immunosuppressive effects were promoted as a result of the greater purity of the MSCs and their major compatibility with culture conditions^[19]. These results reveal the different implications of the application of high passage MSCs in the clinic, it would help increase their production for therapeutic uses but might interfere with their efficacy. The self-renewal of MSCs decrease is caused by shortening telomeres in aged MSCs^[14] and this was also demonstrated when overexpression of hTERT bypassed a replicative senescence in hBM-MSCs^[20]. Kouroupis *et al*^[21] have reported that the number of CD146⁺ UC-derived MSCs decreased with the *in vitro* age and this is associated with the telomere length. This year, it was discovered that epigenetic changes are implicated in the maintenance of stem cell properties of MSCs, demonstrating that expression of the pluripotency marker Oct4 keeps self-renewal and reverse aging in human hair follicle derived-MSCs through the inhibition of p21

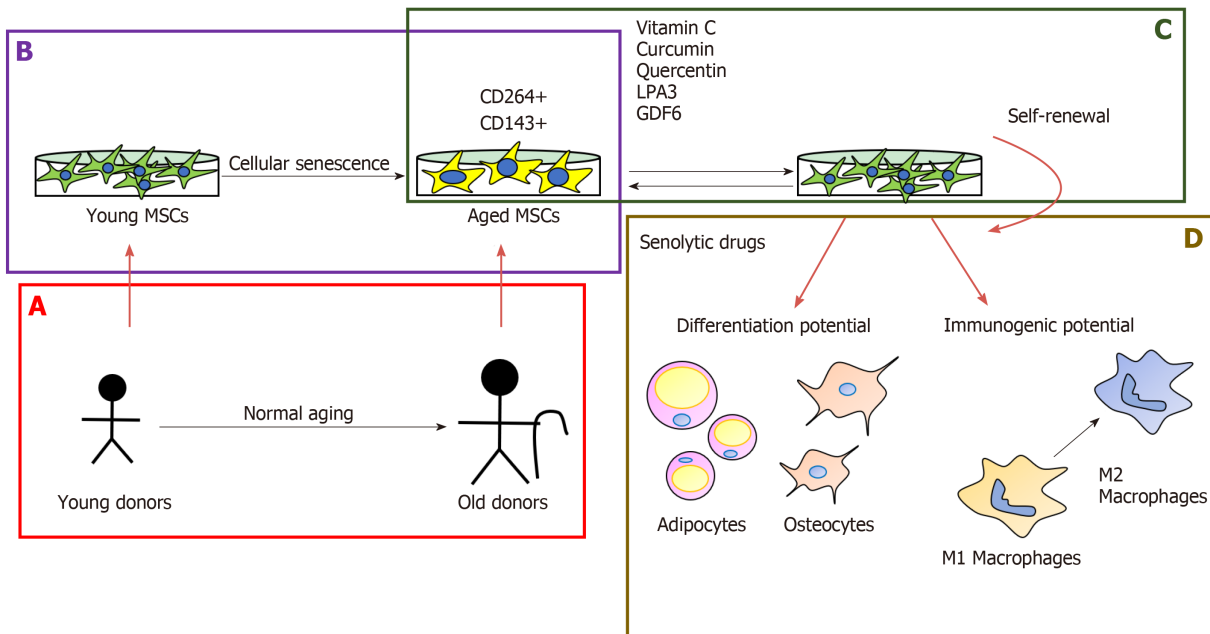


Figure 1 Effect of aging on self-renewal, differentiation and immunogenic potential from mesenchymal stem cells. A, B: Stem cell properties of mesenchymal stem cells (MSCs) are limited by age donor (A), and their long-term *in vitro* culture (B); C: Some new agents can ameliorate the effect of cellular senescence on the therapeutic capacity of MSCs; D: Treatment with senolytic drugs affects the behaviour of MSCs. MSCs: Mesenchymal stem cells; LPA: Lysophosphatidic acid.

by DNA methyltransferases^[22].

Non-coding RNA can play a role in the cellular senescence in MSCs, though the interfering lincRNA-p21 expression might allow the rejuvenation of aged BM-MSCs from C57BL/6 mice *via* the Wnt/b-catenin signalling pathway^[23]. Rn7SK is a conserved small nuclear non-coding RNA, which is overexpressed in senescent adipose tissue-derived MSCs. So, it is directly involved in the decrease of osteogenic differentiation and proliferation^[24].

There is an increase in the number of studies about the effect of natural-origin regulators that prevent or ameliorate cellular senescence in MSCs. Vitamin C also has the potential to re-establish the activity of telomerase reverse transcriptase (TERT) in bone marrow-derived MSCs from senescence-accelerated mouse prone 6 (SAMP6) mice^[25]. Curcumin improves the proliferation of aged rat adipose tissue-derived MSCs through *TERT* gene expression^[26] (Figure 1C). Another option for treating age-related diseases is the use of senolytic drugs, which eliminate target senescent cells and rejuvenate tissues^[27]. Grezella *et al*^[28] have studied the impact of these drugs on human MSCs, such as ABT-263, quercetin, danazol and nicotinamide ribose, which don't have a positive effect on MSCs because they produce changes in the SASP of human femoral bone marrow MSCs. However, Geng *et al*^[29] have proposed quercetin as a geroprotective compound for human MSCs from Werner syndrome. Because it re-establishes the differentiation potential and self-renewal through its antioxidant capacity and growth differentiation factor 6, secreted by young MSCs, it can restore the osteogenic capacity of MSCs from elderly donors^[29,30] (Figure 1D).

Human bone marrow MSCs from young donors have a better monocyte polarization capacity than MSCs from old donors^[31]. Non-senescent MSCs secrete some bioactive factors, which can ameliorate the replicative senescence through enhanced cell proliferation and osteogenic differentiation potential in prolonged *in vitro* culture^[32]. Human umbilical cord blood MSCs stimulate the rejuvenation function in human skin^[33]. Lysophosphatidic acid (LPA) is a bioactive small glycerophospholipid derived from cytoplasm that promotes cell proliferation, survival and migration^[34]. Complementing those results, Kanehira *et al*^[35] have stated that two components of these acids (LPA1 and 3) regulate cellular senescence in MSCs positively and negatively, respectively.

MSCs' BEHAVIOUR *IN VIVO*

MSCs isolated from the term umbilical cord vein have stronger immunomodulatory capacity than preterm ones. Increased immunological maturity of term umbilical cord

vein MSCs may be the explanation for that^[19].

In vivo senescence of MSCs is associated with bone-related disease because the cells lost the osteogenic capacity. In the last year, the number of studies based on gene therapy has increased with a view to improving the stem cell properties in the development of cell-based therapies. Non-coding RNA like miR-1292 was proposed as a senescence regulator in human adipose-derived MSCs and delay bone formation *in vivo* by targeting FZD4 *via* the Wnt/b-catenin pathway. It is a good target for the prevention and treatment of osteoporosis^[36]. The loss of the *in vivo* osteogenesis potential of aged bone marrow MSCs is mediated by p53 through the miR-17 pathway^[37]. In cardiovascular disease, it was found that overexpression of miR-10a in aged human bone marrow MCs activates AKT and improves the angiogenesis in ischaemic mouse hearts^[38]. The overexpression of FOXQ1 in UC-derived MSCs regulates the migration and anti-senescence effects^[39]. SATB2-modified bone marrow-derived MSCs significantly ameliorate ovariectomy-induced alveolar bone loss *in vivo*^[40].

In the last few years, the MSCs from human-induced pluripotent stem cells have had low oncogenic potential and strong immune capacity to regulate T cells^[41]. They modulate CD4 and CD8 cells and lead the upregulation of immune genes and downregulation of c-myc and DNA replicative pathways^[42].

AUTOPHAGY IN MSCs

Autophagy increases when MSCs enter the replicative aging state, and p53 contributes an important role in the upregulation of autophagy in this condition^[43]. In contrast, suppression of the p53 transcriptional activity produced strong cell death of H₂O₂-treated MSCs through autophagy induction^[44]. Autophagy is playing an important role in the mammalian stress response because can be modulated by several ways through hypoxia induced stress in different organelles. Autophagy is deeply linked to senescence, and in some experimental models, the onset of senescence is dependent on a preliminary autophagy induction: For instance, the downregulation of IGF-1 protects senescence MSCs from hypoxic condition by growing the level of autophagy, thereby allowing the survival of senescence bone marrow MSCs after myocardial infarction transplantation^[45] (Figure 2). Brunk and Termal^[46] presented the theory of aging which consisted in accumulation of damage in mitochondrial-lysosomal axis as a result of imperfect autophagocytosis during aging in tissue with limited turnover, and this has remained valid until now, when reversible quiescence is the normal stem cell state throughout life-adds^[46-48]. In the opposite, in other contexts the decrease of autophagy provokes senescence, as shown in several types of MSC acute senescence which the autophagy flux is heavily imbalanced, indicating the autophagy counteracts damaged processes, and its decline produces senescence^[49]. Reconciling these opposite events would be possible by speculating that MSCs try to lead with stress by inducing autophagy that removes damaged components; in this scenario, autophagy would protect from aging and its malfunction might trigger senescence. However, if autophagy cannot counteract stress-induced damage, it could induce senescence. Hyperglycaemia has been reported to MSC senescence^[50]. Chang *et al*^[51] researched the role of high-glucose-induced autophagy in MSC senescence publishing that high glucose increased autophagosome formation, which was linked with the development of senescence process in the cell. 3-methyladenine treatment in MSCs prevented their senescence because of increasing apoptosis. However, N-acetylcysteine or Diphenyleneiodonium, an inhibitor of NADPH oxidase, treatments were effective blocking autophagy and senescence through preventing high-glucose-induced autophagy^[51].

All these results indicate that hyperglycaemia induces MSC aging and an increase of inflammation through oxidant-mediated autophagy, contributing to MSCs' niche dysfunction. On the other hand, methionine restriction may mediate its anti-aging effects through the induction of macroautophagy/autophagy as well^[52].

MSCs are extremely sensitive and very low doses of radiation can induce senescence because of impairing autophagy and their limited DNA repair capacity^[53]. Activation of autophagy restored bone loss in aged mice, suggesting that autophagy has a key role in the aging of MSCs, and an increase of autophagy can partially reverse this senescence process and might represent a new potential therapy for clinically treating age-related bone loss^[54,55].

MSCs in lysosomal storage disorders (LSDs), which impair lysosomal homeostasis, are prone to apoptosis and senescence due to impaired autophagy and DNA repair capacity^[56]. Recently, a study showed that novel small molecules can selectively and sensitively respond to acidic pH, promoting lysosomal acidification and inhibiting

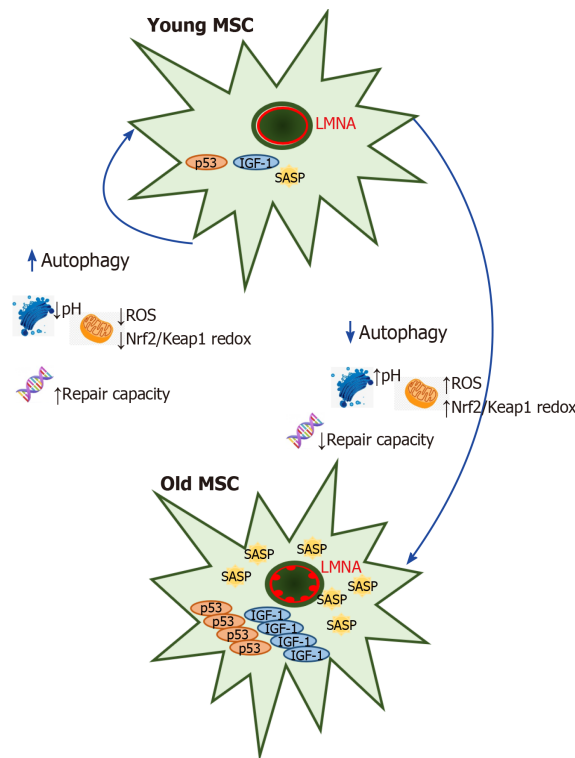


Figure 2 Autophagy influences senescence in mesenchymal stem cells. The self-renewal potential of young mesenchymal stem cells (MSCs) is influenced by their autophagy capacity to regulate the good levels of oncogenic factors like p53 and inflammatory signals like senescence-associated secretory phenotype and IGF-1, which produces overexpression of reactive oxygen species in the mitochondria, accumulation of mutations at DNA levels and acidification in the lysosomal apparatus together with an increase of LMNA in the nucleus. When autophagy is downregulated by the pathologic process, young MSCs become old MSCs in an accelerated way, losing their self-renewal capacity. MSC: Mesenchymal stem cell; ROS: Reactive oxygen species.

senescence in MSCs through autophagy^[57]. Decreased autophagy is one of the mechanisms underlying aging. Yang *et al*^[58] demonstrated that reducing autophagy decreases the hypoxia tolerance of senescent MSCs and Yun *et al*^[59] demonstrated that high p-Cresol serum concentration caused by chronic kidney failure produced cell senescence through the induction of autophagy response and could be potentially rescued by the administration of melatonin through inhibiting mTOR-dependent autophagy^[58,59]. Maintaining optimal levels of autophagy might serve as a new strategy for using MSC transplantation.

MITOCHONDRIAL STRESS IN MSCs

Oxidative stress is characterized by unregulated production and/or the elimination of reactive oxygen and nitrogen species. The main ROS generation sites, under physiological conditions, are found within the electron transport chain in the mitochondria. MSC differentiation processes ROS are mainly generated from mitochondrial complexes I and III and the NOX4 isoform of NADPH oxidase^[60]. The deregulation of ROS generation by CI and CIII can be an important factor for aging and it has been shown that an increase in ROS levels and the resulting oxidative damage are highly correlated with aging^[61-63]. Deschênes-Simard *et al*^[64] linked the bypassing of senescence in premalignant lesions to a decrease of differentiation, an increase of self-renewal potential and an increase in their dependence of mitochondrial functions. Aged adipose tissue-derived MSCs and their adipogenic differentiation are decreased by downregulation of Sirtuin 1 through miR-34a^[65]. Another component, Sirtuin 3 (SIRT3), protects aged human MSCs against oxidative stress through positive regulation of MnSOD and CAT *via* activation of FoxO3a^[39]. Huang *et al*^[66] have reported that the reduction of ERAlpha-directed mitochondrial glutaminase expression suppresses the osteogenic differentiation in aged mice MSCs. Melatonin reduces endoplasmic reticulum stress (ERS) in the liver and several diseases in the nervous system and lung. It is involved in maintaining stemness during long-time *in vitro* expansion^[67]. Yun *et al*^[59] demonstrated that MSCs from rats

with chronic kidney disease exhibited greater senescence induced by oxidative stress than normal MSCs, whereas when treated with melatonin, it protected them from H₂O₂ and excessive associated senescence. Fang *et al*^[68] have reported that it prevents senescence in canine adipose-derived MSCs through activation of Nrf2 with the inhibition of NFK beta and ERS. L-carnitine is a transport of long-chain fatty acids into the mitochondria for degradation by beta-oxidation and it has the potential to increase telomerase activity by changing the methylation status of the human TERT promotor in aged adipose tissue-derived MSCs^[69,70]. Wang *et al*^[57] postulate that treatment with curcumin gives bone marrow MSCs the ability to survive and this could be attributed to their protection in the mitochondrial function, destabilization of HIF-1 α and the activation of the Epac1-Akt signalling pathway. Therefore, they suggest that curcumin influences the preconditioning of MSCs to facilitate cell therapy in the treatment of tissue repair. Oh *et al*^[71] propose the role of 17 β -estradiol (E2) as a potential target to prevent or treat metabolic disorders in the production of reactive mitochondrial oxygen species induced by glucose (mtROS) through signalling mediated by the oestrogen receptor in MSCs from umbilical cord blood *in vitro*, suggesting that E2 serves as a potent antioxidant. Denu *et al*^[72] propose that SIRT3 is a sirtuin involved in aging (it is the main mitochondrial deacetylase) that decreases mitochondrial ROS and promotes an efficient oxidative metabolism. It has been shown that SIRT3 reduces the decrease in function and senescence associated with age in multiple cell types. Then, the increase in nuclear translocation of Nrf2 triggered the positive regulation of SIRT3 and the activation of manganese superoxide dismutase (MnSOD), which plays an important role in the decrease of mtROS levels. During MSC expansion *in vitro*, they experience a replicative senescence that compromises their immunomodulatory and differentiation functions due to increased ROS and oxidative stress in aged stem cells. MSCs accelerate aging and inhibit differentiation in adipocytes and osteoblasts because of the elimination of SIRT3, and because the overexpression of SIRT3 in the last step of the MSC restores its capacity for differentiation and reduces oxidative stress^[73]. The study by Yao *et al*^[74] attempts to demonstrate that human umbilical cord MSC-derived EVs carrying MnSOD could alleviate oxidative stress in liver tissue *in vivo*.

Oxidative stress is a key process in the induction of cellular senescence according to several studies^[75-77]. Afterwards low-grade chronic inflammation during aging and associated pathologies can lead to oxidative stress and rupture of the cells that cause senescence. According to Platas *et al*^[78], chronic oxidative stress related to aging or mechanical stress can cause cellular senescence in joint tissues and age-related alterations in the differentiation and function of MSCs.

MSC-DERIVED EXTRACELLULAR VESICLES

Exosomes and microvesicles are small vesicles included in the term extracellular vesicles (EVs). Recently, it is unravel their function in cell-to-cell communication and their capacity for transporting proteins, signalling lipids and miRNAs which are relieved to target cells *via* endocytosis and membrane fusion. Lately, MSC-derived EVs are being studied for their role in MSC-based cellular therapy. These VEs have the capacity to alter cell or tissue metabolism at short or long distances in the organism. The EVs are influencing tissue responses to infection, injury and disease. MSC-derived EVs could be used for cell-free therapies. However, these therapies might be applied in clinic when parameters as quality, reproducibility and potency of their production can be controlled. In addition, it must be taken into account the MSC-derived EV content is not static, they are produced by MSCs and they are influenced by specific MSC's niche. So, MSC-derived EVs are altered when MSCs are co-cultured with different types of cells *in vitro* or with tumour microenvironment *in vivo*^[79,80]. It has been demonstrated that MSCs can induce tumour growth, and MSC-derived EVs can be very important in the tumour microenvironment transferring information between cells along disease's development. There are some findings supporting a new mechanism, suggesting the contribution of these MSC-derived EVs to tumour growth^[81]. So, EVs secreted by MSCs might have therapeutic effects on the reconstruction process through promoting the cell cycle and inhibiting cell apoptosis, as happens in vaginal epithelium^[82].

Articles focused on a murine model have shown that a brief interaction of old MSCs with young MSC-derived EVs rejuvenated them and restored their functionality *via* inter-cellular communication. These EVs contained autophagy-related mRNAs through inhibition of AKT in aged MSCs increased the levels of autophagy-related mRNAs in their EVs^[83]. MSC-derived EVs are also involved in the transport of anti-inflammatory markers aging depending, confirming variations with aging of

Toll-like receptor 4 pathway activation in rat bone marrow MSCs and containing pro-inflammatory miRNAs (miR-21, miR-155, miR-146 and miR-21) in their MSC-derived EVs^[13]. Surprisingly, recent experiments show that the self-renewal power of these EVs is even better than that of the young MSCs. It has been demonstrated that such *ex vivo* self-renewal from old MSCs could increase the donor cohort improving efficacy in transplantation therapies^[84].

CONCLUSION

Aging affects the behaviour of MSCs in different ways depending on several factors, such as their status, source and pathological process. MSCs *in vitro* go into senescence earlier than *in vivo* and the pathological process stimulates their senescence *in vivo*. Despite this, or perhaps because of it, MSCs are an excellent tool to keep exploring in cellular therapy and to study senescence both *in vivo* and *in vitro* and their versatility seems to be extensively to their derived EVs.

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