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Mini Review

How to improve the regenerative potential of mesenchymal stem cells (MSCs) for the use in regenerative medicine?

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Abstract

Mesenchymal stem cells (MSCs) are widely used in regenerative medicine. They can be isolated from different adult tissues. However, the regenerative potential of MSCs obtained from various sources and from different age donors may significantly differ. Here, we describe the use of MSCs obtained from adipose tissues and focus our attention on the potential use of these stem cells in regenerative medicine and on the possibilities to improve their efficacy.

Introduction

Stem cells, especially the Embryonic Stem Cells (ECMs), are crucial for embryo development, while the Adult stem cells (ASCs), although much less understood, play a role in fetal development and after birth. The adult stem cells, in contrast to the embryonic stem cells, are no ethically controversial and are not subject to restrictive regulatory ethical regiments. They are multipotent because they can differentiate into many cell types within a given germline, and possibly pluripotent if they can manage to differentiate into all cell types of the embryo but the trophoblast. This makes them an excellent alternative to embryonic stem cells for regenerative medicine [1,2]. A low number of ASCs is present in the liver, pancreas, epidermis, cornea, and retina, where they are responsible for local corrective events. Among ASCs, the Mesenchymal stem cells (MSCs) are of special interest for the regenerative medicine. These cells are multi- or possibly pluripotent with the potential to differentiate into osteoblasts, chondrites, myoblasts, adipocytes, neurons, and participate in the angiogenesis [3-5]. Characteristic features that distinguish mesenchymal stem cells from other cells of the body are their abilities to adhere to plastic, a fibroblast-like phenotype, high proliferation rate, and the expression of specific surface antigens (CD105, CD73 and CD90) [6]. The MSCs express the following surface antigens: CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA DR [6].

Adipose-Derived Mesenchymal Stem Cells (AD-MSCs) in Regenerative Medicine

The best-known sources of these stem cells are the bone marrow and adipose tissues. However, the bone marrow includes both hematopoietic and mesenchymal stem cells [7,8]. Also due to the relatively low percentage of MSCs in the bone marrow, obtaining the right number of these cells for medical treatment is quite difficult. Consequently, there is an ongoing search for alternative, easy-to-access, and high-yielding MSCs acquisition sources, and adipose tissue-derived stem cells seem the best. MSCs' ability to differentiate into various cell types can be used in tissue engineering and regenerative medicine. Currently conducted research focuses on the use of MSCs in the treatment of cardiovascular damage, pulmonary fibrosis, spinal cord injury, nervous system, cartilage, bone, tendon, muscle, and skin [9-13]. The MSCs are also used to regenerate lost tissue in the wounds [14,15]. It has been suggested that MSCs can also be used to treat incurable diseases such as imperfect ossification, Parkinson's disease, and muscular dystrophy [16-20]. It is of great importance to evaluate the MSC differentiation potential and their possible use in the regenerative medicine depending on the age of the donors of these stem cells. Here we will focus on Adipose-derived mesenchymal stem cells (AD-MSCs) because they are the best stem cell candidate to be used in regenerative medicine.

Numerous studies describe the possibilities of using MSCs isolated from adipose tissues in tissue reconstruction, stimulation of peripheral nerves repair [21], regeneration of spinal cord injuries [22], treatment of diabetes [23], and repair of liver damage [24]. AD-MSCs are also used in autologous graft repair of knee cartilage [25] and as a filler in plastic and cosmetic surgery [26]. In addition, AD-MSCs are used, in conjunction with fibrin adhesive and biodegradable scaffold, for the repair of jaw bone defects [27].

AD-MSCs may also help in wound healing by accelerating many functions involved in this process [14,15]. They may accelerate the migration of macrophages and neutrophils to the wound via secretion of cytokines, the proliferation of different cell types involved in wound healing, and the process of the neo-angiogenesis of the wound area. They may eventually increase the number of regenerating cells by direct differentiation into different cell types, such as keratinocytes, fibroblasts, muscle cells, or blood vessels within the regenerating tissues.

Potential Improvement of MSCs for the Regenerative Medicine

AD-MSCs activities in wound healing can be enhanced by interactions with endothelial precursor cells (EPCs). It has been suggested that MSCs and EPCs may be involved in specific interactions that increase the regenerative functions of MSCs in the body [28]. This is evidenced by the proximity of the niches occupied by these cells in tissues and by the transmission of information between these cells during the activation of MSCs during trauma [29,30]. The nature of these interactions is not yet well characterized. In vitro studies have demonstrated that bone marrow-derived BD-MSCs co-cultured with precursor endothelial cells increase expression of embryonic genes, such as *Oct 4*, *Nanog,* and *Sox2* [31]. These genes code for transcription factors that are highly expressed naturally in the embryonic cells [32] and their experimental expression in differentiated cells restores their pluripotency [33]. It seems that such a transformation also should occur following the co-culture of AD-MSCs with EPCs, however, this is still hypothetical.

Our previous research has shown that the action of lipophilic compounds such as hexachlorophene (HCP) on various types of MSCs reduces their ability to proliferate and differentiate [34]. The reduction of these abilities by HCP is maintained after the removal of the drug from the culture. It would be interesting to investigate if a co-culture of such AD-MSC, which have decreased ability to differentiate after HCP treatment, with the EPC will restore their regenerative potential.

Our interest in HCP is also linked with the ability of this drug to stimulate the autophagy [35] and thus modify the MSC's physiology. Indeed, HCP was shown to be a competitive inhibitor of the chaperone GRP78- peptide interaction [35]. The consequence of this inhibition is the induction of the unfolded protein response (UPR), autophagy, and cell death through apoptosis [36,37]. HCP induced molecules involved in UPR such as XBP1s, which is the component of the IRE1α pathway,and ATF4 of the PERK pathway. If the UPR is not resolved, all these signaling lead ultimately to CHOP and apoptosis [37]. Apoptotic cell death is dependent on the HCP dose and the time of exposition. The induction of UPR is responsible for the control of ER stress. If the process of degradation of misfolded proteins generated in the ER is insufficient, the apoptotic cell death programs are initiated [37].

HCP is a highly lipophilic chlorinated bisphenol that binds tightly to the cell membrane resulting in the loss of ion gradients [38]. HCP disrupts the efflux of monovalent cations such as K^+ and Na^+, due to the modification of cellular membrane permeability. The perturbed ion transport triggers the direct inhibition of (K^+–Na^+)-activated and $Mg2^+$-dependent ATPase. This, in turn, decreases the efficiency of metabolic reactions [39]. These changes inhibit oxidation and modify the permeability of the cell membrane [40]. The HCP is also a potent uncoupler of oxidative phosphorylation in mitochondria and inhibits mitochondrial respiration. Mitochondrial functions are the major factors inducing apoptosis. HCP affects cell apoptosis throughout Wnt/b-catenin classic pathway [41]. For instance, HCP addition to the colon cancer cell line inhibited Wnt/b-catenin signaling throughout the degradation of the intracellular b-catenin independently of GSK-3 and b-TrCP activation [42]. Wnt/b-catenin signaling pathway controls the functioning of T cells transcription factor (TCF) and modifies various molecular processes impacting embryogenesis, cell survival, differentiation, and proliferation [43]. All these phenomena may be affected when the MSCs are exposed to HCP. As HCP is present in numerous cosmetics used in the everyday life it can accumulate in the body, and especially in the adipose tissues. Consequently, AD-MSCs obtained from the patients with an accumulation of HCP in their adipose tissues may differentially, depending on the HPC amount, modify the regenerative capabilities of AD-MSCs obtained from these patients.

More and more research on the use of different stem cells, both human and murine, focus on examining the relationship between the donor age, the proliferative and differentiative potential, and the number of stem cells. Recent studies have confirmed that mesenchymal stem cells isolated from older donors have lower viability [44], lower number of colonization units [45], lower proliferation [46], differentiation, and lower telomerase activity as compared to the cells from the younger donors. Additionally, the number of AD-MSCs present in adipose tissue has also been shown to be significantly reduced with the increasing age of donors, which lowers their usefulness in regenerative medicine [47]. There are also various chronic diseases common in older donors, such as osteoporosis [48] or diabetes [49,50].

The developmental potential of BD-MSCs was studied in experiments in which these cells were introduced into mouse blastocysts [51]. BD-MSCs have been shown to be pluripotent, i.e. they can participate in all embryonic tissues but trophoblast. It is not known whether AD-MSCs have similar properties because such tests have not been performed on these cells. BD-MSCs have also been used in wound healing tests and have been shown to accelerate wound healing in mice [52]. Interestingly, these studies show that BD-MSCs have the best regenerative potential when derived from the young adult donors. This potential decreases in the cells procured from older individuals. It is not known if also the AD-MSCs regenerative potential changes with the donor age, although several studies indicate a link between the lowered regenerative potential of such donor-aged cells [53,54]. The assessments of the proliferation and differentiation potential of AD-MSCs derived from mice of different ages are now conducted in our laboratory. Our goal is to find the best source of AD-MSC for therapeutic wound healing in mice, and eventually in humans.

MSCs as a potential remedy for COVID-19

Finally, MSCs have an important immunomodulatory and anti-bacterial or anti-viral capabilities making them a good therapeutics

against infectious diseases (e.g. [55]). The outbreak of COVID-19 in China by the end of 2019, and the resulting 2020 pandemic, provoked an urgent need for an efficient remedy to this novel infection disease. Besides numerous potential solutions with the efficient vaccine and anti-viral drugs in the foreground, the hope is also placed in the application of MSCs. In short, as the intravenous transplantation of MSCs results in a significant population of cells accumulating in the lung, the immunomodulatory effect of such transplanted MSCs could have a protecting effect on alveolar epithelial cells during the Acute Respiratory Distress Syndrome (ARDS), which is one of the most severe symptoms of COVID-19. The secretory capacities of MSCs may play a key role in such a potential stem cell cure for COVID-19. The detailed analysis of the ongoing trials, approaches, and potential treatments has recently been discussed by Ali Glochin and colleagues [56].

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