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REVIEW

Aging: A cell source limiting factor in tissue engineering

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Abstract

Tissue engineering has yet to reach its ideal goal, *i.e.* creating profitable off-the-shelf tissues and organs, designing scaffolds and three-dimensional tissue architectures that can maintain the blood supply, proper biomaterial selection, and identifying the most efficient cell source for use in cell therapy and tissue engineering. These are still the major challenges in this field. Regarding the identification of the most appropriate cell source, aging as a factor that affects both somatic and stem cells and limits their function and applications is a preventable and, at least to some extents, a reversible phenomenon. Here, we reviewed different stem cell types, namely embryonic stem cells, adult stem cells, induced pluripotent stem cells, and genetically modified stem cells, as well as their sources, *i.e.* autologous, allogeneic, and xenogeneic sources. Afterward, we approached aging by discussing the functional decline of aged stem cells and different intrinsic and extrinsic factors that are involved in stem cell aging including replicative senescence and Hayflick limit, autophagy, epigenetic changes, miRNAs, mTOR and AMPK pathways, and the role of mitochondria in stem cell senescence. Finally, various interventions for rejuvenation and geroprotection of stem cells are discussed. These interventions can be applied in cell therapy and tissue engineering methods to conquer aging as a limiting factor, both in original cell source and in the *in vitro* proliferated cells.

Key words: Aging; Senescence; Rejuvenation; Geroprotection; Tissue engineering; Stem cell therapy

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Core tip: To attain profitable off-the-shelf tissues and organs, we must deal with the challenge of identifying and isolating an optimal cell source. Different types of stem cells with different properties have been used in tissue engineering and cell therapy to face this challenge. Although aging is an inevitable process that can eventually limit the function and stemness of stem cells, it is a conquerable phenomenon. In this article, we have reviewed several applicable interventions that can be used to overcome cellular aging.

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INTRODUCTION

Anatomical and functional complexities of biological systems challenge the artificial construction of viable human tissues and organs. Proper three-dimensional tissue architecture to maintain blood supply is a key constraint on the size of the *in vitro* fabricated tissues[1]. In addition, biomaterial selection and strategies to design tissue scaffolds are vital for regulating cell signaling pathways that provide appropriate cell-cell interactions such as growth factor delivery, which is essential for cell differentiation. Although numerous attempts were made to overcome these key challenges in tissue engineering, the reproducible *in vitro* construction of artificial vascularized tissue is still needed[2].

The ideal goal of tissue engineering is to create off-the-shelf tissues and organs providing vast opportunities to tackle a group of diseases and to reduce the need for organ donors. This not only would treat millions of patients, but also increase human longevity and quality of life[1,3,4]. As the field of tissue engineering evolves, new obstacles appear in the way of the research and clinical application of these artificial tissues and organs. The fundamentals of this interdisciplinary field not only involves identifying biomaterials and designing scaffolds for *in vivo* cell expansion but also requires addressing the reliable cell sources. Hence, gradual advances in the clinical application of tissue engineering deal with hurdles in diverse aspects of science such as cell biology, bioengineering, and material science[5].

Apart from these engineering challenges, biologic issues and the major concern of identifying the ideal cell source is the other essential principle of tissue engineering[2]. Various stem cell types and sources have been extensively employed in regenerative medicine studies. However, each source has its own practical and technical challenges concerning their availability, isolation and cell expansion, cell delivery, aging, immunological barriers, and clinical and therapeutic efficiency. Furthermore, while major challenges of tissue engineering must be addressed at first, aging, as a cell source limiting factor, should not be overlooked. In this article, we have reviewed the cell sources that are used in tissue engineering and cell therapy techniques and how aging and cell senescence can challenge the isolation of ideal cell source. Also, we have discussed potentially applicable approaches for rejuvenation of aged cells.

CELL SOURCE AS A MAJOR CHALLENGE

First and foremost, the unresolved controversy of identifying the optimal cell types for tissue engineering is still a major challenge[4,6,7]. While cell transplantation, organ transplantation, and tissue engineering are fundamentally different, there are essentially three varieties of sources: Autologous, allogeneic, and xenogeneic cells, each of which can be subdivided into several types of stem cells including adult and embryonic stem cells. In addition, the discovery of induced pluripotent stem cells (iPSCs), which are discussed in the following sections, represent a promising source of cells for all branches of regenerative medicine[8,9].

Autologous sources

In autologous transplantation, the donor and the recipient are the same. Concerning the role of the immune system in potential tissue rejections, utilizing a patient's own

cells or "autologous cells" would be ideal. This method minimizes the chance of graft *versus* host disease and transmitted infections, and more importantly it would eliminate the need for lifetime use of immunosuppressive drugs, which improves the quality of life in post-transplant patients[10]. Despite these benefits, autologous cell therapy brings about several challenges. In fact, using the patient's own cells might not be practical for the majority of cases. Transplant waiting lists are filled with aged patients who suffer from age-associated morbidities and cellular senescence affecting both their somatic and stem cells[11]. In addition, the patients who suffer from gene defects cannot easily benefit from autologous cell therapy[12]. Furthermore, to be viable for tissue engineering, millions of autologous cells should be collected from a donor and expanded *ex vivo*. For many tissue types, harvesting a sufficient number of cells is not applicable, especially when a patient is aged or severely diseased. Moreover, cell culture *per se* can cause undefined complications; the proliferative potential and clonogenicity of stem cells decrease after several cell divisions, which raises concerns about viability and functionality of cells after transplantation. These issues make autologous cell therapy undesirable for clinical applications, especially in emergencies or acute phases of disease[9,13].

Allogeneic sources

As mentioned earlier, the goal of tissue engineering is to manufacture large quantities of off-the-shelf tissues and organs that are immediately available to be administered clinically[14]. Allogeneic cells are cells from a genetically non-identical donor but of the same species. Thus, unaffected cells, tissues, and organs of every healthy donor can be a precious allogeneic cell source. This will rule out the challenges of aging, unavailability, and *in vitro* expansion challenges of autologous cell sources and consequently introduce allogeneic cell therapy as a promising method in case of emergency. This advantageousness paved the way for preparing a master bank of ready-made, clinically practical, and off-the-shelf allogeneic cells. On the contrary, the immunogenicity of allogeneic cells and the major histocompatibility complex (commonly known as MHC) incompatibilities are by far the most formidable barriers of allotransplantation. In addition, the side effects of immunosuppression like metabolic disorders, malignancies, and opportunistic infections can aggravate the outcome of a transplantation[9,12,15].

Xenogeneic sources

Xenogeneic or cross-species transplantation is the process of transplanting living cells, tissues, or organs from one species to another. In recent decades, the ever increasing demand for clinical transplantation and shortage of allogeneic sources for patients on the waiting lists has led to considerable amounts of clinical and experimental research in order to overcome the barriers of xenotransplantation. However, a great number of ethical red tape and immunological roadblocks are yet to be surpassed. Graft rejection and failure to achieve successful long-term outcomes are the main issues to be addressed, as there are great disparities between MHCs of different species. Another concern is the risk of zoonotic infections, particularly unidentified viruses. In addition, xenotransplantation is by itself a controversial ethical issue and sometimes raises religious concerns because it involves sacrificing animals to harvest organs and tissues for human usage[16].

CELL TYPES

Thus far, several stem cell types have been utilized in the field of tissue engineering.

Embryonic stem cells (ESCs)

ESCs are pluripotent stem cells isolated from the inner cell mass of blastocysts up until day 5.5 post-fertilization, right before the stage in which the embryo is ready for gastrulation[17,18]. They have unlimited potential for self-renewal and differentiation to be used as a source for derivation of multiple lineages of adult cells. In spite of these distinctive potentials, studies have raised concerns over the prolonged culture of ESCs. Formation of *in vivo* teratomas has been reported in implantation of *in vitro* cultured undifferentiated ESCs. Additionally, difficulties in finding patient-matched ESCs are an obstacle. Finally, because isolating ESCs involves the destruction or manipulation of pre-implantation stage embryo, there are lots of ethical controversies surrounding their usage[19].

iPSCs

iPSCs are generated *via* the induction of expression of certain genes in non-pluripotent adult cells. This technique was first developed in 2006 by Takahashi and

Yamanaka, who introduced four transcription factors, Oct-4, c-Myc, KLF4, and SOX2, into mouse fibroblasts. These factors contributed to the maintenance of pluripotency in ESCs and are sufficient to generate ESC-like colonies[20]. A year later, Yamanaka improved on the reprogramming approach, leading to generation of iPSCs that were indistinguishable from ESCs[21]. Direct derivation of iPSCs from adult tissues not only helps to bypass the need for embryos as the pluripotent stem cell source but also makes personalized cell therapy a viable option. This method could generate unlimited supplies of young autologous pluripotent stem cells with a promising future in the field of regenerative medicine[22,23].

In contrast, several challenges still exist. Primarily, the efficacy of the reprogramming process is considerably low. For example, the rate at which somatic cells were reprogrammed into iPSCs in Yamanaka's original mouse study was 0.01%–0.1%. Although protocols for the induction of pluripotency are evolving, experimental evidence for appropriate initial cell type, transcription factor combinations, gene vectors, and methods of cell culture still lack the consistency required for clinical applications. In addition, induction of pluripotency and the process of reprogramming, itself causes genomic instability and adversely affects the cellular integrity. Moreover, the reprogramming factors (such as c-Myc) are known to be proto-oncogenes. Also, the retained epigenetic memory of the past somatic identity in newly generated iPSCs may influence the potency and *in vivo* functionality of engineered tissues[24]. However, recent rapid progress of several clinical studies have improved the outlook for this technology[25-27]. The first iPSC-derived therapy was done for age-related macular degeneration patients at Japan's RIKEN Institute[28]. Encouraging results have smoothed the path for other scientific groups to seek clinical trials for the iPSC-based treatment of cardiac diseases, Parkinson's disease, and blood clotting disorders[29-32].

Adult/somatic stem cells

Adult stem cells are populations of undifferentiated cells that unlike ESCs are found in mature tissues and organs throughout the postnatal life. These progenitor cells are responsible for tissue cell turnover and maintenance of injured tissues. Their easy accessibility, availability, and self-renewal ability introduce adult stem cells as a preferred cell source for transplantation. In spite of these great potentials, adult stem cells are not perfect. First, unlike pluripotent ESCs, adult stem cells are usually multipotent and can only give rise to a limited number of cell lineages of their specific tissue. Although adult stem cells can be obtained from both allogeneic and autologous sources, the age-dependent progressive deterioration of stem cell function is an important issue to be expected[11,33]. In addition, due to replicative senescence after prolonged culture periods, the proliferative ability of these cells declines rapidly[9,33].

Genetically-modified stem cells

Genetically modified stem cells are born out of the junction of two focus points of intense research: Gene therapy and stem cell therapy. Gene modification of cells prior to transplantation is one of the proposed solutions to overcome cell source challenges and to enhance cell proliferation and function[34]. Various gene therapy approaches are proposed, including the creation of genetically or epigenetically modified cells expressing useful proteins, growth factors or growth factor receptors, transcription factors, neurotransmitters and their receptors, and neuropeptides or creating cells that have the ability to recruit host cells to the implantation site[35,36].

The promise of using clustered regularly interspaced short palindromic repeats (CRISPR) technology brings about new hope as a tool for the gene editing of stem cells[37,38]. Brunger *et al*[39] used CRISPR for targeted deletion of the interleukin-1 receptor type 1 gene in murine iPSCs to make custom-made inflammation resistant cartilage cells. Genome editing by CRISPR has also been used to correct Duchenne muscular dystrophy patients derived iPSCs successfully to differentiate muscle cells that express functional protein[40]. Moreover, genetic modification of patient-derived iPSCs using CRISPR and other genetic engineering tools has been used for hemoglobinopathies such as β-thalassemia and sickle-cell anemia[41-44].

Immortalized cell lines are genetically mutated cells with unlimited propagation potential that are generated to prevail major challenges of cell source availability, such as early onset of cellular senescence and the consecutive limited cell expansion and differentiation potential. The mutations required for immortality can occur naturally or can be induced intentionally. There are several possible gene modification methods to bypass the senescence block. Viral oncogenes such as SV40 and E6/E7 proteins of oncogenic human papillomaviruses are used for regulating human cellular senescence[45-48]. One possible gene editing approach is artificial expression of key proteins required for immortality such as telomerase (discussed in later parts of this article). However, it was reported that they might be associated with genomic

instability and increased risk of cell transformation[33,49,50].

Conditionally reprogrammed cells are another gene therapy approach used to rapidly and efficiently generate an unlimited number of patient-derived cells. In this technique by using both fibroblast feeder cells and a Rho-associated kinase inhibitor, Liu *et al*[51] indefinitely extend the life span of primary human keratinocytes *ex vivo*. Unlimited propagation of these karyotype-stable and non-tumorigenic cells offer opportunities for regenerative medicine as these cells have a stem cell-like phenotype[52].

In spite of preliminary success, several hurdles prevent both laboratory and particularly clinical applications of these gene-editing technologies. Genetic and epigenetic changes might cause unresolved issues to the patient. Transgenic genes, vector genes, or non-autologous stem cells might trigger immune reactions or even induce neoplastic transformation. In addition, developing an ideal gene vector system is next to impossible; the most common vectors are viruses. Beyond the uncontrollable insertional mutagenesis of viruses leading to increased risk of malignant transformation, viruses can cause adverse events such as toxicity and immune and inflammatory responses[34,53].

Ethical issues of gene editing of stem cells should not be overlooked. Matters like safety and efficacy of gene editing, including off-target mutations, raise concerns regarding human enhancement and eugenics that must be closely regulated. All in all, it is a necessity to set boundaries for techniques that have dire consequences[37,54].

CELLULAR AGING AS A LIMITING FACTOR

Aging, whether it is in a stem cell or a fully differentiated cell, seems to be the result of particularly shared processes. Some believe that aging occurs due to the incapability of senescent stem cells to contribute in tissue repair and regeneration, while others suggest that the vicious cycle of the dysfunctional relationship between stem cells and their niche cells is the leading contributor in the progressive deterioration during aging[55].

Cell intrinsic changes usually occur due to the accumulation of damage caused by normal cellular processes like metabolism and proliferation, while cell extrinsic changes are derived by a factor external to the cell subjected to those changes, such as paracrine and endocrine factors, ionizing radiation. and changes in the extracellular matrix[55]. Sometimes it is almost impossible to delineate the intrinsic and extrinsic changes. For instance, free radicals produced during both oxidative phosphorylation (a cell intrinsic factor) and generated by ionizing radiation (a cell extrinsic factor) can harm cellular components leading to senescence[56]. These intrinsic and extrinsic elements are discussed in detail in the following sections.

Functional decline of aged stem cells

During aging, several functional properties of the stem cells are being affected[55]. For instance, aged stem cells, especially neural stem cells[57-59], germline stem cells[60], and muscle satellite cells[61-65], lose their cellular polarity. As a consequence, they lose their ability to divide asymmetrically, a key feature of stem cells helping them to preserve the stem cell repertoires[55]. This loss of polarity is granted mostly by cell extrinsic factors like aged niche cells, dysfunctional adhesion molecules, disrupted morphogen, growth factors signaling, and inflammation[66-71]. Another phenomenon that is seen in aged stem cells is a lineage bias in the differentiation of their progenies. To enumerate, aged hematopoietic stem cells (HSCs) tend to skew toward the myeloid lineages more prominently compared to young and fully functional HSCs, a circumstance that leads to the incompetence of adaptive immune system in aged individuals[55,72-83].

Another example is loss of osteogenic differentiation and biased adipogenic commitment of mesenchymal stem cells (MSCs), which contributes to osteoporosis and bone marrow fat accumulation in aged individuals. Over-expression of receptor activator of nuclear factor kappa B ligand, down-regulation of peroxisome proliferator-activator receptor gamma, and suppression of forkhead box family O3 by protein kinase B (AKT) signaling in aged MSCs are proposed as the mechanisms responsible in this phenomenon[84-86]. This age-associated skewed differentiation is not completely understood for cells like ESCs and iPSCs. For instance, Xie *et al*[87] showed that H9 ESCs have an increased tendency for ectodermal lineages; however, this may be explained by the culture media composition. However, they observed no difference in teratoma formation between old and young ESCs. iPSCs were found to have a different story; while some studies have claimed that iPSCs have skewed differentiation capacity, probably because of their retained epigenetic memory of their original cell lines[88], other studies have reported that the iPSC differentiation capacity

has no correlation with the cell source they are originated from[24,89].

Additionally, aged stem cells lose their migratory and homing potential, due to both cell intrinsic and cell extrinsic changes. For instance, transplantation of young mouse HSCs to old individuals delivers a lower yield compared to young recipients, which is due to the inferiority of the aged bone marrow niche[90,91]. Additionally, transplantation of old HSCs to young individuals is less effective in contrast to young donor cells, which shows a decline in the homing capacity of old stem cells due to intrinsic factors[72,90,91]. Another interesting aspect of HSCs is that using immunophenotyping, it has been shown that the number of HSCs increases with age; however, functional evaluation of these immunophenotypes shows reduced engraftment and improper differentiation in the new host[55,78-80,92]. This indicates a decrease in the population of functional HSCs or a form of clonality that happens with aging[55,81-83].

Yet, another example is heterochronic transplantation of aged mice muscle satellite cells into young recipients[61-65]. These cells show much lower regenerative capacity in old donors compared to young recipients, mostly due to cell extrinsic factors including, but not limited to, Wnt, Notch, and transforming growth factor beta signaling as well as altered Janus kinase-signal transducer and activator of transcription signal transduction[93,94]. In addition to the declined *in vivo* engraftment potential, aged satellite cells also have a reduced *in vitro* proliferation capacity[95-99].

Replicative senescence, Hayflick limit, and telomere length

Replicative senescence, equally known as Hayflick limit, is a phenomenon observed *in vitro* in which a primary cell or a stem cell stops dividing after a particular number of doublings. While the mechanism of Hayflick limit is not thoroughly understood, many attribute telomere attrition and genomic instability as the principal mechanism of replicative senescence[84,100]. For instance, MSCs stop dividing after 20 to 40 doublings when their telomeres are between 5.8 and 10.5 kb[84,101-103]. Despite the fact that telomere attrition can be considered an intrinsic change in stem cell replicative senescence, several questions remain to be addressed. Considering the fact that non-dividing cells also senesce[104-106], can we really take telomere attrition as one of the integral causes of aging, or is it just one of the many "effects" of the aging process that worsens this vicious cycle? Additionally, if telomere attrition is a deriving cause for aging, is it possible to increase the lifespan of a model organism, like a mouse or a rat, by "telomerization" or telomere lengthening? While the answers to these questions are controversial, it seems possible to immortalize cell lines *via* expression of telomerase subunits. Human telomerase reverse transcriptase (hTERT)-immortalized cells show extended life span with improved functional activities[58]. A successful example of this approach is the use of immortalized human keratinocyte cell lines in the treatment of chronic wounds and complex skin defects[59,60]. Notwithstanding, one study showed that over-expression of TERT only increases the median lifespan of the cancer-resistant mice, implying that telomere attrition might be important only in the late stages of aging[55,107,108]. Additionally, as mice have very long telomeres, it is not clear why they have a much shorter lifespan. Knocking out the RNA component of telomerase has no obvious life-threatening effect up to the sixth generation of these mice. Albeit, HSCs of the fourth generation started to show lineage skewness[109,110].

Stem cells spend most of their life in a quiescent state, probably to avoid the replicative damages, especially those related to DNA duplication. These quiescent stem cells are more likely to acquire destructive DNA damage after a double-strand break compared to a cell in its proliferative state. Quiescent stem cells mostly use the error-prone non-homologous end joining repair mechanism, while proliferative cells utilize homologous recombination, a much more accurate repair mechanism[111,112].

Autophagy

Perhaps one of the most extensively studied factors involved in aging is autophagy. Autophagy is a conserved mechanism that has evolved to recycle the damaged structures and organelles in a eukaryotic cell. This very sophisticated feature integrates the signal from several pathways to regulate the level of protein degradation. AMPK (adenosine monophosphate-dependent protein kinase), mTOR (mechanistic target of rapamycin), and ULK1 (Unc-51 like autophagy activating kinase 1) are the most important upstream signaling pathways of autophagy that regulate atg (autophagy related) genes and autophagosome formation. AMPK senses the ratio of AMP:ATP and activates ULK1 whenever the cell requires more energy. mTOR, on the other hand, inhibits ULK1 and autophagosome formation whenever it integrates the signal from nutrients and growth factors, which are the prerequisites of anabolism[11,113,114]. Every cell tries to strike a balance between the three forms of autophagy (macro-autophagy, micro-autophagy, and chaperone-mediated autophagy) and protein synthesis[115]. It has been shown that autophagy is decreased

in aged cells of both animal models and humans, regardless of whether it is a stem cell or a fully differentiated one. While autophagy declines progressively, tiny amounts of damage gradually accumulate throughout time[115-117]. Stem cells have at least two mechanisms to prevent these damaged proteins and organelles to build-up: the asymmetric division (which diminishes with aging)[55,118-120] and maintaining high levels of autophagy and proteasome activity[55,121].

Aged MSCs and HSCs show accumulation of autophagic vesicles and inclusion bodies with LC3II or ubiquitin expression, which are the features of decreased autophagy with age. Rapamycin or spermidine treatment restores the autophagic capacity, leading to clearance of those accumulated autophagic vesicles and inclusions[115,122,123]. Additionally, Ho *et al*[123] showed that more than two-thirds of the HSCs in an aging population have very low levels of autophagy and skewed and escalated differentiation to myeloid lineages, while only less than a third of them had high levels of autophagy and regenerative potential comparable to that of young HSCs[115,123]. It has also been shown that while young MSCs in GFP-LC3 transgenic mice have high levels of autophagy in the quiescent state, this capacity fades with aging[115]. Furthermore, using conditional knock-out mice, when autophagosome formation is genetically compromised, senescence can rise from impairment of proteostasis[115,122]. These studies substantiate the importance of autophagy for maintaining stemness in a quiescent stem cell[115].

Epigenetic changes

In a fertilized egg, the genome of two mature and non-young individuals get stripped of epigenetic marks (except for the imprinted areas) to form a new very young individual with almost the same lifespan as the parents[124]. This epigenetic reprogramming can be emulated by *in vitro* induction of totipotency/pluripotency. The nucleus of a somatic cell can either be fused with the cytoplasm of an enucleated oocyte (somatic cell nuclear transfer) or be transfected with viruses expressing Yamanaka factors (SOX2, c-Myc, Oct-4, and KLF4)[20] to produce an iPSC[55,125-128]. Although this reprogrammed cell is very similar to a freshly young ESC in many aspects, its epigenome is slightly different[127]. In fact, iPSCs are reprogrammed with regard to the age-, tissue-, and senescence-associated DNA methylation patterns but keep some donor-specific DNA methylation patterns[129]. In 2013, Abad *et al*[130] produced a transgenic mouse expressing the four Yamanaka factors in every cell upon administration of doxycycline. These mice usually develop teratomas in several organs and tissues. Another interesting fact about epigenetic reprograming is that it is possible to make phenotypically young neural stem cells from iPSCs, which are generated from aged fibroblast, while direct transdifferentiating neural stem cells from aged fibroblasts maintains the aged phenotype[55,131].

This reprogramability of the epigenome helps us to unravel detailed mechanisms of aging in order to find a way to conquer it in the future; however, it is obviously not a practical formula for rejuvenation[55]. Perhaps it is better to use epigenomic results to reinforce gene regulatory networks and to decipher what signals are differentially active in old cells compared to their younger counterparts.

miRNA

Among the differentially expressed genes in aged cells in comparison with the young cells, there are several non-coding RNAs, including miRNAs expressed (some of which are even proposed as biomarkers for aging)[56,84,132]. miR-195 is over-expressed in aged cells and reduces the telomerase reverse transcriptase; also, knocking-down this miRNA in MSCs increases their regenerative capacity when transplanted to the infarcted myocardium[56,133]. Another example is over-expressed miR-34a, which is elevated in infarcted mouse hearts and is associated with apoptosis and senescence. Also, its inhibition decreases the number of apoptotic cells in cardiac tissue[56,134,135]. Some of these differentially expressed miRNAs control proliferative and regenerative capacity of the stem cells by regulating cell cycle transition and stemness factors (such as Nanog)[84,133,136-138].

Role of mitochondria in stem cell senescence

Free radicals, otherwise known as reactive oxygen species (ROS), are a well-recognized origin of age-related molecular injuries including but not limited to nuclear and mitochondrial DNA mutations, organelle damages, and lipofuscins. Chronic inflammation, ionizing radiation, and mitochondrial dysfunction are the most prominent sources of ROS in cells[56,139,140]. Stem cells employ several mechanisms to keep ROS and its damage at bay. To enumerate, quiescent HSCs depend predominantly on glycolysis to limit ROS production[75,141].

Sirtuins, (SIRT1–SIRT7) a conserved family of NAD^+-dependent deacetylases of which SIRT1 is the best known, appears to increase mitochondrial turnover by

activation of mitophagy. Activation of SIRTs can considerably extend the replicative capacity of human bone marrow stem cells[142] and human fibroblasts[11,143]. Additionally, SIRTs boost the stress-relieving and antioxidant mechanisms in cells. Studies show that over-expression of certain SIRTs increases catalase and superoxide dismutase, while their knock-down compromises cell proliferation and increases cellular senescence[56,144-147].

On the other hand, stem cells have a unique way to get rid of the damaged proteins and organelles[55,75]. During asymmetrical division, stem cells actively accumulate these injuries in the differentiating daughter cell, while keeping the daughter stem cell almost clean of them[109,118-120,148]. This polarized division is lost in certain stem cells, like HSCs and germline stem cells, during aging. As a matter of fact, less-polarized HSCs are more biased toward myeloid lineages[55,70,71]. Furthermore, autophagy and proteasome-mediated degradation, the other mechanisms that keep even the quiescent stem cells clean, diminish with aging. When dysfunctional mitochondria cannot be recycled by mitophagy (macro-autophagy of mitochondria), it generates more ROS. As a result, we observe a vicious cycle between impaired autophagy, mitochondrial dysfunction, and ROS-mediated injuries[56,139,140,149]. Xie *et al*[87] found that the most prominent changes that occur in long-term passaged ESCs have to do with the mitochondria; older passages of H9 and PKU1 hESC lines have elevated mitochondrial mass, ROS level, and mitochondrial membrane potential. On the other hand, aged iPSCs develop defects in their nuclear envelop[150], which might be the cause of interference in SIRT and NF-kB nuclear transportation and downstream signaling in these cells[151,152].

Above all, some studies contradict ROS as a contributing factor in aging. At the cellular level, Zhu *et al*[153] showed that there is "no evident dose-response effect between cellular ROS level and its cytotoxicity." For instance, they showed that while all three of the piperlongumin, beta-phenylethyl isothiocyanate, and lactic acid increased ROS in the cultured cells, only piperlongumin and beta-phenylethyl isothiocyanate, two ROS-based chemotherapeutic agents, killed the cells and lactic acid "spared them." Additionally, although chemical depletion of glutathione increased ROS much higher than piperlongumin and beta-phenylethyl isothiocyanate, it did not affect the cell growth in cultured samples. However, these results were achieved in cancer cells, and it is unclear if similar mechanisms also happen in stem cells. Le Gal *et al*[154] showed that administration of the antioxidant N-acetyl cysteine to a mouse model of melanoma not only decreased the survival of the mice but also increased the severity of their tumors by increasing metastasis. Biesalski *et al*[155] meta-analytically reevaluated clinical effectiveness of antioxidants on mortality and health. They showed that micronutrients, including those with antioxidant activity, are only effective in those with the deficiencies or the risk of deficiencies, but not effective in individuals with the micronutrients above the minimum required level. All in all, these counterexamples provide sufficient evidence to raise a reasonable doubt toward ROS-based therapeutics.

INTERVENTIONS FOR REJUVENATION OF AGED STEM CELLS

The ultimate goal of unraveling mechanisms of aging is geroprotection (preventing from aging) or rejuvenation (making a senescent cell young again). For this purpose, there are three options: Changing the extrinsic factors, altering the intrinsic factors, or manipulating the genomic targets of those changes. We can either use pharmacological means, modify the environment in which the stem cells reside, or genetically manipulate the stem cells.

Using pharmacological means to prevent aging or even rejuvenate is, perhaps, the most practical measure. Different mechanisms have been targeted pharmacologically. For instance, antioxidants like vitamin C and N-acetyl cysteine have been used to reduce ROS both *in vitro* and *in vivo*[75,154,156]. However, their efficacy is limited, especially *in vivo*. Although antioxidants to some extent show geroprotection in cell culture, the possible life extension by reduction of free radicals is challenged by *in vivo* experiments[115,153-155]. Comparatively, SIRTs are another example of drug targets for geroprotection. Resveratrol, resveratrol-mimicking compounds, and NAD+ seem to hinder aging both *in vitro* and *in vivo* by activating certain members of the SIRT family[157-160]. In particular, resveratrol improves metabolism and enhances DNA repair, which are critically important in aging[11,157].

Metabolic dysfunction is yet another focus for research on geroprotection. Rapamycin, spermidine, quercetin, and metformin are only a few examples of the drugs that increase the lifespan by this mechanism, whether it is in cell culture or *in*

vivo[56,161]. As we previously discussed, the balance between protein synthesis and protein recycling is disrupted in aging. Rapamycin that inhibits mTOR gives an advantage to the autophagic side of the balance between autophagy and protein synthesis[56,114,162]. Likewise, metformin activates AMPK to increase autophagy and other anti-stress mechanisms in the cell and slightly inhibits mTOR complex 1 through targets upstream of mTOR complex 1[11,163,164]. This boosted autophagy helps the cell to get rid of the damaged organelles and macromolecules much faster than it did before. Thus, it delays the damage accumulation, which is an important factor in dysfunctioning of stem cells[73,115,165-167]. Both of these small molecules have been shown to increase the lifespan, decrease the doubling time, and improve functional properties of stem cells, *e.g.*, engraftment, migratory, and regenerative potential[11,115,165-167]. Furthermore, combination treatment of cardiac stem cells with rapamycin and resveratrol improves the cardiac output of the infarcted myocardium in mice[56,168].

Caloric restriction (CR) is the most effective intervention for lifespan extension. Mechanistically, CR exerts its benefits through the alteration of the nutrient/growth factor-sensing mTOR signaling, energy-sensing AMPK signaling, stress-fighting forkhead box family O signaling, and SIRTs[55,169-172]. Therefore, CR not only increases the longevity of stem cells but also enhances the performance of niche cells that support stem cells[55,173-176]. Interestingly, most of the compounds that extend the lifespan by improving metabolism, especially those that promote autophagy like metformin and spermidine, are known as CR mimetics[73,174,177,178]. In fact, the geroprotective activity of CR is repressed by hindering autophagy[73,117]. While CR works best *in vivo*, it is not a practical way to extend the *in vitro* lifespan of stem cells, precisely because it limits the doubling time of cells. Thus, these CR mimetics might be the most practical intervention to be used in cell culture[11].

Although interventions like genetic manipulation might effectively work to counteract senescence in stem cells, their cost and safety concerns limit their application[75,179]. Studies mentioned interventions like over-expression of telomerase as a proposed mechanism for counteracting replicative senescence in MSCs[84,180]. For instance, over-expression of hTERT in MSCs increased their lifespan, while the normal karyotype was maintained[84,180,181]. Another strategy to genetically prevent aging is knocking-down either the retinoblastoma protein gene or the $p16^{INK4a}$ gene[84,182,183]. Retinoblastoma gene silencing decreases the age-related DNA damage and senescence as well as increases the functionality of MSCs[84,182]. Finally, manipulating miRNAs could be an effective strategy, but it needs further experimental support. To enumerate, knock-down of miR-195 leads to increased expression of hTERT, and forkhead box family O3 also intensified phosphorylation of protein kinase B (AKT) in senescent MSCs[84,133].

CONCLUSION

The way toward the production of tissue engineered products still has serious hurdles to overcome: The choice of cell source, proper biomaterial selection, maintaining blood supply by designing suitable scaffolds, and three-dimensional tissue architecture. Combined efforts to prevail over these major obstacles are warranted to pave the way for achieving tissue engineered products at a commercial scale.

With regards to the choice of cell source, aging is a limiting factor. Aging, as inevitable as it seems, is proven to be conquerable. In different cell types the problem of aging is preventable and to some extent reversible. As aging is a very complex and dynamic phenomenon, it would be better to approach it from a systems biology point of view to reach the best results. Perhaps we need to target multiple pathways to find the maximum efficacy. Regardless of the application of the stem cells, *i.e.* tissue engineering and cell therapy, we have to overcome aging, both in the original cell source and in the *in vitro* proliferation.

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