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Review

iPSCs-based anti-aging therapies: Recent discoveries and future challenges

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ABSTRACT

The main biological hallmarks of the aging process include stem cell exhaustion and cellular senescence. Consequently, research efforts to treat age-related diseases as well as anti-aging therapies in general have recently focused on potential 'reprogramming' regenerative therapies. These new approaches are based on induced pluripotent stem cells (iPSCs), including potential *in vivo* reprogramming for tissue repair. Another possibility is targeting pathways of cellular senescence, *e.g.*, through modulation of p16INK4a signaling and especially inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Here, we reviewed and discussed these recent developments together with their possible usefulness for future treatments against sarcopenia, a major age-related condition.
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1. Introduction

Developing countries are aging. This demographic phenomenon poses major issues, including loss of elderly's independence and elevated healthcare and social costs. Aging is characterized by a cumulative loss of biological integrity at the cellular level which in turn affects body physiological functions, ultimately increasing vulnerability to death. The main biological hallmarks of the aging process include (i) a decline in tissue regenerative capacity with attrition of stem cells in virtually all adult stem cell compartments

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and (ii) cellular senescence, that is, as a stable arrest of the cell cycle coupled to phenotype changes (including among others, DNA damage) (Lopez-Otin et al., 2013). Accordingly, research efforts to combat age-related diseases have focused on potential 'reprogramming' regenerative therapies (such as induced pluripotent stem cells (iPSCs)-based therapies) or targeting pathways of cellular senescence. Future efforts in regenerative medicine should also put an emphasis on a major age-associated condition, sarcopenia, that is, an extensive loss of muscle mass and function which affects up to 13% of people aged 60–70 years and 50% of those aged 80+ years (Landi et al., 2012). Sarcopenia is closely linked with the frailty syndrome which is related to falls, disability, dependence, hospitalization, and mortality (Landi et al., 2012; Mohler et al., 2014). The purpose of this perspective article is to review the novel potential therapies, included mainly those based on iPSCs, for regenerative medicine and anti-aging purposes.

2. 'Classic' *vs* 'modern' reprogramming regenerative medicine

The potential of regenerative medicine has grown considerably in the last decade since the Nobel Prize laureate Yamanaka reported that iPSCs could be generated from fibroblasts using four defined transcription factors (Oct4, Sox2, Klf4 and c-Myc) (Takahashi et al., 2007). Thus, at least theoretically, any dividing cell of the body could be converted or 'reprogrammed', into an iPSC. Until now, regenerative medicine has been mainly based on stem cell administration and tissue engineering. Unfortunately, such approaches continue to pose major limitations from an ethical standpoint, particularly in relation to the use of embryonic stem cells. Other important caveats include methodological shortcomings (*e.g.*, cellular viability) and the risk of immunological rejection (Sommer and Mostoslavsky, 2013).

In contrast, iPSCs offer major advantages, including self-renewal and their capacity to differentiate into patient-specific cell lineages (ultimately reducing the likelihood of rejection). In addition, they are easier to obtain than embryonic stem cells, have less ethical limitations, and can capture human genetic diversity. In this scenario, iPSCs could be used in regenerative medicine through a variety of different approaches, including autologous therapies, new outstanding techniques to edit genomic DNA at a precise locus in iPSCs (*e.g.*, the CRISPR/CAS9 system) or 'go fishing' through pharmacological screening with drug libraries (Wilson and Wu, 2015).

3. The need for *in vivo* reprogramming

Two major problems in the use of iPSCs are their administration route and their stability upon tissue injection. Thus, an *in vivo* reprogramming would avoid cell transplantation and provide specific iPSCs *in situ* for tissue repair. In this regard, Abad et al. (2013) recently generated reprogrammable mice through the transitory induction of a drug-inducible polycistronic cassette encoding the aforementioned murine reprogramming factors (Oct4, Sox2, Klf4, c-Myc) in several transgenic mouse lines. These results indicated that *in vivo* reprogramming was feasible and conferred totipotency features that are absent in both embryonic stem cells and standard reprogrammed iPSCs. However, technical improvements are still eagerly awaited before transplantation therapy with iPSCs can be actually established. First, the minimum number of undifferentiated iPSCs that can produce teratomas must be carefully analyzed in autologous transplantation animal models. Indeed, residual undifferentiated cells may still remain after iPSC are differentiated into specific cell lineages and produce tumors after delivery into patients. Second, even with the new non-integrative reprogramming technologies the possibility of tumor generation from the iPSCs derivatives needs to be evaluated before their actual use in regenerative medicine. Additionally, more research is needed to assess the real potential of *in vivo* iPSCs for cell therapy. In this regard, some researchers have reported that incomplete *in vitro* reprogramming can trigger a de-differenciated state with advantageous properties (Kurian et al., 2013; Pulecio et al., 2014; Thier et al., 2012). Thus, partial or transient activation of the Yamanaka factors *in vivo* could be an attractive approach that requires further scrutiny for regenerative purposes.

4. Reprogramming old cells—rejuvenation is possible

iPSCs-based therapies are emerging as a promising tool in the forthcoming anti-aging medicine. Aging impairs, albeit not drastically, the ability of human cells to reprogram into iPSCs (Mahmoudi and Brunet, 2012). Although several studies (especially in mouse models) have shown an age-dependent decline in the reprogramming efficiency (Cheng et al., 2011; Kim et al., 2010; Li et al., 2009; Schnabel et al., 2012; Wang et al., 2011), other research groups have successfully obtained *bona fide* iPSC lines from old humans (Boulting et al., 2011; Ohmine et al., 2012; Prigione et al., 2011; Somers et al., 2010; Suhr et al., 2009; Yagi et al., 2012), including centenarians (Yagi et al., 2012). Reprogramming has the remarkable ability to reverse some cellular and molecular characteristics associated with aging, suggesting that numerous age-associated characteristics are in fact reversible and rejuvenation can actually occur at the cellular level (Freije and Lopez-Otin, 2012; Mahmoudi and Brunet, 2012). For instance, there is evidence supporting an increase in telomere length (Agarwal et al., 2010; Marion et al., 2009) and mitochondrial function (Prigione et al., 2010; Suhr et al., 2010) or loss of senescence markers (Lapasset et al., 2011) in iPSCs from centenarian donors, suggesting that cellular rejuvenation occurs during reprogramming.

5. Targeting pathways of cellular senescence (*e.g.*, NF-κB): recent findings

Cellular senescence, which leads to a virtually irreversible arrest of the cell cycle, is one of the mechanisms explaining partial aging impairment in reprogramming efficiency as we age (Mahmoudi and Brunet, 2012). The number of senescent or pre-senescent cells, increase with normal aging (Dimri et al., 1995; Herbig et al., 2006; Kuilman et al., 2010). Sousa-Victor et al. (2014) recently found that, in geriatric mice, satellite cells lose their quiescent state owing to deregulation of p16INK4a whereas repression of this molecule restores muscle regenerative capacity. Accordingly, we recently hypothesized that modulation of the p16INK4a pathway could be a new potential target for combating senescent-related disorders such as sarcopenia (Pareja-Galeano et al., 2014). Cell senescence also occurs in younger patients with phenotype traits indicative of accelerated aging (*e.g.*, patients with Hutchinson–Gilford progeria syndrome) (Hennekam, 2006; Merideth et al., 2008). In this context, an important question is how to target the molecular pathways involved in cellular senescence in order to boost reprogramming efficiency. In this regard, hyperactivation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in senescent cells, is a hallmark of the aging process (Lopez-Otin et al., 2013), which impairs endogenous generation of iPSCs by eliciting the reprogramming repressor DOT1-like histone H3K79 methyltransferase (DOT1L) (Feng et al., 2002). Soria-Valles et al. (2015) recently demonstrated that iPSCs generation can be stimulated by inhibiting DOT1L. Specifically, DOT1L inhibition allowed progeroid mice to obtain an extended lifespan and a rejuvenated phenotype. The potential clinical implications of this animal-based study were strengthened by the observation that NF-κB

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