Highlights

- No drug has yet proven useful against senescence and its related disorders (e.g. sarcopenia)
- iPSCs represent a potential strategy for regenerative medicine
- In vivo reprogramming may also represent a new promising technique for rejuvenation of tissues

Ageing Research Reviews

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

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Abstract

No drug has yet proven useful to combat senescence *per se* and its related manifestations such as sarcopenia and frailty. Here we review the more recent advances in the field. Regeneration therapies based on induced pluripotent stem cells (iPSCs) represent an intriguing strategy for regenerative medicine and anti-aging purposes, *eg*, to combat sarcopenia. Although much more research is needed, in vivo reprogramming of old cells also emerges as a new promising technique to be explored for the generation of rejuvenated tissues.

Keywords: induced pluripotent stem cells, regenerative medicine, sarcopenia, in vivo reprogramming, DOT1L

Manuscript

1. Introduction

Several major problems are associated with demographic aging. Our research group has experience in studying one of the main age-related alterations, *ie*, loss of muscle mass and function or 'sarcopenia', which affects up to 13% of people aged 60-70 years and 50% of those aged 80+ (Landi et al., 2012). The purpose of this perspective article is to review the potential regeneration therapies, included mainly those based on induced pluripotent stem cells (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 induced pluripotent stem cells (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, *ie*, '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 (*eg*, 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, pose 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 (*eg*, the CRIPSR/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*. 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 (Abad et al., 2013). 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. Albeit not drastically, aging impairs 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 succesfully 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 derived from old donors, suggesting that cellular rejuvenation occurs during reprogramming.

5. Targeting pathways of cellular senescence (*eg*, 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. (Sousa-Victor et al., 2014) recently found that, in geriatric mice, satellite cells lose their quiescent state owing to deregulation of $p16^{INK4a}$ whereas repression of this molecule restores muscle regenerative capacity. Accordingly, we recently hypothesized that modulation of the $p16^{INK4a}$ 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 (*eg*, 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*. (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 inhibition significantly increased the reprogramming efficiency of fibroblasts from Néstor–Guillermo and Hutchinson–Gilford progeria syndrome patients, as well as from advanced aged donors. NF-κB reinforces senescence signals and down-regulates pluripotency genes. Thus, the provocative recent findings by Soria-Valles and co-workers suggest that the development of rejuvenation therapies might not have to be necessarily based on the exogenous administration of rejuvenated iPSCs. Instead,

modulation of the NF-κB signalling pathway through DOT1L inhibition could also serve as a potential therapy target.

On the other hand, Cosgrove et al. (Cosgrove et al., 2014) recently highlighted the potential role of skeletal muscle stem cells (MuSCs) on muscle regeneration. This process is impaired with aging due, at least partly, to cell-autonomous functional decline of MuSCs, and is related with different senescence markers and, importantly, with elevated activity of the p38α and p38β mitogen-activated kinase pathway. Thus, according to these provocative findings, the transient inhibition of p38α and p38β could be a potential therapeutic approach for treating sarcopenia.

6. iPSCs to combat sarcopenia

A major problem of aging is sarcopenia, *ie*, an age-related loss of muscle mass leading to the functional impairment that inevitably occurs at late life in virtually all mammals. It has been reported that 11-50% of people aged 80+ years suffer from sarcopenia (Landi et al., 2012). Besides compromising independent living, sarcopenia contributes to the feared frailty syndrome (which in turn increases the risk of falls, disability, dependence, hospitalization, and mortality, ultimately posing a significant social and economic burden on our society) (Landi et al., 2012; Mohler et al., 2014). Unfortunately, the current pharmacologic approaches for combatting sarcopenia can produce major side effects (Sanchis-Gomar et al., 2014). However, the large size and the homogeneous structure of muscles make them a suitable target for iPSCs therapies. The skeletal-muscle tissue is mainly composed of post-mitotic cells. Accordingly, satellite cells are the only cells within this tissue that are able to proliferate and repair muscle damage over life. However, their number and function decline with aging. Thus,

differentiation of human iPSCs into rejuvenated satellite cells might serve as an autologous therapy against this condition.

7. Concluding remarks

No drug has yet proven useful to combat senescence *per se* and its related manifestations (including sarcopenia and frailty). Thus, a growing public health problem worldwide is the management of our aging populations, with the oldest old representing the most rapidly expanding population segment (Waite, 2004). In this regard, iPSCs-based therapies represent an intriguing strategy for regenerative medicine and anti-aging purposes (see **Figure 1** for a summary) (Pareja-Galeano et al., 2015). However, some considerations must be taken into account before iPSCs can be actually used in the clinic. The isolation of clinical grade iPSCs requires very strict quality controls to avoid possible deleterious effects (Mummery, 2011). It is also important to establish whether the therapy should be autologous or allogeneic (Garber, 2015). Although autologous therapy probably represents the best option, long-term studies are needed to rule out an increased risk of tumor formation, against which the patient is unlikely to develop an efficient immune response. The first clinical trial using autologous cells derived from iPSCs in Japan was in fact suspended in March 2015 (Garber, 2015). The researchers treated a single patient with macular degeneration. The patient suffered no serious adverse effects but the authors decided to stop the trial. The main reason was related to the high frequency of iPSCs mutations, epigenetic, and chromosomal changes in culture (Gore et al., 2011; Hussein et al., 2011; Lister et al., 2011). The trial protocol has been revised by taking into account Japan's new regulations on regenerative medicine. With regard to future allogeneic trials, banked HLA matched cells already validated for genomic stability will be assayed. Thus,

allogeneic therapy migh allow developing well-characterized cell banks, thereby making cell transplantation more affordable, controlled, and industrialized. On the other hand, *in vivo* reprogramming may represent a new promising technique to be explored for the generation of rejuvenated tissues (notably, skeletal muscles) with the ultimate goal of improving not only human life span, but also functional independence in the elderly.

Conflict of interest: None declared

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Figure legend.

Figure 1. Summary of potential future anti-aging therapies based on induced pluripotent stem cells (iPSCs). Abbreviations: DOT1L, DOT1-like histone H3K79 methyltransferase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells.

Figure 1

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