IPSCs, a Promising Tool to Restore Muscle Atrophy

As life expectancy in developed countries rises, the number of elderly persons steadily climbs on the way to form 12% of the population in 2050. A major problem of demographic ageing is sarcopenia, i.e., age-related loss of muscle mass leading to functional impairment. Roughly 5–13% of people aged 60–70 years and 11–50% of those aged 80þ suffer sarcopenia (Landi et al., 2012), which is a main determinant of frailty syndrome. The latter is linked to falls, disability, dependence, hospitalization, and mortality, generating considerable healthcare, and social costs (Landi et al., 2012; Mohler et al., 2014). Although pharmacologic approaches have been proposed to combat sarcopenia, these are not without potential risks and secondary effects (Sanchis-Gomar et al., 2014). A potential alternative is regenerative medicine, whose goal is tissue repair/substitution with transplanted healthy tissue, e.g., embryonic stem (ES) cells from the same individual or a compatible donor. Yet numerous ethical and legal issues have been associated with the use of ES cells which has led to a breakthrough in the form of induced pluripotent stem cells (iPSCs) (Sommer and Mostoslavsky, 2013). iPSCs have the capacity to differentiate into patient specific cell types, therefore reducing the likelihood of immunological rejection. Since the first report by Nobel Prize laureate Yamanaka that iPSCs could be generated from fibroblasts through the introduction of specific transcription factors using retroviral systems (Takahashi and Yamanaka, 2006; Takahashi et al., 2007), more effective, non-integrative techniques involving the use of Sendai virus have been described (Lieu et al., 2013). Thus, it is currently possible to generate iPSCs from a person's somatic cells and differentiate them into the required functional cell type (Wilson and Wu, 2015): notably, a first human clinical trial is using iPSC-derived retinal pigment epithelium cells to evaluate their efficacy in treating macular degeneration (Reardon and Cyranoski, 2014). Further, senescent and centenarians' iPSCs can re-differentiate into fully rejuvenated cells (Lapasset et al., 2011). These results provide strong insights into the potential of iPSCs in anti-aging regenerative medicine. The large size of muscles and their homogeneous structure, compared with other organs, make them a suitable target for iPSCs therapies. The skeletal-muscle tissue is mainly composed by post-mitotic cells, and the only ones which are able to proliferate and thus to promote tissue repair over life, the satellite cells, become scarce and dysfunctional as we age. Thus, because sarcopenia is a naturally occurring event independent from genomic alterations, differentiation of human iPSCs into rejuvenated satellite cells could be used as an autologous therapy against this condition. On the other hand, direct reprogramming of adult fibroblasts to a pluripotent state has opened new possibilities for the generation of patient- and disease-specific iPSCs. In this regard, the skeletal-muscle tissue is frequently deteriorated in inherited neurometabolic diseases. Probably owing to the rare nature of most of these disorders, research efforts are still insufficient. The newly available tools of genomic edition like the CRISPR/CAS9 system could be potentially applied to cure these conditions since the sole edition of the specific genetic alteration in the iPSCs followed by differentiation and cell engraftment could reverse, at least partially, the genetic defect in question (Huang et al., 2015; Song et al., 2015). Darabi et al. (2011) showed that transplantation of iPSCs-derived myogenic progenitors into dystrophic mice resulted in extensive engraftment, which was accompanied by improved contractility of treated muscles. In summary, based on the recent advances, we highlight the potentiality of iPSCs for treating muscle-affecting conditions for which no effective cure is yet available, notably aging sarcopenia but also inherited neurometabolic disorders. Both conditions share common pathways related to senescence and satellite cell loss or dysfunction.

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