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Satellite Cells and Their Potential for Therapy in Muscular Dystrophies

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The muscular dystrophies are a group of more than 30 genetic diseases with no treatment that can stop or prevent the progression of disease in any form of dystrophy. The current treatment of muscular dystrophies consists mostly of palliative and supportive measures. Of the more than 30 forms of muscular dystrophy, Duchenne muscular dystrophy (DMD) is the most common. Becker muscular dystrophy (BMD) is similar to DMD but is milder due to its late onset and slower progression. The prevalence of DMD and BMD combined (D/BMD) has been reported as 1.3-1.8 cases per 10,000 males in the age range of 5 to 24 years in four states reporting to the Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet) [1]. These numbers are limited to data collected from only four states (Arizona, Colorado, Iowa and western NY) and only for those patients that were captured by the health system. Thus, the prevalence of D/BMD is likely to be higher than reported. The prevalence and the devastating effects that these diseases have on patients and their families underscore the need to find therapeutic alternatives that restore muscle integrity or stop the progression of disease.

Forms of therapy aimed at restoring muscle integrity currently under investigation are based in genetic, pharmacological, and cellular approaches. In general, the aim of gene therapy is to deliver a copy of the defective gene carried by viral vectors [2,3] or to restore the reading frame (exon skipping) with antisense oligonucleotides [4-8]. Pharmacological agents have been proposed to read through a premature stop codon in the dystrophin gene (such as gentamicin or ataluren) or to increase expression of utrophin, an orthologue of dystrophin with high sequence similarity [9,10]. Steroid treatment has proven to be beneficial for Duchenne muscular dystrophy (DMD) patients for quite some time and for certain forms of limb-girdle muscular dystrophy (LGMD), although the mechanism of action is uncertain and the secondary effects are multiple [11-15]. In addition to the anti-inflammatory and immunosuppressant effects, glucocorticoid treatment also increases the expression of utrophin in DMD by enhancing the activity of an internal ribosomal entry site in the 5' UTR of utrophin mRNA [16]. Other effects of glucocorticoids in DMD treatment are currently unknown. The principle of cell therapy is to provide cells with a normal gene and with the capacity to divide and fuse with host fibers. These donor cells must also be able to maintain a sustainable population in the host muscle. The source of cells that can be used for this purpose is very diverse and includes satellite cells [17-19], pericytes from skeletal muscle blood vessels [20-22], bone marrow [23-25], embryonic stem cells and inducible pluripotent stem cells [26,27]. Perhaps the most widely studied of all these sources are satellite cells since they are naturally involved in the maintenance and repair of skeletal muscle.

Satellite cells were first identified by Mauro over 50 years ago as cells intimately associated with the periphery of skeletal muscle fibers [28]. As with other cells types currently under investigation for use in cell therapy, satellite cells are selected based on specific markers present in the plasma membrane. The function of the markers varies from regulation of proliferation to cell cycle entry to fusion. However, isolated satellite cells can differentiate into osteocytes or adipocytes in addition to myocytes [29]. Thus, the multipotential ability of satellite cells calls for the need to find a marker indicative of the cells that will have the ability to commit to the muscle lineage. Ideally, the marker would be expressed in satellite cells at different states that is, when cells are quiescent, activated or differentiated. The α2δ1 protein is a potential marker since it is present in freshly isolated satellite cells that will later become myoblasts [30]. Surprisingly, the α2δ1 protein is a subunit of the L-type calcium channel (also called dihydropyridine receptor) involved in excitation-contraction coupling in muscle. Satellite cells without α2δ1 do not differentiate into muscle cells or show delayed differentiation until α2δ1 is expressed. An additional advantage of the α2δ1 protein is that it is present in human satellite cells. Further studies are needed to establish firmly α2δ1 as a marker of satellite cells in the path of muscle differentiation and to identify other markers that will separate the cells that will differentiate into osteocytes or adipocytes. Identification of those markers will be beneficial for the enrichment of satellite cells that can be used to treat other pathological states, such as fractures [31]. Additional studies are also required in other types of stem cells, such as bone marrow mesenchymal stem cells, to determine the presence of α2δ1 and the commitment of those cells to the muscle lineage.

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