Duchenne's muscular dystrophy is a devastating, progressive, X-linked muscle-wasting disease. It is the most common form of muscular dystrophy, affecting 1 in 3500 boys. With an onset in early childhood, the disease progresses to final stages that are characterized by cardiorespiratory failure and death, which usually occurs in the teenage years or early 20s. The disease affects striated muscles of the limbs, diaphragm, and heart and is associated with a progressive loss of muscle mass, leading to impaired ambulation and paralysis. Skeletal myofibers degenerate and undergo necrosis; muscles progressively accumulate calcium deposits and are replaced by connective tissue and fat.

Twenty years ago, mutations in the dystrophin gene were found to be responsible for the disease. Such mutations lead to the production of defective structural proteins and the loss of muscle-membrane integrity. No effective therapy is available, although therapeutic interventions that include pharmacologic agents and genetic alterations to replace the missing dystrophin by exon skipping or viral gene delivery are in clinical trials.

An attractive alternative is a cell-based therapy, and a study recently described by Cerletti et al. demonstrates an interesting strategy. Muscle is composed of multinucleated cells, called myofibers, to which myogenic precursors fuse. If these precursors harbor a normal, healthy gene, they could provide the missing dystrophin protein and rescue the fiber by taking advantage of the normal biology of muscle-tissue formation. Several cell-based strategies have been tested with variable success.

Myoblasts are mononucleated myogenic precursors capable of extensive proliferation and fusion to form multinucleated fibers in tissue culture. The discovery of methods for their purification has led to several clinical trials. Although the injected human cells fused with resident muscle fibers and synthesized the appropriate gene products in patients' muscles, the cells and their products remained extremely localized.

Given the limitations inherent in this native muscle-cell source, researchers have turned to other cell sources and modes of delivery. Bone marrow stromal cells are among the cell types that have been isolated on the basis of their adhesive properties. These cells can be expanded extensively in tissue culture, providing an ample source of cells capable of contributing to muscles of the mdx mouse (a model of Duchenne's muscular dystrophy) after intramuscular injection. In another approach, cells with an exceedingly active efflux pump can be isolated from blood or muscle by flow cytometry. An attractive feature of these cells is that they can be delivered intravenously because they are capable of extravasating from the vasculature and engrafting into myofibers after tail-vein injection. A limitation of these cells is that they cannot be grown in tissue culture.

Efficient transplantation has been observed with the use of another cell type, the blood vessel–associated mesangioblast, which can be expanded extensively in culture and effectively delivered by femoral-artery catheterization. Mesangioblasts are isolated from the outgrowth of small-vessel–containing tissue fragments from muscle-biopsy specimens. Such cells are advantageous because they contribute to muscles throughout the body and have been shown to restore dystrophin and strength to muscles of dystrophic dogs (which best recapitulate the human disease).

In parallel, researchers have become increasingly interested in the satellite cell, which is intrinsic to skeletal muscle and is the natural cell source for muscle regeneration. More than four decades ago, Alexander Mauro first identified...
Purification by flow cytometry of GFP+ skeletal muscle progenitors (SMP) (Sca1+, Mac1−, CD45−, CXCR4+, and β1–Integrin+)

Injection of skeletal muscle progenitor cells into toxin-damaged murine model of muscle dystrophy (mdx)

After 4 weeks

Restoration of contractile forces and detection of dystrophin GFP+ myofibers

Nontreated mouse

GFP+ SMPs–treated mouse
satellite cells using electron microscopy as mononucleated cells ensheathed in their own membrane compartments along the length of the muscle fiber. Recently, isolation of satellite cells has been achieved with the use of diverse protocols. Remarkably, if satellite cells are transplanted as soon as they are isolated, they are capable of extensive dissemination throughout the muscle into which they are injected, a property that is lost as soon as the cells are exposed to culture conditions, whereupon they give rise to more specialized myoblasts.5

The study by Cerletti et al. represents an advance in several respects. The authors describe a subpopulation of freshly isolated satellite cells obtained with the use of a combination of molecular markers, of which CXCR4 (a receptor that responds to signals emitted by muscle damage) may be key. Genetically marked skeletal muscle progenitors, which express green fluorescent protein (GFP), can be recovered from the muscles to which they contribute (Fig. 1). Using a dual marker system, the investigators showed that the cells contributed not only to preexisting muscle fibers but also to newly formed fibers. Most remarkably, this subpopulation of satellite cells contributed substantively to the injected muscles (the authors observed that 90% of muscle fibers were composed of cells labeled with GFP) and led to an unprecedented increase in muscle force in the mdx mouse.

Are CXCR4+ skeletal-muscle progenitors or other satellite cells the long-sought stem cells of adult muscle? To be so, they need to fulfill standard criteria. A single cell must be transplanted and shown both to reproduce itself and to give rise to more specialized progeny. A means of propagating the cells in culture without a loss of their regenerative properties is necessary; without expansion, the low cell numbers would limit therapeutic applications of either genetically corrected autologous cells or heterologous cells used in conjunction with immunosuppression. Moreover, if systemic delivery were possible, it would not be necessary to inject each muscle individually. Finally, the human counterpart of the specialized satellite cell remains to be identified and shown to have similar properties. Nonetheless, the findings of Cerletti et al. are notable and will no doubt fuel interest in a cell-based therapy for Duchenne’s muscular dystrophy.

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