MUSCLE DISEASE

Bone Marrow Cells May Provide Muscle Power

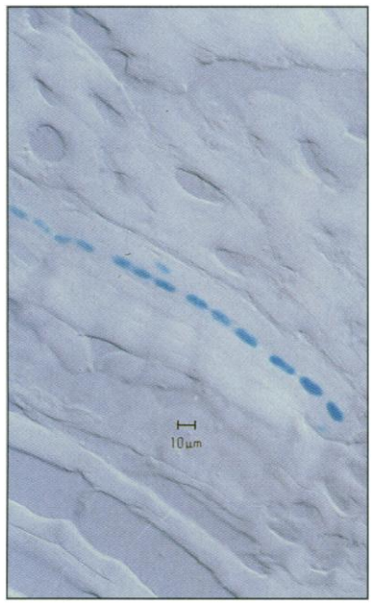
As we age, many of us start hitting the workout trail to stave off the muscular decline that comes as the years go by. But people afflicted with muscular dystrophy or other such degenerative diseases don't have that option. Over time, the dystrophy gradually destroys their muscle cells, eventually robbing them of even the ability to move. Now, a team from Italy has provided preliminary evidence that it may one day be possible to replenish degenerating muscles with fresh cells from an unexpected source: patients' bone marrow.

On page 1528, molecular biologists Giuliana Ferrari and Fulvio Mavilio of the San Raffaele–Telethon Institute for Gene Therapy in Milan, Italy, in collaboration with developmental biologist Giulio Cossu from the University of Rome, show that bone marrow cells can move into damaged muscle and grow into new muscle fibers in mice. The result overturns current dogma that muscles must depend on local cells to repair injury and are not aided by cells migrating through the blood from the bone marrow or elsewhere.

That has clinical implications. Terry Partridge, a cell biologist at the Medical Research Council Clinical Research Centre at Imperial College School of Medicine in London, says the finding presents "a whole avenue of potential therapies that didn't exist before" for muscular dystrophies. For example, researchers might one day be able to introduce a good copy of the defective gene that causes muscular dystrophy into the patient's own bone marrow cells so that they provide decaying muscles with a plentiful source of new—and normal—muscle cells. This might be easier than other strategies now being attempted, such as using viruses or injections of other types of cells to deliver a good muscular dystrophy gene.

Mavilio and Cossu got their first clue that bone marrow might contain cells that could repair damaged muscle about 2 years ago. At the time, most researchers thought the so-called satellite cells that surround skeletal muscle fibers were the usual agents of repair in injured muscles, fusing with damaged fibers to repair or replace them. But because the new muscle cells that grow in an injured region can outnumber the satellite cells there, researchers suspected that other cells might also play a role in regeneration. No one had been able to pin down their source, however.

The group in Italy began to suspect bone marrow after getting some surprising results in experiments aimed at determining whether fibroblasts, cells that normally make connective tissue, could also become muscle. The researchers had injected the forelimb muscles of mice with fibroblasts purified from various tissues. For their controls, they injected other types of cells, including bone marrow devoid of fibroblasts. They then chemically induced muscle damage in all the mice, expecting to see new muscle precursor cells, if at all, only in the mice that got the fibroblasts. But Mavilio recalls, "We obtained better results in the mice receiving bone marrow without the fibroblasts."



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Telltale blue. This muscle's blue nuclei could have come only from bone marrow cells.

They began to wonder whether bone marrow might contain cells other than fibroblasts that can travel through the bloodstream to injured muscle to help with repair. Mavilio notes that there was already some evidence for the possibility. Two other research teams, those of Arnold Caplan at Case Western Reserve University in Cleveland and Darwin Prockop at Allegheny University of the Health Sciences in Philadelphia, had shown that stromal cells—the support cells of the marrow—could be coaxed into becoming precursor muscle cells in lab dishes (*Science*, 4 April 1997, p. 71).

Mavilio and Ferrari wanted to find out whether the same thing could happen in animals, but they realized that the experiment would require a very sensitive means of monitoring the fate of the bone marrow cells they were testing. Help came from Margaret Buckingham and her colleagues at the Pasteur Institute in Paris. For their studies, this group had created a strain of transgenic mice carrying a so-called marker gene that, when activated, causes cell nuclei to turn blue—but only in muscle cells. Thus, it could provide a way of identifying any bone marrow cells that had migrated to damaged muscle and turned into muscle cells.

In her experiments, Ferrari transplanted bone marrow carrying the marker gene into mice whose own bone marrow had been destroyed by irradiation. Then, after several weeks, she injected a toxin into the forelimbs of these mice to damage the muscle there. Two weeks later, Ferrari found that the damaged muscle areas in nine mice not only showed signs of recovery but also had numerous blue nuclei throughout—the nuclei of bone marrow cells that had, when surrounded by muscle, transformed into muscle cells themselves. The results show, says Partridge, that "there are bone marrow cells that are perfectly capable of becoming muscle."

Everyone, including Mavilio, stresses that much more work is required to determine whether bone marrow cell transplants will be of any use to people with muscular dystrophy. Ronald Schenkenberger, director of research administration for the Muscular Dystrophy Association, based in Tucson, Arizona, cautions that while the mice used in the experiments in Italy still had functioning satellite cells in the damaged muscles, that's not the case for people with the disease. Without those cells, muscles might not be able to regenerate usefully even with the aid of normal bone marrow cells.

The Italian team finds, for example, that the bone marrow cells are both slower and less effective at producing muscle cells than satellite cells are. The team is now repeating the bone marrow transplant experiments in mice that have the same genetic defect as people with Duchenne type muscular dystrophy to see whether the marrow cells can produce functional muscle regrowth in these animals as well. If they do, "that would be eureka," Schenkenberger says.

And if the cells responsible do in fact turn out to be stromal cells, the prospects for a useful treatment for muscular dystrophy are even better, says Prockop. Stromal cells, he points out, "are relatively easy to isolate and genetically manipulate," and they will reproduce in the lab. A person with the disease would thus need to donate just a small amount of bone marrow, to which normal copies of the muscular dystrophy gene could be added. Once those cells had been allowed to multiply, they could be injected back into the patient, where they would grow into new and healthy muscle. Partridge cautions, however, that such therapies are "certainly not around the corner."

–Elizabeth Pennisi