Stem cell "gold standard"

A single muscle stem cell implanted in irradiated mouse muscle tissue proliferated, giving rise to more self-renewing stem cells

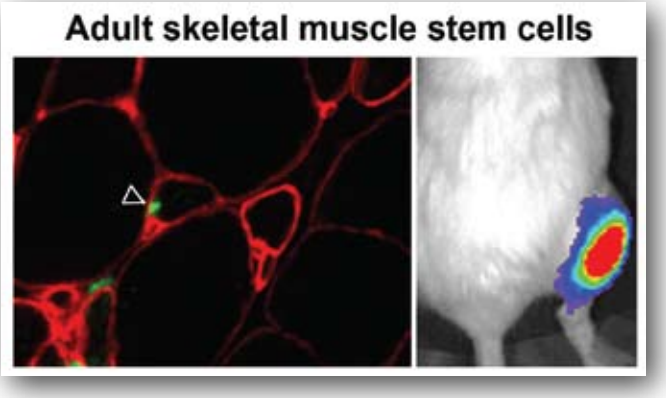
Toti-, pluri-, or multipotent stem cells are sorted out by their unique potency both to change and to remain unchanged. Only a true stem cell can renew itself over a lifetime while still churning out specialized progenitor cells. That makes the "gold standard" test for useful adult multipotent stem cells brutally simple. First you must isolate a stem cell population. Then you must transplant one stem cell into an individual lacking the function supplied by that stem cell and its differentiated descendants. The transplanted stem cell must proliferate and generate both progenitors that participate in tissue regeneration and new stem cells. Then you must recover these new stem cells from the transplant to demonstrate that self-renewal has occurred.

Alessandra Sacco and Helen Blau of Stanford University have applied this gold standard to adult muscle stem cells (MuSCs) isolated from a mixed population of satellite cells in mouse skeletal muscle. Adult MuSCs were thought to be a subset of these satellite cells, living just under the membrane that surrounds muscle fibers. They respond to muscle damage by giving rise to progenitor cells that become myoblasts, fusing into myofibers to repair muscle tissue.

Using a protein marker for satellite cells, Pax7, Sacco and Blau isolated MuSCs from a line of lab mice genetically engineered to express the glowing protein luciferase. Every cell in their bodies glows, making the luciferase and Pax7-expressing MuSCs easy to trace when implanted into a nonglowing mouse. The researchers used special immune-suppressed, nonglowing mice for the transplant test. They first irradiated a hind limb muscle to wipe out the endogenous MuSC population and then implanted one luciferase-expressing MuSC. Using luminescent imaging along with quantitative and kinetic analyses, Sacco and Blau tracked the transplanted stem cell as it rapidly proliferated and engrafted its progeny into the irradiated muscle tissue, forming new myofibers. The researchers then re-isolated the luciferase-glowing MuSCs to demonstrate that the cells' self-renewal powers were intact. The glowing MuSC had met the gold standard.

"We are thrilled with the results," says Sacco. "It's been known that these satellite cells are crucial for the regeneration of muscle tissue, but this is the first demonstration of self-renewal of a single cell." Being able to isolate and then transplant skeletal MuSCs could have a broad effect in a variety of muscle-wasting diseases such as muscular dystrophy and in treating severe muscle injuries or loss of function from aging and disuse.

In other experiments, the researchers transplanted between 10 and 500 luciferase-tagged MuSC into mouse leg muscle. Again the cells proliferated and engrafted, forming new myofibers. Furthermore, the transplanted stem cells reached homeostasis; that is, unlike tumor cells, the transplants grew to a stable, constant level and stopped replicating. Injuring the transplanted muscles set off massive waves of muscle cell growth and repair, demonstrating that this population had rescued the lost muscle healing function.



Freshly isolated skeletal MuSCs (left) tagged with green fluorescent proteins were transplanted into recipient mice. A month after transplant, leg muscle was damaged by injection. Five days later, the fluorescent cells were found engrafted in the satellite cell position (arrow head) indicating MuSC self-renewal. Freshly isolated MuSCs from double-transgenic mice were injected into recipients (right) and imaged four weeks after transplantation.

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Self-Renewal and Expansion of Single Transplanted Muscle Stem Cells

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