

# San Francisco Chronicle

June 16, 2008

## Research illuminates how stem cells may work

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UC Berkeley scientists are a step closer to understanding how a series of molecular switches can turn on or off the regenerative power of stem cells that normally build new muscle tissue after it has been damaged.

The research, conducted on laboratory mice, is years away from practical therapies for human beings. Nevertheless, this latest work, published online Sunday by the journal *Nature*, provides insight into how scientists are dissecting, step-by-step, the processes that govern how stem cells work.

A goal of such research is to find ways to intervene and control these molecular switches - to improve healing and perhaps slow the effects of aging.

"How can you fix a car if you don't know how the engine looks?" said Rik Derynck, co-director of the Institute for Regeneration Medicine at UCSF, who was not involved in the Berkeley research but is conducting similar studies in his lab. "We are all trying to find out what's really happening inside these stem cells."

Although Derynck is skeptical that the work will have much impact in slowing the aging process, he believes the approach could lead, within five to 10 years, to novel therapies against degenerative diseases such as muscular dystrophy.

The UC Berkeley research was carried out by Irina Conboy and her colleagues at the Department of Bioengineering. They are trying to solve one of the mysteries of aging: why muscle cells readily repair themselves when we are young, but are slower to do so as we grow older.

About 2 percent of cells in muscle tissue are "satellite" cells. These tiny powerhouses are adult stem cells, which uniquely can be coaxed into producing new muscle fibers with the right set of chemical signals.

Conboy contends that the stem cells within older tissue are no different from those found in young muscle - the difference over time appears to occur in the chemicals that switch them on or off. In effect, she explained, the stem cells don't wear out, but the switches do.

So the key to repairing older muscle tissue is to understand how these switches work, and how to restore their function as they wear out. An important finding in the newly published research is that these signals compete to turn these stem cells on or off. As muscle tissue ages, the outcome of that competition tends to tip against renewal.

"We need to figure out how the on-and-off switches become deregulated, then how to recalibrate them back to the young state," Conboy said. "Then the stem cells in the old tissue will start working as well as in the young tissue. The goal for humans is to regenerate tissue as if you were 25 years old."

Conboy's research was done with laboratory mice. Both mice and men have similar systems of muscular repair using adult stem cells.

The regenerative capacity in the muscle of a 2-year-old mouse is similar to that of an 85-year-old human. So Conboy's lab studied both young mice and 2-year-old mice to compare how the molecular switches for stem cells perform in the old and young.

In earlier work, Conboy's team identified a protein called Notch that acts as an on switch. It stimulates adult stem cells to begin morphing into new muscle fiber cells and multiplying. The body uses this sequence all the time to repair torn muscles or replace worn-out tissues.

But her work also found that the presence or absence of Notch alone did not fully control the repair process. The latest study identified another protein - with the unfortunate moniker pSmad3 - as an off switch for adult stem cells.

Even if the body were producing Notch to stimulate repair, the stem cells might remain quiet if the body were also churning out more of the off switch pSmad3.

Why would the body want to turn off a repair process? One reason may be that cell growth stimulation can promote cancers. Another reason may be to conserve a limited lifetime supply of adult stem cells, so they are activated only when needed.

The mouse studies showed that the two competing chemical signals strike a constant, shifting balance with each other. In younger mice, there are higher levels of the on switch, and lower levels of the off switch; in older mice, the balance is reversed. As a consequence, muscle tissue is readily repaired in young mice, whereas it is a slower process among the older rodents.

"When the death of tissue is faster than repair, many, many diseases begin to appear," Conboy said.

What remains unexplained is precisely what causes this balance to change - why these chemical switches wear out. That is a topic likely to keep researchers busy in their labs for years to come.

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