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Making Old Stem Cells Act Young Again

In virtually every part of the body, stem cells stand ready to replenish mature cells lost to wounds, disease, and everyday wear and tear. But like other cells, stem cells eventually lose their normal functions as they age, leaving the body less able to repair itself.

Surprisingly, this age-related decline in stem cell potency may be somewhat reversible. A team of Howard Hughes Medical Institute (HHMI) researchers has found that in old mice, a several-week exposure to the blood of young mice causes their bone marrow stem cells to act “young” again.

The researchers have not yet isolated the blood-borne factors that can switch old stem cells back to a more youthful state, but their results are consistent with other recent studies that show stem-cell aging may be reversible. Together those results suggest that it might one day be possible to boost the practical lifespan of stem cells, and thereby increase the body’s resistance to disease and age-related degeneration.

"Knowing what these circulating factors are could enable the development of drugs to boost stem cell functions."

- Amy J. Wagers

The new findings are reported in an advanced online publication in *Nature* on January 28, 2010. Amy J. Wagers, an HHMI Early Career Scientist at Harvard Medical School, was the senior author and principal investigator of the study.

Wagers had participated in two previous studies that found that the blood of young mice appears to contain factors that could improve the repair capabilities of muscle and skin in older or diabetic mice, respectively. In the new work, Wagers and her team decided to find out whether blood-forming (hematopoietic) stem cells in the bone marrow could also be rejuvenated.

Hematopoietic stem cells give rise to all the cells of the blood system, including immune cells and red blood cells. As animals age, these stem cells become more numerous, but less effective at regenerating the blood system, Wagers says. That translates into a less effective immune system and a greater susceptibility to disease.

To see if younger blood could reverse the sluggishness of aging blood cells, the researchers began by surgically joining the bloodstreams of pairs of mice that were of different ages, but nearly clones of one another. Each mouse carried distinctive genetic markers so that researchers could differentiate between its cells and those of its partner. The technique, called parabiosis, enables researchers to test the long-term effects of one animal's blood on the tissues and organs of the other. "It's the only model that really allows us to come close to mimicking an *in vivo* systemic environment," Wagers said. "There is a constant exposure to any cell or soluble factor that circulates, at close to physiologic levels."

After several weeks of sharing their blood systems with young mice, the hematopoietic stem cells of the older mice changed markedly. Exposure to a younger animal's blood somehow pushed the older animal's hematopoietic stem cells back to a more youthful state, in which they were fewer in number but recovered nearly all of their blood-cell-generating capacity. When transplanted into mice whose own blood-producing cells had been eliminated by radiation, the "rejuvenated" stem cells repopulated the blood with a mixture of cell types similar to that generated by transplanted young stem cells. No such changes occurred in the young mice in these pairings, or among age-matched pairs of animals.

Wagers and her team haven't yet discovered the blood-borne factor that triggers this apparent restoration of youthfulness in aged hematopoietic stem cells. But they did find two important clues to how it transmits its effects.

First, they found evidence that this factor works via bone-forming cells known as osteoblasts, which also are present in bone marrow and help regulate hematopoietic stem cells. When old animals were exposed to young blood, their osteoblasts reverted to more youthful numbers. They also behaved more like younger osteoblasts in their interactions with hematopoietic stem cells. Hematopoietic stem cells grown in cultures with these "rejuvenated" osteoblasts regained the blood-cell-generating capacity characteristic of youthful stem cells. For osteoblasts, the opposite was also true: the bone-forming cells of young animals— from humans as well as mice — showed signs of aging when they were exposed to blood from an older animal.

The team also found that the insulin-like growth factor 1 (IGF-1) hormone appears to be necessary to maintain these stem-cell-regulating osteoblasts in an aged state. When they blocked IGF-1 activity in osteoblast cells in culture or in bone marrow, aged osteoblasts reverted to a "younger" state, and could pass that rejuvenation effect on to hematopoietic stem cells. Blocking IGF-1

activity in the bloodstream of mice didn't have the same effect, which suggests that IGF-1 acts specifically through osteoblasts.

Oddly enough, IGF-1 is best known for its growth-promoting and potentially *anti*-aging effects in other tissues, including muscles and bones. "Our findings highlight the fact that IGF-1 signaling is complex and depends in part on the tissue involved," said Wagers.

She and her team are now searching this signaling pathway more carefully for the mysterious factor or factors that circulate in blood and somehow trigger this cascade of marrow activity that rejuvenates hematopoietic stem cells. "Knowing what these circulating factors are could enable the development of drugs to boost stem cell functions, for example to restore a more youthful and healthy pattern of blood cell production in older individuals," Wagers said.

To Wagers, the findings also underscore the importance of the local cellular environment, or "niche," in regulating stem cells' activity. "If you're thinking of transferring stem cells into a recipient to replace cells that have been lost to disease, you have to think a lot about the state of that recipient," she said. "In the wrong environment, even perfectly healthy young stem cells could lose much of their regenerative potential."