

Young Again

NICHE CELLS CAN REVERSE THE AGING OF STEM CELLS.

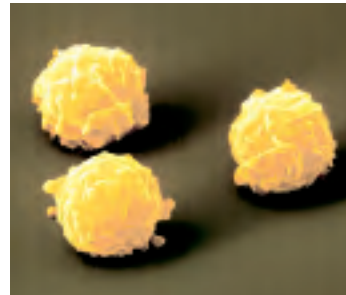
Stem cells don't get wrinkles, but when they're old, it shows. Precursors to blood cells—called hematopoietic stem cells (HSCs)—become sloppy at their job as they age. The result is poorer immune function, increased risk of blood cancers, and an imbalance among the types of blood cells produced. Research has suggested that some of this aging is due to HSCs' intrinsic factors, such as DNA damage that accumulates over time. But HHMI early career scientist Amy Wagers suspected that external factors might also cause the cells to grow old, coordinating aging among organs.

"Different types of stem cells throughout the body all age together, so there could be some kind of global aging signal," says Wagers. "Since blood has access to all organs, it made sense to look there first."

To test whether blood could turn back the clock on stem cell function, Wagers' lab group at Harvard Medical School turned to mice. The researchers joined the circulations of old and young mice and observed the effects on HSCs. The results were dramatic: after 4 weeks of having young blood coursing through their veins, the older mice had HSCs that numbered—and functioned—much more like their younger counterparts. By using markers that distinguished old HSCs from young ones, the researchers verified that the older cells had recovered youthful characteristics (rather than

young HSCs migrating from young mice to older animals). The stem cells in the younger mice appeared unchanged.

Wagers hypothesized that osteoblastic niche cells (ONCs), found at the interface of the bone and bone marrow where blood cells are formed, send aging signals to stem cells. So the researchers exposed stem cells in culture dishes to isolated old and young ONCs. The outcome, published January 28, 2010, in *Nature*, matched that of the first experiment: whereas old ONCs induced signs of age in young HSCs, old ONCs exposed to young blood regained their youthful characteristics.



Stem cells found in bone marrow change as they age, researchers have discovered.

While the scientists haven't yet pinpointed what ages the ONCs, and thereby the HSCs, Wagers suspects that more than one molecule is involved in regulation. She next plans to study the genes that are upregulated and downregulated in the blood and in ONCs as they age. ■ —SARAH C.P. WILLIAMS

IN BRIEF

DNA CRASH TEST

A DNA strand is a busy runway for proteins. A large complex called the replisome separates strands of the double helix and moves in one direction, whereas RNA polymerases—proteins that transcribe the DNA sequence into lengths of RNA—zip back and forth in both directions. HHMI investigator Michael E. O'Donnell wondered what happened when the two inevitably collide.

To find out, O'Donnell's lab group at the Rockefeller University set up crash tests between the complexes. They attached an RNA polymerase to a fragment of DNA and allowed it to move partway down the strand before they stalled it. Then they assembled a replisome at the other end of the DNA and set it into motion toward the polymerase.

They found that the replisome made it all the way down the DNA strand, pushing the stalled polymerase off its tracks and producing a full copy of the genetic material. Moreover, the team showed that another protein, Mfd, helped the replisome sidetrack the polymerase even more efficiently, allowing the complex to make additional copies of the DNA.

The results, which appear in the January 29, 2010, issue of *Science*, provide

evidence that replisomes are more stable than some scientists suspected. O'Donnell is now searching for other factors that help the replisome push through blocks in the bacterium *Escherichia coli* and is studying whether replisomes in other organisms behave similarly.

VESSEL CUES

Turning human embryonic stem cells into cells that build blood vessels, or into any other specific cell type, takes just the right mix of molecular signals. Now HHMI investigator Shahin Rafii, at Weill Cornell Medical College, has identified the most robust signal yet for coaxing stem cells to become blood vessel-forming cells. The finding helps move scientists closer to developing stem cell-based treatments for heart disease and stroke.

Previously, for every five stem cells that researchers treated with particular molecules, one would become a vascular endothelial cell—the cell type that lines blood vessels. To identify new signals that could increase this efficiency, Rafii's lab group engineered a line of embryonic stem cells that glow green when they become vascular endothelial cells. This allowed the scientists to easily screen large numbers of

molecules for their ability to help morph stem cells into vascular endothelial cells. One molecule, a compound that blocks growth factor TGF-beta, caused the most cells to light up.

When the researchers applied this finding to a new batch of stem cells, blocking TGF-beta and inducing the expression of a transcription factor at just the right time, they produced 40 endothelial cells for every five stem cells—a dramatic increase from previous yields. More importantly, a raft of tests showed that the endothelial cells behaved as they should in blood vessels, assimilating into mice circulatory systems and attracting the right types of molecules to their surfaces. The results were published in the February issue of *Nature Biotechnology*.

STOP THAT PROTEIN

Despite their diminutive size, small RNA molecules play a large role when it comes to regulating genes. How certain small RNAs (miRNAs) turn off gene expression, however, has remained poorly understood by scientists. One thing that was known: a family of proteins called Argonautes is required for miRNAs to block production of a protein from a gene. Now, HHMI inves-