Stress Impairs Stem Cell Function in Aging Tissues

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(PhysOrg.com) -- Heinrich Jasper, assistant professor of biology at the University of Rochester, has won a $900,000 Senior Fellow Award from the Ellison Medical Foundation for his work showing how stress affects stem cell function, leading to symptoms of aging.

Jasper's work could help scientists understand what causes organs to malfunction in old age, and why certain cancers are so prevalent in the elderly.

In a recent issue of the journal *Cell: Stem Cell*, Jasper and his colleagues, Benoit Biteau and Christine Hochmuth, showed that an enzyme called Jun N-terminal kinase, or JNK for short, which normally protects cells from stresses such as disease or damage, has deleterious effects when activated in stem cells, where it promotes the accumulation of malformed cells. The team found that JNK activation occurs normally in the intestine during aging, contributing to age-related tissue degeneration.

"In order to prevent this damage and perhaps eventually extend our lifespan, we will have to very carefully balance the costs and benefits of enzymes like JNK," says Jasper. "We're learning more and more that dealing with aging is not a black and white issue of 'turn on that gene' or 'turn off that one.' It's a complicated balance."

Jasper studied the intestinal lining of fruit flies because intestinal cells are shed and re-grown frequently, suggesting that degradation of the

intestines ought to be held to a minimum as new cells quickly replace old. Degradation of the tissue still occurs, however, which led Jasper to believe that perhaps the stem cells which produce new intestinal cells were themselves degrading with age.

In investigating these intestinal cells, Jasper found that something was scrambling the chemical signal that tells stem cells when to create a particular kind of new cell. Without this communication, called a delta-notch signal, the stem cells spawned malformed descendents, which very often formed tumor-like structures.

Jasper knew the enzyme JNK was involved in cell signaling, and that cells activate it to help repair damage when a cell experiences stress, such as from pathogens or injury. What he found was a surprise: JNK disrupted the delta-notch communication, which confused the stem cells and led to the malformation and over-production of new cells. The results he saw in the intestines of a young fly he'd engineered to activate JNK were identical to what he'd expect to see in an aged fly.

"We've shown that by activating JNK, we effectively age the fly's tissue, and that by reducing JNK activity, we can delay age-associated degeneration," says Jasper. "But we can't do away with JNK entirely because it's necessary to help cells fight short-term damage. The whole balance is more complicated than we'd like." He cautions that researchers must be careful of jumping to conclusions because these apparently deleterious aspects of JNK may themselves be consequences of a protective mechanism—an anti-cancer stop-gap measure, for instance.

Jasper is now investigating specifically how JNK disrupts the delta-notch communication to determine if there is a safe way to regulate their interaction. He says he believes that such insight might help to find means to fight aging because "you can't just turn off the cause of aging.

There is a balance to be kept."

The Ellison Medical Foundation, which awarded Jasper the $900,000 to continue his aging research over four years, was founded to support basic biomedical research on aging and age-related diseases and disabilities. In particular, the foundation aims to stimulate new research that may not be currently funded adequately because of its perceived novelty or its high risk.

Provided by University of Rochester