Researchers discover tactic to delay age-related disorders

2 November 2011

Researchers at Mayo Clinic have shown that eliminating cells that accumulate with age could prevent or delay the onset of age-related disorders and disabilities. The study, performed in mouse models, provides the first evidence that these "deadbeat" cells could contribute to aging and suggests a way to help people stay healthier as they age. The findings appear in the journal *Nature*, along with an independent commentary on the discovery.

"By attacking these cells and what they produce, one day we may be able to break the link between aging mechanisms and predisposition to diseases like heart disease, stroke, cancers and dementia," says co-author James Kirkland, M.D., Ph.D., head of Mayo's Robert and Arlene Kogod Center on Aging and the Noaber Foundation Professor of Aging Research. "There is potential for a fundamental change in the way we provide treatment for chronic diseases in older people."

Five decades ago, scientists discovered that cells undergo a limited number of divisions before they stop dividing. At that point the cells reach a state of limbo -- called cellular senescence -- where they neither die nor continue to multiply. They produce factors that damage adjacent cells and cause tissue inflammation. This alternative cell fate is believed to be a mechanism to prevent runaway cell growth and the spread of cancer. The immune system sweeps out these dysfunctional cells on a regular basis, but over time becomes less effective at "keeping house."

As a result, senescent cells accumulate with age. Whether and how these cells cause age-related diseases and dysfunction has been a major open question in the field of aging. One reason the question has been so difficult to answer is that the numbers of senescent cells are quite limited and comprise at most only 10 to 15 percent of cells in an elderly individual.

"Our discovery demonstrates that in our body cells are accumulating that cause these age-related disorders and discomforts," says senior author Jan van Deursen, Ph.D., a Mayo Clinic molecular biologist and the Vita Valley Professor of Cellular Senescence. "Therapeutic interventions to get rid of senescent cells or block their effects may represent an avenue to make us feel more vital, healthier, and allow us to stay independent for a much longer time."

"Through their novel methodology, the research team found that deletion of senescent cells in genetically engineered mice led to improvement in at least some aspects of the physiology of these animals. So, with the caveat that the study involved a mouse model displaying accelerated aging, this paper provides important insights on aging at the cellular level," says Felipe Sierra, Ph.D., Director of the Division of Aging Biology, National Institute on Aging, National Institutes of Health.

How They Did It

Dr. van Deursen and colleagues genetically engineered mice so their senescent cells harbored a molecule called caspase 8 that was only turned on in the presence of a drug that has no effect on normal cells. When the transgenic mice were exposed to this drug, caspase 8 was activated in the senescent cells, drilling holes in the cell membrane to specifically kill the senescent cells.

The researchers found that lifelong elimination of senescent cells delayed the onset of age-related disorders such as cataracts and muscle loss and weakness. Perhaps even more importantly, they showed that removing these cells later in life could slow the progression of already established age-related disorders.

The findings support a role of senescent cells in the aging process and indicate that chemicals secreted by these cells contribute to age-related tissue

dysfunction and disease.

Provided by Mayo Clinic