# Where does the gene activity of youth go? New findings may hold the key

November 26 2008

New evidence may explain why it is that we lose not only our youthful looks, but also our youthful pattern of gene activity with age. A report in the November 26th issue of the journal *Cell*, a Cell Press publication, reveals that a protein perhaps best known for its role in the life-extending benefits of a low-calorie diet also maintains the stability of the mammalian genome—the complete set of genetic instructions "written" in DNA.

The researchers found in studies of mammalian stem cells that the protein SIRT1 controls the packaging of DNA into chromatin, thereby setting the youthful pattern of gene activity by keeping select genes switched off. In response to DNA damage, those SIRT1 proteins leave their posts to go off and assist in the necessary repairs. That change in SIRT1's job description leads to shifts in gene activity that parallel those seen in the aging mouse brain, they show. They suspect similar changes would also be found in other body tissues as well.

" The critical protein controls both which genes are off and on as well as DNA repair; it's used for both processes, and that's the catch," said David Sinclair of Harvard Medical School. "As cells accumulate DNA damage, the protein can't do both jobs sufficiently." Once SIRT1 loses control, gene activity goes haywire, a state of affairs that leads to symptoms associated with aging.

Sinclair's team also found what they consider to be good evidence that the aging process can be slowed. Mice with an excess of SIRT1 had an

improved ability to repair DNA and prevent those unwanted changes in gene expression. The hope is that those improvements could be reproduced with a drug that stimulates SIRT1, they said.

Indeed, the famous red wine ingredient known as resveratrol offers benefits through its effects on SIRT1, as do several more targeted drugs at some stage of development or testing. The new findings offer an explanation for how those life-promoting chemicals may be working. The ultimate test, Sinclair said, will be whether such drugs can indeed maintain a youthful gene profile.

While scientists had long known that gene activity changes with age, the driving force behind those changes remained mysterious, Sinclair said. Many had also proposed a connection between DNA damage and aging. After all, it's common knowledge that UV damage to the skin leaves it looking older. But again, he said, no one had really put their finger on just what the relationship is, or at least they hadn't in mammals.

In fact, scientists had discovered some years ago that Sir2, the yeast equivalent of SIRT1, stabilizes the genome. With age or in response to a DNA break, however, the Sir2 complex takes off for the damaged sites, activating genes that leave the yeast sterile, a characteristic associated with aging.

The new results show that the yeast aging process may be remarkably relevant to mammals. "If you step back and think, it's pretty striking," Sinclair said. "Something as simple as yeast can tell us about the mechanism of aging in mammals."

Source: Cell Press