Wistar Institute team finds key target of aging regulator

June 10 2009

Researchers at The Wistar Institute have defined a key target of an evolutionarily conserved protein that regulates the process of aging. The study, published in *Nature*, provides fundamental knowledge about key mechanisms of aging that could point toward new anti-aging strategies and cancer therapies.

Scientists have long known that a class of proteins called sirtuins promotes fitness and longevity in most organisms ranging from single-celled yeast to mammals. At the cellular level, sirtuins protect genome integrity, enhance resistance to adverse stresses, and antagonize senescence. However, the underlying molecular mechanisms have remained poorly understood. The team, led by senior author Shelley Berger, Ph.D., Hilary Koprowski Professor at The Wistar Institute, demonstrated for the first time a molecular target for a member of this class, Sir2, in regulation of aging in yeast cells. Sir2 removes an acetyl group attached to a specific site (lysine at position 16 or K16) on histone H4—histones are proteins that package and organize the long strands of DNA within the nucleus and also are central regulators in turning genes on and off. The study reveals that removal of this acetyl group by Sir2 near the chromosome ends—the telomeres—is important for yeast cells to maintain the ability to replicate. Researchers found that Sir2 levels decline as cells age, and there is a concomitant accumulation of the acetylation mark along with disrupted histone organization at telomeres.

Deacetylation of H4K16 by Sir2 and consequent telomere stability play a major role in maintaining long lifespan in yeast. Since sirtuins

deacetylate many different proteins, these results clarify a key role of Sir2 protein in control of lifespan.

"Some modifications on histones, like this acetylation on histone H4 lysine 16, are persistent and are maintained through generations of cell divisions. This DNA-independent inheritance is called epigenetics," Berger says. "Characteristic epigenetic features have been discovered for various developmental processes in recent years. Understanding epigenetic changes associated with aging is a hugely exciting direction in aging research. It will provide insights and ideas not only for new therapies to regulate cells that have lost control of proliferation, such as 'immortal' cells found in cancers, but also for new strategies to maintain health and fitness."

"We plan to continue to search for new targets of Sir2 and other aging regulators," says lead author Weiwei Dang, Ph.D., a postdoctoral scientist working with Berger. "We are designing unbiased screens for other aging targets and mechanisms in chromatin. Using yeast as our aging model enables us to do many discovery screens that are impossible with other, more complex organisms. Yet it is remarkable that many of these chromatin mechanisms associated with yeast could turn out to be relevant even for aging human cells."

Source: The Wistar Institute