Unlocking the Secrets of Heart Rejuvenation: The Promising Role of SIRT2

By YAN Fusheng

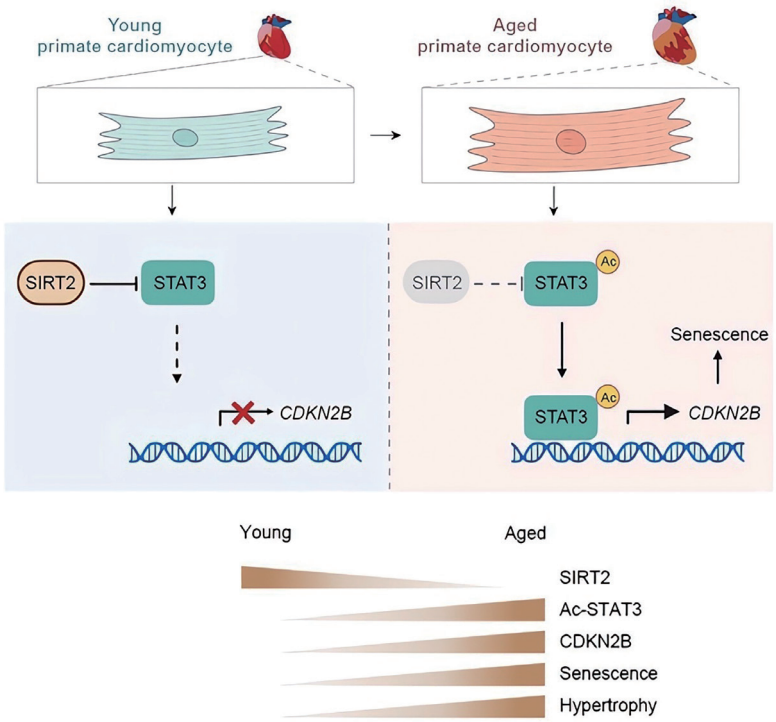
For as long as we've lived, humans have sought the fountain of youth. Today, while the mythical potion remains elusive, scientists are unraveling the mysteries of aging at the molecular level – offering new hope for revitalizing aging hearts.

Weaving a young and healthy heart with SIRT2. (Image by IOZ)

On October 2, 2023, in the prestigious journal *Nature Aging*, a collaborative effort by researchers from the Institute of Zoology (IOZ) and Beijing Institute of Genomics of the Chinese Academy of Sciences has shone the spotlight on a protein named SIRT2. This protein could be the key to turning back time for our most vital organ.

As we age, our hearts gradually lose function and undergo harmful changes like stiffening and hypertrophy. This greatly increases risks for cardiovascular diseases, the leading cause of death globally. Unfortunately, aging hearts in humans are extremely difficult to study, since nearly all elderly individuals already have underlying cardiac conditions.

To solve this, the researchers examined hearts from healthy aged cynomolgus monkeys, whose heart structures and lifespans closely resemble humans. Cynomolgus monkeys have lifespans of around 25 to 30 years. The researchers obtained heart samples from monkeys around 18 to 21 years old, which are equivalent to humans around 65 years old in age.



Molecular mechanisms of SIRT2 delaying myocardial aging in primates. (Image by IOZ)

These monkeys aged normally over their lifespans, allowing the researchers to study how hearts age under natural physiological conditions. This is a key advantage over lab models like rodents that have much shorter lifespans and differ more from humans genetically. More importantly, these aged monkeys were confirmed to be healthy, with no underlying cardiovascular diseases. This let the researchers isolate changes occurring due to normal aging versus disease processes.

Compared to young monkeys, the team found aged monkeys had enlarged, dysfunctional heart muscle cells and increased fibrosis. This confirms similar aging changes occur in healthy primate hearts.

Digging deeper, the scientists performed advanced proteomic profiling to identify proteins altered in aged monkey hearts. One protein called SIRT2 especially stood out, being the only one downregulated that was also linked to human age-related heart diseases. SIRT2 is an important epigenetic regulator controlling gene activity.

Further experiments revealed exactly how SIRT2 protects the heart: it interacts with and inhibits a protein called STAT3. In aged cells, loss of SIRT2 leads to hyperactive STAT3, which activates CDKN2B – a powerful stimulator of cellular senescence. Indeed, the researchers found blocking SIRT2 in healthy heart cells mimicked aging effects.

Excitingly, ramping up SIRT2 levels in old mouse hearts reversed multiple aspects of cardiac decline. This proves replenishing SIRT2 can rejuvenate aged hearts.

While the path from discovery to treatment is long and winding, this study paves the way for a future where therapies based on SIRT2 could help our hearts beat strongly for longer. It's a world where the old saying might need revising – perhaps you can teach an old heart new tricks after all.

Reference

Ye, Y., Yang, K., Liu, H., Yu, Y., Song, M., Huang, D., . . . Liu, G. H. (2023). SIRT2 counteracts primate cardiac aging via deacetylation of STAT3 that silences CDKN2B. *Nature Aging, 3*(10), 1269-1287. doi:10.1038/s43587-023-00486-y