Cellular Time Keepers: Sirtuins as The Aging Clock of Health

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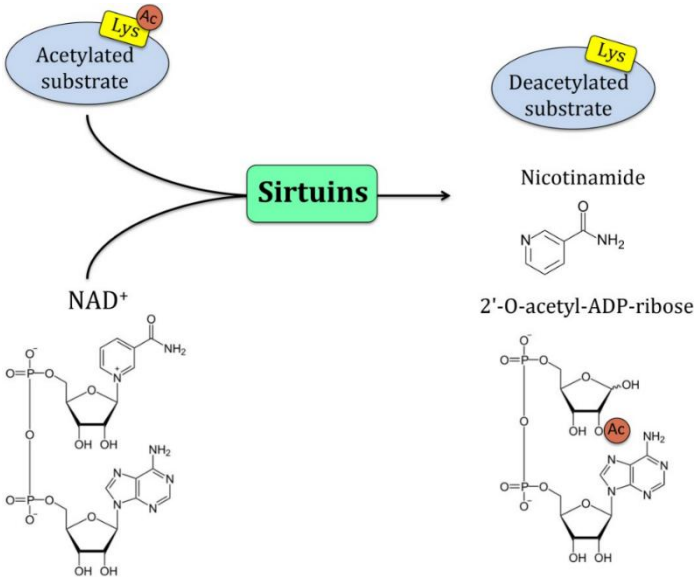
Good nutrition, accessibility to good healthcare and healthy lifestyles have increased human longevity. Cellular ageing is a physiological state with permanent cessation of the cells' ability to replicate and accumulation of damaged DNA which is increased by ageing. Sirtuins are nicotinamide adenine dinucleotide (NAD)+ dependent protein deacetylases that link protein acetylation, metabolism, aging and diseases of aging. They were initially found to slow aging in yeasts and more recently shown to mediate many effects of calorie restriction on metabolism and longevity in mammals with sirtuin protein family (SIRT1 to 7). The search for wholesome foods that can ameliorate metabolic syndromes like malnutrition and over-nutrition is gaining ground. Sirtfood is a new concept diet food, that can target sirtuins (SIRTs). They modulate SIRTs, have strong antioxidant activity, interact with gut microbes and metabolic components. Sirtfoods interfere with many signaling pathways, target genes and exert biological effects through synergistic networks.

The human body is composed of different types of cells, tissues and other complex organs. Our body releases some chemicals to accelerate biological processes such as respiration, digestion, excretion and a few other metabolic activities to sustain a healthy life. "Enzymes can be defined as biological polymers that catalyze biochemical reactions" The majority of enzymes are proteins with catalytic capabilities crucial to perform different processes that are necessary to sustain life.

Sirtuins: Sirt (Silent Information Regulator)

Maintaining metabolic homeostasis is essential for cellular and organismal health throughout life. Multiple signaling pathways that regulate metabolism also play critical roles in aging, such as mTOR, AMPK, and sirtuins (SIRTs). Among them, sirtuins are known as a protein family with versatile functions, such as metabolic control, epigenetic modification and lifespan extension.

One such enzyme is called Sirtuins. The word "sirtuin" was coined from its finding member Sirt2 in budding yeast Saccharomyces cerevisiae. Sirt2 slows replicative aging by promoting genomic stability in the rDNA which causes senescence in yeast cells. It silences all heterochromatin regions like ribosomal gene cluster (rDNA) and telomeres. The gene product Sirt2 protein is an enzyme called histone deacetylase (HDAC, class III) that removes the acetyl group from acetylated lysines.



Exhuming sirtuins

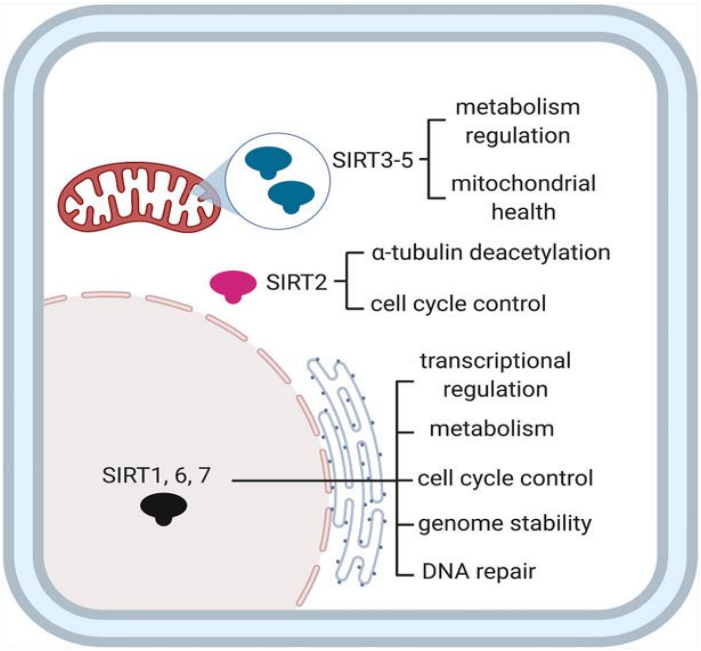
Research on sirtuin protein was started in 1991 by Leonard Guarente of Massachusetts Institute of Technology, Cambridge, United States. In 1995, Brachman discovered 7 more sirts. Involved in silencing mating-type loci, telomeres and genomic integrity. From bacteria to mammals, Sirt2 is a member of a large and ancient family of genes referred as 'sirtuins'. NAD+ metabolism was heightened after 2000 discovery by Shin-ichiro Imai and coworkers in the Guarente laboratory that sirtuins are NAD+ dependent protein deacetylases.

Sirtuins are Class III protein deacetylases with seven conserved isoforms. In general, Sirtuins are highly activated under cellular stress conditions in which NAD+ levels are increased. Nevertheless, regulation of Sirtuins extends far beyond the

influences of cellular NAD+/NADH ratio and a rapidly expanding body of evidence currently suggests that their expression and catalytic activity are highly kept under control at multiple levels by various factors and processes. owing to their intrinsic ability to enzymatically target various intracellular proteins.

Loci and functions of sirtuins

- Core to the science of anti-ageing is group of proteins called sirtuins. In human cells, there are 7sirtuins (SIRT 1 to 7) with various roles
- Three of these sirtuins (SIRT 3,4,5) control the power generation for the needs of cells and function in the mitochondria for cellular antioxidant balance and lipid metabolism
- Another three sirtuins (SIRT 1, 6, 7) control the genetic framework in the cell and function in the cell nucleus with roles in gene expression and DNA repair
- There is one sirtuin (SIRT 2 mainly) which controls the environmental processes within the cell and function in the cytoplasm



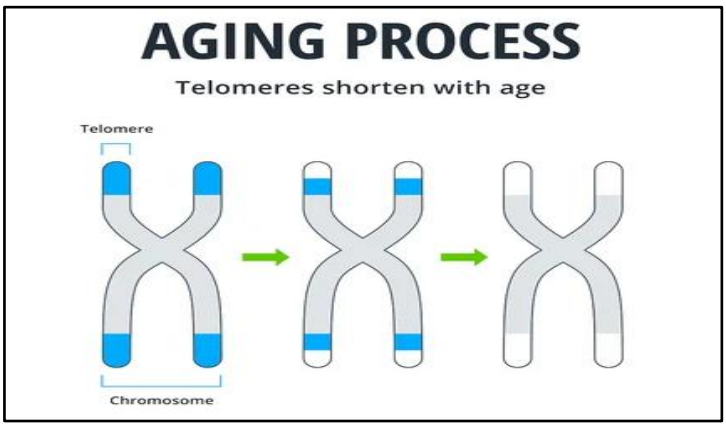
Aging

Aging is accompanied by a decline in the healthy function of multiple organ systems, leading to increased incidence and mortality from diseases such as type II diabetes mellitus, neurodegenerative diseases, cancer and cardiovascular disease.

Aging is known to be accompanied by changes in metabolism. At a general level, aging is associated with a functional decline across various organs in almost all organisms, associated with increased risk of diseases. The global population is therefore predicted to experience overall increased frailty, neurodegeneration, impaired immune function and disability, which in turn segregate with the development of multiple chronic diseases. As a result, characterizing mechanisms of aging and identifying Gero protective approaches are both critical and urgent.

Cell aging or cellular senescence

- Cell aging is a physiological state with permanent cessation of the cells' ability to replicate and accumulation of damaged DNA which is increased by ageing
- This cellular senescence is marked by shortening of the protective terminal ends of the chromosome's telomeres (preventing them from being frayed and damaged)
- Shortening of the telomere is a sign of cellular senescence
- In 1999, a study was published stating that increased sirtuin activity could increase the lifespan of yeast cells by 70 per cent. Since then, there has been a growing interest that the cell has a group of anti-ageing proteins, the sirtuins, that are essential for delaying cellular senescence and increasing the lifespan of organisms.



Sirtuins as regulators of lifespan extension

Calorie restriction without malnutrition, one of the most well-studied metabolic interventions, has long been considered beneficial to health span and lifespan extension in multiple model organisms, ranging from yeast to rodents. During calorie

restriction, numerous metabolic regulatory pathways are altered, including PI3K/AKT, mTOR, AMPK, and sirtuins. These pathways are also the main metabolic control signaling axis, representing the general influence of metabolism on lifespan extension.

The mitochondrial sirtuins, SIRT3, SIRT4 and SIRT5, mainly localize to the mitochondrial matrix, placing them as potential master regulators of metabolism. During calorie restriction, SIRT3 leads to accumulation of long-chain fatty acids and decreases fatty acid oxidation. Metabolism is a central node that governs every aspect of cellular and organismal physiology. Metabolic reactions are necessary for providing energy and fundamental chemical molecules to maintain cellular homeostasis, development, senescence and apoptosis.

Antiquity of sirtfood diet

The sirtfood diet was launched in the year 2016 by two U.K. based nutritionists, Aidan Goggins and Glen Matten. The idea with the sirtfood diet is that by eating certain foods, you can activate "skinny gene". SIRT foods simulate the calorie restriction condition and reduce nutrient intake by 20–40% without causing malnutrition.

The calorie restriction stimulated poly-pharmacological activities regulate epigenetic mechanisms, target numerous substrates, and initiate a two-way interactive reaction between dietary and gut environmental components. The "Mediterranean Asian" diet pattern had a small portion of non-plant components and a significant portion of plant-based low-dense energy and health-promoting SIRT modulators. However, progenitors of modern Sirtfoods claim that their plant-only recipe "turns on consumers' skinny genes", which regulate metabolic disorders and improve lifespans.

"The sirtfood diet claims that certain foods can work on DNA to alter metabolism, health and longevity". The diet is possibly based on sirtuins and it promotes eating sirtfoods while doing a calorie restriction, which is ranging from 1000-1500 calories per day.

The Sirtfood diet promotes a specific green juice, as well as foods that claim to increase sirtuin levels like kale, olive oil, coffee, walnuts and strawberries addition to foods rich in polyphenols, or natural anti-inflammatory components. The Sirtfood green juice is one of the most popular food items on the diet, which includes kale, arugula, parsley, celery, half a green apple, ginger, lemon, and matcha green tea.

Sirtfood diet

The diet is divided into two phases: Phase one, which lasts seven days and phase two, which lasts 14 days

Phase I: 1 to 3 days: Total calories are 1,000 per day, and a day's worth of meals includes three homemade green juices and one meal rich in sirtfoods. Homemade green juices include kale, arugula, parsley, celery, green apple, fresh ginger, lemon and matcha green tea powder

Phase I: 4 to 7 days: Calories are increased to 1,500 per day, where the dieter drinks two green juices and eats two meals rich in sirtfoods

Phase II: 8 to 14 days: A day's worth of meals encompasses one green juice, three sirtfood meals and optional snacks like dates or walnuts.

There are no calorie restrictions with a focus on weight loss maintenance and lasts for 14 days

- The diet encourages repeating the two phases until weight loss goals are met, but recommends waiting at least a month before repeating phase I.
- In addition, the phases should not be repeated more than once every three months.
- Can repeat one or all the days of phase II

Conclusion: Sirtuin activity is indispensable for delaying cellular senescence and appears to protect the body against many age-related diseases. The lifestyle, sirtfood diet practices and pharmacological choices increase sirtuin activity and can potentially elevate the anti-ageing effects by assuring prolonged longevity.

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