Archives of the
International Society of Antioxidants in Nutrition and Health (ISANH)

Vol. 5, Issue 2, 2017
DOI: 10.18143/AISANH_v5i2_5
Extended abstract of Vienna Polyphenols 2017

Sirtuins, a promising target in slowing down the ageing process: regulatory role of polyphenols

Anna Bielak-Zmijewska

Nencki Institute of Experimental Biology PAS, Laboratory of Molecular Basis of Ageing Warsaw, Poland

Corresponding author:

Anna Bielak-Zmijewska
Nencki Institute of Experimental Biology PAS, Laboratory of Molecular Basis of Ageing
Warsaw, Poland
a.bielak@nencki.gov.pl

Abstract

We live longer and longer. Ageing however, is associated with increased incidence of age-related diseases. Fortunately, it is a plastic process and can be successfully modulated. There are some defined promising anti-aging interventions, which can postpone the age-related pathologies and improve the healthspan in animal models. These interventions can be partially transferred to humans. One of the most promising anti-ageing targets are proteins belonging to the sirtuin family. They are called "the enzymes of youth". Sirtuins are evolutionary conserved and are present in bacteria and eukaryotes. It has been shown that sirtuins are responsible for extending the lifespan of model organisms and are strongly connected with the beneficial effect of dietary restriction. In humans, proper lifestyle, including physical activity and diet, can influence the healthspan also via increasing the level of sirtuins. Therefore searching for activators of sirtuins is currently one of the hottest issues in anti-ageing studies. A lot of hopes are put in natural compounds, which can be present in everyday diet; they are non-toxic and commonly available. The well-known natural sirtuin activators include polyphenols.

Introduction

The population of elderly people is growing rapidly. Even though ageing is unavoidable, it is a very plastic process. It can be delayed, its symptoms can be alleviated and the quality of life can be improved. Ageing can be modified by the lifestyle, including proper diet, regular physical activity and avoidance of chronic and severe stress. We want to live long but also to enjoy life. The aim of anti-ageing intervention is mostly addressed to elongate the healthspan, which naturally leads to lifespan extension. Some universal features of ageing, such as impaired wound healing, weak immune system, reduced hearing, poor vision, osteoporosis, hair graying or sarcopenia, impair functioning of people. However, the most destructive ailments impairing the quality of life are age-related diseases, such as neurodegeneration, cardiovascular diseases, lung diseases, type II diabetes and some types of cancer. All age–related diseases are associated with increased inflammation, which is both the cause and the result of ageing. Until recently therapeutic interventions were aimed at particular age-related diseases but the general thinking is now changing and it is believed that prevention of ageing protects from age-related diseases. Such approach could be more justified than treatment of particular diseases

Received: July 27, 2017; Accepted: December 7, 2017 -

separately (Niccoli T and Partridge L, 2012; Muñoz-Espín D and Serrano M, 2014).

The role of cellular senescence in ageing

To find out the successful anti-ageing intervention we have to understand why we age. One of the most important issues is cellular senescence. We are getting older because our cells senesce. Senescent cells impair proper functioning of tissues, including tissue regeneration, and have a strong impact on surrounding cells. They modify the microenvironment by secreting certain cytokines, chemokines and mediators of inflammation and they can induce senescence in neighboring cells and support tumor progression. Such secretory cell phenotype is one of the causes of chronic low grade inflammation observed in old individuals. There is a lot of evidence showing that cellular senescence is actually involved in ageing. It has been observed that more senescent cells are present in tissues derived from old animals. This suggests that senescent cells accumulate with age in tissues and organs. Accumulation of senescent cells is also observed in all age-related diseases. Interestingly, it has been shown that elimination of senescent cells from the animals improved their condition. These animals were genetically modified, but removing senescent cells can be possible also in a less invasive manner, namely by using senolitic drugs, which are currently intensively studied. Remarkably, elimination of senescent cells in naturally aged mice prolongs healthspan and extends lifespan by about 20% (Baker et al., 2011, 2016).

Sirtuins and anti-ageing strategies

Recently, some well-documented anti-ageing strategies have been successfully tested in animals. Dietary restriction (DR) - the reduction of calorie intake without causing malnutrition, is the only known intervention able to increase the lifespan in many species and to delay the onset and progression of age-related metabolic diseases. Some approaches, e.g. exercise and certain pharmaceuticals, can mimic DR. Certain elements of these strategies can be applied to people. It can be expected that the effect will be similar even though the course of ageing in humans is much more complicated. In humans, where dietary restriction is not easy to apply, short-term fasting can mimic DR and be effective in lowering the prevalence of age-related loss of function and protecting against age-related pathologies, as evidenced by changes in the level of markers for type 2 diabetes, hypertension, cardiovascular disease, cancer and dementia. It should be emphasized that, in fact, all of the anti-ageing strategies mentioned above are associated with activation of some proteins, namely, sirtuins. Although some data put in question direct involvement of sirtuins in extending the human lifespan, it was documented that proper lifestyle, including physical activity and diet, can influence the healthspan via increasing the level of sirtuins. It is believed that the sirtuin family is one of the most promising targets for anti-ageing approaches and therefore they are called “the enzymes of youth”. There is a well-documented link between the activity of sirtuins and the ageing process. First, these enzymes are responsible for the beneficial effects of DR (elongation of lifespan of model organisms) and second, the level of sirtuins decreases with age. They are involved in DNA repair (with age, DNA damage increases and DNA repair efficiency decreases). Sirtuins are able to antagonize cellular senescence. Conversely, lack of sirtuin 6 leads to premature ageing and lack of sirtuin 1 increases the expression of genes characteristic for ageing. The activity of sirtuins depends on nutrients availability/intake, and nutrient sensing pathways are strongly involved in the regulation of the ageing process.

Sirtuins are a family of class III histone deacetylases (HDACs). The catalytic activity of these enzymes depends on NAD+ and is regulated by dynamic changes in NAD+ level and the NAD+/NADH ratio. Sirtuins can catalyze deacetylation of histone and non-histone lysines. They play a key role during cell response to a variety of stresses, such as oxidative or genotoxic stress, and are crucial for cell metabolism. In humans, the family consists of seven members (SIRT1-7). Sirtuins are involved in such processes as senescence (counteract cellular senescence), survival, DNA repair, metabolism, development, immune response, genome stability, posttranslational modification of protein, telomere structure maintenance, activation of enzymes involved in antioxidative defense, and inhibition of inflammation (including NFkB inhibition). Sirtuin-knockout mice acquire a premature ageing phenotype (kyphosis, loss of subcutaneous fat, osteopenia, degenerative cardiac hypertrophy, and inflammatory cardiomyopathy). On the other hand, sirtuins are able to inhibit progression of such diseases as neurodegeneration, cardiovascular diseases, adiposity, insulin resistance, liver steatosis and to maintain the homeostasis of glucose (most of them are age-related diseases). These enzymes are activated as a result of exercise, which improves the resistance to oxidative stress. Exercise can influence the pace of ageing and help maintaining brain function. The beneficial effect of exercise can be also observed at the cellular level. Exercise inhibits replicative senescence of adipocytes and decreases the level of apoptosis in rat cardiomyocytes. In humans, expression of sirtuin 1 increases in skeletal muscle of both young and aged subjects after exercise.

Received: July 27, 2017; Accepted: December 7, 2017 -

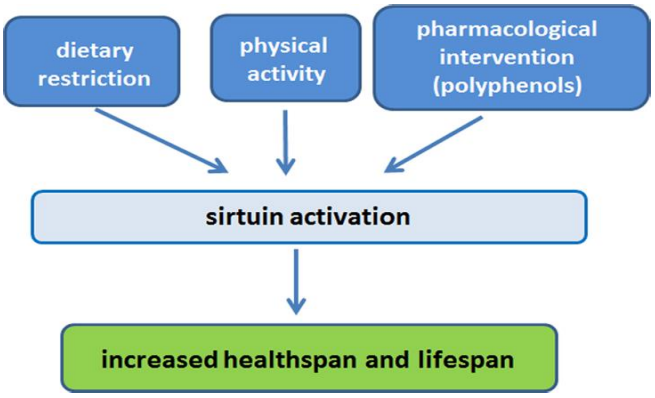

Figure 1 Sirtuins are involved in all currently known anti-ageing strategies

Interestingly, the age-dependent changes in sirtuin level could be used as a diagnostic tool. Serum sirtuins are considered as a novel noninvasive protein marker of frailty, a complex clinical state described as a characteristic set of features among older patients such as sarcopenia, cognitive decline, abnormal functioning of immune and neuroendocrine systems, and poor energy regulation. Diagnosis of frailty is often difficult because of subtle and subjective clinical features, especially at the early stage of the syndrome. As suggested by analysis of people diagnosed as frail in comparison to nonfrail individuals, lower levels of sirtuin 1 and 3 are associated with frailty (reviewed Grabowska et al., 2017).

Polyphenols – activators of sirtuins

Apart from DR and exercise, some pharmaceuticals can be used as sirtuin activators. They are named STACs (sirtuin-activating compounds) and could be both natural and synthetic. The synthetic ones are more efficient but the natural ones are present in everyday diet (fruits, vegetables, herbs, and spices) and can be applied safely and systematically. The use of natural activators of sirtuins, present in diet or acquired by healthy lifestyle, seems to represent a good strategy to delay ageing and age-related diseases. To such natural activators belong many polyphenols. The best recognized and described natural activator of sirtuins is resveratrol. Some data call into question the ability of resveratrol to activate sirtuins. A number of evidence support its role in, at least, sirtuin 1 activation in an indirect manner via increasing AMPK. However, the issue is still open. There are nevertheless many more polyphenols exhibiting similar activity, e.g., curcumin, quercetin, catechin, fisetin, daidzein, silibinin, kaempferol, icariin and piceatannol. One of the most commonly studied polyphenols is curcumin, which shows anti-oxidant, anti-inflammatory and anti-cancer properties, both preventive and therapeutic. Currently, one more activity of curcumin is being studied, namely, the anti-ageing one (Sikora et al., 2010). Curcumin, similarly to other polyphenols, belongs to a specific group of drugs called hormetins. It means that in low doses they bring about a beneficial effect, while they are harmful when taken in high doses. There are some rationales for considering curcumin as a potential anti-ageing factor. Firstly, its anti-inflammatory properties (both ageing and age-related diseases are associated with inflammation). Moreover, experimental data showed that curcumin leads to lifespan elongation of model organisms such as *C. elegans*, fruit fly and mice. Curcumin also alleviates the symptoms of some diseases, including age-related ones, and diminishes the effects of factors which are able to induce diseases or premature ageing/senescence. Moreover, curcumin intake mimics dietary restriction and improves the effectiveness of exercise and, most importantly, it activates sirtuins. There are some examples describing stimulation of sirtuins as a result of curcumin treatment. The most interesting one demonstrates that curcumin could elongate the lifespan of *C. elegans*, but not when the sirt2 (mammalian homolog of sirtuin 1) is mutated (reviewed Grabowska et al., 2017).

Because there are a lot of data showing beneficial role of curcumin in the cardiovascular system and a lot of data showing that sirtuins are essential for its homeostasis, we analyzed the impact of curcumin on human aortic vascular smooth muscle cells. This type of cells is strongly involved in the development and progress of atherosclerosis, which belongs to the most common age-related diseases. Our studies revealed that curcumin (in low doses, which did not impair cell proliferation) was able to activate sirtuins in cells building the vasculature (Grabowska et al., 2016). As it was mentioned before, sirtuins are regulated by the level of NAD+, which is regulated by AMPK (AMP-activated kinase) via stimulation of NAMPT, a transferase involved in NAD+ synthesis. AMPK can be activated by increased ROS production as well as decreased ATP level, and we have shown that curcumin caused both these effects. Therefore we have proposed that sirtuin activation is the result of increased AMPK activity, which is a consequence of ATP decrease and an increase in ROS production in curcumin-treated cells. We have also postulated that AMPK could be responsible for increased expression of sirtuins because AMPK induces the FOXO transcription factor, which is involved in regulation of sirtuin expression. Despite sirtuin activation, curcumin did not delay cellular senescence in our experimental model. It was a surprising result for us. An explanation for this contradiction may be such that the ability of postponing cellular senescence could be cell-type specific. However, in the case of sirtuins, it is not clear what is the cause and what is the result, i.e. we do not know whether cells senesce because the activity of

Received: July 27, 2017; Accepted: December 7, 2017 -

sirtuins is diminished or the activity is lower because of cellular senescence. Further studies to elucidate this contradiction will be necessary.

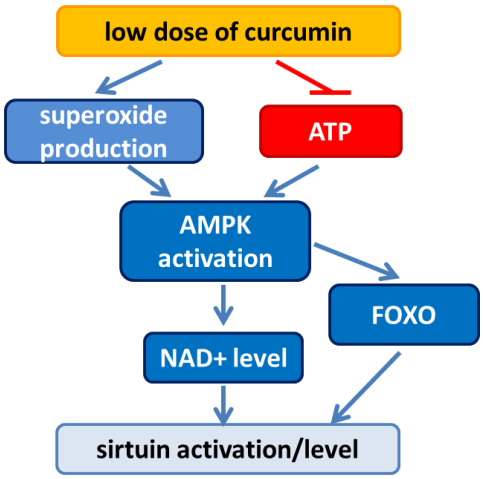

Figure 2 The mechanism of sirtuin activation/elevation by low doses of curcumin

We have demonstrated that surprisingly cytostatic concentration of curcumin (5-7.5 µM) induced cellular senescence in cells building the vasculature (Grabowska et al., 2015). A similar effect was observed by others after resveratrol treatment. All these results can be explained by the hormetic activity of these compounds. It is worth noting that cellular senescence has two faces. On the one hand, it can be detrimental as exemplified by ageing and age-related diseases and, on the other hand, it can be beneficial since it is indispensable for tissue regeneration and protection from tumor progression (López-Otín et al., 2013). The function of cellular senescence is changing with age. In young individuals the beneficial role dominates while in the elderly the detrimental one prevails. Which function could be assigned to curcumin-induced senescence is not clear. Currently, there are some data suggesting that curcumin-induced senescence could be beneficial, e.g. protection from fibrosis (senescence of hepatic stellate cells, HSC) or defense against cancer invasion (senescence of cancer-associated fibroblasts, CAF) (Hendrayani et al., 2013; Jin et al., 2017), but more studies are needed to solve this issue.

Conclusions

To conclude, the sirtuins in modifying the ageing process seems to be very promising and its natural activators, present in everyday diet, might be a good and pretty simple method for staying longer in good health and condition.

Acknowledgements

This study was supported by grant from National Center of Science, UMO-2011/01/B/NZ3/02137 and by the Nencki Institute statutory funds.

References

Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, van de Sluis B et al (2011) Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479(7372):232-236.

Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J et al (2016) Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 530(7589):184-189.

Grabowska W, Kucharewicz K, Wnuk M, Lewinska A, Suszek M, Przybylska D et al (2015) Curcumin induces senescence of primary human cells building the vasculature in a DNA damage and ATM-independent manner. Age (Dordr) 37(1):9744.

Grabowska W, Suszek M, Wnuk M, Lewinska A, Wasiak E, Sikora E et al (2016) Curcumin elevates sirtuin level but does not postpone in vitro senescence of human cells building the vasculature. Oncotarget 7(15):19201-19213.

Grabowska W, Sikora E, Bielak-Zmijewska A (2017) Sirtuins, a promising target in slowing down the ageing process. Biogerontology 18:447–476.

Hendrayani SF, Al-Khalaf HH, Aboussekhra A (2013) Curcumin triggers p16-dependent senescence in active breast cancer-associated fibroblasts and suppresses their paracrine procarcinogenic effects. Neoplasia 15:631-640.

Jin H, Jia Y, Yao Z, Huang J, Hao M, Yao S et al (2017) Hepatic stellate cell interferes with NK cell regulation of fibrogenesis via curcumin induced senescence of hepatic stellate cell. Cell Signal 33:79-85.

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. (2013) The hallmarks of aging. Cell. 153(6):1194-217.

Muñoz-Espín D, Serrano M (2014) Cellular senescence: from physiology to pathology. Nat Rev Mol Cell Biol. 15(7):482-96.

Niccoli T, Partridge L (2012) Ageing as a risk factor for disease. Curr Biol. 11;22(17):R741-52.

Sikora E, Bielak-Zmijewska A, Mosieniak G, Piwocka K (2010) The promise of slow down ageing may come from curcumin. Curr Pharm Des 16(7):884-92.