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Review

Anti-senescence compounds: A potential nutraceutical approach to healthy aging

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ABSTRACT

The desire of eternal youth seems to be as old as mankind. However, the increasing life expectancy experienced by populations in developed countries also involves a significantly increased incidence of the most common age-related diseases (ARDs). Senescent cells (SCs) have been identified as culprits of organismal aging. Their number rises with age and their senescence-associated secretory phenotype fuels the chronic, pro-inflammatory systemic state (inflammaging) that characterizes aging, impairing the regenerative ability of stem cells and increasing the risk of developing ARDs. A variegated class of molecules, including synthetic senolytic compounds and natural compounds contained in food, have been suggested to possess anti-senescence activity. Senolytics are attracting growing interest, and their safety and reliability as anti-senescence drugs are being assessed in human clinical trials. Notably, since SCs spread inflammation at the systemic level through pro-oxidant and pro-inflammatory signals, foods rich in polyphenols, which exert antioxidant and anti-inflammatory actions, have the potential to be harnessed as "anti-senescence foods" in a nutraceutical approach to healthier aging. We discuss the beneficial effects of polyphenol-rich foods in relation to the Mediterranean diet and the dietary habits of long-lived individuals, and examine their ability to modulate bacterial genera in the gut.

1. Introduction

Aging is the result of a continuous interaction between individuals' genetic makeup and environmental factors, characterized by lifelong damage accumulation and progressive loss of tissue and organ functionality (Kirkwood, 2017). Increasingly favorable living conditions − including the availability of food and medical treatment −have been contributing to extend life expectancy in developed countries, raising the proportion of elderly and old individuals in the population (Menotti et al., 2014). However, aging involves a rising risk of developing a number of neurodegenerative disorders, cardiovascular disease, diabetes, osteoarthritis, and cancer, which are commonly referred to as age-related diseases (ARDs) (St Sauver et al., 2015). Notably, a dramatic increase was also observed in the prevalence of multiple chronic diseases and comorbid conditions, *i.e.* hypertension and frailty, especially in elderly subjects (Crimmins, 2015). On the contrary, some individuals reach advanced age in good clinical conditions, demonstrating that healthy aging is possible (Franceschi and Bonafe, 2003). Overall these observations have prompted investigations into how the trajectory of aging can be intercepted to prevent or delay ARD development, increasing healthspan and compressing morbidity (Kennedy et al., 2014). Most of the research work performed to date has focused on interventions against the common ARD risk factors, such as hypertension and high glucose, cholesterol, and triglyceride levels. However, mounting evidence suggests that the most effective strategy would be to target the molecular mechanisms shared by all ARDs,

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rather than try to prevent the separate disorders from arising (Seals and Melov, 2014; Blagosklonny, 2009). Clearly, this requires unraveling the molecular mechanisms that promote aging itself (Fontana et al., 2014; Kirkland, 2013).

The identification of molecular and cellular hallmarks of aging highlighted the potential for lifestyle-behavioral, including nutrition, to improve healthspan in humans (López-Otín et al., 2013).

A large body of data indicates that the burden of senescent cells (SCs) accumulating in aging organisms can contribute to spread inflammaging, a shared risk factor for the most common ARDs (Franceschi et al., 2000; Salvioli et al., 2013; Childs et al., 2015; Franceschi, 2017), pointing at SCs as druggable targets for ARD prevention or treatment (Sikora et al., 2014; Childs et al., 2017; Prattichizzo et al., 2016a,b).

A number of natural and synthetic compounds have been investigated for their anti-senescence and anti-aging potential in cellular and animal models as well as in humans (Vaiserman et al., 2016; Janubová and Žitňanová, 2017). We review the advantages and disadvantages of using medications or natural compounds to counteract or delay senescence and aging and highlight that the safety and efficacy of most potential anti-senescence or senolytic compounds, especially synthetic drugs, are still far from being clearly understood.

Polyphenols (PPs) are natural compounds with documented antioxidant and anti-inflammatory properties that could be harnessed to counteract the signaling through which SCs spread inflammation at the systemic level. Accordingly, PP-rich foods could have “anti-senescence” effects. To substantiate this hypothesis, we analyze and discuss their beneficial effects exerted in the framework of the Mediterranean diet and of the dietary habits of long-lived individuals. Moreover, to assess the mechanisms involved in the putative pro-longevity properties of PP-rich foods, we discuss the interaction of PPs with the gut microbiota in animal models and in humans. Finally, we provide information on some of the best known dietary PPs, with a view to stimulating the consumption of PP-rich foods not only by ARD patients, but also by healthy aging individuals (Neveu et al., 2010). This information was obtained from Phenol-Explorer, a database collecting data on natural phenols and PPs found in food, on their processing, and on the PP metabolites investigated in humans and in experimental animals. Vitamins are not addressed in this review.

2. Cellular senescence

2.1. Phenotypes and signaling pathways

In vitro studies have demonstrated that cellular senescence can occur as a consequence of replicative and non-replicative stress (He and Sharpless, 2017). Investigation of replicative senescence in cell models has shown that it is associated with limited proliferative capacity in cultured human cells (Cristofalo et al., 2004). Non-replicative senescence can be induced by a variety of stressors − including chemical and physical insults like x-ray exposure, oxidative stress, DNA and chromatin damage, and mitochondrial dysfunction – as well as endogenous processes like transcriptional stress, *i.e.* overexpression of activated oncogenes (Coppé et al., 2010; Childs et al., 2015), the latter has been defined as stress-induced premature senescence (SIPS) (Toussaint et al., 2000).

Even if the existence of different senescence programs and the nonspecificity of current senescence markers limit the identification of SCs, a number of features of senescence phenotype can be observed both *in vitro* and *in vivo* (Hernandez-Segura et al., 2018). SCs exhibit distinctive morphological features, such as an enlarged, flattened and irregular morphology, a larger nucleus, a single and larger nucleolus, and an increased number of cytoplasmic vacuoles (Campisi and d'Adda di Fagagna, 2007). The senescence phenotype is characterized by increased activity of senescence-associated (SA) β-galactosidase (β-gal), a typical lysosomal enzyme. SA β-gal activity (measured at pH 6.0) is frequently employed as a marker of SCs both *in vitro* and *in vivo* (Dimri et al., 1995), although according to some researchers it should be combined with other markers, like p16 (Severino et al., 2000; Hall et al., 2016). The main pathways involved in the acquisition of a senescent phenotype have been explored by transcriptomic and pharmacological approaches (Shaohua et al., 2014). SCs are characterized primarily by the loss of proliferation ability. Cell cycle arrest has long been considered as a potent anticancer mechanism preventing premalignant cell expansion (Baker et al., 2017). However, senescence features are expressed in premalignant tumors, where progression to malignancy requires evading senescence (Collado and Serrano, 2010; Campisi and d'Adda di Fagagna, 2007). Recent evidence points at a tumor- and relapse-promoting role for senescence in both cell-autonomous and non-cell autonomous mechanisms (Demaria et al., 2017; Milanovic et al., 2018). The suppression of cell cycle progression in SCs is mediated by the overexpression of inhibitory proteins such as p53, p21, and $p16^{InK4a}$ and by the downregulation of proteins stimulating cell replication, like cyclins, c-Fos, and pCNA (Narita et al., 2003). Therefore, p16 and p21 are extensively investigated senescence-associated biomarkers.

Besides replicative arrest, SCs undergo a number of other changes involving DNA, mitochondrial function, oxidative balance, lipid and glucose metabolism, and inflammatory signaling.

The main senescence-associated DNA markers – SDF (senescence-associated DNA damage foci) and SAHF (senescence-associated heterochromatin foci) – are commonly detected in SCs as are some markers of DNA damage (*i.e.* p-γH2AX and TAF) (Noren Hooten and Evans, 2017). Mitochondrial dysfunction and the resulting oxidative metabolism imbalance have been implicated in the development of cellular senescence (Ziegler et al., 2015; Correia-Melo and Passos, 2015; Correia-Melo et al., 2016). Reactive oxygen species (ROS) are emerging as key signaling molecules responsible for spreading senescence from SCs to neighboring cells (Davalli et al., 2016). Mitochondrial dysfunction also seems to contribute to the impaired fatty acid metabolism seen in SCs, which is related to the development of age- and diabetes-dependent hepatic steatosis (Ogrodnik et al., 2017). Senescence therefore induces extensive metabolic and bioenergetic changes (Quijano et al., 2012). SCs show an increased but inefficient glycolysis, in association with ATP depletion and AMP accumulation, which in turn can promote cell cycle arrest through AMPK activation (Zwerschke et al., 2003). AMPK stimulates ATP production and reduces its consumption, increasing glycolysis and fatty acid oxidation, halting cell growth, biosynthesis, and proliferation, and partially suppressing the mammalian target of rapamycin (mTOR), a nutrient-sensing serine/threonine protein kinase (Vaiserman et al., 2016; Johnson et al., 2015). mTOR is found in cells as two different complexes, complex 1 (mTORC1) and complex 2 (mTORC2) (Laplante and Sabatini, 2012); the former is involved in the response to nutrient signaling and in the induction of cell growth and protein synthesis, and reduces autophagy, whereas the latter has a role in the arrangement of the cytoskeleton (Shaohua et al., 2014). mTOR activity is increased in SCs, playing a pivotal role in a variety of processes like cell cycle arrest, metabolism, lysosome-autophagy proteolytic system, and secretion of pro-inflammatory factors (Laberge et al., 2015; Herranz et al., 2015; Moreno-Blas et al., 2018). Similar to the hypothesis that has been advanced for immune cells, the mTOR network is emerging as a biological mechanism that adjusts the environmental nutritional status to SC activities and fine-tunes the inflammatory response (Weichhart et al., 2015). Notably, mTOR is a key modulator of aging in organisms as evolutionarily divergent as yeasts and rodents, and it is conceivable that this function is to some extent conserved also in humans (Johnson et al., 2013).

Increasing data support a role for silent information regulators (SIRTs/sirtuins), a class of nutrient-sensitive epigenetic regulators, in promoting mammalian health, modulating cellular senescence and lifespan. SIRT1 is a (NAD+) − dependent deacetylase that targets a number of transcription factors such as FOXO1, 3 and 4, p53, NF-κB,