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Review article

In search of nutritional anti-aging targets: TOR inhibitors, SASP modulators, and BCL-2 family suppressors

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ABSTRACT

In pursuit of developing anti-aging or age-delaying strategies, nutritional interventions have long been considered promising candidates. However, emerging advances in the understanding of the causes and effects of senescence per se have enhanced the prospects of a more focused approach in the exploration of therapies aimed at the modulation of aging. The aim of this study was to review recent developments on the molecular basis of aging and provide evidence that regulation of the mechanistic target of rapamycin (mTOR), senescence-associated secretory phenotype (SASP), and apoptotic pathways could be the key mechanistic targets of prospective senescence modulatory interventions. The emerging role of nutraceuticals in specifically targeting these molecular aspects of senescence are reviewed with the rationale of identifying novel opportunities and challenges in formulating food- and nutrition-based anti-aging therapies.

Introduction

The phenomenon of aging is a gradual, deleterious, and multifaceted aspect of life. As we age, major regulatory systems of the body, including immune response, cardiovascular system, and the endocrine network, are categorically affected, causing tissue and organ dysfunction characteristic of the aging phenotype [1,2]. Notable advances in health care and vaccination have immensely contributed to increasing human life expectancy, and as a result, the global geriatric population is on the rise. However, older individuals are dramatically more prone to a vast majority of degenerative diseases including the hallmark disorders of the 21st century (i.e., cancer and diabetes) [3]. It is thus evident that understanding the fundamental causes of aging and identification of its potential therapeutic targets and modulators is of paramount importance in maintaining health and longevity. At present, physical exercise, lifestyle management, and nutritional interventions are the only known considerable non-genetic factors that may promote healthy aging. Among these, nutritional modulation of aging is arguably the most rational and achievable phenomenon [4]. There are several examples of nutraceuticals, including plant secondary metabolites and probiotic bacteria, that have been shown to modulate at least some of the deleterious functional aspects of aging, and in the process, even conferring an extension in the life span of experimental animals [5–9]. However, only emerging evidence has begun to reveal the molecular basis of aging, thereby identifying potential cellular targets for mitigating age-associated cellular and organ dysfunction. The present review describes the current advances in the understanding of the etiology of cellular senescence as well as evidences, underlying mechanisms, and perspectives in the quest for achieving a nutraceutical-based modulation of senescence and aging.

Molecular etiology of aging: Emerging concepts

Organismal aging is essentially a manifestation of collective functional deterioration in almost all cell types. These age-associated aberrations in cellular functions are at least partially attributed to the phenomenon of cellular senescence [10]. Somatic cells have a limited replicative life span, following which the cells cease to proliferate and become “senescent,” ultimately hampering the natural regeneration capacity of worn-out or damaged cells. Although this restriction in cell proliferation is viewed as an evolutionary barrier to tumorigenesis, a causative linkage between cellular senescence and aging has been speculated. Indeed, recent advances in geroscience have demonstrated

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that gradual accumulation of senescent cells in various tissues and organs directly contributes to organ dysfunction and the characteristic aged phenotype [11]. In a breakthrough study, it was shown that selective elimination of senescent cells in vivo could essentially confer anti-aging attributes by delaying tumorigenesis and attenuation of age-related deterioration of several organs including kidney, heart, and fat [12]. In addition, it has been shown that transplanting small numbers of senescent cells from the ear cartilage of luciferase-expressing mice into the knee-joint area of wildtype mice caused the development of leg pain, impaired mobility, and radiographic and histologic changes suggestive of osteoarthritis [13]. Therefore, it is not surprising that cellular senescence has been argued to be the "causal nexus" of aging, and targeting senescent cells appears to be a promising way to mitigate the deleterious effects of aging [11].

Furthermore, it is now understood that senescent cells have unique associated features that greatly enhance their prowess to inflict damage to nearby healthier cells and thus augment tissue and organ dysfunction. This includes the development of characteristic senescence-associated secretory phenotype (SASP) and the resistance to apoptosis-mediated natural cell death. The SASP is a complex milieu of several proinflammatory and prooxidant molecules that, by way of autocrine and paracrine signaling, results in prooxidant, proinflammatory, and protumorigenic environment [14]. SASP could also provide an explanation to the notion of *inflamm-aging*, wherein chronic circulatory presence of inflammatory molecules such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and monocyte chemoattractant protein (MCP)-1 is observed in the elderly, which is thought to invoke systemic inflammatory damage [15]. In young organisms, SASP factors serve to attract immune cells in their localized area for inflammation-mediated clearance of senescent cells, whereas growth factors present in SASP stimulate proliferation in neighboring cells to allow subsequent replacement of senescent cells [16]. However, as we age, both innate and adaptive immune systems have been documented to undergo characteristic and widespread dysregulations that hamper effector functions and thus could possibly relate to the apparent accumulation of senescent cells [17,18]. Therefore, it is evident that strategies aimed at maintaining immunologic homeostasis during aging could result in efficient clearance of senescent cells. Senescent cells are also metabolically active but resist both extrinsic and intrinsic proapoptotic stimuli. This ability prevents the natural elimination of senescent cells from tissues, thereby further aiding in their accumulation and augmentation of the senescent phenotype [19]. Recently, apoptotic resistance in senescent cells was linked to the persistent activation of prosurvival pathways (B-cell lymphoma [BCL]-2 family) with concomitant inhibition of proapoptotic pathways (BCL-2-associated X protein [BAX] family) [20]. It was also observed that inhibition of BCL-2 family proteins resulted in skewing of the cell fate toward apoptosis and their gradual removal in vivo [21]. This discovery has revealed a novel mechanism of triggering self-clearance of senescent cells that could be used in developing therapeutic approaches. Notwithstanding, it is interesting to note that despite the emerging role of senescent cells in driving the aging process, senescent cells have been associated with certain beneficial aspects as well, such as wound healing and control of fibrosis [22,23]. This implies that unabated elimination of senescent cells may also affect some desirable cellular aspects that require further exploration. Nonetheless, evidence suggests that elimination of senescent cells during aging may preserve organ functions and enhance life span. The causes of age-associated activation of the senescence program includes a combination of inherent loss of replicative potential (replicative senescence) owing to telomere erosion, age-associated chronic oxi-inflammatory or genotoxic stress (stress-induced senescence), and defective immune cell-mediated clearance of senescent cells. The oxi-inflamm-aging theory proposes that mitochondrial dysregulation of reactive oxygen species (ROS) production with age is the cellular initiator of the aging process [24]. As ROS-mediated molecular and eventual DNA damage prevails, downstream pathways of cell cycle inhibition ($p53/p21^{WAF1}/p16^{INK4a}$) are activated and the senescence program is triggered. The chronic stress-mediated induction of senescence is arguably more pertinent because it not only represents a modifiable factor of aging, but could also explain the loss of function and development of senescence (mediated by SASP) in non-dividing cells (such as neurons or immune cells). Although different theories have been put forward to explain the mechanisms of aging, why we age is generally regarded as an evolutionary consequence involving age-associated persistent activation of certain nutrient-sensing pathways (such as mTOR) that are otherwise essential for normal growth and development [25].

mTOR, SASP, and BCL-2 family proteins in senescence

mTOR signaling is vital for cellular growth and function because it directly regulates metabolism, translation, and stress response in proliferating cells. Emerging evidence has shown that both cell growth and cell senescence are related to mTOR signaling [26,27]. In quiescent cells, both cell cycle and mTOR are blocked, but if cell cycle is inhibited and mTOR is still activated, cells become hypertrophic and hyperactive, resulting in cellular damage characteristic of cellular senescence (Fig. 1) [25]. There are reports suggesting aberrant mTOR activation both in vitro and in vivo in the pro-aging environment and that the inhibition of mTOR can improve cellular functions and immune responses and enhance life span [28–34]. Despite these observations, reasons for why mTOR is activated during aging and how its inhibition extends the life span remain elusive. At least two potential causes of mTOR activation can be envisaged. First, TOR is essential for development in early life and its knockout in early stages is lethal [35]. Although the growth rate of mammals is maximally achieved near adulthood, the nutritional stimulus continues unabated, rendering persistent TOR activation that contributes to aging. The scenario is compounded by modern lifestyles wherein fast food or overeating, coupled with lack of physical exercise, may further aggravate the nutritional overstimulation of the mTOR (Fig. 1). Second, increased nutritional stimulus also may cause a time-dependent overburden on cellular antioxidant machinery, thereby affecting mitochondrial redox homeostasis and causing accumulation of ROS that has been shown to directly result in mTOR activation. Once activated, TOR results in enhanced oxidative phosphorylation in mitochondria, leading to further generation of ROS [36,37]. Thus, mTOR and ROS mutually complement each other, resulting in a vicious circle of sustained mTOR activity and oxidative damage and thereby driving the senescence program (Fig. 2).

Inflammatory damage owing to SASP is the single most damaging factor of cellular functions and augmenter of senescence. It has been shown that mTOR can directly regulate SASP production by selectively enhancing the translation of the membrane-bound cytokine IL-1A and that rapamycin-mediated amelioration of age-related pathologies, including late-life cancer, could be due to the suppression of SASP [38]. Moreover, the SASP is particularly detrimental because it is prevalent in all senescent tissues, even in terminally differentiated skeletal muscles and immune cells, and thus could augment systemic effects of aging. Another major aspect of senescence is resistance to apoptosis-mediated cell death. Normal cells, when irreparably damaged, undergo programmed cell death in an attempt to prevent gradual injury to healthy cells. However, senescent cells are not only deleterious in functions but also persist in a metabolically active, non-dividing state owing to prevalent

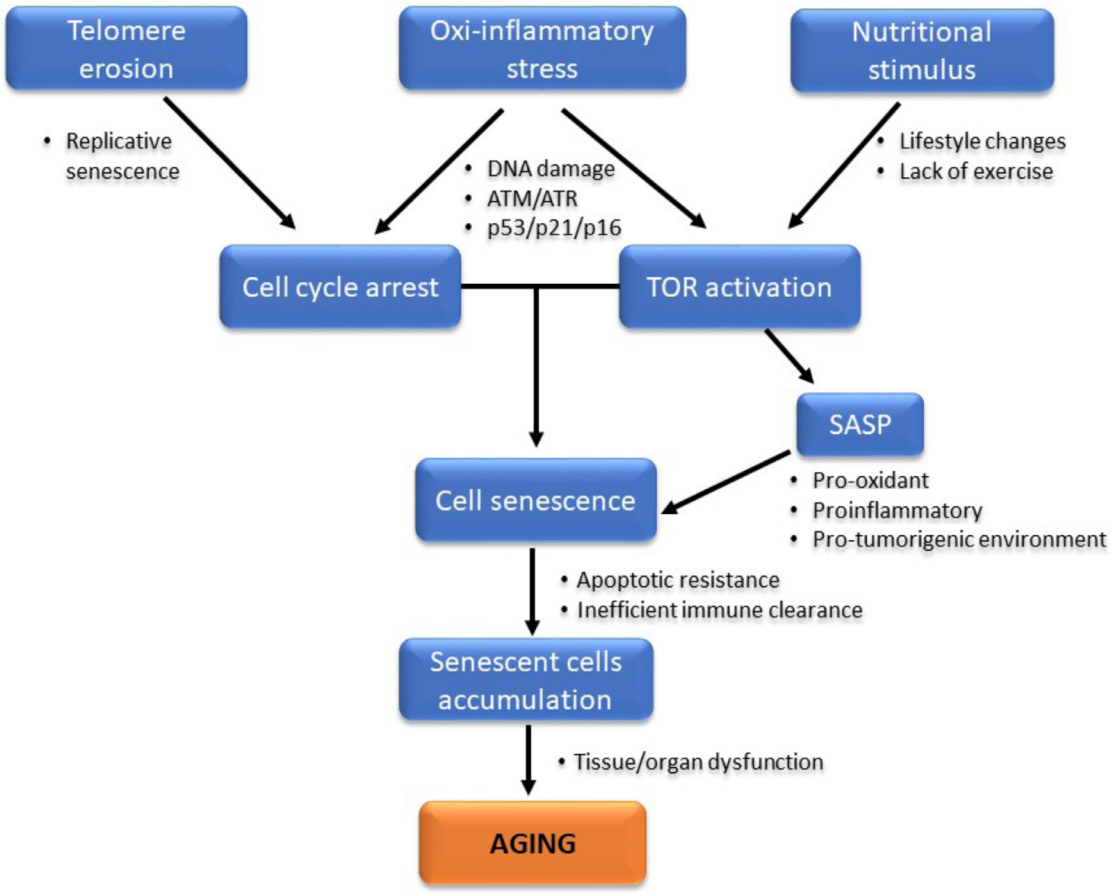

Fig. 1. Schematic diagram of the interplay between cell cycle arrest and mTOR activation in the development of senescent cells and their characteristic features, ultimately leading to the manifestation of aging phenotype. mTOR, mechanistic target of rapamycin; SASP, senescence-associated secretory phenotype.

resistance to apoptosis. Several proteins control the process of apoptosis, including pro-apoptotic regulator BAX and anti-apoptotic regulator BCL-2. BAX regulates the activities of caspases and endonucleases by extricating cytochrome c from mitochondria, whereas BCL-2 prevents the release of cytochrome c and encourages cell survival [39]. Recent studies have shown that apoptotic resistance in senescent cells is caused by the activation of BCL-2 family proteins. Interestingly, there is also evidence that Akt, the upstream activator of mTOR, might directly contribute to stabilization of BCL-2 family proteins, thereby indicating another possible implication of mTOR activation in contributing to senescence and senescent phenotype [40]. Taken together, it is evident that targeting mTOR signaling, SASP progression or BCL-2 accumulation in senescent cells could be a viable strategy for the mitigating of progression of senescence and delaying the development of age-inflicted inflammatory disorders.

Nutritional modulation of mTOR, SASP, and BCL-2 during senescence

Evidence suggests that nutritional components can influence different aspects of aging that are largely attributed to the improved cellular antioxidant and inflammatory homeostasis. A plethora of bioactive molecules including quercetin, resveratrol, and epigallocatechin gallate (EGCG), as well as milk bioactive peptides and probiotic bacteria, have shown promising, functional anti-aging aspects [9,41–45]. Recent evidences suggest that these apparent effects of nutraceuticals could at least be partially attributed to their inhibition of both the development and the progression of cellular senescence as documented in various in vitro experiments [46]. A vast majority of studies pertaining to nutraceutical-mediated modulation of senescence have highlighted the prevention of p53/p21^{WAF1}/p16^{INK4a}–mediated cell cycle arrest in senescent cells [46,47]. However, despite emerging evidence of the crucial role of mTOR in aging pathophysiology, few reports have directly assessed the effects of nutritional interventions considering mTOR signaling as the causative agent of senescence (Table 1). For instance, a report by Yang et al. [33] identified the inhibition of the AKT/mTOR pathway and ROS production as the underlying mechanism of ascorbic acid–mediated prevention of D-galactose–induced cell senescence. Using a rat model of brain aging, Wang et al. [48] showed that saponins of *Trillium tschonoskii* can prevent neural dysfunctions by upregulating Rheb and downregulating mTOR, thereby rescuing dysfunctional autophagy to execute an anti-aging role. Similarly, Park et al. [49] showed that *Kaempferia parviflora* extracts can inhibit AKT/mTOR pathway in stress-induced senescent fibroblasts. Lee et al. [50] observed that isoflavone genistein-induced mTOR inhibition caused activation of autophagy pathway, resulting in attenuation of senescence in vascular smooth muscle cells. Another study observed that alkaloid berberine can suppress stress-induced senescence by the inhibition of mTOR pathway [51]. It should be considered that in the perspective of cancer research, multiple evidences exist wherein bioactive phytomolecules such as polyphenols have shown promise in the inhibition of PI3K/Akt/mTOR signaling, thereby inhibiting cell growth and proliferation. However, to our knowledge, there is a

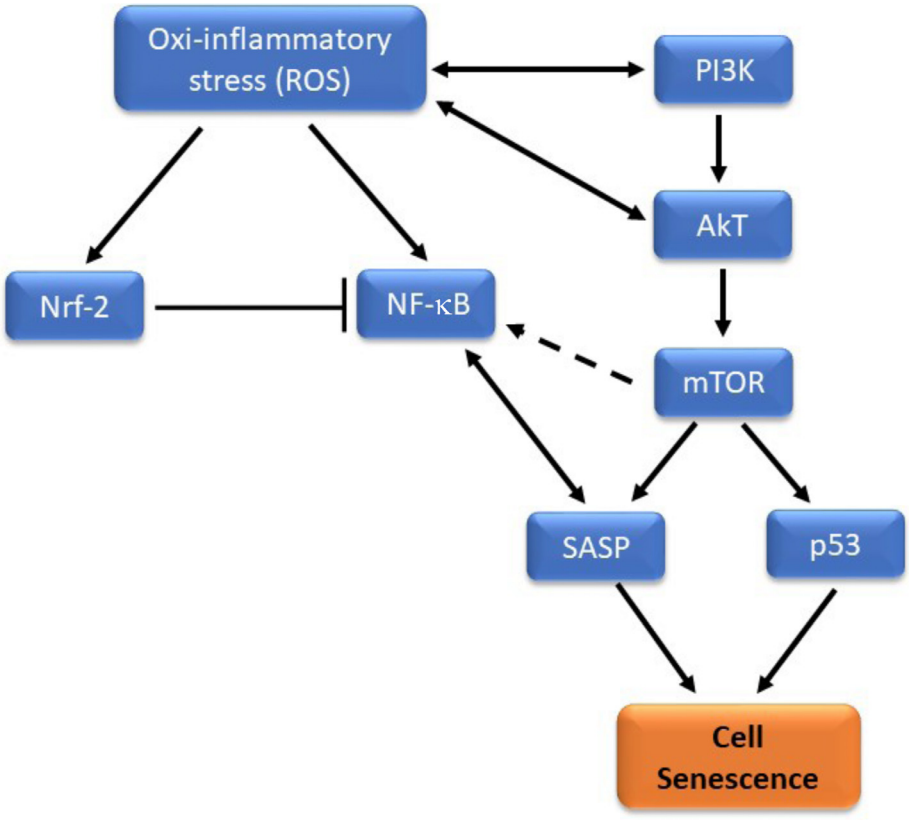

Fig. 2. Schematic diagram indicating the role of ROS and mTOR signaling pathways in driving the senescence process. Persistent age-associated ROS accumulation results in activation of mTOR pathway that further stimulates ROS production while also inducing SASP factors, ultimately causing stimulation of cell cycle inhibitory pathways and thereby augmenting the process of senescence. mTOR, mechanistic target of rapamycin; NF, nuclear factor; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype.

distinct dearth of studies assessing nutritional modulation of mTOR signaling in the context of senescence both in vitro and in vivo. Given the role of nutritional stimulus in activating TOR, reducing the caloric burden by interventions such as calorie restriction have shown to promote health, attenuate age-related morbidities, and enhance the life span [52]. The mechanisms governing these effects have been attributed to a milieu of decreased oxidative stress, enhanced antioxidant systems, epigenetic changes, and the inhibition of TOR [53–56]. Interestingly, dietary supplementation of certain nutraceuticals or drugs, such as the polyphenol resveratrol and the TOR inhibitor rapamycin have been found to "mimic" the phenotypes of calorie restriction [57,58] and therefore represent a more pragmatic approach to attaining health benefits of calorie restriction.

Table 1
Nutraceuticals that target mTOR/SASP and BCL-2 pathways are antisenescence agents

Reported anti-senescence mechanism	Nutraceutical component	Reference
	Epigallocatechin gallate	Kumar et al. [73]
	Ascorbic acid	Yang et al. [33]
	Saponins	Wang et al. [48]
mTOR inhibitors	*Kaempferia parviflora* extract	Park et al. [49]
	Genistein	Lee et al. [50]
	Berberine	Zhao et al. [51]
	Epigallocatechin gallate	Kumar et al. [73]
	Resveratrol	Menicacci et al. [59]; Liu et al. [60]
SASP suppressors	*Ophiopogonis radix* extract	Kitahiro et al. [61]
	Ginsenoside	Tang et al. [62]
	Flavonoids	Lim et al. [63]
	Epigallocatechin gallate	Kumar et al. [73]
	Piperlongumine	Wang et al. [69]; Liu et al. [70]
Senolytic	Fistein	Zhu et al. [71]; Yousefzadeh et al. [72]
	Quercetin	Zhu et al. [64]

BCL, B-cell lymphoma; mTOR, mechanistic target of rapamycin; SASP, senescence-associated secretory phenotype

Studies addressing SASP modulatory attributes of nutraceuticals have only begun to emerge (Table 1). Nonetheless, evidences suggest that various plant secondary metabolites have the potential to attenuate gene and protein expression of several SASP components such as IL-1β, IL-6, IL-8, and TNF-α mediated by the inhibition of nuclear factor (NF)-κB expression. Menicacci et al. [59] observed that resveratrol-treated conditioned media of senescent fibroblasts attenuated IL-8 levels as well as IL8/CXCR2 binding in endothelial colony-forming cells, thereby suggesting inhibition of pro-angiogenic attributes of SASP. Liu et al. [60] showed that chronic resveratrol treatment to annual fish *Nothobranchius guenther* downregulated levels of SASP-associated pro-inflammatory cytokines IL-8 and TNF-α and upregulated expression of anti-inflammatory cytokine IL-10 mediated by NF-κB inhibition in the gut. Similarly, methanolic extracts of *Ophiopogonis radix* showed SASP modulatory potential by inhibiting IL-6 and IL-8 in senescent human dermal fibroblasts [61]. Application of Ginsenoside Rg1 to *tert*-butyl hydroperoxide induced premature senescence in mouse hematopoietic stem cells

and resulted in decreased mRNA and protein expression of NF-κB, signifying attenuation of SASP and resistance to senescence [62]. In a detailed study, various flavonoids such as apigenin, quercetin, kaempferol, naringenin and wogonin were evaluated for anti-SASP attributes in bleomycin induced senescent BJ cells [63]. Some authors have observed that apigenin and kaempferol strongly repressed the expression of SASP factors such as IL-1α, IL-1β, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, CXCL1, monocyte chemoattractant protein-2, and matrix metalloproteinase-3 by inhibiting the NF-κB p65 activity via the IRAK1/IκBα signaling pathway. Furthermore, oral administration of apigenin significantly reduced elevated levels of SASP in the kidneys of aged rats, suggesting that flavonoids are inhibitors of SASP [63].

Since the discovery that the synthetic molecule navitoclax promotes apoptosis and cell death by inhibiting expression of BCL-X_L proteins of the BCL-2 family; there is growing interest in identifying safer yet equally effective natural compounds with such attributes. These compounds that can selectively eliminate senescent cells by regulating mechanisms such as apoptosis are called *senolytics*. Given the fact that various phytomolecules have shown anti-senescence potential, identification of senolytics is a promising area of research in nutrigerontology. However, studies pertaining to identification of natural compounds for their senolytic attributes are still in their infancy (Table 1). The first evidence of a non-synthetic senolytic compound was reported for the flavonoid quercetin in irradiation-induced senescent human umbilical vein endothelial cells (HUVECs) [64]. Since then, using several different approaches in preclinical studies, quercetin and the synthetic drugs dasatinib and navitoclax have been shown to clear senescent cells in vivo [65–67]. Recently, quercetin, in combination with dasatinib, has been shown to selectively eliminate senescent cells, attenuate SASP, alleviate physical dysfunction, and increase post-treatment survival by 36% while reducing mortality hazard to 65% in experimental mice [68]. Similarly, the polyphenols piperlongumine and fistein have been identified as having senolytic potential in senescent human WI-38 fibroblasts and human umbilical vein endothelial cells, respectively [69–71]. More recently, Yousefzadeh et al. [72] observed that acute or intermittent treatment of progeroid and old mice with fisetin reduced senescence markers in multiple tissues, whereas administration of fisetin to wildtype mice late in life restored tissue homeostasis, reduced age-related pathology, and extended the median and maximum life spans. Furthermore, working on green tea catechin EGCG, we observed that EGCG has multifaceted antisenescence attributes because it can enhance immune responses in the older population [9] and inhibit mTOR-mediated activation of senescence and SASP and also can act as a potential senolytic against murine adipocytes [73]. Taken together, a niche research area involving nutritional modulation of mTOR, SASP, and apoptotic cell death during senescence can be envisaged, particularly using known bioactive polyphenols because they appear to be ideal candidates for developing anti-aging therapies.

Conclusion and future perspectives

As of now, human aging is inevitible. However, aging itself is not a disease but rather it predisposes older individuals to recurring infections and inflammatory disorders that contribute to observed morbidity and mortality. The identification of TOR as senescence and life span regulator, coupled with prevalent SASP, are among the factors that predominantly contribute to age-associated tissue and organ dysfunctions and thus have provided novel and exciting therapeutic targets. Indeed, clinical trials of TOR inhibitors and senolytic drugs are presently envisaged so as to assess their anti-aging efficacy [74]. However, diet and nutraceuticals could play a vital role in this regard because of their established role in influencing various regulatory systems of humans, safety, and lack of side effects. Notwithstanding, there is little information as to whether and how nutraceuticals could target TOR or SASP that may affect cellular senescence and ultimately organismal health and longevity. Nutrition-mediated activation of immune surveillance or the identification of novel BCL-2 inhibitors for efficient clearance of senescent cells is another promising therapeutic approach for which little or no reports are available to our knowledge. Thus, emphasis should be placed on identification of nutraceuticals with TOR inhibitory, SASP modulatory, or senolytic attributes or their combinations, which may contribute to the development of a safer and more natural approach to nutrition-based antisenescence and healthy aging strategies.

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