

When Anti-Aging Studies Meet Cancer Chemoprevention: Can Anti-Aging Agent Kill Two Birds with One Blow?

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Abstract Recent evidence has strongly supported that the rate of aging is controlled, at least to some extent, by evolutionarily conserved nutrient-sensing pathways (e.g., the insulin/insulin growth factor 1 (IGF-1)-signaling, molecular target of rapamycin in mammals (mTOR), adenosine monophosphate-activated protein kinase (AMPK), and sirtuins) from worms to humans. These pathways are also commonly involved in carcinogenesis and cancer metabolism. Agents (e.g., metformin, resveratrol, and *Rhodiola*) that target these nutrient-sensing pathways often have both anti-aging and anti-cancer efficacy. These agents not only reprogram energy metabolism of malignant cells, but also target normal postmitotic cells by suppressing their conversion into senescent cells, which confers systematic metabolism benefits. These agents are fundamentally different from chemotherapy (e.g., paclitaxel and doxorubicin) or radiation therapy that causes molecular damage (e.g., DNA and protein damages) and thereby no selection resistance may be expected. By reviewing molecular mechanisms of action, epidemiological evidence, experimental data in tumor models, and early clinical study results, this review provides information supporting

the promising use of agents with both anti-aging and anti-cancer efficacy for cancer chemoprevention.

Keywords Chemoprevention · Aging · Nutrient-sensing signaling pathways · Cancer

Introduction

Aging is a major risk factor for many common cancers, such as bladder, prostate, kidney, lung, colon, and breast cancers [1]. The risk of cancer of those 55 or older increases up to 78 and 58 % in first- and third-world countries, respectively [1]. Due to the dramatically increased life expectancy in the twenty-first century, cancer has become a major health and economic burden in many countries. In the USA, approximately 1.6 million people are diagnosed with cancer and one out of four elderly people die from cancer each year [1]. As populations continue aging, the global cancer burden is expected to increase 50 % by 2020 [2].

Proposed hallmarks of aging include deregulated nutrient-sensing, genomic instability, telomere shortening, mitochondrial dysfunction, cellular senescence, aberrant epigenetic alterations, imbalance of protein homeostasis, loss of proteostasis, stem cell exhaustion, altered inter-cellular and intracellular communications, and inflammation [3]. Notably, all of these hallmarks of aging are also observed during the process of carcinogenesis, suggesting that cancer and aging are both associated at the molecular level. However, the molecular link between aging and the development of cancer, in particular how aging leads to carcinogenesis, remains largely unknown. The current paradigm is that aging and cancer are driven by the accumulation of molecular damage, such as DNA damage [4, 5]. This paradigm has recently been challenged by accumulating evidence demonstrating that

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evolutionarily conserved nutrient-sensing pathways (e.g., insulin/insulin growth factor 1 (IGF-1), molecular target of rapamycin in mammals (mTOR), adenosine monophosphate-activated protein kinase (AMPK), and sirtuins) are, at least to some extent, required for overall life span and healthy aging across different species from worms to humans [3, 6]. Nutrient-excessive conditions activate the insulin/IGF-1 and mTOR pathways, whereas, nutrient restriction activates the AMPK and sirtuin pathways (Fig. 1) [3, 6, 7]. Altering nutrient-sensing pathways by either inhibiting the insulin/IGF-1 and the mTOR pathway or activating the AMPK and sirtuins pathways lead to the longevity of an organism [3, 6]. Anti-aging studies have shown that these nutrient-sensing pathways can be modulated by nutritional approach [e.g., calorie restriction (CR)] [8], a preventive drug (e.g., metformin and aspirin) [9, 10], and dietary supplements (e.g., resveratrol and Rhodiola) [11–14]. Importantly, these nutrient-sensing pathways are also involved in cancer development and progression [15–18]. Therefore, interventions that target nutrient-sensing pathways for slowing down aging may also reduce and delay the process of carcinogenesis and prevent cancer.

Current efforts to treat cancer include radiotherapy, chemotherapy, and surgery. However, many elderly cancer patients are not tolerant of these treatments, which decrease their quality of life [19, 20]. Chemoprevention is an approach to delay the process of carcinogenesis by the use of natural, synthetic, or biological agents in order to reduce cancer incidence, morbidity, and mortality, as well as to improve overall quality of life [21]. The high incidence of many cancers in aging populations suggests that cancer is an age-related disease, and agents that inhibit or delay cancer development and progression in the elderly could yield significant reductions in cancer morbidity and mortality [19, 20]. Therefore, non-toxic or less toxic agents (e.g., metformin, resveratrol, aspirin, and *Rhodiola*) with anti-aging properties are suitable for cancer chemoprevention in the elderly.

In this review, we have attempted to summarize the role of the most common nutrient-sensing pathways at the intersection of aging and cancer (Fig. 1), as well as mechanisms by which anti-aging agents could slow down aging and inhibit carcinogenesis.

Nutrient-Sensing Pathways at the Intersection of Aging and Cancer

The Insulin and IGF-1 Signaling Pathway

The insulin and IGF-1 signaling pathway is an evolutionarily conserved nutrient-sensing and bioenergetic pathway with a major impact on longevity [22, 23]. Constitutively decreased insulin- and IGF-1 signaling can extend the life span of model

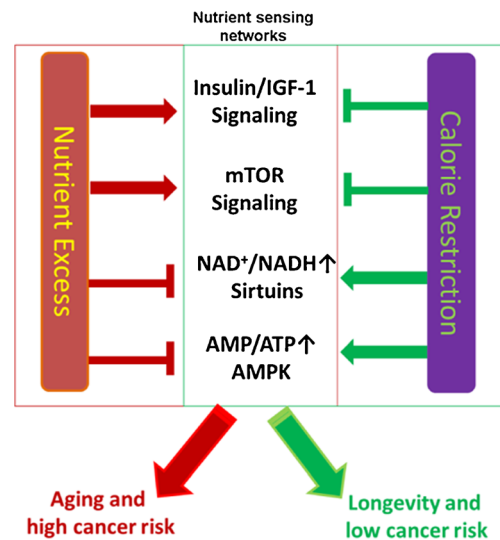


Fig. 1 The effect of nutrient excess and caloric restrictive conditions on longevity and cancer risk via nutrient-sensing signaling networks. Nutrient excessive conditions activate insulin/IGF-1 and the mTOR pathways for promoting aging and cancer risk, whereas, nutrient restrictive conditions activate AMPK and sirtuins pathways for increasing longevity and reducing cancer risk

organisms, such as yeast, worms, fruit flies, and mice [24–27]. On the contrary, studies also showed that supplementation of IGF-1 can improve premature aging in progeroid mice, which have low levels of IGF-1. These results suggest that there may be an important balance in expression of IGF-1 for longevity [28]. The role of insulin and IGF-1 signaling in human aging is also controversial and contradicts animal studies. Some studies reported reduced longevity of patients with growth hormone deficiency [29, 30]. For example, individuals with growth hormone (GH)-resistance dwarfism have a reduced life span [30]. Other studies reported that lower levels of IGF-1 was not a good predictor for longevity; however, lower levels of IGF-1 in cancer patients predicted longer survival [31, 32]. Currently, it remains debatable and largely unknown about the long-term effects of IGF-1 on human aging [24, 33].

Although gene amplification and activating mutations of insulin and IGF-1 receptor family members are not common in cancer, abnormal autocrine or paracrine expression of ligands are common [14]. IGF-1 and IGF-2, which are secreted by mammary adipose tissues, have been shown to have significant paracrine effects and contribute to diabetes associated cancer [34]. Evidences from epidemiological studies have demonstrated that high circulating IGF-1 levels are associated with an increased risk for gastrointestinal, prostate, breast, colorectal, and ovarian cancers and negatively affect cancer prognosis [14, 35–38]. Earlier studies examining the IGF-1 receptor in fibroblast cells showed that it was required for the transforming activity of simian virus 40 large tumor antigen (SV40T) [39]. To characterize the role of IGF-1 in carcinogenesis, Hursting SD et al. [40] generated transgenic mice overexpressing human IGF-1. When the carcinogen, p-

eresidine, was introduced, these transgenic mice exhibited greatly increased bladder tumors compared to nontransgenic mice. In addition, insulin secretion rate as indicated by c-peptide levels influenced cancer risk [41, 42]. Patients with congenital deficiencies in IGF-1 and growth hormone are resistant to cancer and aging development [29]. Taken together, the above results suggest that the modulation of insulin and IGF-1 levels in tissues or the circulation in the body would be promising for both anti-aging and cancer prevention.

The mTOR Pathway

mTOR is a conserved serine/threonine kinase that belongs to the phosphoinositide-3-kinase (PI3K)-related kinase family and consists of two multiprotein complexes, mTORC1 and mTORC2 [18]. mTOR plays a key role in energy management at both the cellular and organismal level by getting cues from cellular nutrients, oxygen, and energy [18]. There have been many reports of the mTOR pathway promoting aging in different model organisms. Inhibition of mTORC1 activity by genetic approaches can extend the life span of yeast, worms, and flies [43–48]. Mice with genetically modified low levels of mTORC1 activity or deficient in its downstream target S6K1, but with normal levels of mTORC2 activity exhibit extended life spans [49]. Rapamycin, a specific inhibitor of mTORC1 normally used to treat various cancers, has been shown to enhance the longevity of mice by 9 to 14 % [47, 48]. Rapamycin can also delay the onset or progression of multiple age-related phenotypes, such as tendon stiffening, liver deterioration, and cardiac dysfunction to name a few [50]. Recently, a clinical trial of rapamycin at half the dose that a kidney transplant patient would receive for slowing aging has been carried out in five men at their late 80s and 90s [51]. Initial results from this trial have shown that men receiving rapamycin have increased walking ability and responsiveness to the hepatitis B vaccine compared to the controls [51]. Therefore, rapamycin which decreases mTORC1 seems to slow down cellular senescence and aging of an already elderly population.

The PI3K/AKT/mTOR pathway is commonly activated in many cancer and tumor syndromes. It has been estimated that mTORC1 is aberrantly activated in up to 80 % of human cancers [52]. The mTOR pathway can be activated by mutations in the PI3K, mTOR, or AKT genes; loss of PTEN, NF-1, PIK3CA, VHL, TSC2, or TSC1; or constitutive activation of Ras, Src, Raf, or MEK [53–55]. During the process of carcinogenesis, multiple rounds of cellular proliferation and selection can transform initially random mutations into non-random activation of the mTOR pathway [53]. Given the oncogenic properties of this pathway, many agents that inhibit the PI3K/AKT/mTOR pathway at different levels, such as mTOR inhibitors, pure PI3K inhibitors, dual PI3K-mTOR inhibitors, and AKT inhibitors are in clinical development

[56, 57]. Several mTOR inhibitors, rapamycin analogs including everolimus and temsirolimus, have shown benefits of overall survival in large clinical trials against angiomyolipoma associated with tuberous sclerosis, metastatic renal cell carcinoma, breast cancer, and pancreatic neuroendocrine carcinomas [58, 59]. The PI3K/AKT/mTOR pathway is also recognized to play a central role in tobacco smoking-induced carcinogenesis, and inhibitors of this pathway, including myoinositol and metformin, are promising agents for lung cancer prevention [60].

Although inhibition of mTOR activity seems to have beneficial effects for anti-aging, cancer prevention, and treatment, adverse events observed in patients treated with mTOR inhibitors (e.g., rapamycin) are fairly common, regardless of each specific indication. These undesirable side effects include stomatitis, skin rash, and non-infectious pneumonitis, as well as elevated blood glucose, cholesterol, and triglyceride levels leading to the development of insulin resistance and increased incidence of infections [61, 62]. Therefore, there is a need for the development of non-toxic mTOR inhibitors for the purpose of cancer chemoprevention for long-term use.

AMPK Pathway

In contrast to the insulin and IGF-1 signaling and mTOR pathways that detect nutrient abundance and anabolism, AMPK and sirtuins are two nutrient sensors that are activated by the increase in cellular AMP and NAD⁺ concentrations, respectively, in response to nutrient scarcity and catabolism [63]. Accordingly, the upregulation of AMPK and sirtuins promote healthy aging.

There are many studies with lower organisms (e.g., worms, fruit flies, and rodents) linking increased AMPK signaling to longevity. Overexpression of AAK-2 (catalytic subunits of AMPK in *Caenorhabditis elegans*) increases life span by 13 % and mimics dietary restriction in well-fed animals [64]. Similar increases in the life span of the fruit fly are also seen in overexpression of the single *Drosophila* AMPK- α subunit in either muscle or the fat body [65]. Additionally, AMPK upstream activator such as liver kinase B1 (LKB1), and its downstream effectors, cAMP-responsive element-binding protein (CREB)-regulated transcriptional coactivators (CRTC), UNC-51-like kinase 1 (ULK1), mTOR, FOXO, and sirtuins have been shown to be involved in life span extension [66–69]. In recent studies, pharmacological agents that directly activate AMPK, such as aspirin and its metabolite salicylate, as well as A-769662 and C24, resulted in similar life extension effects as do AMPK indirect activators (e.g., metformin, dietary restriction, and resveratrol) [10, 70, 71, 72, 73]. Therefore, these results indicated that AMPK has potent ability to modulate life span and it is an ideal target for promoting healthy longevity.

Due to AMPK's important role in maintaining energy balance, perturbation or decreased AMPK activation may be associated with increased cancer risk in human metabolic disorders, such as obesity, diabetes, and the metabolic syndrome. Activation of AMPK by CR and metformin has been considered to be one of the main mechanisms for their cancer prevention benefit in patients with these metabolic disorders [74]. In addition, LKB1 (an upstream activator of AMPK) mutations commonly occur in sporadic non-small cell lung carcinoma [75] and are associated with the greatly increased cancer risk in the inherited Peutz-Jeghers syndrome [76]. In mouse studies, loss of function of LKB1 resulted in increased susceptibility to cancer development [77]. These findings have led to more studies on pharmacological activators of AMPK.

In some studies, AMPK α , β , and γ subunits were also found to be overexpressed in 2 to 25 % of human cancers and cancer cell lines. Therefore, AMPK activation can also promote cancer growth and survival under certain conditions by supporting the metabolic changes needed for tumor growth [17, 78–80]. Thus, approaches of targeting AMPK activation or inhibition for cancer therapy requires further investigation for their context dependent effects and cautious evaluation needs to be done.

Sirtuins

Silent information regulator 2 (Sir2) homologues, named “sirtuins”, function to catalyze NAD⁺-dependent protein deacylation and mono-ADP ribosylation reactions [81]. Sir2 homologues increased the life span and protected against age-related pathologies in nematode worms and fruit fly experimental systems as well as in specific yeast strains and mice [81]. There are seven mammalian sirtuins (SIRT1–7). These sirtuins are differentially located in the cells and have different functions and biochemical activities. SIRT1 shares the most homology with the founding member of yeast Sir2 and is located in the nucleus. SIRT1 overexpression has been shown to delay the onset of many age-related diseases, such as cardiac hypertrophy and neuropathies [82, 83]. SIRT2 is primarily localized in the cytoplasm, but can translocate into the nucleus during the G2M phase of the cell cycle [81]. SIRT3, 4, and 5 localize to the mitochondria [81]. Among the mitochondrial sirtuins, SIRT3 protects against the accumulation of oxidative damage and attenuates age-associated hearing, suggesting its strong association with aging [84, 85]. SIRT6 is expressed in the nucleus and also known to be associated with aging. SIRT6 knockout mice have severely shortened life span, while overexpression of SIRT6 extended their life spans [86]. Moreover, SIRT6 seems to protect against many age-related pathologies, both at the cellular and the systematic level. For example, aging and failing hearts express lower levels of SIRT6, and SIRT6 knockout mice displayed cardiac hypertrophy and heart failure [87]. Interestingly,

SIRT6 overexpression in cardiomyocytes inhibited AKT-IGF signaling and protected against cardiac hypertrophy [88]. Accumulating evidence shows that SIRT6 plays a central role in regulating longevity-related pathways.

Activation of sirtuins appears to be a key mechanism for several anti-aging approaches [89]. Mild caloric restriction and decreased glucose consumption, as well as resveratrol and synthetic sirtuin-activating compounds (STACs) have been used to activate sirtuins because of their effects on modulation of aging and age-related disease in mammals [89].

Sirtuins play a role in proliferation, apoptosis, DNA repair, metabolism, and inflammation under basal or stress conditions [90]. Sirtuins also play a significant role in tumorigenesis. During tumorigenesis, sirtuins function both as a tumor promoter and a tumor suppressor, depending on the cellular context or tumor type. SIRT2 is downregulated in gliomas, breast cancer, head and neck squamous cell carcinoma, and esophagus adenocarcinoma [91–94]. SIRT2 knockout mice develop liver cancer and mammary gland tumors [95]. SIRT3 is downregulated in breast cancer, hepatocellular carcinoma (HCC), and head and neck squamous cell carcinoma [96]. Knockout mice of SIRT3 develop mammary gland tumors [97]. SIRT4 regulates glutamine metabolism and is downregulated in lung cancer [98]. The SIRT6 chromosomal locus was found to be deleted in pancreatic, colon, and liver cancers [99, 100]. Loss of SIRT6 expression resulted in tumor formation by increasing glycolysis [100]. In contrast, there are few reports where sirtuins were overexpressed and promoted cancer. SIRT6 is reported to be overexpressed in pancreatic cancer cells and associated with chemoresistance by increasing inflammation and angiogenesis signaling [101]. SIRT2 is upregulated in acute myeloid leukemia, neuroblastoma, pancreatic cancer, HCC, and regulates the Myc oncogenic pathway [102].

Sirtuins appear to play a complex and diverse role in both aging and cancers. Further studies are needed to define the exact molecular mechanisms by which each sirtuin member functions in a particular cell or organ to affect tumor development. Elucidating the mechanism of sirtuin function would help identify a potential link between aging and cancer and eventually develop cancer chemopreventive agents against age-related cancers.

Approaches or Agents with both Anti-Aging and Anti-Cancer Effects

Caloric Restriction

Long-term CR without malnutrition is the most robust interventions known to increase maximal life span and health span in many organisms [24, 103–106]. Studies in yeast, rotifers, nematode worms, fruit flies, rodents, and non-human primates have demonstrated that reduction of calories 30 to 50 % below

ad libitum levels of a nutritious diet can increase life span [24, 103–106]. In non-human and human primate studies, CR without malnutrition protects against abdominal obesity, diabetes, hypertension, and cardiovascular diseases [106]. However, whether CR can slow human aging remains to be determined and human trials for evaluating CR are ongoing. The early results of CR trials from several published studies [107–109] reported that participants could only reduce caloric intake by 10 to 14 % for a period of 6 to 12 months, even with the highly motivated volunteers assisted by the most up-to-date support and information, which is far lower than the lifetime restriction of 30 to 50 % associated with anti-aging effects in laboratory animals such as rodents and non-human primates. Therefore, these results suggest that application of CR in humans for anti-aging would not be practical due to the degree and length of restriction required. In addition, it is harder to control the degree and time of CR onset and the timing of food intake as well as diet composition in human subjects, although these factors are important in promoting longevity and a healthy life span [8]. The high quality diets consumed by the CR practitioners may have beneficial effects on their metabolic health; however, it may not be entirely dependent on the calorie intake [8]. Therefore, it is important to understand molecular mechanisms of CR's anti-aging effect and develop interventions that would mimic the effect of CR without the difficulties of severely reducing nutrient intake.

Multiple mechanisms have been shown to mediate CR longevity. CR consistently reduces IGF-1 concentration by up to 40 % via the growth hormone (GH)/IGF-1 axis in mice [110, 111]. CR also decreases mTOR activity and mTOR inhibition by both genetic and pharmacological approaches, which phenocopies CR, thus increasing life span [112]. In addition, other factors, including DAF-16 (FOXO), SKN-1(Nrf1/2/3), PHA-4 (FOXA), and AAK-2 (AMPK), that are involved in stress responses and mTOR signaling also play a role in CR mediated longevity [113]. CR also activates sirtuins and increases NAD⁺ by shifting toward oxidative metabolism rather than increasing total respiration. SIRT1 and the nicotinamidase PNC-1, a key NAD⁺ salvage pathway component, are largely required for diet restriction to increase life span [113].

People who undergo long-term CR show a reduction of metabolic and hormonal factors associated with increased cancer risk [114, 115]. Studies over the years have shown that laboratory animals receiving a CR diet had a significantly lower risk of getting tumors compared to animals supplemented with a regular diet. For example, cancer morbidity and mortality significantly decreased in CR monkeys [114, 115]. CR has been shown to inhibit the growth of transplantable, spontaneous, radiation, and chemically induced tumors in mouse models [114–117]. One study showed that CR inhibited p-cresidine-induced bladder carcinogenesis in heterozygous p53-deficient mice via reduction of circulating

IGF-1 levels [117]. However, the protective effect of CR on bladder carcinogenesis was reversed by restoring serum IGF-1 levels via the administration of exogenous human IGF-1 [117]. In addition, mTOR activity can be inhibited by CR and mTOR inhibitors have emerged to mimic CR for delaying cancer development in mice [112]. These results suggest that the inhibition of IGF-1 and mTOR signaling and CR might share similar or overlapping mechanisms for both life span extension and anti-cancer.

Metformin

Metformin is an antidiabetic drug, however, it appears to have various health benefits besides treating type 2 diabetes. In recent studies, metformin treatment increased life span in model organisms. Metformin increased the mean life span of *Caenorhabditis elegans* in a dose-dependent manner via peroxiredoxin PRDX-2 mediated mitohormesis and by altering microbial folate and methionine metabolism [118, 119]. Metformin also increased the life span of mice with different genetic backgrounds and with specific diseases [120]. In R6/2 mice, which develop Huntington's disease, metformin increased the life span of male mice, but not the female mice [121]. Metformin also increased the life span of the transgenic HER-2/neu mice which develop mammary carcinomas [122]. In humans, metformin is associated with the reduction of all-cause mortality and increased life expectancy in diabetic patients [123]. Metformin also reduced cardiovascular mortality in type 2 diabetes patients [123]. These results suggest that metformin may act through both the basic mechanisms of aging and reduction of disease specific mortality to increase longevity in animals.

Epidemiological studies have shown that patients with type 2 diabetes are associated with about twofold or more risk for liver, pancreas, and endometrium cancers and 1.2–1.5-fold risk for rectum, breast, and bladder cancers [124–128]. Other cancers, such as lung cancer, appear not to be associated with type 2 diabetes, and prostate cancer may be detected less frequently in diabetic patients [124–128]. Epidemiological studies have also shown that metformin is associated with reducing cancer risk and/or increasing survival in diabetic patients compared to those diabetic patients who use other therapies [123]. It was estimated that the use of metformin in diabetic patients is associated with an approximately 30 % reduction in the lifetime risk of cancer [123, 129]. The survival benefit of metformin is tumor type specific. Metformin appears to be more effective in increasing the survival of colon and ovarian cancer patients with type 2 diabetes [130, 131], whereas, the survival benefit of metformin is not fully confirmed yet for prostate and breast cancers with type 2 diabetes [132, 133].

However, whether metformin is also beneficial for patients without diabetes or for reducing cancer risk in general populations remains unknown. As metformin is well tolerated and

inexpensive, with a high long-term safety profile, there are currently more than 100 clinical trials of metformin to address this question for cancer in different organs [134]. At least one phase II trial showed that metformin at different doses significantly decreased the level of insulin, testosterone, and other metabolic parameters associated with breast cancer prognosis in post-menopausal breast cancer patients without insulin resistance and with normal baseline insulin serum levels [135]. Hosono et al. [136] also showed that intake of 250 mg/day metformin for 1 month inhibited both colorectal epithelial proliferation and aberrant crypt formation in a pilot randomized trial in nondiabetic patients. Furthermore, evidence from a wide spectrum of preclinical tumor models, including xenografts, chemically induced carcinogenesis, and spontaneous transgenic cancer models have also strongly supported the anti-tumor growth effects of metformin [137–139]. These results suggested that metformin deserves further clinical investigation for its cancer prevention benefits in nondiabetic patients and in general populations.

Molecular mechanisms for the antineoplastic activity of metformin include systemic effects on host metabolism and direct effects on cancer cells [16]. Systematically, metformin inhibits hepatic glucose production, increases insulin sensitivity, and reduces lipolysis in adipocytes and glucose absorption from intestines, which leads to reduced circulating insulin levels and decreased insulin/IGF-1 receptor-mediated activation of the PI3K pathway [16]. The mitochondria respiratory complex I is the central target responsible for metformin's effects [140]. The suppression of the mitochondrial respiratory chain by metformin results in a cellular ATP deficit and the activation of AMP, which in turn inhibits gluconeogenesis to lower blood glucose and subsequently reduces hyperinsulinemia [16, 140]. Additionally, metformin can selectively eliminate cancer stem cells (CSC) and increase the expression of micro (mi)RNA lethal-7 (*let-7*) and miR-200, which inhibits the epithelial-to-mesenchymal transition (EMT) [141–143]. Metformin also activates intracellular DNA damage response checkpoints and attenuates the anti-senescence effects of the enhanced glycolysis of the Warburg effect [144, 145]. Metformin is taken up by the cell surface organic cation transporter 1 (OCT1) [146]. The expression of OCT1 in specific tissues affects whether the drug achieves the pharmacologically relevant concentrations in tissues other than the liver.

Resveratrol

Resveratrol is a stilbenoid present in berries, grapes, peanuts, and wine. Consumption of resveratrol in red wine in some areas of France is associated with the reduced mortality from coronary heart disease despite the consumption of a high-fat diet [147]. Some studies have reported that resveratrol increased longevity in yeast, worms, fruit flies, and short-lived

fish, as well as mice given a high-fat diet [148–151], whereas others also showed that resveratrol had no effect on life span [152–154]. Resveratrol was found to be the most potent SIRT1 activator in a screening assay [148]. Resveratrol is a potent CR mimetic agent and resveratrol at its long-term use overlaps the effect of long-term CR on adipose tissues and shares similar gene expression patterns with CR in mice [154]. In addition, resveratrol increased the metabolic rate and fasting body temperature in mice under a high-fat diet and exerted antidiabetic effects in mice [155, 156••]. In human studies, resveratrol consumption improved cardiovascular function, insulin sensitivity, and HbA1c measurements as well as reduced inflammation with preexisting metabolic disease [155, 156••]. Studies have reported that dietary intake of resveratrol by mice protected against many of the deleterious effects of high-fat diets and provided additional health benefits [155, 156••, 157, 158].

Numerous preclinical studies have been carried out to investigate the cancer preventative and therapeutic effect of resveratrol in a wide variety of animal models, including tumor xenograft models, chemically induced carcinogenesis models, and transgenic spontaneous cancer models [164, 165]. Mixed results have been generated from these studies. In general, resveratrol is ineffective in treating preexisting tumors, whereas, resveratrol seem to be a promising cancer preventive agent for inhibiting tumor initiation, promotion, and progression [159, 160]. Limited clinical trials of resveratrol in cancer with small sample sizes also suggest that resveratrol may serve as preventive agent rather than a therapeutic agent for treating cancer [161]. For example, one phase I clinical trial reported that resveratrol and grape powder administration only inhibited the expression of Wnt target genes in normal mucosa, but not in cancerous mucosa [161]. The bioavailability of resveratrol is a critical issue for its use as a cancer preventive agent. The reported peak plasma concentrations of resveratrol are about 2–4 μM [162]. However, it is also important to know whether resveratrol can reach to the bioactive levels in target organs where it may have the strongest preventive potential.

The anti-aging and anti-cancer mechanisms of resveratrol's actions are mainly mediated by inhibition of cAMP phosphodiesterases (PDEs), particularly PDE4, which leads to activation of AMPK/SIRT2 axis signaling, as well as expression of p21 and p27 for cell growth inhibition [156••]. Other potential resveratrol targets such as cyclooxygenases 1 and 2 have also been reported [163, 164].

Aspirin/Salicylate

Aspirin is an over the counter nonsteroidal, anti-inflammatory drug (NSAID) for treating pain and inflammation. Aspirin has been shown to extend the life span of *Caenorhabditis elegans* via AMPK and FOXO transcriptional factor-dependent

manners [165]. Aspirin is rapidly metabolized to salicylate, which binds to AMPK β 1 and directly activate AMPK thereby increasing longevity of organisms [10]. Aspirin also inhibits oxidant stress and reduces age-associated functional declines and diseases [166]. Finally, aspirin also improves glucose metabolism, decreases fatty acid levels, and reduces all-cause mortality in patients with type 2 diabetes by likely activating AMPK signaling [166].

Substantial evidence has been generated from observational studies indicating that aspirin can protect against cardiovascular events and reduce incidence and mortality in a wide variety of cancers, including colorectal, oesophageal, gastric, breast, prostate, and lung cancers [167]. However, aspirin use is also associated with deleterious effects, such as gastrointestinal bleeding and hemorrhagic stroke [167]. For individuals 70 and older, aspirin associated gastrointestinal bleeding is minimal and the duration of aspirin use for reducing cancer risk requires no less than 5 years [168, 169]. A recent, large population study indicated that prophylactic and daily use of aspirin in the general population 50–70 years old for a minimum of 5 years resulted in a net overall benefit, which outweighed the potential harms [168]. A randomized clinical trial of a daily 100-mg aspirin tablet or a matching placebo for 5 years in 19,000 older healthy individuals (Aspirin in Reducing Events in the Elderly, or ASPREE) has also been initiated to determine the risks and benefits of a daily aspirin dose and its potential for cancer prevention in this elderly population [168].

***Rhodiola rosea* L**

Rhodiola rosea L is a perennial herbaceous plant of the Crassulaceae family that is widely distributed at high altitudes (up to 2280 m) in the arctic and mountainous regions throughout Europe, Asia, and North America [169]. *R. rosea* has been used for centuries to enhance both the physical and mental performance in healthy populations [170]. Swedish herbal *Rhodiola-5* (SHR-5) is a standardized *R. rosea* extract used as a nutrient supplement that the Swedish Herbal Institute (SHI) has been manufacturing since 1985 [171]. SHR-5 increased the mean and maximum life span of the fruit fly up to 24 and 31 %, respectively [172]. *R. rosea* extracts also extended the life span of yeast and worms, and delayed the age-related decline of physical activity and increased stress resistance [11, 12, 172]. The effect of *R. rosea* extracts on life span has been shown to be independent of CR-related signaling pathways, including SIR2 proteins, insulin, and insulin-like growth factor signaling, and the TOR in fruit flies [12], but dependent on diet composition (in particular protein-to-carbohydrate ratios or sucrose contents) and expression of Msn2/Msn4 and Yap1 regulatory proteins [14].

In human urinary bladder cancer cells, SHR-5 induced apoptotic cell death via inhibition of the mTOR pathways

[173]. We have recently demonstrated a marked chemopreventive efficacy of SHR-5 in the UPII mutant Ha-ras bladder cancer transgenic model: approximately 95 % of transgenic mice, which drank 1.25 mg/ml of SHR-5 containing water daily, survived over 6 months of age, versus 33.3 % of mice, which drank normal water ($p < 0.0001$); Additionally, SHR-5 exposure reduced tumor bearing bladder weight by 67 % [174]. Anecdotal evidence from a study involving 12 patients with superficial bladder cancer showed that *R. rosea* extracts decreased the median recurrence rate by 50 % [175]. Salidroside is the main bioactive compound in *R. rosea* extracts. Salidroside prevented the loss of hematopoietic stem cells in mice under oxidative stress via activating DNA repair enzyme poly (ADP-ribose) polymerase-1 (PARP-1) activity [176]. Salidroside also inhibited cancer cell migration and invasion, as well as xenograft tumor growth of human glioma cells in nude mice [177, 178]. Studies also showed that *Rhodiola* improved chemotherapy drug-induced toxicities in cancer patients, such as oral mucositis [179]. Thus, these results suggest that *Rhodiola* is a novel anti-aging herb with great promise for cancer chemoprevention.

Lithocholic Acid and L-theanine

Lithocholic acid (LCA) is a cholesterol-derived bioactive lipid that was identified as a potent, anti-aging, natural compound in a high-throughput screening assay for extending yeast longevity [180]. LCA delayed chronological aging in yeast by causing an age-related remodeling of glycerophospholipid synthesis leading to substantial changes in mitochondrial membrane lipidome and by altering the age-related chronology of mitochondrial respiration [181].

LCA has also demonstrated broad growth inhibitory effects on cancer cell lines derived from different organ sites via induction of apoptosis. The mechanisms of LCA-induced apoptosis involved both extrinsic (death receptor) and intrinsic (mitochondrial) apoptosis pathways by engagement of plasma membrane-bound protein TGR5 (G protein-coupled bile acid receptor 1) on the cell surface, leading to activation of caspase 1, 8, and 9 mediated apoptosis cascades [182, 183]. LCA also showed the in vivo anti-cancer efficacy in xenograft models [184]. However, in carcinogenesis models, LCA acted either as a tumor suppressor or promoter [185]. The anti-carcinogenic effect of LCA remains debatable.

L-theanine (γ -glutamylethylamide) is a unique amino acid that was identified in green tea (*Camellia sinensis*) and in some mushrooms [186]. L-theanine extends the life span of worms, but has no effect on fruit flies [187]. L-theanine also demonstrated its anti-cancer effect by inhibiting growth of cancer cells both in in vitro cell culture system and in vivo xenograft models [188, 189]. L-theanine works by inhibiting glutamate transportation leading to a decrease of intracellular glutathione (GSH) [190, 191]. L-theanine appears to improve

Table 1 Agents with both anti-aging and anti-cancer efficacies

Agents	Anti-aging efficacy	Anti-cancer efficacy	Mechanisms of action
Metformin	<i>C. elegans</i> , mice	Xenografts (breast, colon, gastric, head and neck, kidney, liver, lung, oral, ovarian, pancreatic, prostate, and skin cancers, and leukemia and sarcoma); chemically induced carcinogenesis models (skin, lung, mammary, colorectal, liver, oral); and transgenic spontaneous cancer models (mammary) and patients with type 2 diabetes	Inhibition of the mitochondria respiratory complex I leading to AMPK activation; decreasing the levels of insulin and IGF-1 in the circulation in the human body
Resveratrol	<i>C. elegans</i> , fruit flies	Chemically induced carcinogenesis models (mammary, lung, colon, and skin), and transgenic spontaneous cancer models (prostate and liver)	Inhibition of PDEs leading to activation of AMPK and SIRT2 axis signaling
Aspirin/Salicylate	<i>C. elegans</i>	Xenograft, chemically induced carcinogenesis models (colon and bladder cancers); and transgenic spontaneous cancer models (neuroblastoma, islet cell tumors, breast and prostate); and general populations	Salicylate binding to AMPK β 1 and directly activating AMPK.
<i>Rhodiola rosea</i> L.	Yeast, <i>C. elegans</i> , and fruit flies	Xenograft (breast cancer), and transgenic spontaneous cancer model (bladder)	Inhibition of the mTOR pathway
Lithocholic acid	Yeast	Xenograft cancer model (cervix carcinoma)	Remodeling of glycerophospholipid synthesis leading to substantial changes in mitochondrial membrane lipidome; activation of TGR5 receptor leading to apoptosis.
L-theanine	<i>C. elegans</i>	Xenograft cancer model (lung cancer)	Inhibiting glutamate transportation leading to a decrease of intracellular glutathione levels

the efficacy of chemotherapeutic agents as well by increasing their accumulation in the tumor cells [190, 191]. L-theanine was also shown to protect normal cells from damage caused by chemotherapeutic agents via its antioxidant activity [190, 191]. Further studies are needed to determine whether L-theanine can be effective as a cancer preventive agent against carcinogenesis.

Conclusions and Perspectives

Many common cancers happen at an older age of human life. Interestingly, both slowly aging centenarians and naked mole-rats are particularly resistant to cancer development [192, 193], whereas, rapidly aging mice develop cancer within 2 years [192]. Evidence has also emerged that slowing down aging can, in turn, delay cancer occurrence, improve cancer prognosis, and increase the overall quality of cancer patients' lives. Therefore, we can argue that anti-aging agents are a viable option for cancer prevention in the elderly.

Nutrient-sensing pathways, such as insulin/IGF-1, mTOR, AMPK, and sirtuins play major roles in aging-associated cancer initiation and progression. Aberrant alteration in these nutrient-sensing pathways are associated with increased risk of other age-related diseases and conditions, such as type 2 diabetes, obesity, hyperglycemia and hyperinsulinemia, and metabolic syndrome. These pathways mainly regulate cell metabolism and the whole body metabolism. Therefore, unhealthy lifestyles such as overeating and consumption of high-fat diet, can lead to changes in these nutrient-sensing pathways and increased cancer risk.

Agents with both anti-aging and anti-cancer effects (e.g., metformin, resveratrol, *Rhodiola*, aspirin, lithocholic acid, and L-theanine) often confer cellular and systemic benefits of metabolism similar to the effect of positive lifestyle interventions. Chemoprevention by these agents could potentially target normal postmitotic cells (i.e., aging cells) and no selection for resistance will be expected. It is also possible that the chemopreventive efficacy of these agents does not depend on the genetic background of cancer cells and these agents may be able to prevent cancer even with the loss of tumor suppressors (e.g., p53 and Rb) or the gain of oncogenic functions (e.g., ErbB activation). Therefore, agents with both anti-aging and anti-cancer effects are very promising candidates for cancer prevention as summarized in Table 1.

Many basic questions regarding how aging leads to carcinogenesis and cancer progression remain unanswered. Whether cancer prevention by agents with both anti-aging and anti-cancer properties can target cancer cells directly and/or indirectly by slowing down the aging process is still undetermined. However, it is clear that nutrient-sensing pathways governing cellular metabolism and growth are

common alterations in both cancer and aging. Agents targeting these pathways are moving to the forefront of cancer and aging research as a safe and efficacious means to reduce cancer morbidity and mortality as well as improve cancer prognosis and overall quality of life.

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Compliance with Ethics Guidelines

Conflict of Interest Noriko N. Yokoyama, Andria Denmon, Edward M. Uchio, Mark Jordan, Dan Mercola, and Xiaolin Zi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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