Repurposing metformin and rapamycin to target age-related diseases

Qian Feng[1], Bangwei Chen[1], Chuyao Wang[2], Xiao Liu[1], Chao Nie[1], and TAO LI[1]

[1]BGI-Shenzhen
[2]University of California Davis

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Abstract

The growing epidemic of many age-related chronic diseases, such as cardiovascular diseases, diabetes, cancer, and neurodegenerative diseases, especially Parkinson's and Alzheimer's disease, places an increasing burden on the healthcare systems worldwide. In recent years, efforts to manipulate the consequences of aging have yielded some success, and naturally, identifying effective ways to slow down or even reverse aging has become increasingly popular. Importantly, existing drugs can be repurposed for anti-aging effects. Studies from model organisms and early stage human clinical trials have found that metformin and rapamycin, which respectively are an effective anti-diabetic medication and an immunosuppressant, have promising results in slowing aging and treating age-related diseases. These findings point to the possibility that these two anti-aging drug candidates, and especially their derivatives which may reduce side effects, are likely to become the first genuine rejuvenation medications to achieve healthy aging. Here, we present knowledge on the mechanisms that are involved in the anti-aging effect of the two molecules, followed by an outline of a host of potential aging-related clinical applications. We finally provide insights on the considerations and further directions for the development of anti-aging drugs.

Abstract

The growing epidemic of many age-related chronic diseases, such as cardiovascular diseases, diabetes, cancer, and neurodegenerative diseases, especially Parkinson's and Alzheimer's disease, places an increasing burden on the healthcare systems worldwide. In recent years, efforts to manipulate the consequences of aging have yielded some success, and naturally, identifying effective ways to slow down or even reverse aging has become increasingly popular. Importantly, existing drugs can be repurposed for anti-aging effects. Studies from model organisms and early stage human clinical trials have found that metformin and rapamycin, which respectively are an effective anti-diabetic medication and an immunosuppressant, have promising results in slowing aging and treating age-related diseases. These findings point to the possibility that these two anti-aging drug candidates, and especially their derivatives which may reduce side effects, are likely to become the first genuine rejuvenation medications to achieve healthy aging. Here, we present knowledge on the mechanisms that are involved in the anti-aging effect of the two molecules, followed by an outline of a host of potential aging-related clinical applications. We finally provide insights on the considerations and further directions for the development of anti-aging drugs.

Introduction

Advances in nutrition, sanitation and, hygiene, together with the use of antibiotics and vaccines, have resulted in a dramatic increase in life expectancy for people across the globe. Over the last two centuries, the global life expectancy has nearly doubled, increasing from around 30 years in 1800 to around 70 in 2015 [1, 2]. By 2030, the life expectancy in many countries is projected to exceed 85 years—e.g. women in South Korea will likely break the 90-year barrier[3]. Globally, one quarter of the population is expected to be in their sixties or older in 2050 [4].

Nonetheless, the unprecedented longer life expectancy and the expanding aging population have led to an epidemic of chronic age-related diseases such as cancer, cardiovascular diseases, Type 2 diabetes, and dementia, including Alzheimer's disease (AD) and Parkinson's disease (PD)[5]. These diseases are all known to impair the quality of life for individuals. Additionally, the staggering number of people who live with these aging-associated diseases place a considerable burden on the social, economic, and healthcare systems worldwide. Therefore, from both an individual and a societal standpoint, there is pressing need to combat the challenges posed by age-related diseases and increase the health span of humans [6, 7].

In the last few decades, intensive efforts have been made to improve the clinical outcomes of age-related diseases, such as diabetes and many types of cancer, but not AD. However, those efforts have been largely unsuccessful in preventing the fast-growing prevalence of multiple co-existing conditions, defined as more than two co-existing chronic conditions in one individual. The majority of the elderly population (individuals aged 65 and above) now are affected by chronic multi-morbidities, whereas the current delivery of health services and the research interests have continued to focus on combating the chronic diseases individually [8]. Clearly, this insular approach is inefficient for preventing the development of age-related diseases more broadly [9, 10].

In contrast, aging mechanisms that account for the phenotypic characteristic of old age, such as sarcopenia, frailty, impaired metabolic profiles, and neurodegeneration, have been shown to be the underlying determinants of many different chronic diseases[11]. Therefore, modifying the mechanisms of aging directly seems to be a more productive approach to fundamentally curb the escalating epidemic of chronic diseases.

Although aging has historically been considered an irreversible process; this perception has already started to change. Encouragingly, emerging clinical trials of anti-aging drugs have shown promising results in various animal models [12]. Early human trials have begun, with hundreds of anti-aging drug candidates already registered for clinical trials [13]. It is important to clarify that the focus of these studies is not to eliminate aging and pursue immortality, but instead to extend healthspan, the length of time during which people are living disease-free and in vitality. The current body of promising animal studies, and commercial interests, have resulted in swift growth of biotech companies that focus on developing anti-aging therapeutics commercially [14]. The anti-aging approaches piloted by these start-ups range from modern artificial intelligence-driven methods to life-extension drugs[15].

Among all the anti-aging strategies, calorie restriction (CR) without malnutrition is one of the most reliable approaches in expanding both lifespan and health-span in various vertebrate and non-vertebrate species. While the exact molecular mechanisms associated with CR's health benefits remains not fully understood so far, emerging evidence suggests that CR's beneficial effects in slowing down the aging process can be attributed to the nutrient-sensing pathways (NSP), including the mTOR, AMPK, and IIS pathways. Under CR, the NSPs trigger an array of processes to promote autophagy, a potent cellular mechanism that degrades and recycles dysfunctional components and thus maintain the cellular nutrient and energy balance. However, CR is difficult to sustain and implement since individuals must remain in a state of hunger and endure feelings of starvation, fatigue, and irritations. Besides, the individuals who practiced CR have been reported to be more susceptible to viral infections [16] and resistant to wound-healing [17], both of which impede its widespread use.

To circumvent its impracticality, calorie-restriction mimetics (CRM), drugs that up-regulate autophagy by triggering the NSPs without actually restricting calorie intake, are considered worthy of investigation. Typical pharmaceutical CRMs include resveratrol, aspirin spermidine, metformin, and rapamycin [18]. Among them, both rapamycin and metformin have been used extensively in clinical settings and have well-documented side effects. While they have distinct prescribed use in clinical setting, they have been investigated for many off-label uses for their pleotropic effects against aging, cancer, and cardiovascular diseases.

In this review, we first present a brief overview of the mechanisms of nutrient sensing pathways. We then review the pre-clinical and clinical studies on the effects of metformin and rapamycin in anti-aging, and its association with nutrient-sensing pathway. Finally, considerations and insights for the future directions of anti-aging drug development are offered to guide the next wave of research in the anti-aging field.

Box 1 Aging-related diseases

Advanced age is the major risk factor for developing multiple chronic diseases [19]. In this review, two of the geropreventive medicines, metformin and rapamycin, are discussed with respect to their potential for delaying the age-related diseases that are described in the following sections below. Since age-related diseases is a broad concept that recapitulates a wide range of conditions, including but not limited to sarcopenia, osteoporosis and chronic obstructive pulmonary disease, we here only list age-related diseases whose treatments have been shown by research to benefit from metformin or rapamycin.

Cardiovascular Diseases

Cardiovascular Diseases (CVD) include coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart diseases, deep vein thrombosis and pulmonary embolism[20]. Cardiovascular diseases are characterized by lipid-rich plaques accumulating in blood vessels. The establishment and development of plaque is a result of an interplay of chronic inflammation, endothelia dysfunction, and fibrosis of vascular muscle cells. CVDs are the leading cause of death globally, claiming around 17.9 million people's lives per year [21]. CVDs arise from the complex combination of hereditary predisposition and environmental factors such as lifestyle that depends on educational level, income, and advanced age, leading to a progressive deterioration of cardiovascular structure and function. Amongst all the risk factors, aging dominants [22]. Roughly 70-75% of Americans who aged 60-79 are affected by CVDs [23].

Alzheimer's Disease

The Alzheimer's Disease (AD) is a degenerative neurological disorder, accounting for 60-80% of dementia [24]. AD affects up to one third of the population aged > 65 years, making it the fifth leading cause of death globally [25]. Although causal determinants of AD remain not fully understood, impaired mitochondrial autophagy (termed mitophagy), the accumulation of amyloid-β (Aβ plaques) and neurofibrillary tangles (tau), neuro-inflammation, and altered cerebrovascular reactivity appear to be the contributors to the pathogenesis of AD [26, 27].

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease, which is caused by the dysfunction of the motor system with symptoms such as tremors, difficulty in walking and muscle rigidity [28]. PD affects around 1% of people aged > 60 years[29]. Genetic predisposition plays a vital role for its onset [30-32]; moreover, multiple conditions including diabetes, Polycystic Ovary Syndrome (PCOS), obesity, early menopause in women, and physical inactivity are associated with an increased risk of PD [32].

Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder that is characterized by hyperglycemia, insulin resistance and an endogenous shortage of insulin. In the US, over a quarter of people aged > 65 years have T2DM, resulting in staggering health-care cost and substantial loss of working hours. Genetic susceptibility and environmental factors such as sedentary lifestyle, obesity, and the Western diet are considered as the main factors in the etiology of this disorder [33, 34].

Cancer

Cancer refers to a group of diseases characterized by the uncontrolled growth and invasion of abnormal cells in a healthy body[35, 36]. Activation of oncogenes and tumor suppressor gene mutations are responsible for the development of cancer. The risks of cancer development and a fatal outcome increase exponentially with age, and around 60% of cancers are diagnosed in people 65 years of age or older [37].

2.Target nutrient-sensing pathways on aging-related diseases

Almost all life forms constantly sit on a balance between production and maintenance. Numerous studies involving C*aenorhabditis elegans (C. elegans)* , a nematode that is commonly employed as a biological model for studying aging, *Drosophila melanogaster (D. melanogaster),*also known as fruit flies, mice, and humans have shown that reduced reproduction is linked to increased lifespan [38, 39]. The reason lies in the fact that reproduction is an energetically expensive process. Therefore, under low nutrient conditions when reproduction is more challenging, such as during CR, in order to ensure reproductive success, increasing somatic maintenance is necessary to prolong the reproductively competent period and consequently, lifespan. Hence, the signaling pathways that can sense and respond to the changing intracellular and extracellular energy and nutrient levels grow central in the research of anti-aging drugs. Four such pathways, the mechanistic target of rapamycin (mTOR), 5'-AMP-activated protein kinase (AMPK), sirtuin, and insulin/insulin-like growth factor signaling (IIS) (Figure 1), are particularly important [40].

2.1 **mTOR Pathway**

The mechanistic target of rapamycin (mTOR) is a protein kinase that receives nutrient level information and coordinates a wide range of cellular metabolic processes concerning production, growth, and somatic maintenance, such as protein synthesis, mitochondrial function, and cell proliferation. Low surrounding nutrients levels, especially reduced amino acids and growth factors, have been reported to suppress mTORC1 signaling, resulting in suppressed metabolism and extended lifespan during fasting and intermittent fasting [41]. Not surprisingly, mounting studies have shown that deregulated mTOR signaling is implicated in the aging process and the progression of age-related disease such as cancer and diabetes [42, 43].

The mTOR kinase is found in two functionally different complexes, mTORC1 and mTORC2 [38]. Between the two, mTORC1 is the one with better characterized activities; under nutrient-rich conditions, mTORC1 upregulates the anabolic processes in the cell and represses autophagy by directly acting on the unc-51 like autophagy activating kinase (ULK) complex and inhibiting the expression of the genes that are required for autophagy [42]. Meanwhile, mTORC2 has been reported to phosphorylate and activate Akt, which upregulates mTORC1[44].

Activated mTORC1 enhances mRNA translation and protein synthesis in the cell by phosphorylating the p70 ribosomal protein S6 kinase (S6K) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1)[38]. Interestingly, S6K also negatively regulates the IIS pathway by inhibiting the insulin receptor substrate 1 (IRS1), giving mTORC1 some feedback control over its upstream pathways[44].

The ULK complex is made of ULK1 or ULK2 [45], autophagy-related protein 13 (ATG13), focal adhesion kinase family-interacting protein of 200 kDa (FIP200), and autophagy-related protein 101 (ATG101), and it is essential for autophagosome formation. By phosphorylating ULK1, ULK2, and ATG 13 in the complex, mTORC1 prevents complex's activation, which would otherwise promote autophagy. mTORC1 can also inhibit autophagy by phosphorylating the transcription factor EB (TFEB), thereby preventing its nuclear translocation that leads to the expression of the genes required for lysosome biogenesis and other autophagy mechanisms [42]. The mTOR pathway makes its regulatory decisions based on intracellular and extracellular nutrient levels that are inputted either directly from the environment or via other pathways.

The depletion of amino acids inactivates the mTOR pathway, and growing cellular amino acid level increases its activity and terminates autophagy [40]. When intracellular amino acids level is high, the Rag GTPases recruit mTORC1 to the outer lysosome surface, at which mTORC1 is activated by the Ras homolog enriched in brain (Rheb). In addition, high cellular glucose level also activates the Rag GTPases. The amino acids availability can be communicated to mTORC1 by the taste receptors T1R1/T1R3 as well [46].

The nutrient levels also control the mTOR pathway through the AMPK and the IIS pathway. Once activated by nutrient scarcity, AMPK inhibits mTORC1 by phosphorylating and activating the tumor sclerosis complex (TSC), a component of the TSC1-TSC2 complex, which is an inhibitor of Rheb, and by directly phosphorylating and inhibiting the Raptor component of the mTORC1 complex [47]. The IIS pathway upregulates the mTOR pathway when nutrient is abundant through its two branches of downstream pathways, the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway and the Ras/mitogen-activated protein kinase (Ras/MAPK) pathway. The PI3K/Akt pathway culminates in the activation of Akt, which then enhances mTORC1 activity by repressing the TSC1-TSC2 complex and by phosphorylating the FOXO family of transcription factors, excluding them from the nucleus. The exclusion of FOXO3a, for example, reduces the transcription rate of TSC1 [48]. Another inhibitor of mTORC1 activity, the proline-rich Akt substrate of 40 kDa (PRAS40), is also inactivated by Akt phosphorylation[49]. The Ras/MAPK pathway modulates the mTOR pathway via RSK and ERK, both of which can activate mTORC1 by the inhibitory phosphorylation of TSC2 [47].

2.2 AMPK Signaling

AMPK, the upstream controller of the mTOR pathway, exists among many mammalian species, functioning as an exquisite cellular energy sensor and regulator of nutrient and energy homeostasis. AMPK contains a catalytic α subunit, a regulatory β subunit, and a regulatory γ subunit[50]. On the contrary to the mTOR pathway, the activation of the AMPK pathway under energy deficiency drives catabolic processes and induces autophagy. Numerous studies have indicated that the activating capacity of the AMPK signaling pathway declines with aging, and its decline disturbs autophagy, increases cellular stress, and promotes inflammation, which further provoke many age-associated diseases, such as cardiovascular disease, diabetes, and cancer[38, 51]. Correspondingly, increased activation of the AMPK pathway has been shown to extend lifespan in lower organisms in response to CR and pharmaceutical agents, such as metformin[52]. Aside from promoting autophagy by activating the TSC1-TSC2 complex and inhibiting the Raptor component of mTORC1, AMPK can independently phosphorylate and activate ULK1 of the ULK complex[40]. AMPK also activates the FOXO transcription factors, which transactivate the genes involved in detoxification, autophagy, tumorigenesis suppression, and energy homeostasis[40].

Furthermore, AMPK activation attenuates the aging process by inhibiting NF-κB, the major regulator of innate and adaptive immunity. Inflammation is a crucial step for the immune system to defend against pathogens. Nonetheless, chronic inflammation that is harmful for the host can be triggered by endoplasmic reticulum (ER) stress and oxidative stress. ER stress and oxidative stress are caused by nutrition overload, the aging process, and the production of reactive oxygen species (ROS). Those stresses are implicated in many metabolic disorders, such as obesity and type II diabetes [53]. AMPK inhibits NF-κB indirectly via several downstream targets, including SIRT1, PGC-1α, p53, and FOXO. It can also relieve ER stress and oxidative stress by promoting the expression of the mitochondrial uncoupling protein 2 (UCP-2), which inhibits the production of ROS in mitochondria, suppressing the ROS produced by the NAD(P)H oxidase, and inducing the expression of thioredoxin (Trx) by activating FOXO3. The reduction of oxidative stress improves homeostasis in ER and relieves ER stress [53].

Nutrient scarcity and energy depletion are detected by several upstream sensors of AMPK. AMPK can be activated by increasing AMP:ATP and ADP:ATP ratios as well as by directly AMP binding [38]. Moreover, the AMPK pathway can be activated by two adipokines, which are cytokines secreted by adipocytes, leptin and adiponectin (ADIPOQ), whose quantities positively and negatively correlate with lipid storage[40]. Leptin stimulates phosphorylation and activation of the α subunit of AMPK. It can also activate AMPK via the hypothalamic and sympathetic nervous system [54]. ADIPOQ binds the adiponectin receptor 1 (AdipoR1) and initiate a cascade to activate AMPK and sirtuin 1 (SIRT1) [55].

The AMPK pathway may also be activated by Sestrins, which is a family of proteins that is activated responding to genotoxic stress, hypoxia, and oxidative stress. Genotoxic stress, defined by the accumulation of compounds that are harmful to the DNA, induces p53 and stimulates the Sestrin genes. Hypoxia causes energy deprivation and the activation of the Sestrin genes as well. Oxidative stress induces Sestrins in different ways for different Sestrins family member[56]. Once activated by Sestrins, the AMPK pathway drives autophagy to clear the cell of the harmful compounds such as ROS.

2.3 Sirtuin Pathway

SIRT1 is the most studied family member of the mammalian sirtuins 1-7, which are class III histone deacetylases that utilize NAD+, a coenzyme involved in many biological reactions, to improve longevity. Many have reported that sirtuins are major nutrient-sensing proteins that promote health span from yeast to mice, and its activity seems to explain the beneficial effect of CR [57, 58]. Moreover, the life-extending effects of CR are abrogated when sirtuins are deleted in various animal models [57]. Induced overexpression of SIRT1 has been shown to suppress malignancies partly via p53 signaling. SIRT1 and AMPK share many downstream targets, including PGC1α, FOXO, and eNOS [59, 60]. They also induce similar biological actions such as stimulating the mitochondrial biogenesis and attenuating inflammation. Specifically, SIRT1 can deacetylase FOXO3 and induce ROS detoxification to ameliorate oxidative stress [61]. SIRT1 also deacetylases FOXO4 and increases its transactivation capacity. Furthermore, deacetylation of p65 by SIRT1 inhibits NF-kB signaling, resulting in an anti-inflammatory effect[50].

As mentioned above, SIRT1 is a downstream target of AMPK. However, SIRT1 can also activate AMPK, forming a positive feedback loop. AMPK can activate SIRT1 by raising cellular NAD+ levels, raising NAD+:NADH ratio, and enhancing the transcription of Nicotinamide phosphoribosyltransferase (NAmPRTase or Nampt), a regulator of the intracellular NAD pool [62]; in turn, SIRT1 activates AMPK by deacetylating and triggering the liver kinase B1 (LKB1). LKB1 can also be triggered by energy stress to activate AMPK and several related kinases [63] .

2.4 IIS Pathway

The IIS pathway acutely senses nutrient levels and regulates energy homeostasis by controlling the AMPK and mTOR pathway. The IIS pathway has been documented to play a major role in the control of lifespan in various invertebrate species. Specifically, *C. elegans* with mutations that inhibit IGF-1 signaling displayed an extended lifespan[64]. Mutations in the IIS pathway have also been reported to increase the lifespan of mice [65].

The IIS pathway is activated by the binding of insulin-like peptides (ILP) to the IIS tyrosine kinase receptors. At least 10 ILPs exist in mammals; of those, only insulin, insulin-like growth factor 1 (IGF-1), and IGF-2 are IIS tyrosine kinase receptor ligands. Insulin is produced in pancreas responding to increasing glycaemia [66]. Glucokinase (GCK), a hexokinase that phosphorylates glucose to glucose 6-phosphate (G6P), and glucose transporter 2 (GLUT-2), serve as glycaemia sensors since they are only responsive to high glucose levels. The oral taste receptors T1R2-T1R3 sense glucose as well and initiate a signal transduction cascade to trigger insulin release. The release of insulin can also be enhanced by incretins, which are produced when fatty acids or amino acids are detected in the gut. The G protein coupled receptor 120 (GPR120) senses fatty acid and promotes the production of the incretin glucagon-like peptide-1 (GLP1). Amino acids can be sensed in the gut by the taste receptors T1R1-T1R3. Rather than inciting a gustatory sense in the brain, the detection triggers incretin release into the circulation [40].

In contrast to insulin, IGF-1 and IGF-2 are regulated by the growth hormone (GH), and both IGF and GH decline continuously to extreme low levels during advanced age. Multiple species have been demonstrated to have lower GH/IGF-1 signaling when their lifespan is extended. Reduced GH/IGF-1 signaling has also been observed during CR mode, suggesting the critical role of GH/IGF-1 signaling during life-extending strategies[67]. In addition to extending lifespan, GH can promote the hepatic production of IGF-1 and alter the insulin sensitivity by acting on the IIS pathway. Mice and humans with reduced GH/IGF-1 axis have been shown to have improved insulin sensitivity, protecting them from cancer and diabetes mellitus, two major ageing-related diseases[68].

The activated IIS pathway branches off into the PI3K/Akt pathway and the Ras/MAPK pathway. The activated IIS tyrosine kinase receptor phosphorylates and activates PI3K, which generates phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3). PI(3,4,5)P3 then activates 3-phosphoinositide-dependent protein kinase-1 (PDPK1), which subsequently leads to the activation of Akt, whose regulatory functions on the FOXO transcription factors and the mTOR signaling pathway have been described above. The binding of ILPs to the IIS kinase receptors also sequentially starts the activation cascade of Ras, Raf, MAPK kinase 1 (MEK1) and MEK2, and extracellular signal-regulated protein kinase 1 (ERK1) and ERK2, which are also known as mitogen-activated protein kinase 3 (MAPK3) and MAPK 1 [38]. ERK and its downstream target, RSK, are able to suppress TSC2 and enhance mTORC1 activity[47].

Metformin

Metformin is a common oral antihyperglycemic drug that has been widely prescribed in the management of T2DM. This biguanide class drug exerts its glucose lowering effect via multiple mechanisms, including increasing insulin sensitivity, lowering hepatic glucose production, and decreasing intestinal glucose absorption [4]. Metformin was discovered in 1922 and received its approval in 1994 in the US[69]. After decades of clinical use, metformin has been found to be generally safe and well-tolerated by humans. Each year, metformin is taken by more than 125 million people world-wide, making it one of the top 10 best-selling generic drugs [70]. Common gastrointestinal discomforts such as nausea, loss of appetite, and vomiting often resolve spontaneously. The most serious side effect is lactic acidosis, but the incidence is very low [71].

In recent years, accumulating evidence has supported the safe and efficacious use of metformin beyond its glucose-lowering effects. Its usefulness ranges from countering tumorigenesis properties to inducing

ovulation in women with PCOS [72, 73]. Moreover, metformin has been shown to extend lifespan in short-lived organisms as well as in diabetic patients, suggesting its great potential to become one of the first effective geroprotective agents on the market[74, 75].

1 Mechanisms of metformin in improving healthspan

3.1.1 Metformin's effects on the cardiovascular system

Obesity, dyslipidemia, and insulin resistance are all known risk factors of cardiovascular diseases. Mechanisms that reduce these risk factors underpin the cardiovascular protective effect of metformin. Indeed, AMPK activation by metformin can suppress fatty-acid desaturase (FADS) genes, reducing the circulating levels of lipid metabolites and LDL cholesterol[76]. In addition, metformin treatment also improves insulin sensitivity and has weight loss effect, which reduce perceived hunger and food intake [77].

The traditional risk factors of cardiovascular diseases such as smoking, high blood pressure, and diabetes cause chronic inflammation and subsequent endothelial dysfunction, both of which play a central role in the development of atherosclerosis. Accumulated data have shown that metformin inhibits vascular inflammation mainly by blockading the PI3K–Akt pathway and suppressing the downstream NF-κB pathway by blockading the PI3K–Akt pathway [78]. In diabetic patients, individuals who initiated treatment with metformin have been reported to have lower levels of neutrophil-to-lymphocytes ratio, a marker of systematic inflammation. In non-diabetic patients who have an history of heart failure, metformin treatment has been shown to suppress the circulating pro-inflammatory cytokines, including the aging-associated cytokine CCL11[79]. Besides, metformin also exerts vascular protective effect by regulating endothelium-derived nitric oxide (NO) produced from nitric oxide synthase (eNOS), two substances that have major roles in maintaining vascular homeostasis and its integrity, including regulating vasodilation and vascular permeability, inhibiting platelet activation, and preventing thrombosis formation. Zou et al shows that when bovine aortic endothelial cells are exposed to clinically relevant amounts of metformin, increased activities of eNOS, NO, and AMPK can be observed while no such effect is observed in AMPK-1 knockout mice, suggesting that AMPK activation by metformin exerts vascular-protective effects [80, 81].

3.1.2 Metformin's effects on tumorigenesis

Reprogrammed energy metabolism is one of the hallmarks of cancer. The IIS and AMPK pathways, which are associated with maintaining energy homeostasis, have thus been seen as dominant factors in how metformin exerts antineoplastic effects. First, metformin can suppress the IIS pathway by reducing circulating insulin and IGF 1 levels. Subsequently, the downstream PI3K-Akt and mTOR signaling pathways are down-regulated, attenuating the proliferation of cancer cells and inducing autophagy. Memmott et al. have demonstrated that metformin inhibits the cellular proliferation in 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung cancer in mice by decreasing the levels of circulating insulin and IGF-1 [82]. Secondly, metformin can inhibit the growth of cancer cells by activating AMPK and inhibiting mTOR directly. Multiple studies have backed this mechanism and shown that various cancers including lung cancer, breast cancer, and colorectal cancer are suppressed by metformin via the AMPK/mTOR pathway[83] .

3.2 Effect of metformin on longevity in animals

Numerous *in vivo* studies have shown that metformin can increase longevity and maintain healthspan in short-lived organisms including flies, roundworms and mice [84-86]. Thus, metformin has been shown to extend healthspan and lifespan in the roundworm*C. elegans* [87]. Consistently, metformin has also been shown to retard aging in rodents. For example, low dose (0.1%) of metformin for middle-aged male C57BL/6 mice's diet lead to a 5.83% extension of mean lifespan, while a higher concentration of the metformin (1%) was shown to be toxic [84]. In addition, when supplementing 5mM metformin to the food of *D. melanogaster,*a rigorous activation of AMPK and suppressed lipid storage were observed. However, metformin treatment did not increase the lifespan in either male or female fruit flies. This could be due to the dosage of metformin that was administered to activate AMPK was high to an extent that it became toxic to fruit flies and reduced their survival[85].

In addition to retarding aging, both *in vivo* and *in vitro*studies have shown that metformin has a protective role of attenuating tumorigenesis

[88, 89]. For example, metformin was shown to delay the first tumor onset by 22% and 25% respectively in female mice at the age of 3 months and 9 months [90].

3.3 Metformin improves healthspan in humans

3.3.1 Effect of metformin in cancer

To further investigate the anti-aging benefits of metformin seen in animal models, numerous studies have been conducted to replicate these results in humans [89]. In 2005, a case-control study first suggested that the use of metformin in diabetic patients was associated with reduced risk of cancer [91]. Since then, the anti-tumor effect of metformin has been extensively investigated in multiple observational studies. In particular, Libby et al. and his colleagues compared new users of metformin and those who were taking sulfonylurea, insulin, or other anti-diabetic drugs. Their results showed that in patients with T2DM, metformin users (n= 4,085) have a significant lower risk of cancer than non-users (n= 4,085) do after adjusting for covariates (Hazard Ratio [HR] 0.63, 95% Confidence Interval [CI] [0.53-0.75]) [92].

Although a large body of subsequent observational studies have supported the positive relationship between metformin use and its anti-cancer effect, the evidence from Randomized Control Trials (RCTs) has been largely inconclusive [93, 94]. For instance, Home and his colleagues compared the malignancy rates among diabetic patients who were initially treated with different glucose lowering medications. Their results did not support the view that metformin had a protective effect against cancer compared with rosiglitazone and sulfonylureas[95]. Consistently, multiple meta-analysis did not find any evidence showing metformin treatment being associated with a reduction of cancer incidence [96, 97].

Taken together, metformin use in animal studies and some observational studies have indicated its great potential as a cancer protective agent, which has sparked great interest for expansion to human clinical trials. Encouragingly, multiple RCTs that aim to investigate the anti-aging properties of metformin in non-diabetic individuals are on the horizon. In particular, the Targeting Aging with Metformin (TAME) trial, a large placebo-controlled trial that has been designed to enroll 3000 subjects, was launched in 2017. This study intends to compare the metformin users with placebo controls, and might offer stronger evidence for the protective role of metformin in cancer, cardiovascular disease and other age-related diseases [98, 99].

3.3.2 Effect of metformin on CVD

Mounting data from observational studies have indicated that metformin exerts more CVD benefits than other hypoglycemic drugs do in T2DM patients [91, 100, 101]. In a retrospective study, Roumie et al. compared the CVD events and mortality risk of diabetic veterans who initiated monotherapy with four different medications (metformin, sulfonylureas, rosiglitazone, and glibenclamide). They found that compared with metformin, the other three glucose-lowering drugs were all associated with significantly increased CVD events incidence or mortality [102]. A large-scale prospective study also confirmed the protective CVD effect of metformin over diet. In the United Kingdom Prospective Diabetes Study (UKPDS), Holman and his colleagues compared the cardiovascular events between diabetic patients who underwent dietary therapy and obese diabetic patients who received metformin. Their results showed that metformin was associated with a significantly lower incidence of myocardial infarction (33%, P =0.005) compared with the diet-alone group[103]. Consistent with the UKPDS study, a small clinical trial by Hong et al. compared the effect of two glucose-lowering drugs, glipizide (30 mg daily) and metformin (1.5 g daily), in a 3-year treatment of 304 diabetes patients who had a history of coronary artery disease. The metformin group was found to have a significant reduction of major CVD events (HR 0.54 ,95% CI 0.30–0.90; $P = 0.026$) compared with glipizide group, after a median of 5.0 years of follow-up period [104].

IIn addition to diabetic patients, metformin has also been shown to prevent the development of CVD in pre-diabetic individuals. A clinical trial compared the coronary calcium score, a proxy for CVD, between the pre-diabetic patients who used metformin versus those who used placebo. Compared with the placebo group, the metformin group showed a significantly lower coronary calcium score in the male group but not the female group. This could be due to the interactions occurring between testosterone and metformin in male subjects [105].

Moreover, metformin treatment has been shown to reduce the risk of CVD in non-diabetic individuals. In a study, three hundred and eighty non-diabetics patients with ST-segment elevation myocardial infarction (STEMI) were assigned to receive metformin or placebo for 4 months. Lexis et al. found that CVD proxies, which included glycated hemoglobin, total cholesterol, low-density lipoprotein cholesterol, and body weight, were reduced in the metformin group relative to the placebo group (Lexis et al., 2015). Furthermore, multiple meta-analyses have also shown metformin use in non-diabetic subjects to beassociated with reduced systolic blood pressure, which is the one of most important risk factors for CVD. This effect was particularly prominent in those with impaired glucose tolerance or were obese [105].

Studies that investigate the CVD risk after treatment with metformin or other anti-diabetic drugs are also affected by bias in the experimental design. For example, both sulfonylureas and rosiglitazone are associated with CVD events [106, 107]. Thus, using these hypoglycemic drugs as a comparison could not determine whether the reduced CVD events were due to the protective effect of metformin or the increased CVD risk associated with sulfonylurea and rosiglitazone.

In summary, compelling evidence from observational studies has suggested that the role of metformin in preventing CVD in people with and without diabetes. However, further elucidation of the role of metformin in retarding CVD is critically needed from well-designed large-scale clinical trials.

3.3.3 Effect of metformin on age-related neural disorders

Metformin has been shown in many studies to have positive effects on age-related neural disorders, such as Alzheimer's disease and Parkinson's disease. Compared to the symptomatic treatments that are currently used, repurposed drugs such as metformin show a promising prospect by targeting these diseases closer to their root. However, the benefits of metformin found in the studies should be taken with a grain of salt, as there are also opposite outcomes and remaining risks.

Currently no drug exists to treat or slow down the development of AD. Instead, patients are treated with drugs that improve their impaired cognitive functions. Cholinesterase inhibitors, such as Aricept, Exelon, and Razadyne, prevents the breakdown of acetylcholine and improve neurological function in patients [108-110]; Another treatment is Namenda, a memantine that inhibits glutamate to prevent over-excitation of the neurons in AD patients [111].

Applying metformin, an antidiabetic drug, to treat AD stems from the widely observed association between AD and type 2 diabetes mellitus (T2DM) [112]. The immediate difference seen here is that unlike the other AD drugs already mentioned, metformin is not used for a specific mechanism of action but repurposed based on observation and logical reasoning, and multiple studies have committed to validate this reasoning. In a study that involves 20 non-diabetic AD patients, the patients were treated with metformin for 8 weeks and showed improved cognitive functions [112]. Nonetheless, a larger study that analyzed data from 7,086 dementia patients and matching number of healthy controls from the United Kingdom-based General Practice Research Database (GPRD) concluded otherwise. Their analysis showed that individuals who did not receive any drug for diabetes mellitus (AOR=0.88, 95% CI=0.71–1.10) or those who took antidiabetic drugs (AOR=1.03, 95% CI=0.90–1.19) had a similar risk of developing AD as individuals without diabetes (AOR=1). Furthermore, long-term use of metformin increased the risk of developing AD, which was attributed by the authors to the production of A-β peptides, a hallmark for AD, induced by metformin. However, the increased risk was not confirmed in patients who had only taken metformin, and there was no trend of increasing risk of AD with increasing number of metformin prescriptions[113]. The increased production of A-β peptides caused by metformin was shown on cell cultures of primary cortical neurons and N2a neuroblastoma cells expressing human amyloid precursor protein (APP). Metformin upregulates the transcription of beta-secretase, which cleaves APP into A-β peptides. The study has also shown that metformin combined with insulin reduces A-β peptide levels [114]. This effect was also found to be true in a mice study, in which diabetes model mice were used to evaluate AD-like brain changes and the effect of metformin on those changes. The study found that metformin attenuated the increase of total tau, phospho-tau, and activated JNK, a tau kinase, in the mice. Metformin also attenuated the decrease of synaptophysin and preserved the neural structures of the mice. However, metformin did not improve the spatial learning and memory abilities of the mice[115]. These studies together seem to suggest that having taken metformin in the past does not reduce the risk of AD, but metformin may be used with insulin as an effective short-term treatment of AD.

The loss of dopaminergic neurons is characteristic of PD and leads to a decreased amount of dopamine and imbalance between dopamine and acetylcholine. According to the acetylcholine-dopamine balance hypothesis, over-activation of cholinergic system activity causes motor and cognitive disturbances. Hence, the current PD drugs either provide more dopamine or reduce the amount of acetylcholine to restore the balance. Levodopa is a dopamine precursor that is commonly used to deliver dopamine to the brain, and it is often used with catechol-O-methyltransferase inhibitors to reduce side effects and release of dopamine to other parts of the body [116, 117]. Monoamine oxidase inhibitors are another type of drug that acts by inhibiting the degradation of dopamine [118]. Amantadine and anticholinergics also boost dopamine level in the brain, but they are less used due to a number of side effects including dry mouth, headache, nausea, orthostatic hypotension, and visual hallucinations[119, 120]. Like AD, current treatments of PD work as a remedy instead of neuroprotective agents.

Several studies have found metformin to alleviate PD. PD, diabetes, and dementia share the disorder of mitochondrial bioenergetics and abnormal protein folding in their pathogenesis. An analysis of a cohort of 800,000 people from the Taiwan National Health Insurance database showed that having T2DM increased the risk of PD 2.2 fold, and metformin-inclusive sulfonylurea therapy reduced the risk (HR=0.78 relative to diabetes-free, 95% CI=0.61-1.01) . A mice study suggests that the reason has to do with metformin's ability to reduce α-synuclein release, a component of the Lewy bodies and Lewy neurites that are characteristic of PD. The researchers gave MPTP, a prodrug to a the neurotoxin MPP+, to mice to model PD [121]. MPTP caused damage to the dopaminergic neurons of the mice and led to astroglial activation, which promotes inflammation in the nervous system, and increased release of α-synuclein [121, 122]. Metformin was found to mitigate astroglial activation and promote methylation of protein phosphatase 2A (PP2A) that is related to α-synuclein dephosphorylation. Metformin has also been known for activating AMPK, which activates ATP production in mitochondria and restores mitochondria function. However, the timing and dosage of metformin was also critical. When MPTP and metformin were given in the same day, 75% lethality ensued in the mice. Although metformin increased the levels of BDNF and GDNF, two neurotrophic factors, high dosage (400 mg/kg) killed all the mice [121]. In another study, metformin was found to rescue tumor necrosis factor type 1 receptor associated protein (TRAP1) mutation associated changes in mitochondrial protein balance. TRAP1 is a protein associated with stress sensing in mitochondria, and its absence due to mutation has been identified to increase the risk for PD. The study found that the loss of TRAP1 causes elevated mitochondrial respiration, reduced mitochondrial membrane potential, and imbalance of nuclear and mitochondrial protein production. Metformin was shown to reverse the imbalance and restore mitochondrial membrane potential[123]. In summary, metformin intervenes the pathogenesis of PD by preserving neurons, reducing inflammation, and protecting mitochondria functions. It is a promising new way to help PD patients, but further studies are still needed to understand the influence of dosage and timing.

Rapamycin

Rapamycin, also known as sirolimus, is an antifungal macrolide that is produced by *streptomyces hygroscopicus* . It was first discovered in the Easter Islands in the 1970s, and subsequent studies have identified various uses of rapamycin that extend beyond fighting fungal infections [124-126]. Rapamycin was initially prescribed as an immunesuppressant for organ, especially kidney, transplantation[127, 128]. It has also been used to coat coronary stents, which prevents coronary re-narrowing after stent implantation[129]. However, the side effects of rapamycin, which include ulcer, diarrhea, hyperglycemia, and hyperlipidemia, which have largely impeded its widespread use.

Despite the earlier challenges, a renaissance of rapamycin came when studies consistently reported that rapamycin slowed aging in various model organisms. Consequently, this has led to a flurry of interest in repurposing rapamycin as a geroprotector [130]. Although the adverse effects of rapamycin remain a major concern, new efforts to minimize them have been explored in many directions. For example, the development of rapamycin analogs, tweaking the dosage, and searching for options to combine rapamycin with other drugs have all shown promising results [131, 132].

4.1 Mechanisms of Rapamycin in improving healthspan

Rapamycin suppresses mTOR signaling by first binding to its immunophilin FK binding protein (FKBP12) and then acting upon mTORC1 and mTORC2[133, 134]. While the inhibition of mTORC1 extends life expectancy and confers protection for age-related diseases, mTORC2 is associated with unwanted effects such as glucose intolerance and abnormal lipid profiles. Furthermore, rapamycin can acutely suppress mTORC1, whereas mTORC2 is less sensitive to rapamycin and its inhibition can only be achieved through long-term treatment [135].

4.1.1 Rapamycin retards neurodegeneration via mTORC1 inhibition

Alzheimer's disease is characterized by the aggregation of amyloid-β and tau in the brain tissue. Hence, mTOR signaling, the main regulator of protein synthesis and clearance, has been considered a promising target for treatment. Mice with increased mTOR activity have shown higher levels of tau and Aβlevels [136]. Dysregulated mTOR activity and autophagy have been observed in patients with early Alzheimer's disease [137]. Rapamycin, the main mTOR inhibitor, has therefore been widely studied as a promising treatment for Alzheimer's disease. Administrating rapamycin to young 3xTg-AD mice induces mTOR-mediated autophagy and reduces Aβ and tau levels[138]. Moreover, when administrated early, rapamycin reduces the formation of tau and Aβ plaques and tangles via mTOR-mediated autophagy before their formation [139].

4.1.2 Rapamycin effects on cancer

To fuel proliferative growth and division, tumor cells must reprogram their energy metabolism to maintain an adequate energy supply—a process that is regulated by the mTORC 1 complex. First, the activation of mTORC1 promotes aerobic glycolysis by increasing the amount of hypoxia inducible factor (HIF)-1α, a transcription factor that is associated with metastasis by promoting angiogenesis responding to hypoxia [139]. Also, activated mTORC1 increases lipid synthesis by phosphorylating Lipin-1 and S6K1, thereby activating sterol regulatory element binding factor (SREBP)-1, a lipogenic transcription factor whose binding to the genes involved in lipogenesis upregulates their transcription [140, 141].

Moreover, mTORC1-mediated phosphorylation of S6K1 can enhance the biosynthesis of purine and pyrimidine, two amino acids that are required for cancer cell proliferation [142] . Indeed, over-activation of mTORC1 signaling has been observed in many types of cancer such as lymphoma, endometrial cancer, and renal cell carcinoma[143-145]. Therefore, as a potent inhibitor of mTOR 1, rapamycin can put a brake on the defective tumor metabolism and thus is considered as a promising drug for combating cancer.

4.2 Pre-clinical studies of rapamycin in anti-aging

Rapamycin has been found to extend lifespan in diverse model organisms, including yeast, fruit flies, and nematodes [146-148] . Thus, studies have suggested that treating yeast with rapamycin, although making them smaller, can extend their longevity in a process that has been postulated to mimic caloric restriction[149]. Similarly, a landmark study by Harrison et al. revealed that rapamycin extends longevity in mammals[150]. They found that when treating genetically heterogeneous mice beginning at the age of 20 months with a daily dosage of 2.24 milligrams per kilogram of body weight, rapamycin can extend the lifespan of male mice by 9% and lifespan of female mice by 14%[150]. Remarkably, when increasing the dosage of rapamycin 3-fold compared to the previous study, the lifespan of mice was increased by up to 26% in female mice [151]. Moreover, rapamycin has also been demonstrated to have protective effects against aging, which has been demonstrated in a high-profile study, the Intervention Testing Program (ITP) [152]. This study used genetically outbred mice to test the potential of multiple anti-aging manipulations, including drugs, diets, and other interventions [153]. Surprisingly, rapamycin is one of the only two drugs (the other is acarbose) that had robust anti-aging effect in the ITP experimental animal models.

4.3 Rapamycin improves healthspan in human

4.3.1 Effect of rapamycin on immunity

The encouraging anti-aging effects of rapamycin in animal studies have spurred a great interest in translating these results to human. Intriguingly, rapamycin at a high dose is known to suppress the immune system, which is why it has been used as an immunosuppressant in organ transplantation. However, when tweaking rapamycin to a lower dosage, rapamycin appears to stimulate immunity. In 2014, a milestone study on the immunity-boosting effect of rapamycin was reported by researchers at Novartis [154]. In a double-blind randomized study, they administered everolimus, a derivative of rapamycin, to 218 healthy subjects aged 65 and older for 6 weeks and then stopped the use for 2 weeks before giving them a flu shot. A twenty percent increase of immune response was observed in the everolimus-receiving group, indicating that rapamycin and its analogs (rapalogs) may boost immunity in humans. Furthermore, to minimize the adverse effects of rapamycin, a combination of rapamycin and rapalogs have been subsequently explored. A low dose of rapalogs combined with catalysts have been shown to induce a 40% infection reduction in the healthy elderly (aged 65 and older) subjects who received the rapamycin treatment before flu shot —and more importantly, this combination of therapy was suggested to be well-tolerated in the majority of the subjects [155].

4.3.2 Effect of rapamycin on AD

In addition to extending lifespan and boosting the immune system, rapamycin has been shown to be efficacious in attenuating one of the most common neurodegenerative disease, AD, in animals. Specifically, in 2010, researcher found that rapamycin administered to AD mice in early life protected against cognitive deficits and resulted in a reduction of amyloid-β and tau [156, 157]. However, there has been varied evidence regarding the effect of rapamycin on AD. For example, Oddo et al. reported that when starting treatment of rapamycin AD mice at 2 months, a significant reduction of tau and plaques were observed, whereas treating with rapamycin at 15 months had no such effect. This indicated that rapamycin can only accelerate autophagy before the formation of tau and plaques in AD.

Although tau tangles and plaques are considered hallmarks of AD, cerebrovascular pathological alterations are also commonly found in AD patients. Rapamycin appears to alter cerebrovascular circulation. For example, administering rapamycin to APOE4 mutant carrier mice, a transgenic AD mice model, can result in a restored cerebral blood flow and maintenance of blood-brain barrier integrity, suggesting that rapamycin may have a putative role in reducing vascular progression in AD mice [158].

4.3.3 Effect of rapamycin on cancer

In 2002, rapamycin was first reported to have antineoplastic properties in mice by suppressing cancer metastasis and angiogenesis[159]. Since then, overwhelming *in vivo* and*in vitro* studies have reported that rapamycin and its derivatives have the potential of ameliorating cancer onset and development[90, 150]. So far, rapalogs have been approved for treating multiple cancers, including renal cell carcinoma, hepatocellular carcinoma and mantle cell lymphoma [160, 161]. Moreover, hundreds of clinical trials have been conducted to test either monotherapy of rapamycin or combination therapy with other drugs in treating various cancers such as breast cancer and endometrial cancer[13]. However, the actual clinical benefits of rapamycin in treating cancer have been modest [162, 163].

Importantly, rapamycin has also been tested for its potential to prevent cancer. For example, administrating rapamycin to transgenic HER-2/neu cancer-prone mice has been reported not only to extend the lifespan of the mice, but also to result in a delay in the spontaneous tumor onset[90, 164]. However, the same study found that rapamycin fails to extend the lifespan of the mice with established tumors. In addition, rapamycin has been shown to inhibit the development and progression of tobacco-induced lung cancer. Granville et al. exposed mice with the tobacco carcinogen NNK before administering rapamycin to these mice. The results showed that both phenotypic progression of the tumor as well as tumor size underwent a dramatic decrease. These findings point to the possibility that rapamycin might be used as a cancer prevention agent for those smokers who are at high risk of lung cancer [165].

Discussion

Despite the promising effects that metformin and rapamycin have shown against aging, intensive work is still required to explain several outstanding questions. On the basic level, the full extent of metformin and rapamycin's effects have not been fully understood. Recently, researchers have attributed growth differentiating factor 15 (GDF15), which interacts with the GFRAL receptor in the central nervous system to suppress appetite, to the weight loss effect of metformin through a mechanism independent from insulin sensitization and glucose lowering mechanisms [166, 167]. Furthermore, metformin and rapamycin have been shown gender-specific difference, suggesting the need to investigate the drug-hormones interactions [151, 168] .

Safety of long-term is another concern. Although metformin has been used safely in diabetic patients for a long time, the chronic use of metformin has been associated with the dose-dependent Vitamin B12 deficiency, which is a cause of anemia and neuropathy[169, 170]. To maximize the safe use of metformin, an assessment of the serum level of Vitamin B12 may be needed before prescribing metformin. In addition, the response to metformin also varies from person to person. From the results of genome-wide association study, a locus on chromosome 11 (rs11212617) is associated with the glycemic response [171]. Although this association remains disputable, it may be helpful to develop an approach to predict the response of metformin treatment in clinical settings.

The issue of drug safety also stifles the progress of repurposing rapamycin to anti-aging use - the common side effects of using rapamycin such as diarrhea and nausea have been reported in over a third of rapamycin users, resulting around 5% of treatment discontinuation[172]. Recent results suggest that designed dosage could be effective in easing the incidence of side effects. A small RCT suggests that the short-term use of rapamycin (8 weeks) to be a relatively safe approach [173]. In a mice study, the intermittent use of rapamycin (administrating 2mg/kg rapamycin every 5 days) has also been shown to reduce the incidence of side effects[174]. However, these results are still at the preliminary stage and should be validated by in substantial basic and clinical studies. Tweaking the chemical structure of rapamycin by developing rapalogs without compromising the anti-aging effect and engineering controlled release of rapamycin from biodegradable biomaterial scaffolds are also prospective directions.

Another concern is whether the positive results obtained from animal and clinical studies can be fully translated to humans. Current model animals have large physiological and genetic differences from human. Although many studies that have obtained positive results, the dosage of metformin used in these studies exceeded the limit for humans[175, 176]. Thus, the results obtained from mice, yeast, and fruit flies will require further effort to validate.

The anti-aging effects of metformin and rapamycin studies in human have been inconsistent and varied in their strength of evidence, and many of these epidemiological studies are at high risk of bias. This has generated heterogeneous associations, and further studies are required to determine the genuine extent of their anti-aging effects[177]. It is hoped that the results of the large ongoing study—TAME trial—will shed more light on the anti-aging effect of metformin [178].

Conclusion

Although efforts have been made to ease the progression of diseases from a disease-centric level, less has been done to elucidate the shared mechanisms of aging and the broad effects on a host of diseases. Here, we have discussed two repositioned drugs, metformin and rapamycin, which have had encouraging results both in animal and in human studies in counteracting aging and age-related diseases. Nonetheless, these two drugs still have a long way to go from becoming the ultimate solution to age-related diseases, but the hope will be that they will succeed in helping to extend the healthspan of humans.

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Conflicts of interest

We have no conflict of interest to declare.

Author contributions

Q.F. and C.Y.W. wrote the manuscript. T.L. and C.Y.W. revised the manuscript for intellectual content. B.W.C., C.Y.W. prepared the figures. T.L., N.C. and X.L. conceived the study and were in charge of overall direction and planning. Q.F. and B.W. C. collected relevant literature. The final version of the manuscript was approved by all authors.

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Figure captions

Figure 1. **Metformin and Rapamycin could decrease the incidence of age-related diseases.** In terms of mechanism, metformin and rapamycin achieve similar calorie restriction effect in different ways. Metformin can activate AMPK like calorie restriction and further cause a series of pathways changes, which could arouse anti-aging effects such as Inhibition of pro-inflammatory effect and ROS detoxification. Rapamycin can inhibit mTORC1, which relate to Autophagy and Protein Synthesis pathway.

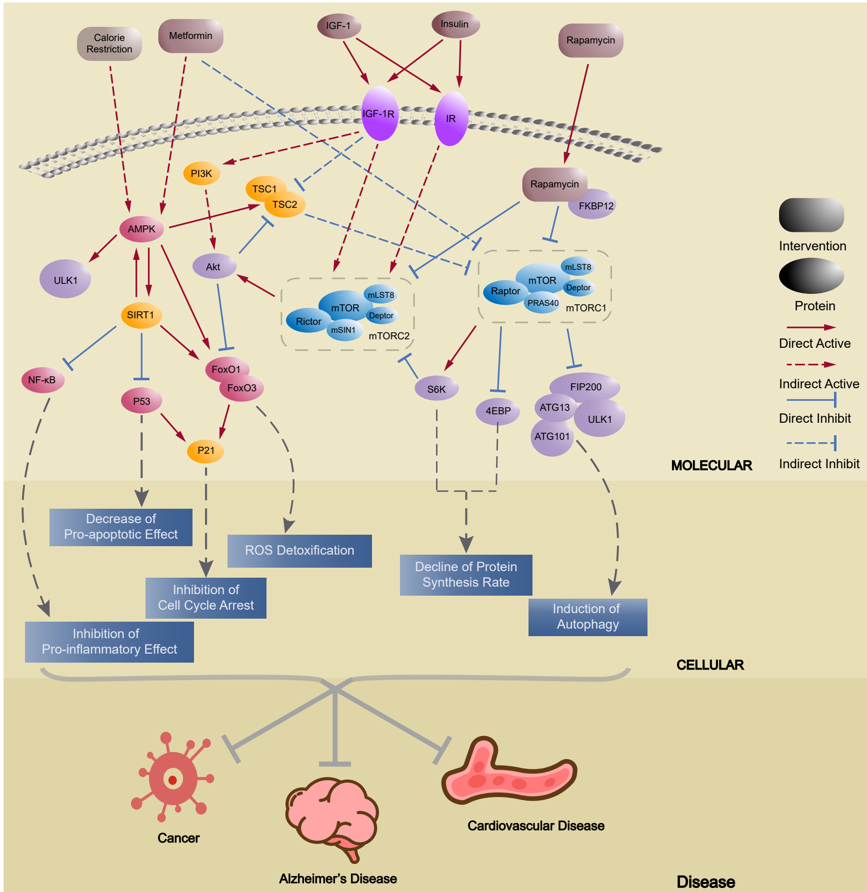
Table

Table 1. A summary of major studies that have shown the effects of metformin and rapamycin

Study	Organisms	Application scheme	Effect
Metformin Life extension effect Slack 2012	Metformin Life extension effect Fruit flies	Metformin Life extension effect 1,10,100 mM, every day	Metformin Life extension effect 1-10 mM, no effect on survival; >10mM, lifespan decrease Increase mean lifespan by 18%, 36%, 3%

Study	Organisms	Application scheme	Effect
Cabreiro 2013	C. elegans	25, 50, 100 mM, every day	Increase mean lifespan by 14%, 6%, 0%
Anisimov 2011	Mice	100 mg/kg, every day, started at 3, 9 or 15 months	0.1%, lifespan increase by 5.83%; 1%, lifespan decrease by 14.4%
Martin-Montalvo 2013	Human	0.1%, 1% metformin (w/w) for 30 weeks	All-cause mortality decrease
Anticancer effect	Anticancer effect	Anticancer effect	Anticancer effect
Mitsuhashi 2014	Human	1500-2250 mg/day, for 4 to 6 weeks	Inhibited endometrial cancer cells grow in vivo
Reduce cardiovascular disease risk	Reduce cardiovascular disease risk	Reduce cardiovascular disease risk	Reduce cardiovascular disease risk
H. P. Chen 2013	Human	Based on the condition of patients with type 2 diabetes mellitus	Hepatocellular carcinoma risk decreases
Lexis 2015	Human	ST-segment elevation myocardial infarction (STEMI) patients, 500 mg twice daily, for 4 months	Cardiovascular risk decreases
Goldberg 2017	Human	850 mg twice daily, for over 3.2 years	Coronary atherosclerosis risk decreases
Anti-Alzheimer's disease effect	Anti-Alzheimer's disease effect	Anti-Alzheimer's disease effect	Anti-Alzheimer's disease effect
Chen 2009	Mice	2–5 mg/mL for 6 days	Both intracellular and extracellular Aβ species increases
Li 2012	Mice	200 mg kg^{-1} d^{-1} for 18 weeks	AD-like biochemical changes decrease
Koenig 2018	Human	Metformin or placebo for 8 weeks	Executive functioning improves
Anti-Parkinson's disease effect	Anti-Parkinson's disease effect	Anti-Parkinson's disease effect	Anti-Parkinson's disease effect
Katila 2017	Mice	200 mg kg^{-1} d^{-1} for 7 days	Metformin provides neuroprotection against MPTP neurotoxicity
Rapamycin			
Life extension effect	Life extension effect	Life extension effect	Life extension effect
Holman 2008	Yeasts	100, 300, 600, 1000pg/mL in the culture medium	Lifespan increase in a dose-responsive manner
Bjedov 2010	Fruit flies	200µM, for 14 days	Lifespan increase
Vellai 2003	Nematodes	Using let-363-(RNAi) treated worms from hatching	Increase mean lifespan by 100%

Study	Organisms	Application scheme	Effect
Harrison 2009	Mice	Begins at 600 days, 14.7 mg/kg	females' lifespan increases by 14%; males' lifespan increases by 9%
Anisimov 2010	Mice	1.5mg/kg, 3 times a week for 2 weeks, followed by a 2 weeks break	Increase mean lifespan by 4.1%
Miller 2014	Mice	Begins at 3 months, ever day	females, lifespan increase by 26%; males, lifespan increase by 23%
Anticancer effect	Anticancer effect	Anticancer effect	Anticancer effect
Guba 2002	Mice	1.5 mg/kg/d, begins on day 0 or 7 relative to tumor implantation	Inhibited liver tumors grow
Granville 2007	Mice	1 weeks after NNK administration	Tumors show decreased phenotypic progression and a 74% decrease in size
Anisimov 2011	Mice	Begins at 2 months ,3 times a week, for 2 weeks, followed by a 2 weeks break, for 2 years	Shifted the tumor-yield curve to the right and prolonged mean lifespan
Anti-Alzheimer's Disease effect	Anti-Alzheimer's Disease effect	Anti-Alzheimer's Disease effect	Anti-Alzheimer's Disease effect
Caccamo 2010	Mice	2.24 mg/kg, every day	RAPA improves learning and memory and reduces Abeta and Tau pathology.
Spilman 2010	Mice	2.24 mg/kg, for 13 weeks	AD-like cognitive deficits are prevented and levels of Abeta is lowered
Lin 2017	Mice	14mg/kg, every day	Block progression of early cognitive deficits



Calorie Restriction
Metformin
IGF-1
Insulin
Rapamycin
IGF-1R
IR
PI3K
TSC1
TSC2
Rapamycin
FKBP12
AMPK
Akt
ULK1
SIRT1
mLST8
mTOR
Deptor
Rictor
mSIN1
mTORC2
mLST8
mTOR
Raptor
Deptor
PRAS40
mTORC1
NF-κB
P53
FoxO1
FoxO3
P21
S6K
4EBP
FIP200
ATG13
ULK1
ATG101
Intervention
Protein
Direct Active
Indirect Active
Direct Inhibit
Indirect Inhibit
MOLECULAR
Decrease of Pro-apoptotic Effect
ROS Detoxification
Inhibition of Cell Cycle Arrest
Inhibition of Pro-inflammatory Effect
Decline of Protein Synthesis Rate
Induction of Autophagy
CELLULAR
Cancer
Alzheimer's Disease
Cardiovascular Disease
Disease