Prospective Treatment of Age-Related Diseases by Slowing Down Aging

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Atherosclerosis, hypertension, obesity, diabetic complications, cancer, benign prostate hyperplasia, Alzheimer and Parkinson diseases, age-related macular degeneration, osteoarthritis, osteoporosis, and seborrheic keratosis are strongly associated with aging, implying a common underlying process. Each disease is treated separately and, in most cases, symptomatically. Suppression of aging itself should delay or treat all age-related diseases, thus increasing healthy life span and maximal longevity. But, is it possible to slow down aging? Recent evidence indicates that the target of rapamycin signaling pathway is involved in cellular senescence and organismal aging. Preclinical and clinical studies demonstrated the therapeutic effects of rapamycin in diverse age-related diseases. One simple reason why a single drug is indicated for so many age-related diseases is that it inhibits the aging process. (Am J Pathol 2012, 181:1142–1146; http://dx.doi.org/10.1016/j.ajpath.2012.06.024)

mTOR and Geroconversion
Mammalian target of rapamycin (mTOR) is a cytoplasmic kinase that regulates cell growth and metabolism. The mTOR pathway is activated by mitogens (eg, insulin-like growth factor-1 and insulin) and nutrients (amino acids, glucose, and fatty acids), hormones, and oncogenic proteins (eg, Ras, Raf, MEK, phosphatidylinositol 3-kinase, and Akt; Figure 1). The mTOR pathway stimulates cell growth (causing cell hypertrophy), ribosome biogenesis, and protein synthesis (including aggregation-prone proteins) and inhibits digestion of defective mitochondria and aggregation-prone proteins. In proliferating cells, active mTOR stimulates cellular mass growth and metabolism. When the cell cycle is arrested, still active mTOR causes hypertrophy and, eventually, cellular senescence, characterized by large-cell morphological features and irreversible loss of proliferative/regenerative potential. The process of conversion of reversible arrest into senescence is termed geroconversion. Rapamycin and other inhibitors of the mTOR pathway decelerate geroconversion in cell culture. Rapamycin also prevents hyperactivation and exhaustion of stem cells in the organism, and it reverses cellular phenotypes and enhances mutant protein clearance in Hutchinson-Gilford progeria syndrome cells.

From Gerogenic Cells to Diseases using Atherosclerosis as an Example
In arrested cells, mTOR increases cell size, differentiation, and differentiation-related cellular functions. Therefore, senescent/gerogenic cells with active mTOR are

Humans and other mammals often die from age-related diseases, such as cancer, ischemic heart disease, hypertension, stroke, and complications of osteoporosis, type 2 diabetes mellitus, and Alzheimer and Parkinson diseases. Each disease is treated separately, for example, diabetes is commonly treated with insulin. However, insulin does not treat cancer; instead, it stimulates cancer. Furthermore, insulin promotes obesity and atherosclerosis, and insulin therapy likely worsens retinopathy. In addition, insulin-activated pathways promote aging. Therefore, while compensating for insulin insufficiency and insulin resistance in diabetes, insulin therapy may accelerate aging. Similarly, while treating cancer, radiation does not treat diabetes and other age-related diseases, if cancer were to be cured, other diseases would continue to limit life span. To prevent age-related diseases and, therefore, to extend healthy and maximal life span, it is necessary to slow down the aging process.
hypertrophic and hyperfunctional or hyperactive.9 Functions of differentiated cells are tissue type specific. For example, fibroblasts, adipocytes, and immune cells secrete cytokines. Therefore, hyperfunctional fibroblasts, adipocytes, and immune cells cause pro-inflammation and fibrosis. Moreover, mTOR is involved in the hypersecretory phenotype of senescent cells.15 As another example, hyperfunctional osteoclasts resorb the bone, thus potentially causing osteoporosis. Liver cells produce lipoproteins, contributing to accumulation of lipids in the arterial wall; and platelets aggregate, leading to thrombosis. For example, atherosclerosis depends on hyperfunctions of local cells [endothelial cells, smooth muscle cells (SMCs), and macrophages] and distant cells (hepatocytes, bone marrow cells, and adipocytes). Atherosclerosis is associated with hypertrophy of arterial SMCs and activation of macrophages in the arterial wall.16,17 The development of atherosclerotic plaque involves endothelial activation, hypertrophy and hyperplasia of SMCs, monocyte migration, macrophage activation, uptake of lipids by activated cells, accumulation of fat, and formation of foam cells (Figure 2). Rapamycin inhibits monocytic/macrophage migration and their accumulation in carotid lesions of cholesterol-fed rabbits.18 Hyperfunctional adipocytes and hepatocytes increase levels of lipoproteins, such as low-density lipoprotein and procoagulation and pro-inflammation factors. Hyperfunction of bone marrow–derived cells, such as monocytes, lymphocytes, and platelets, contributes to atherosclerosis and thrombosis. Increased propensities to thrombosis, hyperlipidemia, pro-inflammation, and high blood pressure, which are systemic manifestations of cellular hyperfunctions, all contribute to atherosclerosis. In animal models, rapamycin slows the progression of atherosclerosis in apolipoprotein E–deficient mice that have elevated levels of cholesterol.19,20 Rapamycin (sirolimus) in heart transplant recipients prevents coronary artery disease.21 In patients with coronary atherosclerosis, oral rapamycin prevents restenosis after implantation of a metal stent.22

Cancer

Despite the common misconception that rapamycin may cause cancer, it has been known for a decade that rapamycin prevents cancers in renal transplant recipients.23–25 At 2 years after renal transplantation, patients receiving rapamycin (sirolimus) as a base therapy do not develop any malignancies.23 In addition, rapamycin prevented tumors and cured pre-existing tumors.26 For example, kidney transplant recipients who had biopsy-proved Kaposi’s sarcoma were switched to rapamycin therapy. Three months after the initiation of rapamycin therapy, all cutaneous Kaposi’s sarcoma lesions had disappeared in all 15 patients.26 Rapamycin is also extremely effective in the prevention of cancer in animal models.27 The cancer preventive effects of rapamycin may be the result of its anti-aging effect.28 In fact, calorie restriction (CR) that decelerates aging delays cancer. CR may slow aging by inhibiting mTOR.29

Rapamycin for Diverse Diseases

Preclinical studies in animals and retrospective clinical studies in humans suggest that rapamycin has the potential to prevent or treat osteoporosis;30 obesity;31,32 neurodegenerative diseases, including Alzheimer, Parkinson, and Huntington diseases and spinocerebellar ataxia; osteoarthritis;34 liver, renal, cardiac fibrosis, and organ hypertrophy; and age-related macular degeneration and diabetic retinopathy.38 Also, lifelong rapamycin administration ameliorates age-dependent learning and memory deficits in old mice.39 Increased activation of the mTOR pathway in liver and skeletal muscle of obese rats is involved in obesity-linked insulin resistance.40 The simplest explanation for the effectiveness of rapamycin in the prevention of so many age-related diseases is the fact that it decelerates a common underlying cause: aging or, on cellular levels, cellular geroconversion.

Inhibition of mTOR Extends Life Span

In fact, inhibition of the TOR pathway extends life span in yeast, flies, and mice.41–49 For example, when fed late in life (at the age of 600 days), rapamycin increased life expectancy by 38% in genetically heterogeneous female mice.43 In another study, rapamycin was administered to mice from the age of 9 months and produced significant increases in life span, including maximum life span.47

**Figure 1.** mTOR-dependent conversion from cell cycle arrest to senescence. When the cell cycle is blocked, active growth-promoting pathways, such as mTOR, cause cellular senescence (geroconversion). Cellular senescence is an irreversible state characterized by cellular hypertrophy, hyperactivity or hyperfunction, hypersecretory and pro-inflammatory phenotype, an inappropriate drive into S-phase—associated with loss of regenerative potential, and resistance to signals (eg, insulin). Rapamycin decelerates or suppresses geroconversion. IGF, insulin-like growth factor; PI-3K, phosphatidylinositol 3-kinase.
The median survival was extended by an average of 10% in males and 18% in females. The causes of death were similar in control and rapamycin-treated mice, consistent with a scenario that rapamycin delayed death from all causes. In inbred female mice, rapamycin (administered intermittently: six times per month) increased life span (especially in the last survivors) and delayed spontaneous cancer. More important, intermittent (acute) treatment with rapamycin in mice does not inhibit mTOR complex 2, otherwise indirectly inhibited by high long-term doses of rapamycin. Yet, even starvation-like metabolic alterations, caused by high long-term doses of rapamycin, are not necessarily harmful.

Calorie Restriction

There is a remarkable example that diseases can be delayed by slowing down aging. CR extends life span in a variety of species, including primates, rats, mice, fish, flies, and worms. CR slows down organismal aging and, thus, delays age-related diseases. CR delays the onset of age-associated pathological conditions in primates. Specifically, CR reduces the incidence of diabetes, cancer, cardiovascular disease, and brain atrophy. Furthermore, CR slows aging and delays age-related diseases in nonobese humans. Some impressive examples include memory improvement in elderly humans and the attenuation of sarcopenia in rhesus monkeys and rodents by CR. In humans, obesity accelerates sarcopenia, whereas weight loss slows sarcopenia. Furthermore, visceral adipose tissue modulates mammalian longevity. In humans, visceral fat accumulation is strongly associated with diabetes, atherosclerosis, thrombosis, hypertension, and other age-related diseases. Reduction of body weight decreases the risk of type 2 diabetes, hypertension, coronary heart disease, cancer, and dementia. Nutrients (food) directly and indirectly (via insulin secretion) activate the mTOR pathway. It was recently reviewed that CR may slow aging by inhibiting the mTOR pathway. Finally, dietary (calorie) restriction reduces cell senescence in mice, consistent with suppression of senescence by rapamycin in cell culture.

When Is It Too Late to Use Anti-Aging Drugs?

Age-related diseases culminate in acute catastrophes, leading to disability and death. For example, atherosclerosis can lead to sudden death because of ventricular fibrillation or myocardial infarction and stroke. When these catastrophes occur, the process becomes a medical emergency and drugs that slow down aging will be useless. However, anti-aging drugs may prevent new catastrophes (eg, new infarctions). Osteoporosis coupled with sarcopenia and neurodegenerative conditions
may ensure a broken hip after an elderly person falls. Anti-aging therapy will be of little or no use in emergencies, such as ventricular fibrillation and a broken hip. But, it will be useful to prevent and decrease atherosclerosis, osteoporosis, and neurodegeneration, which eventually lead to either a myocardial infarction or a broken hip. Anti-aging therapy will be most useful to prevent diseases or stop their progression, rather than to treat short-term complications.

References

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