Aging metabolism: intervention strategies

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ABSTRACT
Human beings are subjected to aging and age-associated diseases. Life expectancy has improved impressively in the last century due to social and economic development, but despite increasing improvement is still more limited than average in those ones with chronic diseases such as treated HIV infection. There has been a substantial research on the underlying factors responsible for aging both in the general and the HIV-infected populations. Several specific targets for potential intervention have been identified but studies so far have been limited to small experiments in cultured cells or living beings other than humans such as mice or flies. Time has come for designing and developing human studies with those candidate therapies showing most promising benefits and least potential toxicities to treat age-related diseases.

Introduction
Human aging and age-associated diseases have become one of the greatest social and economic challenges beyond health. Although average life expectancy has improved impressively in the last century, this fact has not been associated with a similar advance in healthy life prospect. This situation has been changing in recent years due to a better knowledge of the mechanisms involved in aging and to the results of different studies supporting that interventions addressed to slowing aging may be feasible. Several hallmarks of aging to which address potential interventions have been proposed. Primary hallmarks such as genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis are considered to be the primary causes of cellular damage. Antagonistic hallmarks such as deregulated nutrient sensing, mitochondrial dysfunction, and cellular senescence are considered to be part of compensatory or antagonistic responses to the damage; these responses initially mitigate the damage but they may become deleterious if maintained. Integrative hallmarks such as stem cell exhaustion and altered intercellular communication are the end result of the previous 2 groups of hallmarks and are ultimately responsible for the functional decline associated with aging.

As other chronic diseases, HIV has turned into a long-term manageable disease thanks to the effectiveness and availability of specific therapy. However, HIV-infected patients are still at risk of excess morbidity and mortality due to different factors. Modifiable contributing factors to the quantity and quality of life in adults aging with HIV include the injury from HIV infection (earlier diagnosis and treatment), the burden of harmful health behaviors (decreasing smoking, alcohol, and illicit drug use, and improving life style), the antiretroviral toxicity (safer drugs), and the general burden of age-associated comorbidities (better prevention and management). Although adults aging with HIV are subject to similar risk factors for age-related diseases and conditions as uninfected adults, they differ in the prevalence of harmful behaviors. They also experience ongoing HIV-associated inflammation and immune activation and adverse effects of chronic exposure to antiretroviral therapy leading to excess organ injury. The extent to which this excess is expressed in cellular aging, including cellular senescence, mitochondrial dysfunction, telomere attrition and epigenetic alteration is currently an area of active research.

Although HIV-infected adults tend to be less obese than uninfected adults, the prevalence of obesity has increased over time both in the general and the HIV-infected populations. In HIV patients, obesity is associated with the general aging process, earlier antiretroviral initiation, and increasingly widespread coverage. Weight gain after starting antiretroviral therapy is well documented and increase in weight usually surpasses that expected of demographically matched uninfected comparators. This weight gain is due in part to decreased metabolic...
demand from therapy-induced viral suppression coupled with therapy-induced fat accumulation and changes to appetite. In those HIV-infected patients that are overweight or obese, weight gain following antiretroviral therapy should be avoided as it may have a negative impact on survival. Furthermore, therapy-associated weight gain is associated with incident cardiovascular disease and diabetes. Increased visceral adipose tissue (VAT) is particularly problematic in HIV patients. Even with current antiretroviral therapy, VAT increases by 30% in the 2 y following therapy initiation. Increased VAT and peripheral lipoatrophy are associated with cardiovascular disease, and the risk is higher in HIV patients compared with uninfected adults irrespective of VAT level. Moreover, renin-angiotensin-aldosterone system activation associated with VAT accumulation contributes to insulin resistance in HIV infection, which contributes to the excess risk of diabetes associated with weight gain after antiretroviral therapy initiation.

Dietary interventions involving calorie restriction

The best characterized form of fasting evaluated has been the feeding every other day for a long period. Prolonged fasting, in which no food is taken for more than 2 consecutive days, has been investigated in lower eukaryotes and rodents. The pathways of fasting comprise downregulation of the Tor-S6K and Ras-adenylate cyclase-PKA, followed by a stimulation of stress resistance transcription Ms2/4 and Gis1, which protectively govern many metabolic genes. Prolonged fasting reduced both inflammatory markers and clinical symptoms in adults with rheumatoid arthritis and decreased adverse effects of chemotherapy in humans. The consequences of intermittent fasting have been more comprehensively assessed than those of prolonged fasting in humans. Reductions in weight, body fat, abdominal fat, insulin resistance markers and blood pressure have been consistently reported. Prolonged or intermittent fasting should be done under medical supervision because they may have adverse effects that could be life-threatening for persons with very low weight, those who are old and fragile, or insulinized diabetic patients. These issues emphasize the need of diets that imitate the effects of fasting while diminishing associated-adverse effects.

Drugs imitating the effects of calorie restriction

Inhibitors of the TOR pathway

mTOR plays a critical role in determining antigen-induced effector and regulatory T cell (Treg) fate decisions. mTOR activation is essential for T cell commitment for Th1, Th2, and Th17 effector lineages. When mTOR is blocked, naïve T cells preferentially differentiate into Treg cells. There are 2 complexes of mTOR kinase: mTORC1 and mTORC2. Reduction of mTORC1 blocks cellular growth. The drug sirolimus (also called rapamycin) used to prevent organ transplant rejection is a specific inhibitor of mTOR. Sirolimus is well known in clinical practice. However, it may have important adverse effects including insulin resistance and hematopoietic proliferative defects, which seriouly limit any further development as anti-aging therapy. The metabolic effects have been attributed to mTORC2 inhibition, suggesting that more specific inhibitors of mTORC1 could retain efficacy while being safer.

Inhibitors of glycolysis

Several studies in animals with inhibitors of glycolytic enzymes show effects similar to those of dietary restriction, although at the expense of important adverse effects. The first candidate in this category, 2-deoxyglucose as an inhibitor of the phosphoglucone isomerase, produced cardiotoxicity in rats. Mannohexotulose as an inhibitor of the hexokinase improved insulin resistance and increased lifespan in mice.

Inhibitors of the GH/IGF-1 axis

Persons with reduced IGF-1 have a lower risk for cancer and diabetes. Inhibitors of the IGF-1 receptor have been used in clinical trials as antineoplastic agents, but they are not approved for clinical use. Somatostatin analogs have been used to treat acromegaly by suppressing pituitary GH secretion and ultimately reducing IGF-1, but they may be associated with adverse effects. Another agent used to treat acromegaly, pegvisomat, does not decrease GH secretion but inhibits its action through blockade of GH receptor leading to a decrease of IGF-1. Pegvisomat has few adverse events and therefore it could be potential agent to test for longevity studies.

Activators of the sirtuin pathways

Some deacetylases called sirtuins produce effects similar to dietary restriction ultimately leading to longevity. Several metabolites derived from plants such as anthocyanidins, chalcones, flavones and stilbenes are potent sirtuin-activating compounds (STACs). Resveratrol is the best known natural compound activating sirtuins and attempts have been done to synthetize more potent
compounds. Another way of activating sirtuins is to increase NAD\(^+\) levels with NAD precursors, activators of NAD synthesis, or blockers of NAD hydrolysis.

**AMPK pathway activators**

The AMP-activated protein kinase is stimulated when cellular energy declines, promoting an increase in AMP levels. AMPK activation increases insulin sensitivity raising muscular glucose uptake, diminishing hepatic glucose production and promoting fatty acid oxidation. Exercise naturally stimulates AMPK. The biguanide metformin is a drug of choice for type 2 diabetes mellitus; it stimulates AMPK in the liver and, in contrast with other antidiabetic agents, has been shown to reduce the risk of cardiovascular disease, cancer incidence, cognitive decline, and overall mortality in diabetic patients.

**Inhibitors of inflammation**

Low-grade inflammation is involved in the pathogenesis of multiple comorbidities that may develop with the process of aging. Tissues in which chronic inflammation has been identified include the immune system, fat, muscle, liver and gut. The gut contains huge amounts of bacteria that can translocate or release substances into the circulation and both factors may promote systemic inflammation. However, the mechanistic processes triggering chronic inflammation are largely unknown. Stimuli can be chronic infections by agents such as cytomegalovirus, but also by-products of cellular turn-over such as reactive oxygen species and circulating mitochondrial DNA. The Mediterranean diet or diets enriched with omega-3 fatty acids may be an strategy to reduce chronic inflammation. Data from a recent systematic review on the effects of probiotics in HIV infection suggest possible benefits for CD4 count, recurrence or management of bacterial vaginosis and diarrhea management.

**Epigenetic pathways modulating agents**

Epigenetics refers to heritable phenotypic abnormalities induced by changes in the chromatin after cell replication. Studies in twins point out that genetics at birth may exert a relatively small influence on lifespan, suggesting that epigenetics (influenced by diet, lifestyle, and exogenous stress) contribute in a much higher proportion. Therefore, strategies addressed to these targets can improve age-associated cellular dysfunction. Inhibition of histone acetyltransferases in human and yeast cells has resulted in higher resistance to oxidative stress and lower cell death.

**Other promising potential targets**

Statins have shown clear beneficial effects in different types of aging-related morbidities and overall mortality human beyond reductions in lipids, blood, pressure, or cardiovascular disease. Considering the wide availability of statins, it seems worth to assess further its potential consequences on lifespan of healthy adults irrespective of cholesterol-lowering targets. Also, chronic \( \beta \)-blockers, nordihydroguaiaretic acid, activation of hexosamine pathway, deletion of upstream DNA damage responses, stem cell-based interventions, and blockers of retrotransposable elements could be also potential targets to prevent age-associated abnormalities and extending healthy lifespan.

**Conclusions**

There has been substantial research on the underlying factors responsible for aging both in the general and the HIV-infected populations. Several specific targets for potential intervention have been identified but studies so far have been limited to small experiments in cultured cells or living beings other than humans such as mice or flies. Time has come for designing and developing human studies with those candidate therapies showing most promising benefits and least potential toxicities to treat age-related diseases.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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