AJKD

Narrative Review

Chronic Kidney Disease: A Clinical Model of Premature Aging

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Premature aging is a process associated with a progressive accumulation of deleterious changes over time, an impairment of physiologic functions, and an increase in the risk of disease and death. Regardless of genetic background, aging can be accelerated by the lifestyle choices and environmental conditions to which our genes are exposed. Chronic kidney disease is a common condition that promotes cellular senescence and premature aging through toxic alterations in the internal milieu. This occurs through several mechanisms, including DNA and mitochondria damage, increased reactive oxygen species generation, persistent inflammation, stem cell exhaustion, phosphate toxicity, decreased klotho expression, and telomere attrition. Because recent evidence suggests that both increased local signaling of growth factors (through the nutrient-sensing mammalian target of rapamycin) and decreased klotho expression are important modulators of aging, interventions that target these should be tested in this prematurely aged population.

Am J Kidney Dis. xx(x):xxx.

INDEX WORDS: Chronic kidney disease; aging; cardiovascular disease; mammalian target of rapamycin (mTOR); klotho; phosphate; inflammation; oxidative stress.

Peter Stenvinkel, MD, PhD, was an International Distinguished Medal recipient at the 2012 National Kidney Foundation Spring Clinical Meetings. The International Distinguished Medals are awarded to honor the achievement of individuals who have made significant contributions to the field of kidney disease and extended the goals of the National Kidney Foundation.

The prevalence of chronic kidney disease (CKD) has reached epidemic proportions, and today ~10% of the population shows signs of decreased kidney function.[1] Patients with CKD are at increased risk of premature death, mainly due to a high risk of cardiovascular disease and infections, which often occur in combination with protein-energy wasting.[1] Cardiovascular risk increases early in the course of CKD progression,[2] and the non-normalized cardiovascular mortality risk in European patients starting dialysis therapy is 15-fold higher than that in the general population,[3] with the relative death risk being even higher in the United States.[4] Because the uremic phenotype is characterized by many features of aging, such as osteoporosis, atherosclerosis, poor wound healing, sarcopenia, infections, inflammation, oxidative stress, insulin resistance, frailty, hypogonadism, infertility, skin athrophy, cognitive dysfunction, and disability, CKD could be seen as a premature aging (or progeroid) syndrome. Because kidneys are among the organs most sensitive to the aging process,[5] the link between aging and decreased kidney function is birectional. Yang and Fogo[6] have suggested that manipulation of cell senescence, which is an important mechanism for preventing the proliferation of potential cancer cells, may be a future way to manipulate the age-associated decrease in kidney function.

THE BIOLOGICAL PROCESS OF AGING

As a consequence of improvements in life conditions and medical care, today humans can live longer than 100 years, a considerably longer time than that of our ancestors. The longest documented human life span is that of Jeanne Calment (1875-1997), a French woman who lived long enough to both meet Vincent van Gogh and experience the internet. Research in aging is a young field and aging has turned out to be a complex process controlled by many transcription factors and signaling pathways.[7] Although aging seems to occur in most species, many animals living in the natural environment do not become senescent because they die of disease, starvation, and predation before they reach old age.[8,9] Even so, the phenomenon of negligible senescence, which is characterized by an attenuated age-related change in reproductive and physiologic functions, as well as no observable age-related gradual increase in mortality rate,[9] has been documented. Among long-lived animal species such as turtles and rougheye rockfish, the naked mole rat has attracted much interest because recent data show that this eusocial mammal lives up to 8 times longer than mice. In addition, naked mole rats are extremely

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Received August 22, 2012. Accepted in revised form November 19, 2012.

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0272-6386/$36.00

http://dx.doi.org/10.1053/j.ajkd.2012.11.051

Box 1. Examples of Main Theories of Aging

- Evolutionary theory: based on Darwin's theory of natural selection
- Free radical theory: oxidative stress is considered a major cause of premature aging
- Mitochondrial theory: extension of the free radical theory
- Gene regulation theory: cellular senescence is the result of changes in gene expression
- Inflammation hypothesis: inflammation is considered a major part of the aging process
- Telomere theory: a limitation in replicative capacity after a certain number of cell divisions
- Immune theory: the immune system is a powerful mechanism to face stressors
- Neuroendocrine theory: aging is due to changes in endocrine and neural function
- Neuroendocrine-immuno theory: a combination of the immune and neuroendocrine theories
- Phosphate retention theory: a novel theory based on the finding that dietary restriction of phosphate attenuates the aging characteristics in klotho null mice[13]

Source: Tosato et al.[12]

resistant to neoplasia, oxidants, toxins, and oxygen deprivation.[10] Lewis et al[11] recently demonstrated that enhanced cell signaling through the tumor suppressor protein p53 and the transcription factor Nrf2 protects cells in naked mole rats, suggesting that further studies of the role of these proteins in the aging process are warranted. Improved understanding of the processes that have evolved in these specific species to increase healthy life spans provides unique opportunities to develop novel treatment strategies against human aging.

Aging commonly is defined as the progressive accumulation of deleterious changes in cells and tissues that are responsible for deterioration in physiologic functions coupled with increased vulnerability and risk of death. Tosato et al[12] discussed several different hypotheses of aging (summarized in Box 1). The permanent and irreversible growth arrest of cell senescence is a central paradigm of aging. Although senescent cells remain viable, they are unable to divide and their morphologic characteristics change and undergo significant transcriptional changes accompanied by delayed repair, as well as alterations in nuclear structure, gene expression, protein processing, and levels of growth factors (Fig 1). Recent evidence suggests that the mammalian target of rapamycin (mTOR) is involved in the hypersecretory senescent phenotype.[15] Among tumor suppressor proteins that are crucial in the induction of senescence, p53 (the "guardian of the genome") has an especially important role in protecting against DNA damage, oxidative stress, and telomere attrition. Cellular senescence may occur prematurely in response to a variety of stress factors, such as oxidative stress, DNA damage, and inflammation.[16] Notably, decreased kidney function per se and the uremic mileu affect most of the factors known to accelerate aging, including DNA damage, inflammation, phosphate toxicity, klotho deficiency, oxidative stress, exhaustion of stem cells, and telomere shortening.[17]

THE ANTAGONISTIC PLEIOTROPHY HYPOTHESIS

Of the multiple theories to explain exceptional longevity, the most robust has centered on the decreased signaling of anabolic hormones: growth hormone (GH), insulin-like growth factor (IGF), and insulin. Despite ample evidence in the literature that deficiencies in GH and IGF-1 contribute to several aspects of the natural aging process, animal studies show that disrupting the signaling pathways for these hormones exerts antiaging effects.[18] Potential mechanisms linking decreased signaling of these hormones with delayed aging include increased hepatic sensitivity to insulin actions, decreased plasma glucose levels, increased resistance to oxidative stress, and decreased mTOR signaling.[18] Thus, familial longevity usually is associated with better insulin sensitivity.[19] At least 7 genetic mouse models (including mice null for either GH receptor/binding protein or mice heterozygous for the IGF-1 receptor) have been reported to show increased life span and a delay in aging-related diseases.[20] Sonntag et al,[21] who recently summarized the literature on GH and IGF-1 and aging processes, suggested that the perceived contradictory roles of these anabolic hormones are explained by their differential effects on health during specific life span stages. In this context, the antagonistic pleiotrophy hypothesis[22] should be mentioned; this hypothesis posits that gene products have opposite effects on biological fitness at different stages of life. Based on this hypothesis, Blagosklonny[23] suggested that although mTOR activation by IGF-1, GH, insulin, and nutrients may provide a selective survival advantage to young males (because it stimulates muscle growth and increases competitive and reproductive ability), mTOR overactivation may accelerate age-related diseases (Fig 2). It recently was shown that increased mTOR signaling in hypothalamic neurons that express pro-opiomelanocortin contribute to age-dependent obesity.[24] Moreover, interventions that inhibit mTOR, such as rapamycin and caloric restriction, lead to changes in gene expression and to increased life span in both animals[25] and humans.[26] Thus, because single-gene mutations in those genes involved in insulin/IGF and mTOR signaling pathways extend life span,[27] dampening the mTOR pathway may protect from age-related diseases.