Aging Biology in the Kidney

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The notion that kidney function declines with age in the general population is well known in the Nephrology community and the average loss of glomerular filtration rate (GFR) about 1ml per year in most longitudinal studies. There is much debate within the community about whether this represents "normal aging" or whether this constitutes a form of renal disease. However this debate turns out, the real question is whether this decline is preventable - can it be modified or slowed? Efforts to find drivers of this decline are still in the very earliest stages, but have shown some promise at elucidating some of the pathologies involved. This article will address both the wider issue of the biology of aging as well as the specific pathologies of the aging kidney.

INTRODUCTION

The notion that kidney function declines with age in the general population is well known in the nephrology community and the average loss of glomerular filtration rate about 1 mL per year in most longitudinal studies. There is much debate within the community about whether this represents "normal aging" or constitutes a form of kidney disease.[1,2] However, this debate turns out, the real question is whether this decline is preventable—can it be modified or slowed? Efforts to find drivers of this decline are still in the very earliest stages but have shown some promise at elucidating some of the pathologies involved. This article will address both the wider issue of the biology of aging and the specific pathologies of the aging kidney.

GENETIC DRIVERS AND SIGNALING PATHWAYS REGULATING AGING

Research into the aging process has been pursued by only a hand full of scientist mainly in the basic science departments; also, because such research was felt to be futile, as aging was thought to be the natural and inevitable consequence of "wear and tear" of life. The idea that aging could be influenced by the genetic code and had a modifiable biologic component is less than 20 years old. Since then, we have come to understand that aging is a complex biological process controlled by signaling pathways and transcription factors, very similar to disease processes.

Research into the biological basis of aging was accelerated by a chance finding in 1993 by Cynthia Kenyon and colleagues. She was studying the biology of the nematode *Caenorhabditis elegans*, and happened on a spontaneous gene mutation that prolonged the worm's life by one third.[3] These mutant worms were healthy, active, and fertile but lived much longer than their wild-type controls. In 1997, a different group cloned this first gene called daf-2 and showed it to be insulin-like growth factor 1 (IGF-1) receptor.[4] This pathway affects expression of a DNA FOXO transcription factor, which controls expression of activity in multiple metabolic pathways, which ultimately results in life span extension. Inhibiting IGF pathways extends life span through changes in the expression of genes involved in multiple pathways, and these are reviewed in detail in the study by Kenyon.[5] Soon, similar life span extension was shown for mutations in other genes within the same signaling pathway. It was initially thought that a process that worked in a small simple organism, such as *C. elegans* was unlikely to have a parallel in highly complex larger organisms. However, manipulation of this pathway has now been successfully used to extend life span in multiple organisms, including mice.[6] Although it is clearly not possible to experimentally modulate activity in this pathway in humans, there are cohorts of centenarians in whom mutations affecting activity in IGF-1 signaling have been identified.[7] Importantly, calorie restriction, which has been shown to extend life span in non-vertebrates and most vertebrates, also alters the activity of this pathway (see in the following section).

In the 20 years since this seminal discovery, 3 other signaling pathways have been found to be capable of modifying the aging process. These include "target of rapamycin (TOR) signaling". TOR inhibition increases life span in all experimental models from yeast to mammals.[5] This pathway is implicated in mediating the longevity effects of calorie restriction, and calorie restriction of an animal harboring a mutation in the TOR pathway does not further extend life span.[8,9] TOR interacts with pathways that control messenger RNA (mRNA) translation, autophagy, and mitochondrial metabolism. Although the exact mechanism whereby mTOR inhibition slows aging is still unclear, current evidence supports the idea that mTORC1 modulates aging by mechanisms that overlap but are distinct from insulin/IGF-1–like signaling, consistent with the model that mTORC1 acts mainly downstream of dietary restriction.[10] As noted in the following section (under calorie restriction), experiments are currently underway in mice to try and extend life span by using rapamycin.[11] On the other hand, the effects of rapamycin on

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organ-specific aging phenotypes remain unclear.[12] Clearly careful thought will need to be given to the use of rapamycin to slow the aging process in humans in view of its unclear mechanisms and many side effects. However, the significant work on this pathway does hold the promise of finding ways to slow age-related pathologies and facilitate healthy, disease-free aging.[13]

A signaling mechanism that promotes longevity includes Sirtuins, a broadly conserved family of enzymes found in all phyla of life from the simplest to the most complex. The sirtuin pathways are believed to be the target of resveratrol, the much-touted "healthy ingredient" in red wine. These ancient proteins have a common biochemistry, which allows them to interact with nicotinamide adenine dinucleotide (NAD^+), and deacetylate proteins. The first link with aging was the discovery of SIR2 (Silent Information Regulator) in yeast, which controlled healthy extension of life span.[14,15] There are 7 mammalian homologues called SIRT1 to 7.[16] Knockout of at least 1 family member, SIRT6 causes premature aging.[17] There is also research implicating the sirtuins in metabolic dysfunction such as diabetes, in cancer suppression and in cardiovascular disease—the world's leading cause of death.[18] As this field continues to grow, new roles for these ubiquitous molecules are continually being added. They have been shown to be important in adaptation to low-nutrient conditions, mitochondrial function, DNA repair, neuronal survival, and the maintenance of a youthful pattern of gene survival. Which of these functions is responsible for the increase in life span is not yet clear. Of note, SIRT1, SIRT3, and SIRT6 are all induced by calorie restriction, suggesting a mechanism for the benefits seen in calorie-restricted animals. The current emphasis of sirtuin research focuses as much on the benefits to "healthspan" as it does on the extension of life span. The key is to understand how to achieve healthy extension of life. There is significant effort to develop small molecule activators of sirtuins, and these have already shown promise in mice.[19,20] This is a rapidly expanding field with as yet, no clear link to the kidney, although SIRT1 is believed to provide some renoprotection through reduction of fibosis and through anti-inflammatory effects.

Klotho was the Greek goddess who spins the thread of life, and the name was given to a gene that characterized an accelerated aging phenotype. The role of klotho in aging was an accidental finding published in 1997.[21] A group making a transgenic mouse had fortuitously inserted their transgene randomly into the promoter region of the klotho gene and produced a prematurely aged mouse that lives only 5% to 6% of normal captive mouse life span. Subsequent work with an overexpressing model produced a mouse that lives 20% to 30% longer than wild-type littermates.[22] Klotho is expressed as both a membrane protein and a secreted protein, primarily in the distal tubular cells of the kidney. Its primary role appears to be as a cofactor or coreceptor regulating fibroblast growth factor 23 signaling and activation of the ion channel TRPV5. It plays an important role in phosphorus homeostasis. Klotho promotes phosphate excretion, and reduced expression of klotho is associated with ectopic calcification, increased concentrations of $1,25(OH)_2$-vitamin D_3, hyperphosphatemia, and therapy-resistant hyperparathyroidism.[23,24] Although these functions are important in the context of kidney disease, the aging phenotype appears to be modulated through the IGF-1 signaling pathway. Secreted klotho inhibits insulin/IGF-1 signaling, and klotho-deficient mice are hypoglycemic and highly insulin-sensitive, whereas mice overexpressing klotho are resistant to IGF-1. It is this interaction with an evolutionary conserved mechanism for regulating aging that appears to confer the aging phenotype. Reduced expression of klotho has been observed in patients with chronic kidney disease (CKD).[25] Some single nucleotide polymorphisms in human klotho are associated with altered life span and increased vascular disease.[26] Klotho is clearly an interesting protein with a role to play in the complications of CKD and maybe in the altered life span associated with this disease. It has potential both as a biomarker to define which patients with CKD are progressors and as a therapeutic intervention to slow progression.

CLINICAL SUMMARY

- Aging affects all components of the kidney in distinct ways and leads to age-associated loss of kidney function.
- Aging is a molecular process that can be interrogated and potentially manipulated.
- Identification of avenues to modulate aging-associated molecular events can potentially increase healthspan.

At this time, the only gene-specific intervention to retard aging is to inhibit mTOR, but several research groups are actively pursuing the IGF-1 and the Sirtuin pathways as potential targets for intervention. Experiments in rodents are currently ongoing and attempting to slow the aging process using rapamycin (sirolimus) to interfere with mTOR signaling.[11] Results from this study so far are modest with an increase in maximum life span of 14% for female mice and 9% for male mice. This does show promise for pharmacologic interventions that prevent age-related diseases, but it remains to be shown that age-associated glomerulosclerosis can be slowed. There is also the consideration of significant side effect profile associated with rapamycin. Therefore, several newer studies are testing low-dose and intermittent regimens to assess efficacy without side effects.

DNA Damage and Progerias

Maintaining the integrity of DNA is essential for normal "healthy" cellular function. Not only can point mutations in the DNA sequence of single genes be the cause of cancer and many diseases related to aging but DNA is continuously damaged by free radicals including reactive oxygen species (ROS) generated by errors in enzymatic reactions