Molecular mechanisms of renal aging

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Epidemiologic, clinical, and molecular evidence suggest that aging is a major contributor to the increasing incidence of acute kidney injury and chronic kidney disease. The aging kidney undergoes complex changes that predispose to renal pathology. The underlying molecular mechanisms could be the target of therapeutic strategies in the future. Here, we summarize recent insight into cellular and molecular processes that have been shown to contribute to the renal aging phenotype.The main clinical finding of renal aging is the decrease in glomerular filtration rate, and its structural correlate is the loss of functioning nephrons. Mechanistically, this has been linked to different processes, such as podocyte hypertrophy, glomerulosclerosis, tubular atrophy, and gradual microvascular rarefaction. Renal functional recovery after an episode of acute kidney injury is significantly worse in elderly patients. This decreased regenerative potential, which is a hallmark of the aging process, may be caused by cellular senescence. Accumulation of senescent cells could explain insufficient repair and functional loss, a view that has been strengthened by recent studies showing that removal of senescent cells results in attenuation of renal aging. Other potential mechanisms are alterations in autophagy as an important component of a disturbed renal stress response and functional differences in the inflammatory system. Promising therapeutic measures to counteract these age-related problems include mimetics of caloric restriction, pharmacologic renin-angiotensin-aldosterone system inhibition, and novel strategies of senotherapy with the goal of reducing the number of senescent cells to decrease aging-related disease in the kidney.

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While life expectancy in developed countries has constantly increased in the last century, incidence rates of acute kidney injury and chronic kidney disease have also grown and will continue to grow in proportion to the expanding geriatric population. Although the aging process *per se* does not cause renal disease, the kidney undergoes distinct physiologic changes during the lifespan, predisposing to renal pathology. Renal volume and the number of functioning nephrons decrease progressively, and the glomerular filtration rate declines with advancing age. In parallel, the kidney develops reduced capacities for adaptation to stress and for structural repair. Combined with the cumulative impact of age-associated risk factors, these features lead to renal disease in the elderly. From a cellular and molecular point of view, considerable advances in identifying some of the mechanisms involved have been made. A comprehensive view of these findings may provide insight into novel therapeutic possibilities. In this review, we discuss specific cellular and molecular processes that show promise for elucidating the complex biologic events that lead to normal and pathologic renal aging.

Structural and functional changes of kidney cells

The aging process *per se* is characterized by a progressive decline in intrinsic physiologic function of all organs.[1] The kidney is one of the best organs to study this decline because age-associated functional changes are easily detectable by standard clinical measures. The glomerular filtration rate drops by approximately 5%–10% per decade after the age of 35 years.[2,3] The structural correlate for this decline is a loss of functioning nephrons. It was recently observed that kidneys from healthy donors aged 70 to 75 years had 48% fewer intact nephrons than kidneys from donors aged 18 to 29 years.[4] An estimated 6000–6500 nephrons are lost per year after the age of 30.[4,5] Compared with this loss, the corresponding drop in glomerular filtration rate is proportionally smaller because the remaining nephrons undergo hypertrophy, resulting in partial functional compensation. A crucial and still largely unresolved question is why do nephrons perish during healthy aging? Although all renal compartments and cell types might contribute to the underlying process, research during recent years has focused on podocytes and intrarenal microvasculature.

Podocytes. As terminally differentiated cells, podocytes play a central role in renal aging. Podocyte proliferation and replacement capacity are minimal in the adult mouse under normal conditions.[6] When challenged by the progressive loss of neighboring cells during the lifespan, podocytes are driven

into hypertrophy.[7–10] Podocyte hypertrophy seems to be compensatory for a long time (Figure 1). With a gradual loss of nephrons, however, the need for hypertrophic enlargement of the remaining glomeruli causes persistent stress that gradually becomes overwhelming. In turn, podocyte detachment, secondary tuft vasoconstriction, capillary collapse, parietal epithelial cell activation, periglomerular fibrosis, and global glomerulosclerosis may ensue.[7,9,11] Eventually, globally sclerosed glomeruli involute and become increasingly difficult to recognize by light microscopy.[12] The involution of entire nephrons with the disappearance of glomerular structures explains the poor correlation between age-related loss of renal function and detectable glomerulosclerosis in morphometric studies.[13] Diagnostically, it has been suggested that the individual podocyte density per glomerulus could serve as a biomarker read-out in biopsies to determine biologic kidney age.[14] Despite a well-justified interest and an increasing focus on podocytes in recent years, it is important to recognize that podocytes are not the only cell type contributing to nephron loss in the aging kidney.

Capillary network. Regardless of the etiology of chronic kidney disease, loss of peritubular capillaries is strongly associated with interstitial fibrosis and predicts renal functional decline.[15–17] A decrease in peritubular capillary density can also be observed during kidney aging.[18,19] However, it is presently unclear to what extent the age-related reduction in renal microvessels is a secondary effect of glomerulosclerosis or instead an independent cause of nephron loss. Considering the "rete mirabile" organization of the renal microvasculature, glomerulosclerosis and nephron loss are necessarily paralleled by a gradual reduction in peritubular capillary density. On the other hand, there is also evidence for direct age-associated changes in capillary health and maintenance. An imbalance of endothelial cell–derived factors alters vascular tone and vasomotor activity in aging.[20,21] Decreased abundance of nitric oxide and increases in endothelin-1 lead to an impaired

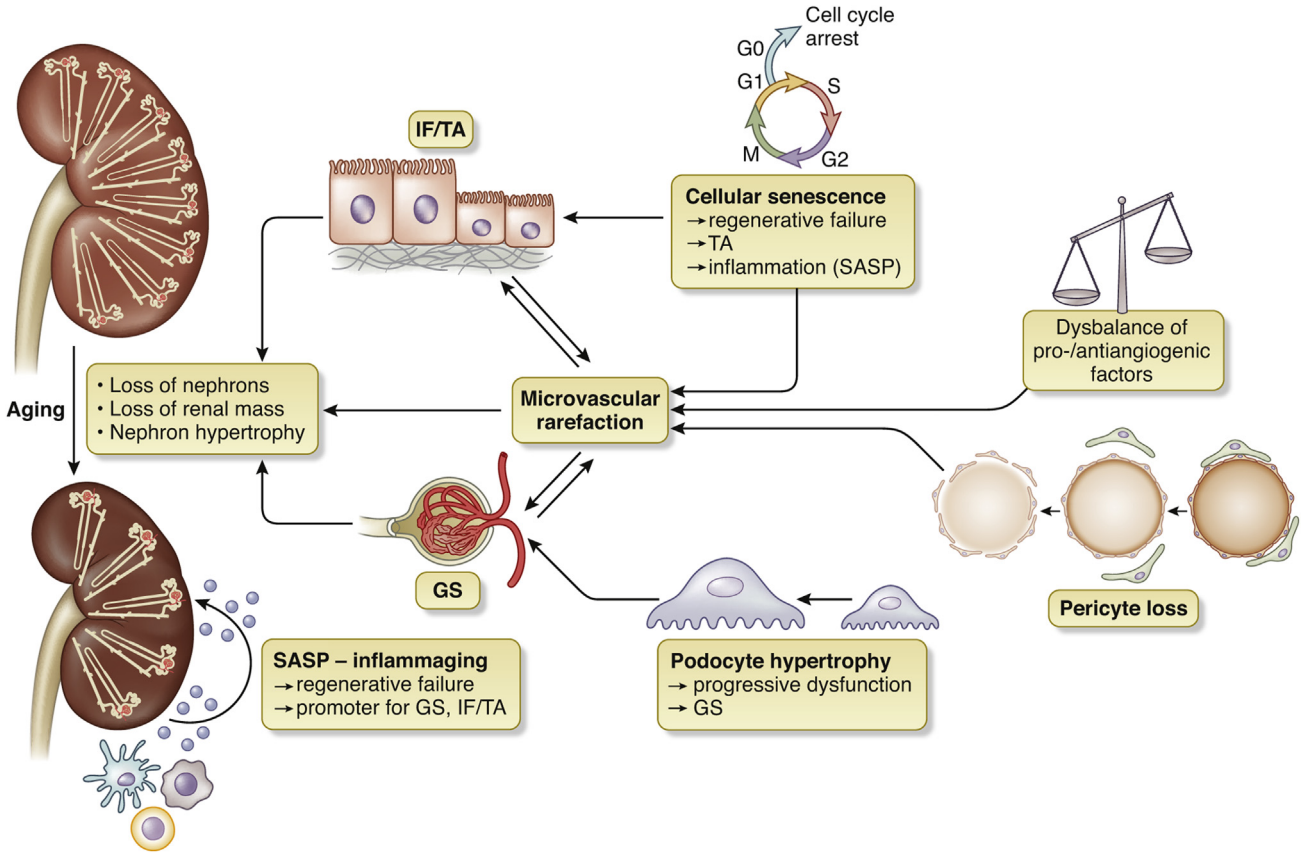

Figure 1 | Changes occurring in the aging kidney. The aging kidney loses nephrons and mass; in turn, the remaining nephrons compensate for this loss by undergoing hypertrophic adaptation. The figure illustrates driving mechanisms for the aging-associated macroscopic and microscopic findings and the regenerative failure seen with older age. The histologic features interstitial fibrosis and tubular atrophy (IF/TA), glomerulosclerosis (GS), and microvascular rarefaction are partly interdependent. The importance of cellular senescence for tubular changes has been nicely demonstrated, but a contribution of cellular senescence to microvascular changes through endothelial or vascular senescence is also conceivable. Pericyte loss and an imbalance of pro- and antiangiogenic factors further contribute to the vascular phenotype with age. The age-related reduction in renal microvasculature may be an independent cause of nephron loss but could be also secondary to GS. Podocyte hypertrophy and the associated dysfunction are driving GS. SASP, senescence-associated secretory phenotype.