# Aging biomarkers in CKD: Time for rejuvenation?

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Aging is a physiological process occurring in all organisms and gradually leading to progressive functional decline and, eventually, death. The field of biomedical research on aging has evolved considerably over the last decades focusing on the biochemical, genetic, and physiological mechanisms underlying the process of biological aging. Although the current understanding of aging remains limited, certain common cellular and molecular traits have been identified associated with its progress.

**The hallmarks of aging**

The hallmarks of aging should ideally fulfill the following criteria: they should manifest during normal aging, their experimental aggravation should accelerate aging, and their experimental amelioration should postpone the normal aging process. The primary hallmarks include the factors that cause aging-associated damage, those responding to the damage, and the consequences of the response and culprits of the aging phenotype. Nine hallmarks are considered to contribute to the aging process and jointly determine the aging phenotype: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Aging is regulated by specific signaling pathways, and among them, the mTOR, the p53, the p16, the IGF1/insulin pathway, and the mitochondrial dysfunction pathway play critical roles. Novel research suggests active interactions between these aging models.

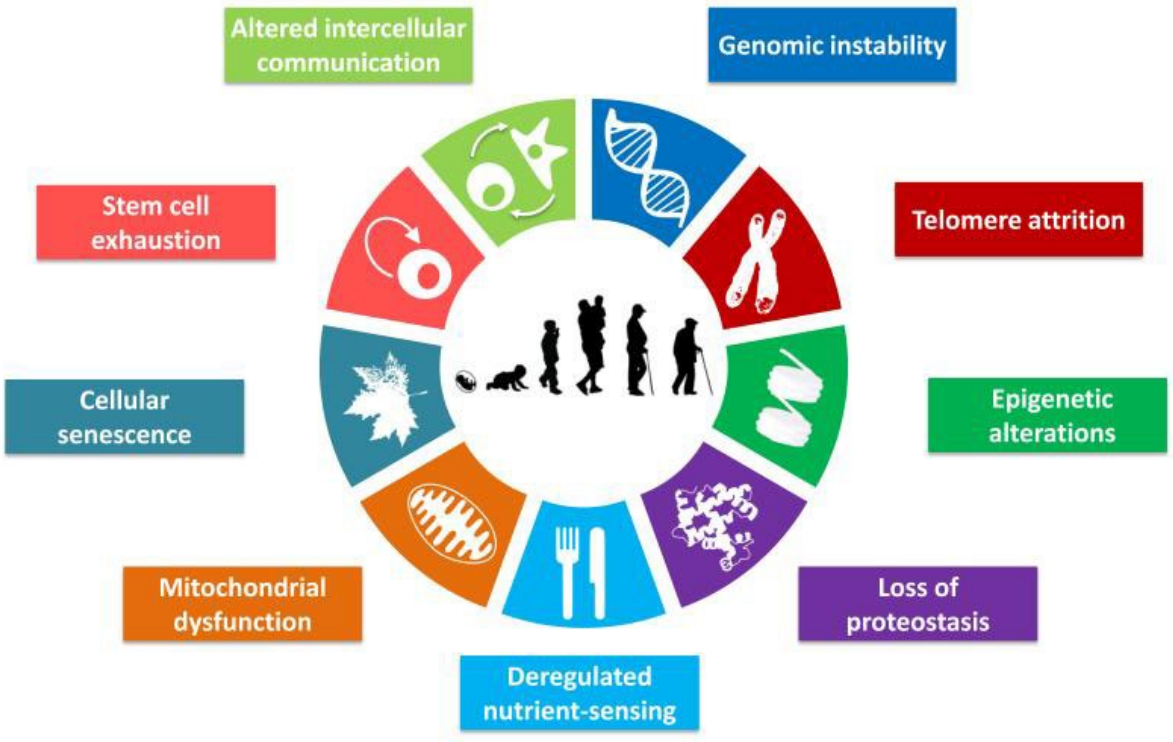


Figure 1. The hallmarks of aging

**Senescence**

Senescence is a cellular response that limits the proliferation of aged or damaged cells. Besides playing a physiological role in normal development, it is also necessary for tissue homeostasis and is a powerful mechanism of tumor suppression. It also constitutes a stress response associated with genomic instability and telomere attrition, which are also the hallmarks of aging. The possible relationship between senescence and aging was first suggested in the early research by Hayflick and Moorhead during the serial passage of human fibroblasts. The aberrant accumulation of senescent cells with age results in potential detrimental effects, but there is a hypothesis that senescence itself can provoke aging processes.

The major feature of senescent cells is their stable growth arrest in the G0 phase related to telomere shortening. Senescent cells remain metabolically active but undergo several morphological and physiological alterations, including the upregulation of beta-galactosidase activity and acquisition of a proinflammatory pro-fibrotic senescence-associated secretory phenotype (SASP). There is an intimate link between senescence and other antagonistic hallmarks of aging. For example, senescent cells display decreased removal of damaged mitochondria, which may accumulate and contribute to metabolic dysfunction.

Cell cycle arrest in senescence is largely mediated through p16 and p53 pathways. In normal cells activation of these pathways is crucial for maintaining genomic integrity. The p16-mediated senescence acts through the retinoblastoma pathway inhibiting the action of the cyclin dependant kinases leading to the arrest of the G1 cell cycle phase. The p53 pathway activates in response to DNA damage and also causes cell growth arrest.

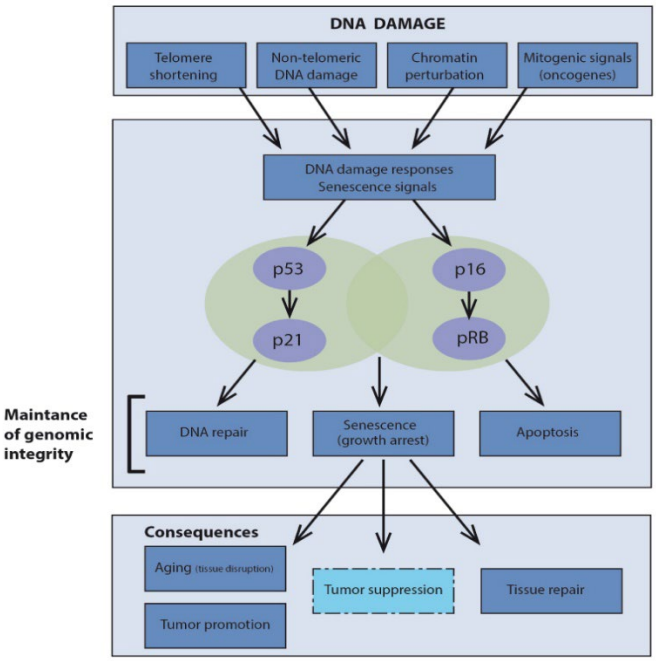


Figure 2. Senescence pathways

**Aging and CKD**

Aging and chronic kidney disease (CKD) are bidirectionally related – the prevalence of CKD increases with aging, while the disease itself accelerates biological aging through four major mechanisms: by increasing allostatic load, activating age-promoting mechanisms, triggering stress-resistance pathways, and through impairment of anti-aging pathways. Stress resistance may be central to the hallmarks of aging and enhanced adaptation to stress appears to retard aging. The major pathways involved in stress resistance are the insulin-like growth factor-1 (IGF1) pathway, the target of rapamycin (mTOR)-S6K1 pathway, and the FOXO3 pathway. The IGF1 and mTOR pathways normally stimulate cell growth and protein synthesis in states of energy excess, thus playing a critical role in cell proliferation, survival, and energy metabolism. Alterations to each of these pathways have effects on aging and age-dependent diseases. FOXO3 is a key player in the control of skeletal muscle protein turnover and its downregulation accelerates cellular senescence. All these pathways share AMP-activated protein kinase (AMPK) as the common element, which plays a major role as a master regulator of cellular energy homeostasis and manages cell growth and autophagy. AMPK is inactivated in senescent cells.

In CKD patients, premature aging at a cellular level typically manifests by accelerated shortening of telomeres and an accumulation of growth-arrested cells that express p16. The pathophysiologic substrate of CKD is renal tissue fibrosis, accompanied by an upsurge of senescent cells, developing either due to renal injury or related to aging. Senescent cells accumulate in many renal diseases, including IgA nephropathy, several types of glomerular nephritis, hypertensive and diabetic nephropathy, and delayed graft function.

**Senescence in lupus nephritis**

Accelerated senescence may be one explanation for some excess morbidity and mortality seen in lupus patients. Very recent data show biomarkers of cellular senescence in experimental models and human lupus, including telomere shortening and upregulation of the p16 pathway. The increased activity of the p16 pathway is associated with higher proteinuria levels and worse renal outcomes, but not with parameters of disease activity in lupus nephritis. Telomere shortening in lupus nephritis does not appear to reflect disease activity or immune cell turnover, but is associated with lower vitamin D levels and improves with vitamin D replenishment.

The exact causes for senescence activation in lupus nephritis still need to be elucidated, but the inflammatory-oxidative environment is the most likely trigger. The detrimental effect of senescence in lupus nephritis manifests through SASP-associated fibrosis. Accumulation of senescent cells impedes tissue repair processes, thus leading to organ failure.

**Key points**

1. Aging is a physiological process characterized by progressive functional decline.
2. Senescence is characterized by an irreversible growth and division arrest of aged or damaged cells. It is mediated through p16 and p53 pathways and represented by telomere shortening.
3. Aging and CKD are bidirectionally related - the prevalence of CKD increases with aging while CKD itself accelerates biological aging.
4. The major pathways involved in CKD-related senescence are the IGF1 pathway, the mTOR-S6K1 pathway, and the FOXO3 pathway.
5. Accelerated senescence is also seen in lupus nephritis, but more research is needed to identify the exact causes of its activation.

**Further reading**


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