Chronic Inflammation Potentiates Kidney Aging

Changlin Mei, MD, and Feng Zheng, MD†*

Summary: Chronic inflammation, characterized by increased serum levels of tumor necrosis factor-α, interleukin-6, C-reactive protein, and plasminogen activator inhibitor-1, and the presence of inflammatory-related diseases, are seen commonly in aging. Both the dysregulation of immune cells and phenotypic changes in parenchymal cells may contribute to chronic inflammation in aging. Moreover, senescent cells are an important source of inflammatory factors. Oxidative stress, via activation of p38 and c-Jun N-terminal kinase and induction of cell senescence, is likely to play a critical role in inflammation. Endoplasmic reticulum stress also may be present in aging and be involved in inflammation. Advanced glycation end products also are important contributors to inflammation in aging. Because the kidney is a major site for the excretion, and perhaps the degradation, of advanced glycation end products and small inflammatory molecules, reduced renal function in aging may promote oxidative stress and inflammation. Chronic inflammation in turn may potentiate the initiation and progression of lesions in the aging kidney.

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Aging is associated commonly with various degrees of reduced renal function.[1] Because reduced renal function occurs in 11% of older individuals who did not have an obvious intervening disease such as diabetes, hypertension, and drug toxicity,[1] a process of kidney biological aging may be the cause in a segment of the aging population. Kidney aging is an important health problem because, although it may not progress often to end-stage renal disease, it very likely increases the risk of cardiovascular diseases.[2] Multiple factors including oxidative stress, the accumulation of advanced glycation end products, the loss of sex hormone(s), cell senescence, and the dysregulation of vascular tone have been implicated in the development and progression of kidney aging.[3-5] A role for chronic inflammation also recently has emerged and is the center of this review. This review begins with a description of the association of chronic inflammation with aging and aging renal function decline, and then specifically discusses the likely cell sources and mechanisms of chronic inflammation in aging. The last section focuses on a possible role of chronic inflammation in the progression of kidney aging.

THE ASSOCIATION OF CHRONIC INFLAMMATION WITH AGING AND AGING RENAL FUNCTION DECLINE

Accumulating evidence suggests that aging often represents a state of chronic low-grade inflammation characterized by increased serum levels of tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), IL-1–receptor antagonist, fibrinogen, and C-reactive protein (CRP).[6-8] For instance, the levels of fibrinogen and CRP were higher in healthy elders older than 60 years than in adults younger than 45 years.[7] Chronic inflammation may play an important role in aging-related diseases such as atherosclerosis, type 2

*Nephrology Institute of PLA, Department of Medicine, Changzheng Hospital, Second Military Medical University, Shanghai, China.
†Division of Experimental Diabetes and Aging, Department of Geriatrics, Mount Sinai School of Medicine, New York, NY.
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Address reprint requests to Feng Zheng, MD, Assistant Professor, Division of Experimental Diabetes and Aging, Department of Geriatrics, Mount Sinai School of Medicine, Box 1640, One Gustave Levy Pl, New York, NY 10029. E-mail: feng.zheng@mssm.edu
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diabetes, and neurodegenerative diseases.[8] Inflammation is also a critical player in many forms of chronic kidney disease (CKD).[9,10] Patients with CKD, especially those with advanced disease, are known to have higher levels of TNF-α, IL-6, and CRP.[11] Because dialysis may have a major impact on immune cells and body homeostasis, Pecoits-Filho et al[12] specifically examined the levels of CRP and IL-6 in predialysis renal failure patients (estimated glomerular filtration rate [eGFR], 1.8-16.5 mL/min/1.73 m^2) and found that patients with the lowest eGFR had higher CRP and IL-6 levels. Thus, renal failure per se is associated with increased inflammation. An association of moderate eGFR decline (30-60 mL/min/1.73 m^2) with inflammation also was found in patients with CKD. The increase was even more obvious in older patients with a similar degree of renal function decline. Moreover, a report from the health, aging, and body composition study showed that 70- to 79-year-old individuals with mild renal function decline (eGFR $\geq$ 60 mL/min/1.73 m^2 but Cystatin C $\geq$ 1 mg/L) had significantly increased serum TNF-α and its soluble receptor levels than age-matched controls with Cystatin C levels of less than 1 mg/L.[13] These data suggest that decreased renal function, especially when it occurs in aging, may be an independent risk factor for inflammation. Because the kidney is a major site for the removal of small molecules, it may be reasonable to speculate that reduced renal function would promote inflammation via retention and perhaps less degradation of molecules such as advanced glycation end products (AGEs), TNF-α (25 kd), and IL-6 (21-28 kd).

THE CELLULAR SOURCES OF CHRONIC INFLAMMATION IN AGING

The cellular basis of chronic inflammation in aging is unknown. A dysregulation of the immune system in aging is believed to play an important role in chronic inflammation.[14] Generally, the functions of immune cells are decreased in older people. Fewer B and T cells are produced in older human beings.[14,15] In addition, B cells from older individuals generated antibodies with lower affinity to antigen and had an impaired ability to undergo class-switch recombination compared with B cells from the young.[16,17] Alterations in the T cells, including an increase in memory CD4+ T cells and a decrease in naive CD4+ T cells, in aging also have been reported.[14,15] Interestingly, stimulation of CD4+ T cells from aged mice with antibodies to CD3 plus CD28 resulted in a more robust increase in IL-17 and IL-6 production, but a significant decrease in IL-21 production compared with CD4+ T cells from young mice,[18] suggesting a change in T-cell response and cytokine profile that favors chronic inflammation. Macrophages from aged mice also showed a more significant increase in lipopolysaccharide (LPS)-stimulated expression of cyclo-oxygenase 2 and production of prostaglandin E2.[15] Thus, age-related abnormalities in T cells and macrophages may contribute directly to the increased levels of serum inflammatory markers in aging.

A role for parenchymal cells, including kidney cells, in chronic inflammation in aging has gained attention recently. Parenchymal cells actively are involved in inflammatory responses by producing chemokines, cytokines, and growth factors, and by expressing adhesion molecules. For example, adipocytes from obese, type 2 diabetic patients, and aging individuals have been found to produce significant amounts of TNF-α and IL-6.[19-21] Moreover, we found that the upregulation of cytokines (ie, IL-6), chemokines (ie, monocyte chemoattractant protein-1 [MCP-1], macrophage inflammatory protein-2 [MIP-2]), and adhesion molecules (ie, intracellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1]) occurs before the appearance of inflammatory cells in aging kidneys in mice (unpublished data). Therefore, proinflammatory changes in parenchymal cells may be an early event. This hypothesis is supported by a similar study in human aging kidneys. Microarray analysis showed that aged human kidneys have increased expression of VCAM-1, C-X-C motif ligand 2 (CXCL-2), CXCL-14, and complements (C1 and C4) in the absence of an obvious immune cell infiltrate.[22] Because we have found a proinflammatory phenotype in mesangial cells from aging mice,[23, 24] phenotypic changes may be a mechanism to explain the increased expression of proinflam-