In-Depth Review

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Cellular Senescence and Inflammation: A Noteworthy Link

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Interleukin-6 · Atherosclerosis · Chronic kidney disease · Telomeres

Abstract
Although cellular senescence and inflammation have been indirectly associated, a direct connection was absent until recently, when two studies proved that senescence at a cellular level is directly linked to an interleukin (IL)-dependent inflammatory network. IL-6 and IL-8, two well-known proinflammatory cytokines, seem to play a central role in premature cellular senescence induction. Activation of the abovementioned molecules and their receptors is necessary for the initiation of senescence while their deactivation ceases the process. Taking in consideration that atherosclerosis is an inflammatory process and cellular senescence is an emerging cardiovascular risk factor, these new data may be of great importance, especially for chronic kidney disease patients who suffer from increased cardiovascular disease morbidity.

Cellular senescence, a process similar to apoptosis, induces irreversible growth arrest. Cells remain viable but display characteristic changes in their morphology, physiology and gene expression, and are unable to divide [1]. While senescence usually occurs after an extensive number of cell divisions (replicative senescence), it also appears prematurely, independently of the number of cell divisions, in response to various physiological stresses (oncogene activity, radiation, oxidative stress, DNA damage, etc.) [2].

Until recently, cellular senescence was connected mostly indirectly to inflammation. Microarray analysis showed that senescent fibroblasts demonstrate a strong inflammatory type response [3]. Ageing CD8+ T cells produce increasing amounts of interleukin (IL)-6 and tumor necrosis factor-α [4]. Finally, in a recent interesting publication it was shown that reactivation of endogenous p53 (a tumor suppressor factor implicated in apoptosis and senescence induction) in p53-deficient tumors induced cellular senescence that was associated with differentiation and upregulation of inflammatory cytokines [5].

Two new studies published in the same issue of *Cell* have proven an unexpectedly tight link between the process of cellular senescence and an IL-dependent inflammatory network [6, 7]. Two groups of researchers worked on an oncogene-induced model of premature cellular senescence. Kuilman et al. [6] found that IL-6 is a central regulator of an inflammatory network mediating oncogene-induced senescence (OIS) and upon its depletion the network collapses and cells bypass OIS. Specifically, IL-6 was upregulated in cell lines expressing an oncogenic allele of BRAF (cells programmed to enter prematurely in OIS). When IL-6 or its receptor (IL-6 receptor) was suppressed, the cells re-enter the cell cycle and proliferate, so bypassing OIS. This effect of IL-6 was medi-

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ated through the RB tumor suppressor pathway (the second principal pathway of cellular senescence induction, excepting p53). They also found that suppression of IL-8 is similar to the IL-6 effect [6]. This latter finding was also confirmed by Acosta et al. [7]. With a similar approach they found that overexpression of chemokine receptor CXCR2 or its ligands IL-8 and GROα/Gro-1 induce replicative and premature OIS. This latter induction was dependent on the p53 pathway. It is worth mentioning that CXCR2 was regulated by the transcription factor nuclear factor-κB (NF-κB) [7, 8] (fig. 1).

These new data are shedding light on the process of atherosclerosis, which also affects chronic kidney disease (CKD) patients in whom atherosclerotic cardiovascular disease (CVD) is the leading cause of morbidity and mortality in a large number of cases [9].

Atherosclerosis is recognized as an inflammatory process that is initiated by oxidized LDL or other stimuli in arterial intima [10, 11]. Vulnerable atheromatous plaque development and rupture has dramatic consequences (e.g. myocardial infarction) [10, 11]. Recent studies have shown that many CVD risk factors like diabetes, obesity, hypertension, cigarette smoking, etc., are associated with cellular senescence in diverse cell types [12]. Depending on the phase of atherosclerotic plaque development, the senescence phenotype seems to be atherogenic [12]. In concert with inflammation, cellular senescence makes atherosclerotic plaque vulnerable and thus really dangerous [13, 14]. Finally, in an increasing number of clinical studies, some biomarkers of cellular senescence, especially telomere – the end of eukaryotic cell chromosomes – attrition, in circulating leukocyte DNA, correlated with incident or prevalent atherosclerotic CVD [15]. The new biological data emphasize the strong, inflammation-senescence relationship and support the experimental and clinical data mentioned above linking cellular senescence with the inflammatory process of atherosclerosis.

According to a number of recent publications, cellular senescence, at least in circulating monocytes-leukocytes, seems to develop prematurely in CKD patients [12]. Telomere length as well as the activity of telomerase – that protects telomere structure – in circulating cells, are reduced and inversely correlated to renal function in the same patients [16–18]. Furthermore, both senescence biomarkers were found to be associated with the micro-inflammatory state – and probably with the oxidative stress – which characterizes these patients [17, 19, 20]. Moreover, new data showed that inflammation may be the link between diverse processes like vascular calcification [21, 22] or factors (like sialic acid [23]) and CVD in

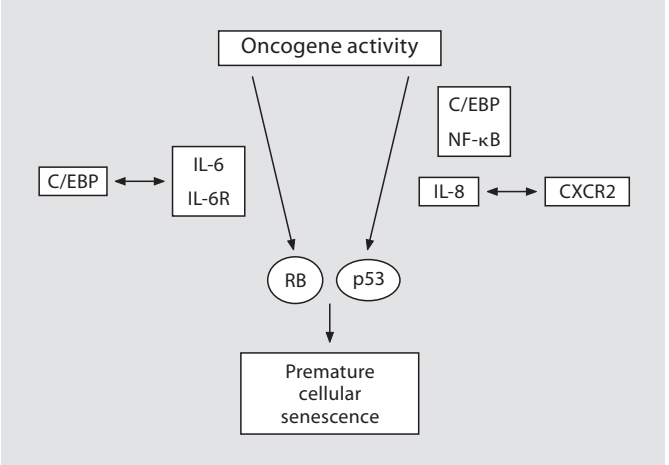

Fig. 1. Induction of premature cellular senescence by oncogene activity via activation of an IL-dependent inflammatory network. The transcription factor C/EBP (CCAA enhancer-binding protein) promotes expression of IL-6. The activity of IL-6 is mediated by IL-6 receptor (IL-6R). Both molecules promote premature cellular senescence induction via tumor suppressor factor RB activation (left side). Chemokine receptor CXCR2 and its ligand IL-8 (and GRO-α, not shown) promote cellular senescence via tumor suppressor factor p53. IL-8 upregulation is dependent on C/EBP and NF-κB transcription factors (right side).

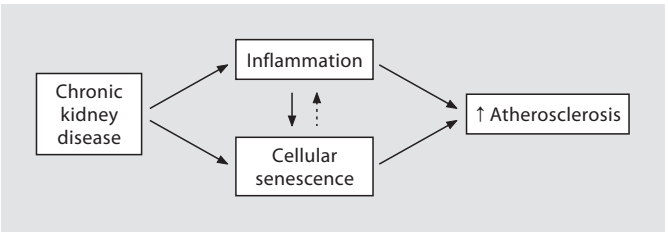

Fig. 2. Inflammation, cellular senescence and atherosclerosis relationships in CKD. Inflammation and cellular senescence are induced in CKD due to multiple, not fully determined factors (oxidant stress seems to be a common causative factor). Both processes seem to be also implicated in the process of atherosclerosis (see text), the main cause of CVD mortality in CKD patients.

CKD patients. In addition, any attempt to alleviate oxidative stress [24, 25] or inflammation [26] may be of importance in CVD prevention in the same population.

The above-mentioned new biological data may explain the findings of the cross-sectional studies associating cellular senescence and inflammation in CKD patients. The link seems to be strong. As these new data show, premature senescence induction depends on some

of the stronger 'players' in the inflammatory cascade at a cellular level, one of which is IL-6. This molecule of note was found to be a significant mortality prognostic factor in CKD patients [26], besides its close relationship with hepatic C-reactive protein production [27]. Combined with the new finding in the field of biology of the relationship between cellular senescence-inflammation and probably atherosclerosis, these data may provide catalytic information for the explanation of the large number of CVD morbidity and mortality cases among CKD patients. Thus, hand-in-hand inflammatory network hyperactivity, premature cellular senescence induction and early atherosclerosis development may explain the premature biological, vascular aging with dramatic cardiovascular consequences in CKD patients (fig. 2).

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