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Review

Cellular Senescence and Vascular Disease: Novel Routes to Better Understanding and Therapy

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ABSTRACT

Cellular senescence is a definable fate of cells within aging, diseased, and remodelling tissues. The traditional hallmark of cellular senescence is permanent cell cycle arrest but the senescent state is also accompanied by secretion of proteins that can reinforce the senescent phenotype and adversely affect the local tissue environment. Assessment for cellular markers of senescence has revealed the existence of senescent smooth muscle cells and senescent endothelial cells in vessels of patients with atherosclerosis and hypertension. This raises the possibility that cellular senescence might contribute to the initiation or progression of vascular disease. Potential disease-promoting pathways include blunted replicative reserve, reduced nitric oxide production, and increased cellular stiffness. Moreover, the secretory phenotype of senescent vascular cells might promote vascular degeneration through chronic inflammation and extracellular matrix degradation. Slowing of vascular cell aging and selective clearing of cells that have become senescent are emerging as exciting possibilities for controlling vascular disease.

RÉSUMÉ

La sénescence cellulaire est l'état définissable auquel sont vouées les cellules constituant les tissus vieillissants, malades ou en cours de remodelage. La caractéristique traditionnellement associée à la cellule sénescente est l'arrêt complet de son cycle de croissance. Cependant, la sénescence cellulaire s'accompagne également d'une sécrétion de protéines qui peuvent renforcer le phénotype de sénescence et nuire aux tissus qui l'entourent. La recherche de marqueurs cellulaires de sénescence a révélé l'existence de cellules sénescentes dans les muscles lisses et l'endothélium des vaisseaux des patients atteints d'athérosclérose et d'hypertension. Cela évoque la possibilité que la sénescence cellulaire contribue à l'installation ou à la progression de la maladie vasculaire. Parmi les voies possibles d'installation de la maladie vasculaire, on note l'épuisement du potentiel de réplication, la diminution de la production d'oxyde nitrique et une augmentation de la rigidité cellulaire. De plus, le phénotype sécrétoire de la cellule vasculaire sénescente pourrait favoriser la dégénérescence vasculaire par l'intermédiaire d'un processus inflammatoire chronique et de dégradation de la matrice extracellulaire. La capacité de retarder le vieillissement cellulaire ou d'éliminer de manière sélective les cellules sénescentes constituerait donc une piste de recherche intéressante dans la lutte contre la maladie vasculaire.

The powerful association between age and vascular disease is captured by the quotation "a man is as old as his arteries," attributed to the 17th-century physician Thomas Sydenham.[1] Notwithstanding the sex exclusivity of the phrase, it is remarkable that its inherent premises—that the vascular system undergoes an aging process and that this process determines health and longevity—hold true today. It is also noteworthy that after 4 centuries, the well recognized linkage between age and vascular disease has had modest practical effect on the management on individuals at risk of vascular events. As a vascular risk factor, age has been placed firmly in the unmodifiable category.

However, the idea that aging is an immutable process is changing. Several advances underlie this conceptual shift. First, there has been an explosion in understanding aging at the molecular level. This has revealed aging to be not simply on the basis of the stochastic accumulation of stressful insults but on a definable set of molecular cascades that either promote or resist age-related tissue dysfunction.[2] Second, there are now several examples whereby the life span of certain animals and lower organisms can be extended by specific genetic manipulations.[2-9] A third advance that has reshaped the understanding of aging is the discovery and elucidation of cellular senescence, a cellular fate that provides an exciting parallel between aging at the cellular level and aging of the entire organism.[10,11]

In this review the phenomenon of cellular senescence, with particular emphasis on the vascular system, is addressed. We

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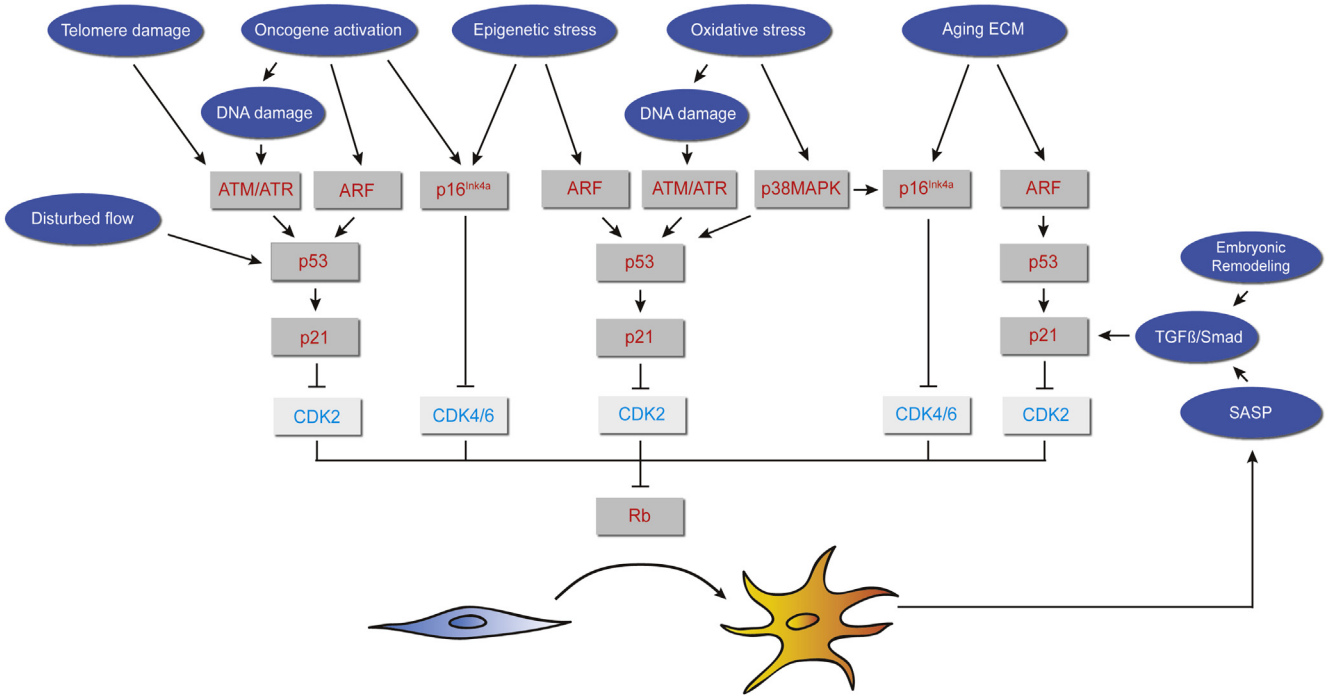

Figure 1. Molecular pathways of vascular cell senescence. A range of stressors can trigger cell senescence. These include DNA damage, including critical telomere shortening, as well as oncogene activation, oxidative and epigenetic stresses, altered extracellular matrix, hemodynamic forces, and TGFβ produced either during normal developmental remodelling or from senescent cells themselves. These stressors engage different signalling cascades that induce expression of p16 and/or p21. The resulting inhibition of cyclin-dependent kinase activity prevents Rb inactivation, leading to cellular senescence. ARF, alternative reading frame; ATM, ataxia telangiectasia mutated kinase; ATR, ataxia telangiectasia and Rad3-related kinase; CDK, cyclin-dependent kinase; ECM, extracellular matrix; Rb, retinoblastoma protein; SASP, senescence-associated secretory phenotype; TGF, transforming growth factor.

review cascades that underlie cellular senescence, the contexts in which senescent cells have been found in the vessel wall, and emerging strategies for inhibiting senescence *in vivo*. We propose that by understanding aging at the cellular level, productive new insights into managing vascular disease will emerge.

Senescence as a Cellular Fate

Cellular senescence is a process whereby cells enter a state of essentially permanent cell cycle arrest, typically after a severe insult. This process is commonly considered in the context of tumour protection,[12] where proliferative arrest occurs in response to severe or unrepairable DNA damage, typically a double strand DNA break, that could otherwise lead to oncogenic transformation. Thus, senescence serves a vital protective mechanism engaged by the cell to safeguard against cancer.

However, it is also well recognized that cellular senescence can proceed in circumstances partly, or entirely, unrelated to tumour control. Indeed, the term senescence was first introduced to describe the proliferative arrest that occurs after long-term culture of human diploid fibroblasts.[13] This form of senescence is termed replicative senescence and has been linked to progressive shortening of telomeres. When telomeres become critically short, the cell is signalled to enter senescence to avoid the consequences of severe chromosomal abnormalities. This response is consistent with the notion of tumour protection but it also links cellular senescence with an aging process, at least in culture. Further studies have supported a relationship between cellular senescence and aging and have also extended the relevance of senescence to other biological processes, including embryonic development, tissue repair, and aging-related diseases.[10]

Importantly, senescent cells are defined not only by proliferative arrest but also by the secretion of a set of proteins that can affect the senescent cell and also the local tissue. This phenomenon is referred to as the senescence-associated secretory phenotype (SASP).[14,15] The SASP develops because of extensive chromatin remodelling, which leads to suppressed transcription of the nuclear lamina protein, lamin B1.[16] This, in turn, drives expression and secretion of a host of inflammatory cytokines and chemokines, growth factors, and proteases, which collectively define the SASP.[16]

Mechanisms of Cellular Senescence

Understanding the molecular cascades underlying age-associated cellular senescence is at a relatively early stage. However several components, from the triggers to the effector mechanisms, are being delineated (Figs. 1 and 2). As noted, progressive shortening of telomeres upon repeated cell replication is an established pathway mediating replicative senescence.[17] As first described by Hayflick and Moorehead, cultured cells have a finite capacity to replicate[13] and it is now known that the resulting senescent state is produced by a critical loss of telomeres.[18] However, senescence can also occur independent of continuous cell replication and critically