Editorial

Cellular Senescence: The p53/Senescence-Messaging Secretome Connection

Advanced age, regardless of species, contributes to the development of chronic and acute disorders that impact mammalian longevity. While mechanisms underlying physiological aging and dictate life span are not well understood [1,2], senescence is a key proliferative "brake" that may limit cellular and tissue regenerative capacity and contributes to the age-associated decline in stem cell renewal. In this issue of the *Journal of Aging and Gerontology*, Igor Popov provides novel insights that address species senescence as it relates to the fractal properties of aging.

The relationship between cellular senescence and physiological aging remains an area of intense investigation; it is increasingly evident, however, that the two processes are fundamentally linked. Senescent cells accumulate in aging tissues as well as in certain pathophysiologic settings (detected usually as β-galactosidase-positive elements) where they are largely perceived as having negative consequences on tissue regeneration and repair. Aging is linked to the expression of the senescence-associated secretory phenotype [3] consisting of a distinct subset of proteins including insulin-like growth factor-binding proteins, several interleukins, transforming growth factor-β (TGF-β) and, most prominently, plasminogen activator inhibitor-1 (PAI-1) [4,5]. This restricted repertoire of expressed factors is collectively termed the "senescence-messaging secretome" (SMS) [5] and is a signature of various cell types (fibroblasts, skeletal muscle cells, melanocytes, keratinocytes, endothelial and retinal epithelial cells among others) as they enter into a replicative end-state. Activation of the SMS appears to be a consistent repeating pattern in the biology of replicative senescence suggesting that expression of this gene set and acquisition of the senescent phenotype are causatively associated. Indeed, the serine protease inhibitor PAI-1 is a critical regulator of replicative senescence in several cellular lineages. RNAi-mediated PAI-1 knockdown results in senescence escape in fibroblasts while PAI-1 deficiency prevents the development of senescence and increases the lifespan of mice genetically-null for the *Klotho* (*kl*/kl) gene [6,7]. Klotho's aging-suppressor activity likely involves inhibition of several signaling pathways including those activated by Wnt, TGF-β and IGF1 [7, for references]. *kl/kl* mice have a severe phenotype that includes a significantly shortened lifespan (8–12 wk) with onset of multiple fibrotic disorders [8]. *BubR1*$^{H/H}$ progeroid mice also exhibit an age-dependent elevation in PAI-1 expression in various tissues [9] and, like the *kl/kl* stain**,** have a shortened lifespan although not as dramatic as in the *Klotho*-null genetic background.

The tumor suppressor protein p53 is a major effector in the induction of replicative senescence. p53 regulates the transcription of key genes in the related genomic programs that control cell cycle arrest and apoptosis [6, for references] although the identification of specific genes involved not in just growth arrest but entry into senescence has been more difficult. The senescence response of human fibroblasts is primarily dependent on p53 and, similar to mouse embryonic fibroblasts, PAI-1 is both upregulated during aging and a marker of senescence. Recent findings, however, confirm that it is much more than just a biomarker. *In vivo* approaches clearly implicate PAI-1 as a critical contributor to the senescent phenotype in *kl*/kl mice [7] and *in vitro* studies established that PAI-1 is both necessary and sufficient for induction of replicative senescence downstream of p53 [6]. p53 controls growth factor-

dependent proliferation by upregulating PAI-1 transcription, leading to down-regulation of PI(3)K-AKT signalling and nuclear exclusion of cyclin D1 [6]. One model by which PAI-1 acts to limit cyclin–CDK activity during the induction of replicative senescence suggests its role as a secreted modulator of fibroblast proliferation. The mitogen-stimulated PI(3)K-AKT pathway is causally involved in the senescence-bypass of fibroblasts; overexpression of its antagonist, PTEN, can reverse this process while knockdown of **PTEN** in wild-type mouse embryo fibroblasts results in senescence bypass and activation of PI(3)K-AKT signaling [6]. The available evidence suggests that PAI-1 may be part of a growth factor-stimulated negative feedback loop that is constitutively activated by p53 in aging or senescent fibroblasts. As a consequence, senescent fibroblasts may induce a state of growth-factor unresponsiveness by secreting PAI-1 which further implicates this SERPIN as well as other members of the SMS in a cell-nonautonomous model [7] of growth control. These data indicate that targeting individual members or the collective repertoire of the SMS may have therapeutic implications in the management of age-related diseases. Since multiscale fractal concepts are being applied to gene expression displays, the findings of Popov in this issue may well have significant implications on our understanding of the complex relationship between the senescent phenotype and organismal aging.

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ACKNOWLEDGEMENTS

Supported by NIH grant GM057242 and funding from the Graver Family Foundation.

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