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Commentary

# Cellular senescence, cancer mortality, and organismal aging: A paradigm shift

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**Abstract**

Cellular senescence is an anti-cancer mechanism and may contribute to organismal aging. A change in paradigm has been proposed that cellular senescence may reduce cancer mortality rather than promote it late in life, and thus positively contributes to longevity in organisms with renewable tissues as a common mechanism across the species.


*Keywords:* Cellular senescence; Replicative senescence; Organismal aging; Cancer; Cancer mortality; Longevity; Oxidative damage; Tumor suppressor; p53; ATM

Each cell division of normal cells results in the gradual shortening of telomeres. After completing a limited proliferative potential and reaching a critically short length of telomeres, normal cells enter into a state of a permanent growth arrest resembling flattened fried eggs due to a process termed replicative senescence (RS) [1]. It was proposed that telomeres are cellular or organismal clock that controls cellular or organismal aging. Mounting evidence revealed that the telomere theory of aging is a misnomer due to many problems in correlating telomere length with cellular or organismal aging [2], leading to the proposal that telomere structure, not telomere length, induces the cellular senescent phenotype manifested by the enlarged, multinucleated, and irregular shapes. Regardless of remaining proliferative potential, normal cells respond to potentially cancer-causing signals such as oncogene activation, ionizing radiation/DNA damage, oxidative damage, and short or dysfunctional telomeres by entering into a state of cellular senescence (CS), which is to prevent cells from neoplastic transformation, suggesting that cellular senescence is a tumor suppressor mechanism [2]. In addition, senescent cells are found in aged human tissues [3]. These findings have contributed to rationalizing a cellular senescence hypothesis of aging. Cellular senescence may be beneficial early in life and becomes deleterious late in life probably because cellular senescence promotes aging by exhausting stem cells or progenitor cells and also because senescent cells secrete harmful factors that can destroy tissue structure and function, promoting late life cancers, which supports the hypothesis that cellular senescence may be antagonistically pleiotropic [4]. Pompei and Wilson recently proposed a model based on available statistical data on cancer mortality and aging, revealing that cellular senescence may contribute to markedly decreasing cancer mortality, resulting in increase in longevity late in life [5]. Lim thus proposed that cellular senescence may not be an example of antagonistic pleiotropy [6]. Whether the cellular senescence hypothesis of aging contributes to organismal aging has remained to be determined. Study by Gu et al. reported the first epidemiological study in humans that increased incidence of cancers is directly linked to defects in surveillance mechanisms of genomic instability such as impaired cellular signaling pathways mediated by Ataxia-Telangiectasia-mutated (ATM), p53, and dysfunctional telomeres [7], supporting the likelihood that failure of cells or tissues to enter into cellular

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senescence due to defects in genomic maintenance mechanisms leads to cancer, resulting in shortening of longevity. In addition, recent evidence reveals that as baboons age, skins of baboons ranging in age from 5 to 30 years accumulate cellular senescence [8], arguably supporting the possibility that cellular senescence may increase organismal longevity. Taken together, it is my view that cellular senescence may prevent cancer late in life rather than promote it, and thus positively contributes to longevity in organisms with renewable tissues as a common mechanism across the species.

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