Directed elimination of senescent cells for targeting of age-related diseases

Valery Krizhanovsky

Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel

Senescent cells accumulate in mammalian organisms with age and they are present in sites of age-related diseases. While senescence aids embryonic development and limits oncogenic transformation and tissue damage, the presence of senescent cells in tissues of the adult organism can promote tumorigenesis, decline in tissue function and tissue aging in a cell non-autonomous manner. When senescent cells gradually accumulate in tissues they promote a chronic “sterile” inflammation which is a hallmark of unhealthy aging. Several genetic studies in mice suggested that elimination of senescent cells from the organism leads to extension of healthspan and lifespan in mice. Therefore, pharmacological tools allowing efficient elimination of senescent cells *in vivo* is a promising strategy for treatment of age-related diseases associated with accumulation of senescent cells. The accumulation of senescent cells in tissues can result from the resistance of these cells to pro-apoptotic stimuli. Molecular mechanisms underlying this resistance are not well understood. We show that senescent cells from both human and mouse origin upregulate the anti-apoptotic proteins Bcl-w and Bcl-xL. Joint inhibition of Bcl-w and Bcl-xL by siRNAs or by a small molecule induced selective apoptosis of senescent cells. We eliminate senescent cells from mice using this pharmacological approach and study the effects of such elimination on organismal aging as a whole and on specific age-related diseases. In humans, a few age-related diseases account for most of the mortality causes in aged populations. We study the effect of the elimination of senescent cells in mouse models of these diseases. One of these diseases, Chronic Obstructive Pulmonary Disease (COPD), is one of the leading causes of death in humans. Chronic lung inflammation is the main component of the disease. To understand the role of airway epithelial senescence in chronic lung inflammation we subjected mice with specific deletion of p53 in bronchial epithelia Club cells to repetitive LPS inhalations. Surprisingly, Club-cells-p53-knockout mice mounted reduced airway senescence and bronchitis in response to chronic LPS exposure and were significantly protected from global lung destruction. Furthermore, pharmacological elimination of senescent cells protected wild type mice from chronic LPS induced bronchitis. Our results provide the first positive link between epithelial cell senescence and progression of chronic airway inflammation and lung destruction. Altogether, these studies focus on **elimination of senescent cells as a promising strategy for extension of healthspan and lifespan as well as directed treatment** of age-related diseases, and uncover the molecular mechanisms of the effect of senescent cells on these conditions.