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Aging mechanism

A critical role of serine protease inhibitor B2 (SerpinB2) in senescence

Normal cells have limited proliferative capacity. They eventually enter a terminal nondividing state termed cellular senescence, which is caused by the incomplete replication of linear chromosomes in cells. Due to the end-replication problem, the telomere (the end of chromosomes) length is shortened upon each cell division. Critically short telomeres are then recognized as DNA strand breaks, and cell cycling is accordingly through a p53-mediated DNA damage response pathway. Although the main players in the process have been identified and characterized, the mechanism of how the DNA damage response pathway is maintained and regulated is less clear.

SerpinB2 is a serine protease inhibitor that binds to both urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA). It is also known as plasminogen activator inhibitor type 2 (PAI-2). Because of its ability to bind uPA and tPA, most research on serpinB2 is related to its extracellular function. Interestingly, it has also been known for over 10 years that the serpinB2 level in senescent cells is increased. However, its role in senescence was not defined. We found that elevating serpinB2 levels is sufficient to induce senescence and that reducing serpinB2 levels greatly decreases the number of senescent cells. These results establish an important role for serpinB2 in senescence. We also showed that senescence induced by serpinB2 is not related to its extracellular function, suggesting an intracellular role of serpinB2.

The mechanism of how serpinB2 is involved in senescence was also analyzed. We found that serpinB2 is a direct target of p53 that can be induced through a DNA damage response pathway in senescent cells (Fig. 1). The induced serpinB2 then binds and stabilizes p21 levels in senescent cells. p21 is an important downstream target of p53. It binds CDKs and inhibits their activities to stop the cell cycle. p21 must be efficiently removed from CDKs for cells to undergo normal cell cycle progression. Thus, the stabilization of p21 by serpinB2 explains how elevated serpinB2 functions in senescent cells. It also provides a novel mechanism for the maintenance of p21 levels in senescent cells.

We also analyzed the expression of serpinB2 under various stresses, including UV irradiation, oxidation damage by hydrogen peroxide exposure, and DNA damage by an anticancer drug, cisplatin. The results showed that the role of serpinB2 is not limited to cellular senescence. SerpinB2 activation might be considered a common stress response that is induced to help cells accommodate stress. The binding and stabilization of p21 by serpinB2 might stop unchecked cell proliferation, providing an opportunity for cells to adjust to various types

of stress.

During the aging process, senescent cells are not efficiently cleared and therefore accumulate. The accumulation of senescent cells is associated with many age-related human pathologies. It has been reported that the removal of senescent cells in model animals would extend the lifespan and delay age-related diseases, including stroke and diabetes. The finding that reducing serpinB2 levels can decrease the number of senescent cells suggests that serpinB2 might have the potential for further development as a drug target candidate for treating age-related degenerative diseases.

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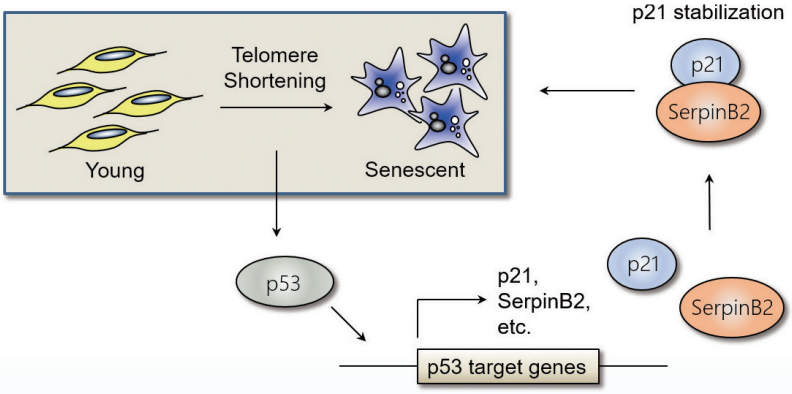

Figure 1. Schematic of serpinB2 involvement in senescence

Chinese dietary patterns associated with cognitive decline in the elderly

There are substantial differences in cooking styles, dietary habits, food items, and nutrients in foods across geographical regions, and dietary patterns (DPs) identified in Western countries (e.g., the Mediterranean diet) are inapplicable to Asian populations. No study has explored the association between DPs and cognitive impairment in the Chinese population. In addition, studies relating specific cognitive domains to DPs are limited. This study was led by Professor Yen-Ching Karen Chen at the Institute of Epidemiology and Preventive Medicine, National Taiwan University, in collaboration with Dr. Meei-Hsuan Lee at National Defense College. Three DPs were identified in the elderly Chinese population, and the article detailing these findings was published online by the *Journal of the American Geriatrics Society* on January 16, 2017 (http://onlinelibrary.wiley.com/doi/10.1111/jgs.14741/full).

This was a cohort study, in which 475 participants aged ≥ 65 years were recruited from the elderly health checkup program at National Taiwan University Hospital, Taiwan, from 2011 to 2013. For each participant, global and domain-specific cognitive function data were collected at