The role of cellular senescence in aortic dissection

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Background: Aortic dissection (AD) is a catastrophic disease that occurs suddenly. The acute mortality is high and those who survived frequently suffer from serious complications such as aneurysm formation and distal ischemia due to progressive destruction of the aortic walls. Currently, no predictor of AD onset is available nor therapeutic intervention to specifically prevent the progressive destruction in AD, because the molecular pathogenesis is largely unknown. Clinical and experimental studies highlighted the importance of inflammation in AD, although the regulatory mechanism of inflammation remains unclear. Recently, we found that cell proliferation precedes the inflammatory response in AD. Because cell proliferation causes cellular senescence that can induce inflammatory response, we hypothesized that cellular senescence participates in AD pathogenesis.

Objective: We investigated if cellular senescence contributes to AD development and progression in mouse AD model.

Methods and results: A mouse AD model was created by continuous infusion of beta-aminopropionitrile and angiotensin II (BAPN+AngII), where AD starts to develop in 3 days and occurs to most of the mice in 14 days accompanied by frequent AD rupture and death. Infusion of BAPN+AngII resulted in the induction of senescence markers Ink4a from day 3 before AD onset and persisted for the 14 days of the observational period. Cellular senescence, as demonstrated by the expression of senescence-associated beta-galactosidase, was evident in intimal endothelial cells, medial smooth muscle cells, adventitial macrophages and fibroblasts. We examined the role of cellular senescence in AD pathogenesis by oral administration of ABT263 which is known as “senolytics” that eliminates senescent cells. ABT263 treatment reduced the expression of the senescence marker, prevented the death by AD rupture, and ameliorated the severity of AD lesion compared to the vehicle treatment. Transcriptome analysis revealed that ABT treatment suppressed the immune and inflammatory response in AD. Quantitative RT-PCR confirmed that ABT treatment prevented the induction of p21Cip1, interleukin-6, several chemokines and their receptors by 3-day infusion of BAPN+AngII.

Conclusions: These findings demonstrated that senescence of multiple cell types precedes AD development, which is likely to induce the inflammatory response. Elimination of senescent cells effectively prevented AD progression and death. Therefore, cellular senescence represents a potential predictor and a therapeutic target for AD.