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A novel senolytic drug, seno-7284 ameliorates age-related cardiometabolic diseases

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Background: Senescence at cellular level develops with various genotoxic stresses and it plays a pivotal role in aging and age-related disorders. Recently, it was shown that elimination of senescent cells, so called “senolysis” has potential to become a next generation therapy for age-related disorders including cardiovascular diseases, pulmonary emphysema, Alzheimer's diseases, etc. However, currently there is no senolytic agent available in clinical settings.

Purpose: Present study was aimed to identify a novel senolytic agent effective for cardiometabolic diseases in compounds already available in clinical settings. Here we demonstrate a compound called “seno-7284” exhibits senolytic effect in murine models of type 2 diabetes, atherosclerosis and progeroid.

Methods: We generated 1) diet-induced obese and diabetic model by imposing a high fat diet for two months, 2) atherosclerosis mice model by imposing western diet to ApoE homozygous knockout mice (ApoE-KO mice) for three months, and 3) Zmpste24 homozygous knockout mice (Zmpste24-KO mice) as a progeroid mice model. We administrated seno-7284 by mixing it into the diet (0.03% w/w). In one, two or four weeks after the administration of seno-7284 to each mice model, we collected tissue samples for further analyses.

Results: Seno-7284 reduced the accumulation of senescent cells in visceral adipose tissue of dietary obese mice as senescence-associated beta-galactosidase (SA-beta-gal) staining exhibits (Figure a). This effect was associated with the suppression in systemic glucose intolerance (Figure b), and adipose tissue inflammation in four weeks after the administration of seno-7284. Administrating seno-7284 for two weeks also reduced accumulation of senescent cells in atherosclerotic lesion in aorta of ApoE-KO mice (Figure c), and inhibited the progression of atherosclerosis (Figure d). Surprisingly, this drug significantly improved the lifespan of Zmpste24-KO mice by administering it from 12 weeks old. Further analysis including RNA-seq or metabolomic analysis suggested that seno-7284 stimulates endogenous senolytic function of NK cells and CD8+ T cells.

Conclusion: Our results indicate that seno-7284 mediates its biological effects by inducing senolysis in some murine aging models. Seno-7284 would become a promising therapeutic agent for age-related cardiometabolic diseases.
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