【Grant-in-Aid for Scientific Research (S)】

Comprehensive basic research for the development of therapies targeting senescent cells and their clinical applications

Principal Investigator	Juntendo University, Faculty of Medicine, Professor MINAMINO Tohru　　Researcher Number:90328063
Project Information	Project Number : 23H05487　　Project Period (FY) : 2023-2027 Keywords : cellular senescence, atherosclerosis, diabetes, seno-antigen

Purpose and Background of the Research

●Outline of the Research

The age-related increase in the incidence of lifestyle-related diseases such as diabetes, atherosclerosis, and hypertension has been implicated in the shortening of healthy life expectancy by causing the development of ischemic heart disease and stroke. It has been suggested that age-related organ dysfunction (pathological organ aging) is one of the causes of the onset and progression of these lifestyle-related diseases, but the mechanism is unknown. We have focused on "cellular senescence" as a mechanism that promotes pathological organ aging and have studied the molecular biological properties of senescent cells that accumulate in tissues and the feasibility of therapies targeting them.

When the genome is damaged by aging or metabolic stress, cells senesce to prevent cancer. Senescent cells are thought to activate the immune system by secreting inflammatory cytokines called SASP factors and are then removed from the tissues. However, when this removal mechanism is impaired by aging or disease, the accumulation of senescent cells becomes prolonged, and chronic inflammation of tissues caused by SASP factors is triggered. Such chronic inflammation is thought to trigger various aging-related diseases, but there are still many unknowns.

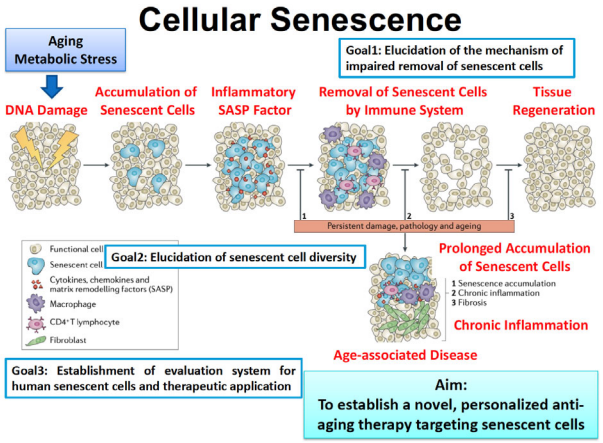

Figure 1. Cellular Senescence

Therefore, this study aims to establish a novel, personalized anti-aging therapy targeting senescent cells accumulated in tissues by achieving the following goals:

1. to elucidate the mechanism of impaired removal of senescent cells associated with aging
2. to develop personalized anti-aging therapies by clarifying the diversity of senescent cells
3. to establish an evaluation system for human senescent cells and to verify the clinical feasibility of human senescent cell removal therapy

●How did I come up with the idea for this research?

I have been promoting aging research based on the cellular aging hypothesis, which states that aging at the cellular level is responsible for some traits of individual aging, especially age-related pathological aging traits. As a result of these activities, I have shown that senescent cells accumulate in human atherosclerotic lesions, visceral fat of obese patients, and heart, and that accumulated senescent cells secrete inflammatory cytokines called SASP factors, which are involved in the onset and progression of atherosclerosis, diabetes, and heart failure, respectively (Circulation 2001, Nat Med 2009, Nature 2007). More recently, we identified seno-antigens specifically expressed in senescent cells and succeeded in establishing a vaccine to eliminate senescent cells by targeting these antigens (Nat Aging 2021). Based on these studies, we believe that it is necessary to develop new, more personalized anti-aging therapies, which led us to the conception of this research proposal.

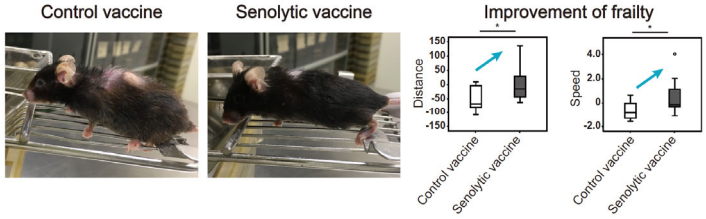

Figure 2. Improvement of aging phenotype by senolytic vaccine

Expected Research Achievements

● Elucidation of the mechanism of impaired removal of senescent cells

It is believed that the removal mechanism of senescent cells is impaired in aged mice and mice with aging-related diseases. Therefore, we will elucidate the mechanism of the impairment by performing single-cell transcriptome analysis in senescent cell transplantation mouse models and senescent cell-specific genetically engineered mice.

● Elucidation of senescent cell diversity

To analyze the diversity of senescent cells, we first established senescent cell reporter mice. From these mice, we isolated senescent cells that accumulated in a cell-/tissue-specific manner and performed omics analysis and single-cell omics analysis to identify cell-/tissue-specific seno-antigens and to clarify differences in their senescence traits. By verifying the diversity of accumulated senescent cells as described above, we aim to develop cell- and tissue-specific senescent cell removal therapies with fewer side effects.

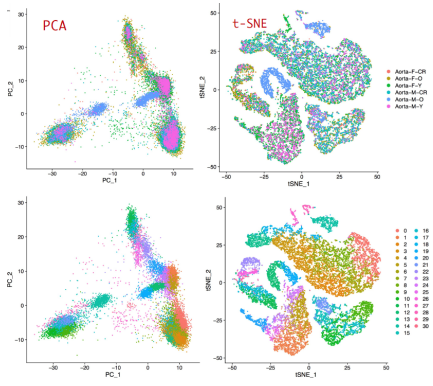

Figure 3 single-cell omics analysis

● Establishment of evaluation system for human senescent cells

We will establish an evaluation system for human senescent cells targeting the seno-antigens that we have already identified. The clinical feasibility of a vaccine against the seno-antigens will be confirmed by testing its reactivity with human peripheral blood mononuclear cells.

Homepage Address, etc.	Department of Cardiovascular Biology and Medicine Juntendo University Graduate School of Medicine : https://juntendo-cvbm.com/