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

A Study of Aging Reprogramming and Its Mechanisms in Gastrointestinal Diseases

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Project Information	Project Number : 25H00445　Project Period (FY) : 2025-2029 Keywords : Reprogramming, Cellular senescence, Gastrointestinal disease, Tissue regeneration, Multi-omics analysis

Purpose and Background of the Research

●Outline of the Research

Gastrointestinal diseases encompass a wide range of conditions affecting the digestive tract, as well as the liver, gallbladder, and pancreas. Ulcerative colitis, a refractory disease of unknown cause, leads to inflammation of the colonic mucosa, resulting in symptoms such as diarrhea, abdominal pain, and bloody stools. There is currently no curative treatment, and the number of patients continues to rise. Meanwhile, cases of metabolic dysfunction-associated steatohepatitis have also been rapidly increasing in recent years, posing a significant risk of progression to liver cirrhosis and cancer. In decompensated liver cirrhosis, where fibrosis has advanced, no effective non-invasive treatments are currently available, necessitating liver transplantation from brain-dead or living donors. However, due to the shortage of donor organs and compatibility issues, transplantation is often unfeasible, highlighting the urgent need for alternative therapeutic approaches.

In severe gastrointestinal diseases, the affected cells often exhibit characteristics of cellular senescence. This study focuses on cellular senescence and aims to develop a novel approach to improve disease conditions by rejuvenating senescent cells within gastrointestinal tissues and organs through “aging reprogramming” while elucidating its molecular mechanisms. If aging reprogramming can suppress the onset and progression of currently incurable gastrointestinal diseases, it may bring a paradigm shift in the treatment of refractory gastrointestinal disorders. Moreover, the process of cellular senescence is intrinsically linked to the cellular rejuvenation induced by aging reprogramming. Understanding this relationship could provide fundamental insights into the core principles of cellular senescence and serve as a foundation for its regulation.

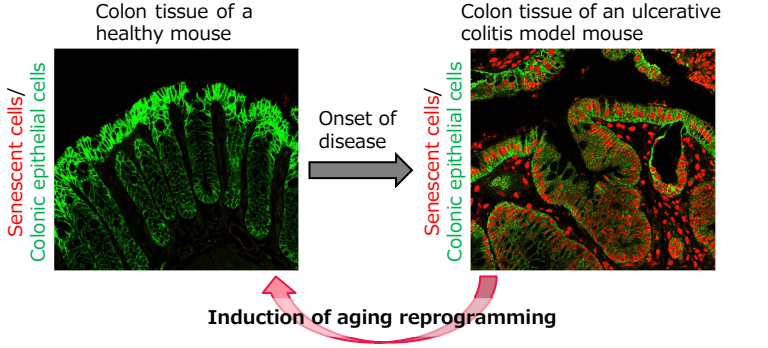


Figure 1. An illustration of this study

●Research Background

Recent studies have shown that the removal of senescent cells from the bodies of mice using genetic engineering techniques or specific drugs leads to improvements in aging-related phenomena and pathological conditions in various tissues and organs. This concept of removing senescent cells from tissues and organs to control aging and age-related diseases is called Senolysis. For future applications in humans, it is crucial to continue exploring and testing new methods for eliminating senescent cells, as this will play a key role in the development of new therapies based on the control of diseases associated with cellular senescence, and for elucidating the mechanisms underlying the onset of these diseases.

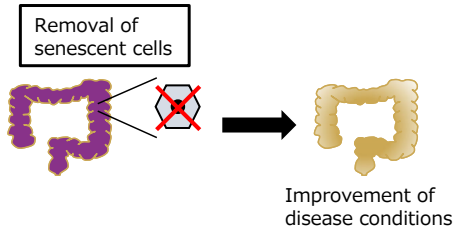


Figure 2. The conceptual diagram of disease control through Senolysis

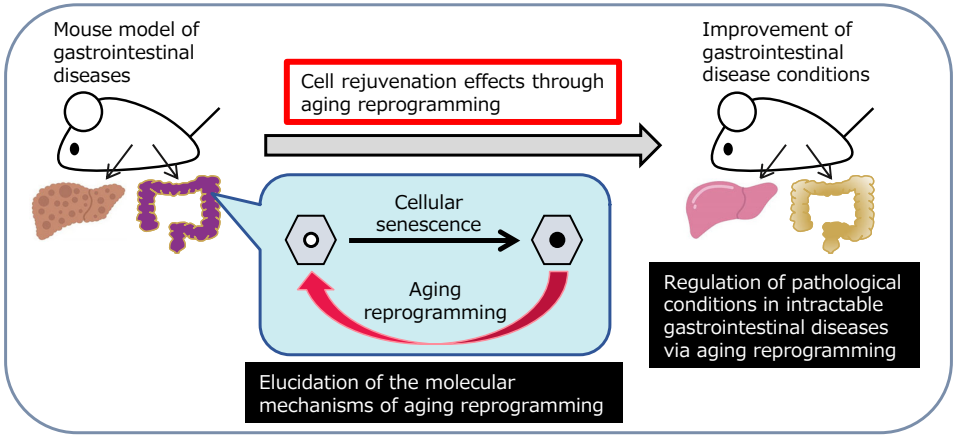
Expected Research Achievements

●Regulation of Pathological Conditions in Intractable Gastrointestinal Diseases via Aging Reprogramming

In this study, we focus on liver cirrhosis and ulcerative colitis as target diseases among intractable gastrointestinal disorders. By inducing aging reprogramming to rejuvenate senescent cells, we aim to develop a method to remove senescent cells from tissues and organs and improve the pathological conditions of these diseases.

●Elucidation of the Molecular Mechanisms of Aging Reprogramming

Utilizing single-cell multi-omics and spatial transcriptomics analyses, we will uncover the molecular mechanisms of aging reprogramming. This will provide a deeper understanding of cellular senescence in gastrointestinal diseases and pave the way for its regulation.



This approach is expected to be applicable not only to gastrointestinal diseases but also to various tissue and organ disorders associated with cellular senescence.

Figure 3. An overview of the research plan

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