【Grant-in-Aid for Transformative Research Areas（B）】

Elucidation of the Aging Clock Revival Mechanism - A New Paradigm Shift in Aging Research (Aging Revival)

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Research Area Information	Number of Research Area : 23B301　Project Period (FY) : 2023-2025 Keywords : Cellular senescence, Fibrosis, Regeneration, Partial reprogramming, Multi-omics

Purpose and Background of the Research

●Outline of the Research

Aging progresses as a result of irreversible changes such as cellular senescence, fibrosis, and a decline in regenerative capacity, leading to dysfunction at various hierarchical levels of cells, tissues, and organs. Initially, aging was thought to be caused by the loss of genetic information due to the accumulation of DNA mutations and increased genome instability with advancing age. However, reports of the creation of individuals with healthy and normal lifespans through somatic cell nuclear transfer, and the reprogramming of somatic cells to induced pluripotent stem cells, have led to the belief that epigenomic information more strongly dictates aging and lifespan. These findings suggest the possibility of reversing the aging clock (revival) if conditions are right. However, there have been no reports of reversing the irreversible biological processes leading to aging, such as cellular senescence, decline in tissue regenerative ability, fibrosis, and disease formation. However, an unprecedented research field, the revival of irreversible higher life processes, is currently burgeoning, centered around the group members of this field.

However, when considering future medical applications, it is believed that a different feasible approach based on the elucidation of molecular mechanisms is necessary. Furthermore, clarifying the commonalities and differences among individual revivals will not only elucidate the molecular mechanisms of specific revivals but will also lead to a deeper understanding of other revivals. In addition, by clarifying these molecular mechanisms, it is thought possible to more precisely depict the relationships between cellular senescence, a decline in tissue regenerative ability, and disease formation, which are at the core of aging.

The development of analytical methods such as transcriptome, open chromatin region analysis, and DNA methylome using next-generation sequencers in recent years has greatly contributed to the elucidation of the molecular mechanisms of life processes. On the other hand, the fact that mRNA expression does not always reflect protein quantity and the large fluctuations in mRNA expression and DNA methylation mean that it is difficult to identify which molecular pathways are truly key to a given life phenomenon using the above analytical methods. To overcome these issues, it is considered very important to perform a trans-hierarchical analysis using a multi-omics approach that includes comprehensive analysis of proteins, which are the entities governing life phenomena, as well as the final metabolic products such as amino acids, lipids, and glycans that reflect the results of protein activity, especially in uncovering "unexplored life phenomena" such as the revivals targeted by this field, where an integrated understanding of molecular mechanisms is lacking. Indeed, Shiromura, the leader of the field, has reached the hypothesis that glutamine metabolism is an important molecular pathway for the survival of senescent cells by comparing and validating transcriptome data with metabolome data in a joint study with team member Ikeda (Science 2021).

In this field, we aim to fully elucidate the revival of irreversible processes directed towards anti-aging. Each research team will leverage their unique revival systems and strengths to analyze the cellular dynamics when revival is induced in each system and to acquire epigenomic and transcriptomic information. In addition, we will analyze the proteome and end-productome (metabolome, lipidome, glycome), which are directly involved in the cellular phenotype. Furthermore, we will perform innovative multi-omics analysis using the acquired multi-dimensional, multi-tiered data and AI technology to highlight theories of revival and individual specificities. alone.

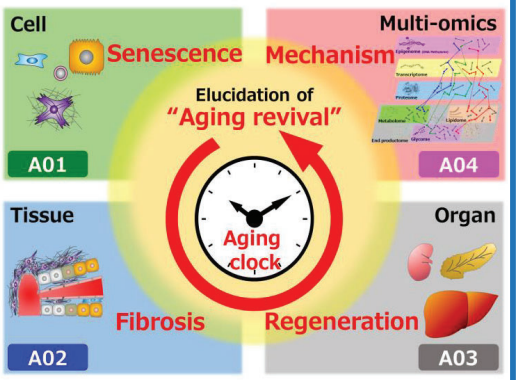

Figure 1. Conceptual diagram of this research field

Expected Research Achievements

●Research area's objectives

Research Project A01: "Elucidation of the revival mechanisms of cellular senescence, the starting point of chronic inflammation"

Using novel mouse models that can visualize aging cells and transiently express "Yamanaka factors" specifically in senescent cells, we will conduct multi-omics analyses of aging cells in the liver, kidneys, and pancreas, as well as of aging cells induced with partial reprogramming. This will elucidate the molecular mechanisms of cellular rejuvenation and extract key epigenomic information pivotal for cellular aging.

Research Project A02: "Elucidation of the revival mechanisms of tissue fibrosis, a key factor in disease formation"

We will elucidate the molecular mechanisms of revival in fibrogenic cells such as fibroblasts and myofibroblasts derived from human iPSCs that are responsible for tissue fibrosis in the liver, kidneys, and pancreas. This will be achieved by conducting multi-omics analyses during quiescent, activated, and de-activated states to extract critical epigenomic information.

Research Project A03: "Elucidation of the revival mechanisms for decreased tissue regenerative capacity by in vivo reprogramming"

Using unique mouse models that can transiently express reprogramming factors specifically in various tissues, we will elucidate the molecular mechanisms of revival for decreased tissue regenerative capacity in the liver, kidneys, and pancreas.

Research Project A04: "Development and application of multi-omics analytical methods for elucidating the revival mechanisms of the aging clock"

In collaboration with each team, we will analyze the end-productome during the revival process in aging and fibrosis to investigate the behavior and relationships of molecules in each life process. This will not only allow us to identify aging and anti-aging marker molecules from the end products but also enable us to depict metabolic pathways strongly correlated with the revival phenomenon.

●Ripple effect of the research field

a) expansion into biology, medical science, and disease biology for chronic diseases
b) expansion of the research area by targeting diverse organs
c) emergence of a composite research area that targets the boundaries of chronic inflammation, fibrosis, and decreased tissue regenerative ability
d) establishment of innovative multi-omics analytical methods

Homepage Address, etc.	https://www.kazusa.or.jp/aging/