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

Elucidating the Antagonistic Regulation of Stem Cell Fate in Degenerative Tissue Aging and Carcinogenesis

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Project Information	Project Number : 25H00439　Project Period (FY) : 2025-2029 Keywords : Tissue stem cells, Aging, Cancer, Hair graying, Melanoma

Purpose and Background of the Research

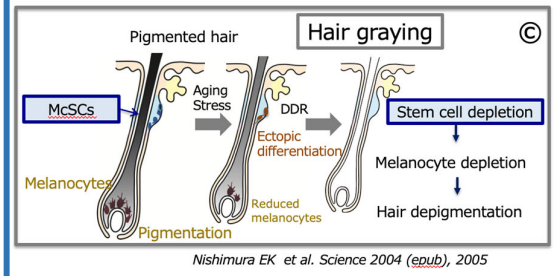
●Outline of the Research

Tissues maintain their function by continuously reconstructing the stem cell pool in response to various aging-related stresses. However, over time, they undergo degenerative tissue aging, occasionally generating the origin of cancer development. The detailed mechanisms by which those different fates are determined at the stem cell level remain unclear.

In our study, we exposed mouse skin to various environmental stresses and found that genotoxic environmental stress can be broadly categorized into two types. The first type, **degeneration-promoting stress**, includes radiation and chemotherapy agents, which accelerate the elimination of stem cells, leading to hair graying. The second type, **carcinogenesis-promoting stress**, stimulates stem cell expansion, thereby promoting the formation of pigmented lesions. Despite inducing DNA double-strand breaks (DSBs), these two types of stress lead to completely opposite stem cell fates, exhibiting remarkable **antagonism** at the single-cell level, which is ultimately reflected in tissue-level outcomes.

To elucidate the antagonistic nature of stem cell fate decisions, we have developed a system to induce DNA double-strand breaks (DSBs) specifically in mouse melanocyte stem cells. Using this system, we track the fate of damaged stem cells at a single-cell resolution and employ a combination of **single-cell omics analysis, organoid technology, and live imaging** to gain deeper insights.

Based on these findings, we aim to achieve a fundamental understanding of **CSD melanoma development in humans**, paving the way for **early cancer diagnosis and precision medicine**.



Nishimura EK et al. Science 2004 (epub), 2005

Figure 1. Mechanism of age/stress-induced stem cell depletion and hair graying

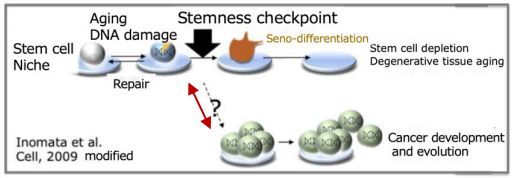


Figure 2. The concept of stemness checkpoint

●Research Objective

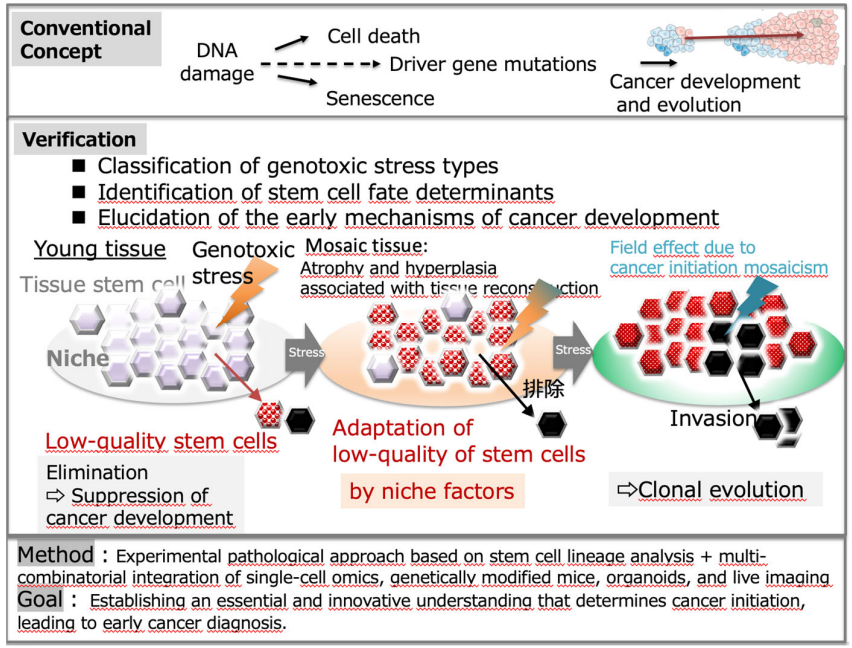
This study aims to investigate the presence of antagonistic regulation at the stem cell level in the manifestation of degenerative aging traits and cancer development. We will analyze the fate and dynamics of tissue stem cells at a single-cell resolution. In particular, we will focus on the stem cell microenvironment (niche) in aging tissues to gain insights into the early initiation and progression of cancer, ultimately contributing to early diagnosis.

●Originality and Creativity

This study employs a unique experimental system for stem cell lineage analysis to elucidate the concept of the **"self-renewal checkpoint"** (Figure 2: *Cell*, 2009), which is central to our original framework. By investigating the molecular mechanisms and functional dynamics of checkpoint regulation, we aim to uncover how unlimited stem cell proliferation is restrained. Furthermore, we will explore the relationship between aging-related degeneration and cancer development using our distinctive research approach.

Expected Research Achievements

●Elucidation of the initiation and progression mechanisms of cancer-initiating clones in aging tissues



●Clinical Applications

Determination of the early cancer initiation sites and tumorigenic niche regions in human tissues

→ Risk assessment at surgical margins and application to ultra-early melanoma diagnosis

Homepage Address, etc.	https://www.ims.u-tokyo.ac.jp/aging-regeneration/