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

Studying the boundary between regeneration and fibrosis: unraveling the highest degree of de-differentiation that newts fascinate us with.

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Project Information	Project Number : 23H05483 Project Period (FY) : 2023-2027 Keywords : regeneration, fibrosis, de-differentiation, newt, mouse

Purpose and Background of the Research

●Outline of the Research

Regeneration and fibrosis are two sides of the same coin. Regeneration here refers to the regeneration of adult newts. In this project, we focus on the boundary between regeneration and fibrosis, or "de-differentiation," to identify the intracellular and extracellular factors that have determined regeneration or fibrosis in newt evolution, and that may also determine regeneration or fibrosis in medicine.

Regeneration and fibrosis: two sides of the same coin

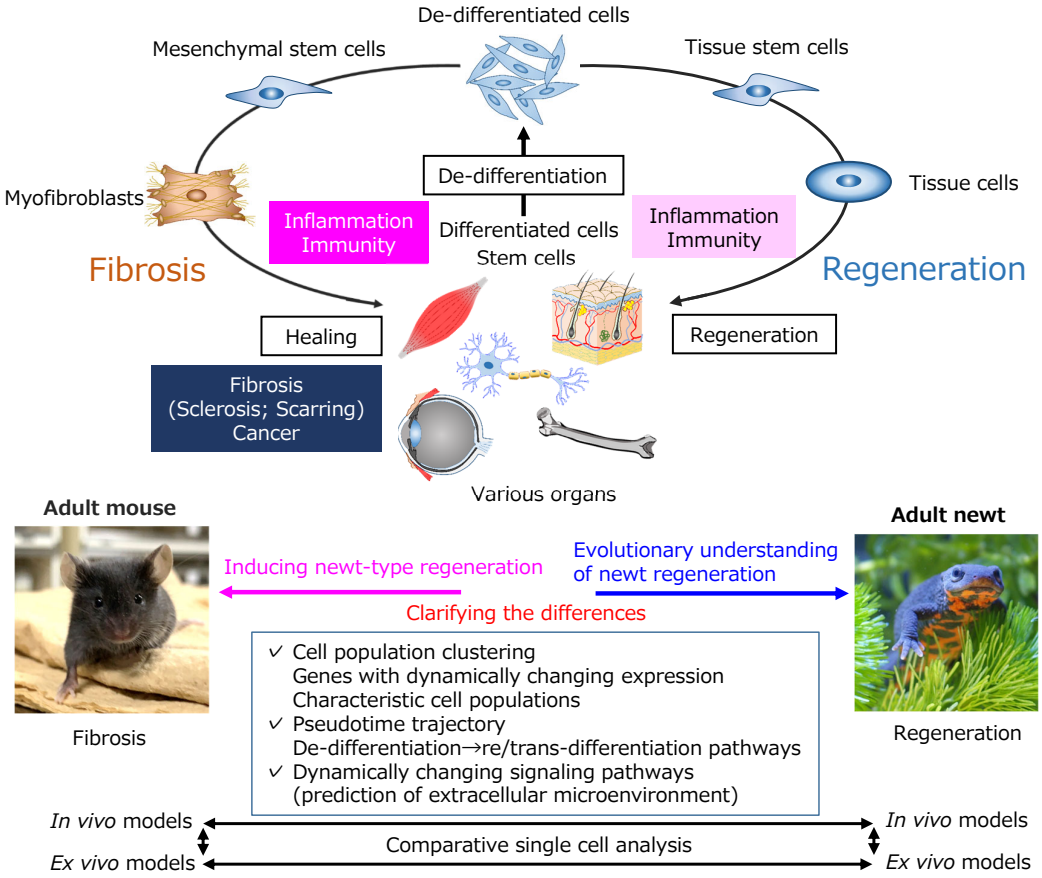

Figure 1. Image of the whole project

●Regeneration and fibrosis

Adult newts have the ability to de-differentiate terminally differentiated somatic cells, which have lost their undifferentiated nature, ceased dividing, and become highly specialized for certain physiological functions, and to mobilize these cells for the regeneration of damaged organs. This highest degree of de-differentiation is thought to have evolved on the basis of a mechanism of fibrosis common to tetrapods (four-limbed vertebrates), including humans. What and how did newts change fibrosis over the course of evolution? Once this academic question is answered, the difference between regeneration and fibrosis will become clear, and we will have a much better understanding of the principles of regeneration in newts, and can apply these principles to the treatment of fibrosis and regenerative medicine. The focus is on the boundary between regeneration and fibrosis, i.e., "de-differentiation" and "fate control of de-differentiated cells.

●Purpose

This project will clarify the differences between adult newt regeneration and adult mouse fibrosis at the molecular and cellular levels, focusing on three cell types with different degrees of difficulty in de-differentiation, i.e., skeletal muscle fiber cells in the limb; retinal pigment epithelial cells in the eye; fibroblasts in the skin.

Expected Research Achievements

We will uncover the mysteries of the evolution of regenerative capacity in newts and the conditions that induce newt-type regeneration in adult mice by clarifying the differences between the regenerative process in adult newts and the fibrotic process in adult mice.

- Focusing on skeletal muscle fiber cells in the limbs, retinal pigment epithelial cells in the eyes, and fibroblasts in the skin, we will identify the intra- and extracellular factors that regulate de-differentiation. For this purpose, we will compare *in vivo* and *ex vivo* models of regeneration in adult newts and those of fibrosis in adult mice.
- Predicting the composition and dynamics of all cells (cell populations), including inflammatory and immune cells, and the molecular networks involved in cell-cell interactions, we will uncover the cellular composition and extracellular environment that suppresses fibrosis and promotes regeneration.

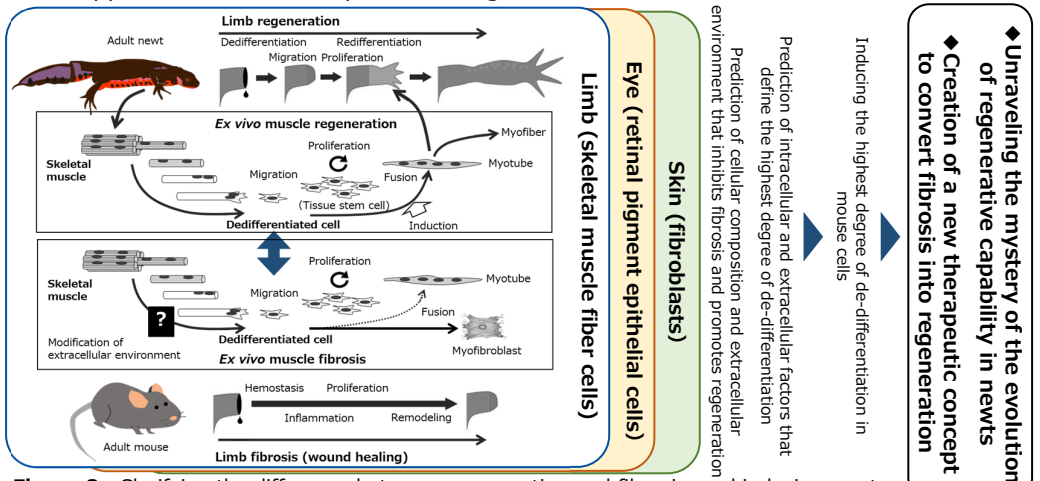

Figure 2. Clarifying the difference between regeneration and fibrosis, and inducing newt-type de-differentiation (regeneration) in adult mice.

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