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

Title of Project Evoking limb regeneration from non-regenerative animals

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Research Project Number : 16H06376 Researcher Number : 70167831
Research Area : Biology
Keyword : Development & Differentiation, Organogenesis, Regeneration, Epigenomics

【Purpose and Background of the Research】

We found a new principle of regeneration, called <distalization & intercalation> (ref.1). To restore lost portions of bodies after amputation, animals regenerate the most distal portion at first and then reorganize intermediate regions between the newly formed distal portion and remaining tissues by intercalation. Based on this new principle, we have succeeded in inducing dormant regenerative ability from non-regenerative animals by artificial manipulation (ref.2-4).

Thus, as s next target, we focus on limb regeneration. Newts can regenerate limbs after amputation. However, in the case of frogs, they lose limb regeneration ability after metamorphosis. It is known that frogs stop expressing the *Shh* gene after metamorphosis, and that a limb specific enhancer (MFCS1) may have an important role to form positive feedback between FGF and Shh for inducing intercalation. Therefore, in this study, we are trying to activate *Shh* expression in frogs even after metamorphosis by modulating the frog MFCS1 sequence.

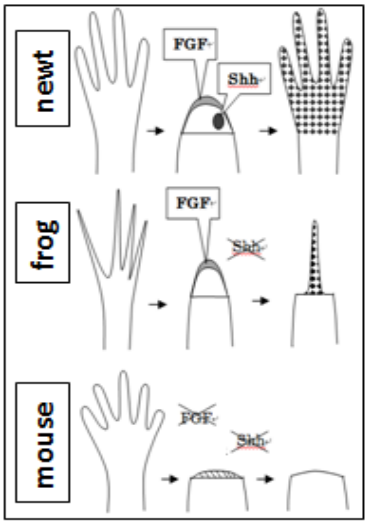

Fig. 1. Comparison of regenerative ability among newt, frog and mouse.

【Research Methods】

As the first step, we investigate the reasons why MFCS1 does not work after metamorphosis in frogs. A Tohoku University group suggested that MFCS1 is highly methylated after metamorphosis. So, we plan to replace the frog MFCS1 with newt MFCS1 by a genome editing technology, such as the CRISPR/Cas9 system, and vice versa. Through these analyses we will be able to elucidate the reason why frog MFCS1 is inactivated after metamorphosis. We will also analyze how MFCS1 functions to form the FGF/Shh positive feedback loop. Based on these analyses, we will also attempt to induce limb regeneration in mouse limbs.

【Expected Research Achievements and Scientific Significance】

When we succeed in inducing limb regeneration from frog and mouse, we will be able to provide a new strategy for regenerative medicine.

【Publications Relevant to the Project】

1. Unifying principles of regeneration I: epimorphosis versus morphallaxis.
K. Agata, Y. Saito and E. Nakajima
Dev. Growth Differ., 49, 73-78 (2007)
2. The molecular logic for planarian regeneration along the anterior-posterior axis
Y. Umesono, J. Tasaki, S. Yazawa, K. Itomi, O. Nishimura, Y. Tabata, F. Son, N. Suzuki, R. Araki, M. Abe and K. Agata
Nature, 500, 73-76 (2013)
3. Reintegration of the regenerated and the remaining tissues during joint regeneration in newts, *Cynops pyrrhogaster*.
R. Tsutsumi, T. Inoue, S. Yamada and K. Agata
Regeneration, 2, 26-36 (2015)
4. Functional joint regeneration is achieved using reintegration mechanism in *Xenopus laevis*.
R. Tsutsumi, S. Yamada and K. Agata
Regeneration, 3, 26-38 (2016)

【Term of Project】 FY2016-2020

【Budget Allocation】 136,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.gakushuin.ac.jp/univ/sci/bio/laboratory/detail_agata/theme.html