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

In vivo enhancer reprogramming for regulation of biological function at the organismal level

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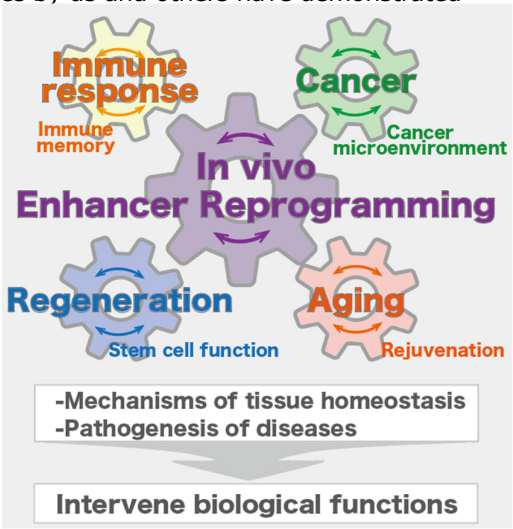
Project Information	Project Number : 23H05485　Project Period (FY) : 2023-2027 Keywords : In vivo reprogramming, Enhancer, Cell fate, Cancer, Aging

Purpose and Background of the Research

●Outline of the Research

Cellular differentiation is accompanied by the establishment of enhancer landscapes, and the identity of somatic cells is stably maintained by the enhancer activity. Moreover, emerging evidence suggests that the impairment in the enhancer landscape is critical in the pathogenesis of various diseases, indicating that the enhancer landscape safeguards the homeostasis of tissues and organisms. Accordingly, it is expected that the global repression of enhancer activity should enhance the cellular plasticity of somatic cells, and that enhancer reprogramming, the forced rewiring of the enhancer landscapes, alters somatic cell fate, which also could alter cellular function. Previous studies by us and others have demonstrated that short-term induction of reprogramming factors (OSKM) results in the recruitment of OSKM at cell type-specific enhancers and globally repress the activity both in vitro and in vivo (Nature Commun. 2018, Cell Reports 2022). These findings raised the possibility that transient expression of OSKM can enhance cellular plasticity, which could be further applied to control somatic cell fate at the organismal level. This project aims to devise a novel method that alters somatic cell fate in vivo by targeting enhancer activity, and apply the means for intervening biological functions at the tissue and organismal levels.



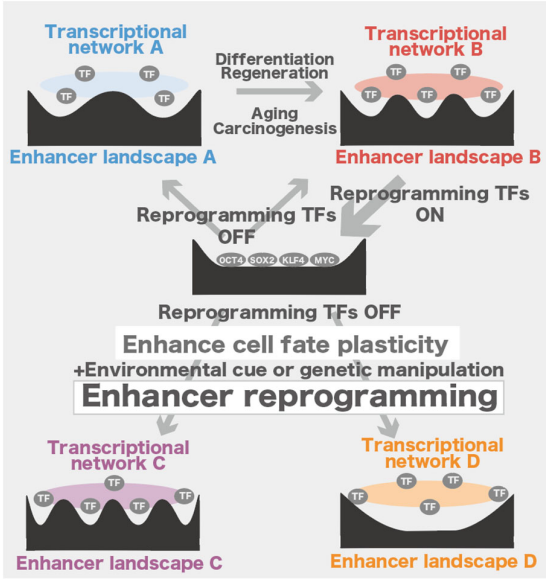
Outline of the research project

●Background of the Research

In our previous studies, we have generated mice capable of inducing reprogramming factors (OSKM) in vivo and demonstrated that somatic cells are reprogrammable to iPS cells in living mice (***Cell*** 2014, ***Nature Commun.*** 2018, 2019, 2021). Analysis of these mice revealed that, at the initial stage of the in vivo reprogramming, the reprogramming factors are directed to cell type-specific enhancers and strongly suppress their activity (***Cell Reports*** 2022, ***Nature Commun.*** 2018). Furthermore, we showed that short-term induction of OSKM can reversibly suppress enhancer activity while maintaining the memory of somatic cell lineage in vivo (***Nature Commun.*** 2018). Taken together, we assumed that this approach can be applied to temporarily reset epigenetic memory and enhance cell fate plasticity of somatic cells at the organismal level.

●Purpose of the Study

In this study, we will develop a technology to suppress enhancer activity in vivo. To this end, we will first generate mice capable of inducing OSKM in a cell type-specific manner in vivo. Taking advantage of the in vivo reprogramming system, we will enhance cell fate plasticity in vivo and evaluate tissue responses to various environmental perturbations, such as tissue regeneration and immune reaction, as well as pathological conditions including cancer and aging-related diseases. The efforts should uncover the mechanisms of tissue homeostasis and the pathogenesis caused by the impairment of enhancer activity. Finally, we aim to devise a technology to control somatic cell fate and eventually intervene individual biological functions through in vivo enhancer reprogramming.



Enhancer reprogramming for cell fate control

Expected Research Achievements

Cancer arises through the accumulation of genetic abnormalities. In our previous studies, we have uncovered the impact of epigenetic regulation in cancer development using an in vivo reprogramming system (***Cell*** 2014, ***Nature*** 2017, ***Nature Commun.*** 2018, 2019, 2021). We showed that even cancer cells with genetic mutations are reprogrammable into non-neoplastic cells (***Nature Commun.*** 2019), indicating that reprogramming technologies could be a powerful tool to alter cell fate and eventually intervene the biological function. The core question of this research project is to present the possibility of controlling cell fate and subsequent biological functions at the organismal level through enhancer reprogramming. Particularly, taking advantage of partial reprogramming to repress global enhancer activity, we aim to intervene in immune memory, tissue regeneration, and cancer. These efforts should also clarify the mechanisms underlying tissue homeostasis and the pathogenesis caused by altered epigenetic regulation.

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