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

Resilience Biology -What are the molecular mechanisms that support the resilience of life?- (Resilience Biology)

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Research Area Information	Number of Research Area : 23B305　Project Period (FY) : 2023-2025 Keywords : resilience, phospholipids, cytoskeleton, channel, stress response

Purpose and Background of the Research

●Outline of the Research

"Resilience" is defined in this research area as the reserve capacity of cells against various stresses. We conduct academic transformational research to create "Resilience biology" to quantify cellular resilience and clarify its physiological significance. For example, the heart adapts to hemodynamic loads (stress), such as blood pressure, by optimizing its structure and function. The resilience of the heart is supported by the resilience of the cardiomyocytes responsible for beating the heart. Until now, it has been thought that cellular transformation (remodeling) after stimulus reception, such as the activation of transcription factors, is important for flexible stress responses. However, our research focusing on membrane lipids and mechanosensitive channels revealed that the flexible behavior of animals and tissues is supported by the dynamics of hotspots (critical membrane sites) before stimulus reception. In this research area, we aim to clarify the nature of the critical membrane site by quantifying the dynamic instability of the cytoskeleton, focal adhesions, lipids, and ionic environments at the molecular level and by evaluating the mechanisms by which the critical membrane site controls cellular resilience in adaptation to environmental stimuli.

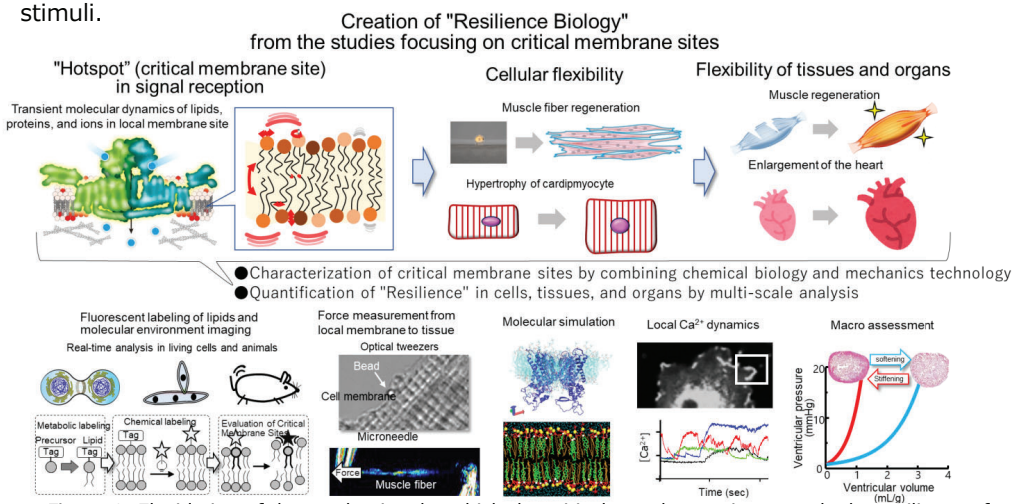

Figure 1. Elucidation of the mechanism by which the critical membrane site controls the resilience of living organism

● Research goals of each group

Group A01: Mechanical quantification of critical membrane sites and evaluation of resilience dependent on unique membrane structures

To assess the mechanical nature of the critical membrane sites and the mechanism by which the critical membrane site supports the resilience of life.

Group A02: Development of critical membrane site imaging technology for visualizing local changes in membrane lipids

To explore the relationship between the behavior of critical membrane sites and cell function by observing the transient state of membranes composed of dynamic biomolecules.

Group A03: Membrane lipid-mediated regulation of cellular resilience in response to environmental stresses

To elucidate how cells control the functions of cells, tissues, and organs by regulating the composition and distribution of membrane lipids to adapt to environmental stress.

Group A04: Maintenance of cardiac plasticity through critical membrane site control by resilience mediator TRPV2

To identify the mechanisms that maintain cardiac plasticity in response to hemodynamic stress by elucidating the process of muscle maturation in the syncytium.

Expected Research Achievements

●Creation of "Resilience biology"

This research area aims to create "Resilience biology," assuming that the critical membrane sites before stimulus reception determine the flexibility of cells and tissues. The goal is to reveal the nature of critical membrane sites consisting of mechanosensitive ion channels and specific lipids, based on novel biophysics and chemical biology techniques. Furthermore, we will elucidate the functional interplay between mechanosensitive ion channels and specific lipids for the quantitative analysis of resilience at the molecular, cellular, and organ levels.

●Ripple Effects on Research Areas

The elucidation of the mechanism by which the critical membrane site determines cellular resilience and the proposal of a novel index of cellular resilience will not only advance our understanding of the morphogenesis and pathogenesis mechanisms of tissues and organs but also provide innovative new concepts in a variety of fields, including early detection and prognostic markers for disease, pathophysiological mechanisms in geriatrics and regenerative medicine, and the basis of biological evolution and biodiversity.

For example, the "Resilience biology" based on the critical membrane site is expected to clarify the regeneration of skeletal muscle and the maturation of cardiomyocytes. However, it is also expected to bring about academic innovation in various life phenomena dependent on membrane lipid dynamics, such as fertilization, bone formation, neurotransmitter release, and vesicle transport.

It will also deepen our understanding of various organisms from a bird's eye perspective, including differences in membrane composition among species, mechanisms for controlling cellular functions unique to each species, and strategies for maintaining resilience during biological evolution. Furthermore, the visualization and manipulation technologies for membrane microdomains developed in this research will not only contribute to cell biology but will also impact pathology diagnoses and explain disease mechanisms at the molecular level, thereby creating innovative developments in medical treatment using resilience as a diagnostic indicator.

Mechanosensitive channels and various membrane proteins are thought to be affected by the formation of critical membrane sites. In the future, understanding the regulatory mechanisms of membrane protein activity at critical membrane sites will reveal the universal principles of life brought about by cellular resilience at the cellular, tissue, and organism levels.

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