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

Unraveling Tissue Regulation Mechanisms through Physiological Hypoxia: Pioneering the Field of Oxygen Dynamics Biology

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Project Information	Project Number : 25B305　Project Period (FY) : 2025-2027 Keywords : Oxygen, Tissue microenvironment, Optical imaging, Electrochemical chip device, Single-cell omics

Purpose and Background of the Research

●Outline of the Research

Oxygen (O_2) deprivation is an immediate emergency for most aerobic organisms. For this reason, hypoxia has long been oversimplified as a severe cellular stress. This view led to the discovery of hypoxia-inducible factors (HIFs) that have since become central players in both basic and clinical oxygen research for the past two decades. However, emerging evidence suggests that physiological hypoxic environments exist within the body, particularly in the bone marrow and brain. In these contexts, hypoxia is not only a stressor, but a functional signal involved in a variety of cell/tissue fate processes. This underscores the need to reinterpret hypoxia as an "oxygen signal" that modulates homeostatic biological responses in living tissues. Despite this conceptual advance, existing research approaches to study oxygen signaling in living tissues remain limited by several technical challenges. Our research project employs unique technologies—such as multi-scale optical molecular imaging and reconstruction of the tissue microenvironment in electrochemical devices—to investigate biological processes in animal models involving oxygen signal-driven hematopoiesis, innate fear responses, and germ cell storage mechanisms.

Through these integrative approaches, we aim to elucidate the dynamic regulation of oxygen signaling in controlling physiological functions and to establish a new interdisciplinary field of research: Oxygen Dynamics Biology (Fig. 1).

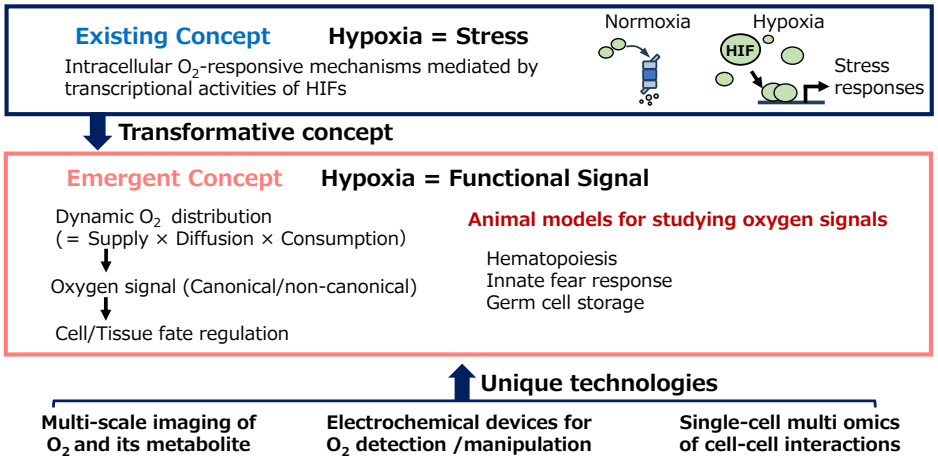

Fig. 1 Pioneering the field of Oxygen Dynamics Biology

●Unique technologies for pioneering the Oxygen Dynamics Biology

Luminescence creatures illuminating oxygen signals

We have synthetically redesigned luciferin-luciferase reactions (LL reactions) identified in natural fireflies to generate tissue-penetrating near-infrared (NIR) bioluminescence (Fig.2) By incorporating sensing functions into the NIR LL reaction, we will visualize oxygen signals in the tissues of model animals.

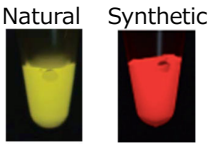

Fig.2 NIR LL reaction

Electrochemical micro/nanodevices controlling oxygen signals

We have developed electrochemical devices incorporating micro/nanoelectrodes and microfluidic channels (Fig. 3). These devices can consume and generate oxygen in situ and in real time, and can also function as cell culture platforms. We will validate the oxygen signals using these devices.

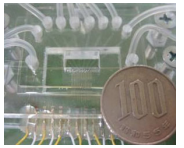

Fig. 3 Electrochemical device

Expected Research Achievements

In this project, we aim to uncover biological processes that contradict the “more oxygen is always better” paradigm. To achieve this, interdisciplinary project members—including biology, medicine, mechanical engineering, chemistry, and physics—will come together to exchange ideas.

Research Group A00 (Kuchimaru, Takubo, Ino, Gotoh)
This group aims to maximize interactions among the groups A01-A03, foster the development of early-career researchers, and promote outreach activities.

Research Group A01 (Takubo, Kobayakawa, Gotoh)
This group focuses on three distinct biological processes—hematopoiesis, innate fear responses, and long-term germ cell preservation—to elucidate the dynamics of O_2 as a signaling mediator, primarily through multi-scale optical imaging and electrochemical nanodevices. Through these efforts, the group aims to clarify the molecular basis of oxygen signaling-driven biological processes.

Research Group A02 (Kuchimaru, Kiyama, Nakashiba, Yamamoto)
This group will design genetically-encoded optical imaging sensors for detection of O_2 and its metabolites. Furthermore, genetic reporter systems for recording cell-cell interactions will be implemented for projects in group A01. These genetic tools will be integrated with nanodevices provided by the group A03.

Research Group A03 (Ino, Suzuki)
This group will develop electrochemical nanodevices capable of measuring and manipulating oxygen signals. These nanodevices are also designed to reconstruct tissue models that recapitulate organ-level physiology and oxygen signaling that drives cell fate decision that is focused in the group A01.

The knowledge gained from this project will elucidate how oxygen signals regulate the functions of our body. Such knowledge also holds promise for broad applications in future society, including the development of therapeutic strategies for oxygen-related diseases and the advancement of innovative regenerative medicine.

Homepage Address, etc.	https://www.jichi.ac.jp/bioconvergence/oxygenb/

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