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

Section III

Title of Project： Establishment of pH Biology

TAKAHASHI Nobuaki
(Kyoto University, The Hakubi Center for Advanced Research, Program-specific associate Professor)

Number of Research Area：20B308　Researcher Number：70604635

【Purpose of the Research Project】

Cell survival is dependent on sensing and responding to a wide variety of stresses. While the mechanisms underlying hypoxia and oxidative stress sensing have been highly investigated to date, it is poorly defined how cells sense and respond to changes in cellular pH, one of the most fundamental parameters in biochemical reactions.

pH sensing and adaptation are of particular importance in cancer cells. Most cancer cells rely on glycolysis to generate ATP regardless of O_2 availability. This causes intracellular acidification because glycolysis leads to the generation of H^+ – one glucose generates two H^+. While cancer cells are known to upregulate a series of acid extruders, the mechanisms underlying sensing and responding to pH changes remain unknown. There could be a selection of tumor cells that enhance the pH sensing mechanisms that all organisms are supposed to have in order to adapt to harsh pH stress conditions. Interestingly, such an evolution can be also seen in shell-building marine organisms, including coral. During the 4.6-billion-year history of Earth, the atmospheric partial CO_2 pressure, which can affect pH of see water, has fluctuated greatly. Given that $CaCO_3$, the main component of the shell, is highly vulnerable to low pH, there may be a selection of shell-building marine organisms that enhance pH adaptation mechanisms to protect the shell from low pH.

Moreover, accumulating evidence has suggested that higher organisms utilize low pH to induce signaling pathways. For example, anterior–posterior pH gradient, which changes the activities of Wnt in a spatial manner, has been recently demonstrated in embryos. It is likely that life dare to create low pH fields within the cell or body in order to change signaling pathways. However, pH-induced signaling pathway remains largely unidentified yet.

To address these questions, the team of this research project is made up of talented scientists who are engaged in cutting-edge research on pH adaptation and pH-induced signal in the field of cancer, development, neuroscience, and marine biology. Through this project, we will establish a new research field, “Biology of pH", which can change our understanding of pH in life.

【Content of the Research Project】

This project focuses on “mechanisms of pH adaptation” and “pH-induced signal” in order to understand fundamental roles of pH that life has evolved to acquire through interdisciplinary areas of research (**Fig. 1**).

A01: Elucidation of pH response/adaptation mechanisms in higher organism

This group aims to elucidate pH response/adaptation mechanisms that enable cancer cells to tolerate pH stress.

A02: Elucidating pH adaptation mechanisms from pH-tolerant marine organisms

This group focuses on shell-building marine animals, including corals and foraminifera, to elucidate how these animals have evolved to acquire pH tolerant mechanisms through selective pressure.

A03: Evaluation of in vivo pH field as a signaling factor

This group aims to analyze unique signaling pathways driven by pH fields within the cell and body and investigate the significance of pH field in life.

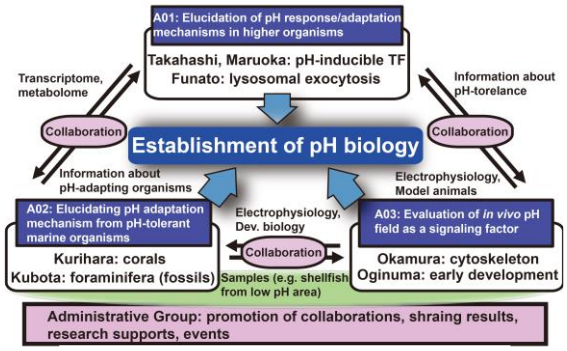

Fig. 1. Organization of this project

【Expected Research Achievements and Scientific Significance】

(A) Impacts on basic medical science

Given that the biology of O_2 and oxidative stress have exerted great impacts on life science, this research project concerning biology of pH will definitively provide novel insight into physiology and pathology.

(B) Impacts on the issues on ocean acidification

The information on the history of selection of the organisms that exhibit pH tolerance will allow you to discuss the future direction concerning the current global issues of the ocean acidification.

【Key Words】

“Stress”: People usually use “stress” as the meaning of “Mental strain"; however, in the field of biology, stress is used as “a mediator that perturb cellular homeostasis”.

【Term of Project】

FY2020-2022

【Budget Allocation】

122,000 Thousand Yen

【Homepage Address and Other Contact Information】

https://www.ph-biology.net/