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

Establishment of pH Biology

Principal Investigator	Team Director, RIKEN Pioneering Research Institute (PRI) / RIKEN Center for Biosystems Dynamics Research (BDR) OGINUMA Masayuki　Researcher Number : 50825966
Project Information	Project Number : 25A304　Project Period (FY) : 2025-2029 Keywords : pH, Stress-response, signaling, bicarbonate ion

Purpose and Background of the Research

●Outline of the Research

pH is a fundamental physicochemical parameter that profoundly influences cellular physiology. Traditionally, cytoplasmic pH was considered stable, which led to a lack of attention to its dynamic nature. However, recent advances in pH imaging technologies have shown that intracellular pH is highly dynamic, influenced by both extracellular environmental fluctuations and endogenous metabolic activities. For instance, changes in atmospheric CO2 levels can alter water acidification, which, in turn, affects intracellular pH. Moreover, acid production through cellular metabolism makes cytoplasmic pH inherently unstable. Aberrant pH dynamics are now recognized as key features of pathological states, such as cancer and aging, where homeostatic regulation is disrupted. These insights suggest that organisms have evolved conserved mechanisms to detect and adapt to pH fluctuations, and that pH itself may function as a signaling cue regulating diverse biological processes. Despite these emerging perspectives, the field remains underexplored, primarily due to the long-standing assumption that pH within cells is invariant.

This research area is based on the novel perspective that life has evolved fundamental mechanisms not only to respond and adapt to pH fluctuations "pH stress response mechanisms" but also to actively harness pH as a signaling modality "pH signaling". By utilizing cutting-edge technologies for pH visualization and manipulation, we employ an interdisciplinary and integrative approach across an unprecedented diversity of organisms and biological phenomena. Through this approach, we aim to fundamentally revise existing paradigms surrounding pH and establish a new academic discipline—"pH-responsive biology" (Figure 1).

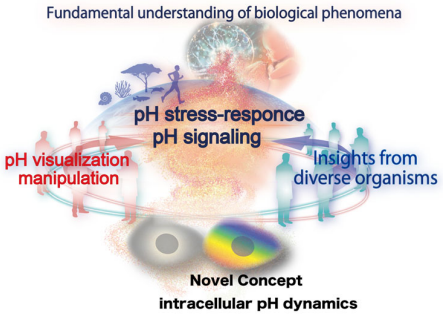

Figure 1. Overview of the "Establishment of pH-Responsive Biology"

●Formation of this Research Domain

The "Birth of pH-responsive Biology" project, led by Shigenari Takahashi at Kyoto University under Transformative Research Area (B), began with young researchers challenging the assumption that "cytoplasmic pH is invariant." The project revealed fluctuating intracellular pH and responsive mechanisms across various biological systems (Figure 2). Interdisciplinary collaboration has fostered innovative research perspectives. Building on this, Transformative Research Area (A) expanded the research to include more species and life phenomena, with a new technical team focused on advancing pH visualization and manipulation techniques, challenging current understanding of life processes through pH-responsive mechanisms.

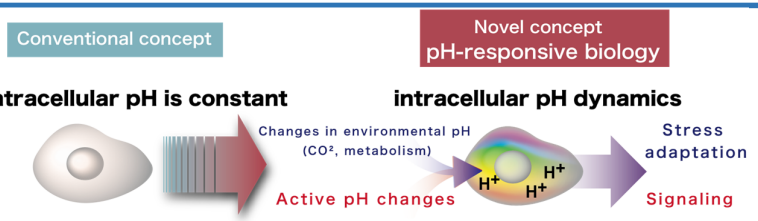

Figure 2. The Emerging Concept of a New pH Biology in this Transforming the Field

Expected Research Achievements

Cutting-edge pH visualization and manipulation techniques will be employed to uncover the molecular mechanisms underlying pH responses—an area that remains poorly understood—across a wide range of species and biological phenomena (Figure 3). Through this approach, three foundational projects will challenge conventional views of pH biology and aim to open a new chapter in the life sciences.

Project 1: pH Stress Response Mechanism:

This project will explore the molecular mechanisms of pH stress response using cancer cells, which are known for their strong tolerance to pH stress. Additionally, pH-tolerant organisms, such as foraminifera, corals, and plants that have adapted to environmental pH fluctuations, will be investigated. This will reveal both common principles and diverse adaptation mechanisms across species.

Project 2: pH Signaling Mechanisms:

This project will investigate pH dynamics and functions both inside and outside cells during key life processes such as development, dormancy, aging, and cancer. It aims to elucidate the regulatory mechanisms of pH signaling and establish it as a universal system underpinning fundamental biological processes. In addition, the project will explore novel signaling pathways regulated by bicarbonate ions, the primary physiological buffer in vivo.

Project 3: pH Visualization and Manipulation Technology:

This project aims to develop advanced pH sensors to improve pH visualization technologies and enable precise manipulation of intra- and extracellular pH using optogenetics. Furthermore, acidic and alkaline metabolites in cells will be identified through MRI-based pH visualization techniques, facilitating the study of species and tissues that were previously difficult to examine. These technologies will serve as a cornerstone for accelerating research across the entire field.

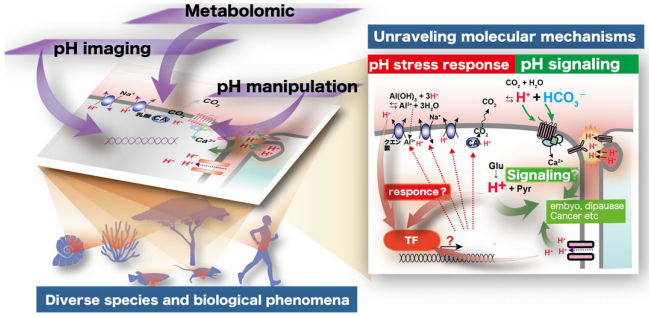

Figure 3. Central Research Challenges in the Establishment of pH-Responsive Biology

Homepage Address, etc.	https://phbiology.rcast.u-tokyo.ac.jp/