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

A Study of thermogenesis and thermal response in muscle over the range of scales from molecule to individual animal (Trans-scale thermal signaling in muscle)

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Research Area Information	Number of Research Area : 22B209　Project Period (FY) : 2022-2024 Keywords : heat dissipation, malignant hyperthermia, microscopy system, quantum beam science, molecular dynamics simulation

Purpose and Background of the Research

●Outline of the Research

Thermogenesis is one of the important functions in muscles. Some diseases are known to be caused by unregulated thermogenesis. However, it is largely unclarified how the heat released from a heat source in a cell affects the tension production or other biochemical reactions that take place in the vicinity of the intracellular heat source.

In this project, we doubt our common knowledge that "the cellular thermogenesis is solely used to maintain the body temperature of the living organism." Then, we propose a new hypothesis that there is an intracellular processes mediated by heat, or "thermal signaling." We examine experimentally the "thermal signaling" effects, establish theoretical background, and uncover the biological significance of thermal signaling in muscle that is initiated at the scale of biological molecule but largely affects the individual.

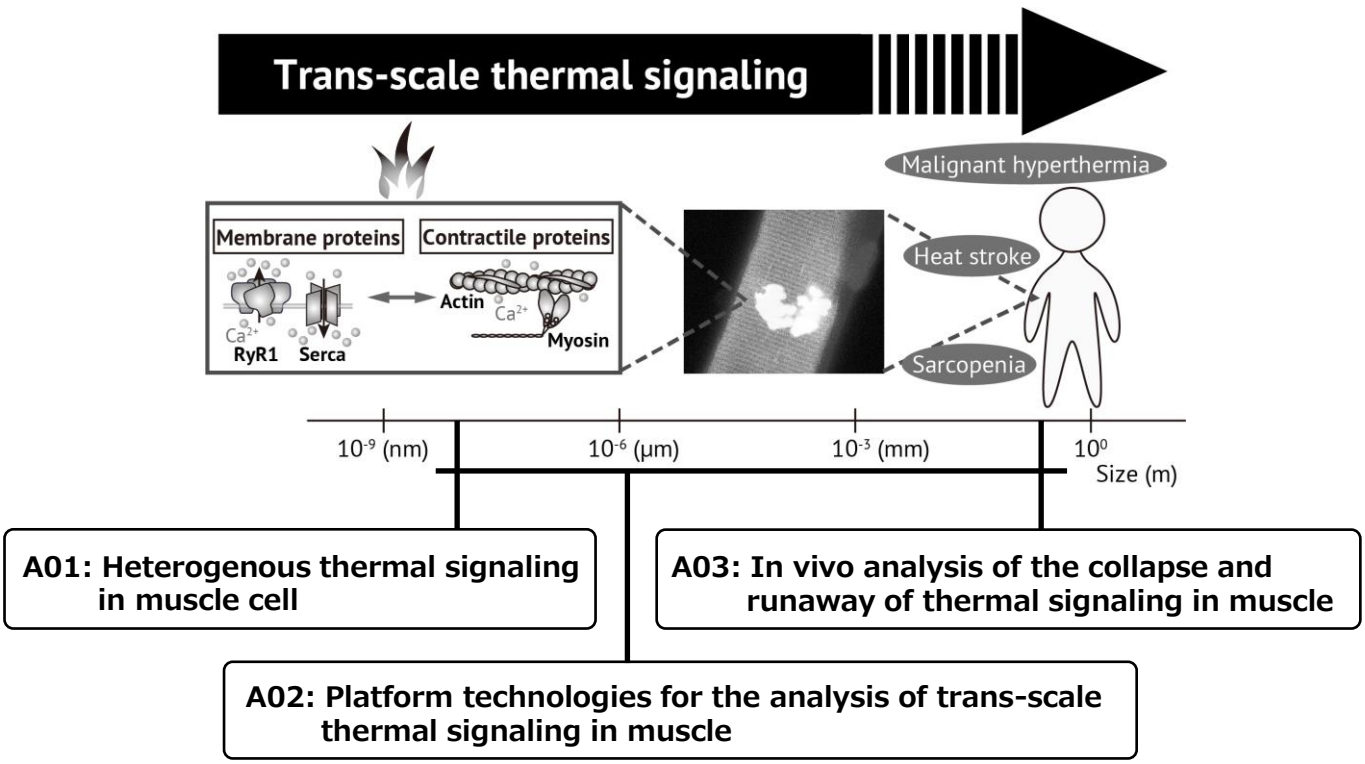

Figure 1. Overview of the project. Here, the intracellular processes mediated by heat, i.e., thermal signaling, that is initiated in biological molecules then transfers to individuals is defined as "trans-scale thermal signaling." We aim to elucidate details of the trans-scale thermal signaling effects, and develop new methods to control them. Specifically, we establish a new research area in muscle physiology, where the regulation and collapse of physiological functions of muscle will be explained comprehensively throughout the hierarchy of biological systems. In *X*-axis ("Size"), 1 nm (nanometer) and 1 μm (micrometer) are approximately 1/100,000 and 1/100 of the thickness of a human hair, respectively.

● **Group A01**
Protein molecules are aligned regularly in muscle cells to produce tension for contraction. How does the heat dissipate in such the intracellular space? Group A01 use quantitative optical microscopy and molecular dynamics simulation to understand the heat diffusion in a local volume in a cell.

● **Group A02**
A02 provide platform technologies to analyze microscopically the thermal signaling in muscle using the quantum science and technology. The new technologies are expected to cover the range of scales from a molecule to tissue.

● **Group A03**
A03 employs animals as disease models. By using the tools provided from Groups A01 and A02, A03 examines the effects (mainly the negative effects that may relate to the diseases) of thermogenesis in cells to the temperature and functions of muscle, which is the largest thermogenic organ in our bodies.

Expected Research Achievements

● **Novel research area that we aim to create**
We consider the temperature as a parameter in a space as small as or smaller than a cell. We measure the thermal signaling effects on the biological processes in the small space in muscles. For example, thermal responses of proteins and biochemical reactions in the muscle are considered as physico-chemical phenomena that necessarily respond to the heat dissipating through the space. We reveal the biological significance of thermal signaling, and develop new methods to control it. These research area is denoted as "trans-scale thermal signaling." Here, we focus more on muscle physiology, where the regulation and collapse of physiological functions of muscle will be explained comprehensively based on the new concept, i.e., thermal signaling.

● **Scientific achievements expected**
Each one of the team members joins a collaborative project(s) to achieve two goals of the current research area:
(1) To create a new platform of science and technology by studying thermal signaling in muscle in a trans-scale manner.
(2) To understand the detailed mechanisms of malignant hyperthermia and heat stroke that are caused by the collapse and runaway of thermal signaling in muscle, and to propose the strategy of their treatment.

● **Significance on the public expected**
Research area on muscle thermal signaling examines the development of muscle and the collapse of its functions. Thus, firstly, the studies are directly related to aging and disability of muscular functions, which are important subjects for maintaining the quality of life in our society. And, secondly, these studies provide the essential knowledge to understand the mechanism of thermogenesis as well as of pathophysiology. Based on the knew knowledges obtained from the current project, we expect to propose in near future the strategy for the treatment of diseases related to the thermal runaway, such as malignant hyperthermia and heat stroke.

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