【Grant-in-Aid for Scientific Research (S)】

Broad Section H

Title of Project : Sulfur-mediated energy metabolism, sulfur respiration: Its discovery and physiological functions

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Keyword : Reactive sulfur species, energy metabolism, sulfur respiration

【Purpose and Background of the Research】

Many organisms utilize the oxygen-dependent energy metabolism, known as oxygen respiration. Because of hypoxic and anaerobic environments for the cells and tissues such as stem cells, muscles and tumors, any alternative energy-producing pathway is required to maintain the homeostasis of cellular physiological functions. Versatile reactive sulfur species has been suggested to be involved in the oxygen-independent energy production system for ancient cells, and prokaryotic organisms, because of its similar chemical properties to molecular oxygen and of its widespread presence in the natural environments like volcanos, hot springs, etc.

We have clarified the abundant formation of reactive sulfur species (RSS), like cysteine persulfide (CysSSH) which has an additional sulfur atom to cysteine (CysSH) in various organisms, including prokaryotes and mammals. More recently, we identified a novel metabolic pathway for CysSSH biosynthesis, mediated by cysteinyl-tRNA synthetases and revealed that CysSSH and its metabolites can be utilized for the energy production process instead of oxygen. This finding is groundbreaking and paradigm-shifting indeed, and we termed the new energy metabolism as the "sulfur respiration (Figure 1)".

Our particular research project aims therefore to comprehensively understand the molecular mechanism and physiological functions of sulfur respiration, which is the most fundamental system of life but is yet almost unknown, and finally aims at establishing the new central dogma, which would greatly promote the human health, disease control, and improved longevity.

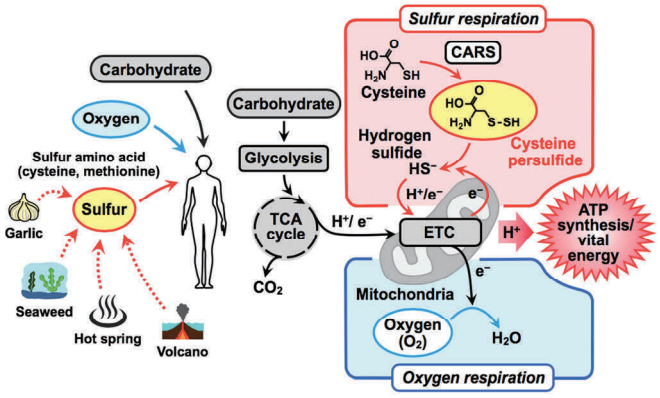

Figure 1. Sulfur respiration

【Research Methods】

We will clarify the mechanisms of the sulfur respiration in vivo, based on the chemical biology, biochemistry, cell biology and redox biology of RSS, as well as by using animal models to be develped herein for the sulfur respiration utilizing gene-editing techniques (Figure 2). The translational applications based on the insights obtained from this proposed research will be also conducted.

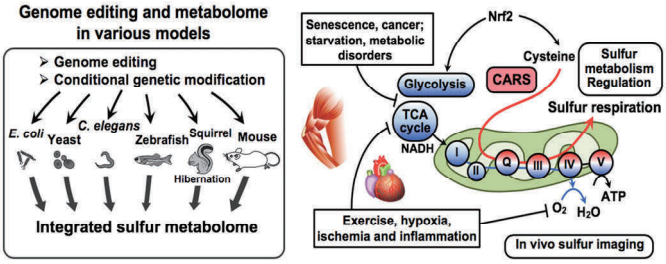

Figure 2. Research plans

【Expected Research Achievements and Scientific Significance】

The theoretical and molecular basis for the sulfur respiration that will be established by this project could provide novel strategies for anti-aging or improving human longevity and contribute to newly develop diagnoses, preventions and therapeutic approach for various diseases, including chronic or intractable cancer and infections, atherosclerotic vascular and cardiac diseases. In addition, the sulfur metabolites, or reactive sulfur species (including their antidotes) can be capitalized as biomarkers, and applicable for regulating the sulfur respiration, on which several malignant cancers may be addicted or the stem cells and other particular cells and tissues may depend especially under hypoxic and anaerobic conditions.

【Publications Relevant to the Project】

・Ida T et al. Reactive cysteine persulfides and S-polythiolation regulate oxidative stress and redox signaling. *Proc Natl Acad Sci USA* 111: 7606-7611 (2014).
・Akaike T et al. Cysteinyl-tRNA synthetase governs cysteine polysulfidation and mitochondrial bioenergetics. *Nat Commun* 8: 1177 (2017).

【Term of Project】 FY2018-2022

【Budget Allocation】 148,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.toxicosci.med.tohoku.ac.jp/index.html