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

Exploring supersulfide that mediates energy metabolism and redox signaling

Principal Investigator	Tohoku University, Graduate School of Medicine, Professor AKAIKE Takaaki　Researcher Number : 20231798
Project Information	Project Number : 24H00063　Project Period (FY) : 2024-2028 Keywords : supersulfide, supersulfide imaging, energy metabolism, oxidative stress, redox signaling

Purpose and Background of the Research

●Outline of the Research

Electron coupling via supersulfides is a fundamental biological process in nature. The redox reaction that is mediated by electron transfer, governs cellular activities, including energy metabolism, signal transduction, and gene expression, thereby controlling the life and death of all organisms. While the major focus of redox biology has been on oxygen, oxygen only accounts for a small part of redox reactions in the organisms. This project aimed at establishing a brand-new field, "supersulfide redox biology," focusing on redox-active polysulfide derivatives that are abundant in organisms but largely unexplored. Recent studies by our group reveal the diverse physiological functions of supersulfide molecules, which in fact lay the foundation of this innovative research (Fig. 1, 2).

Fig. 1. Brand-new concept of supersulfide biology

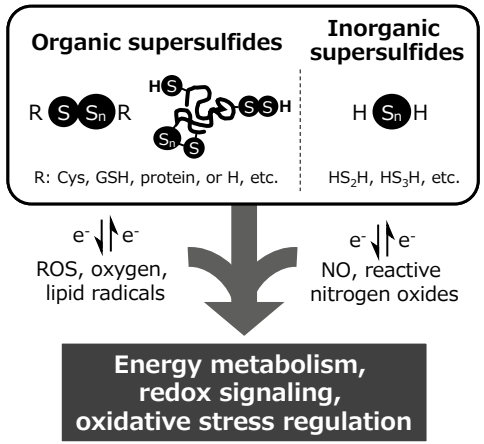
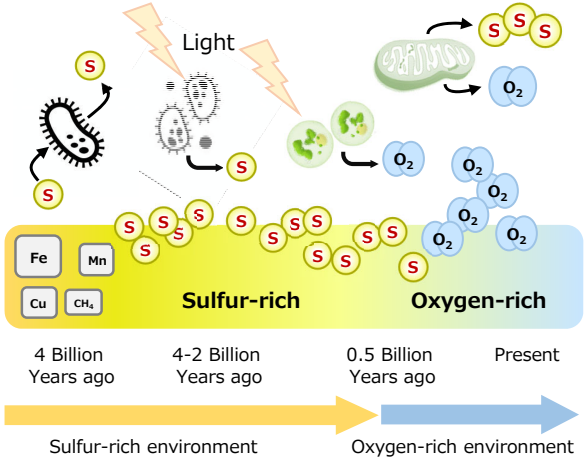
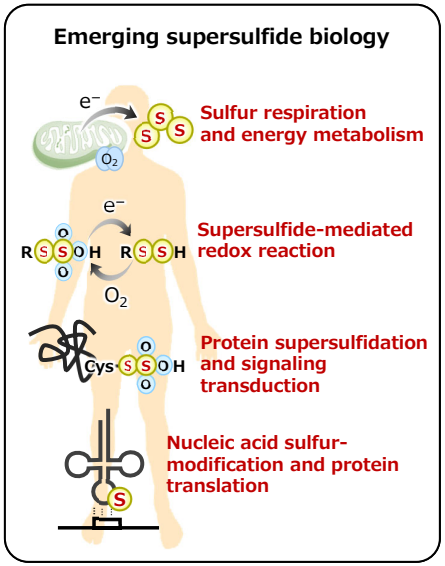


Fig. 2. Supersulfides in life evolution and their biological perspectives

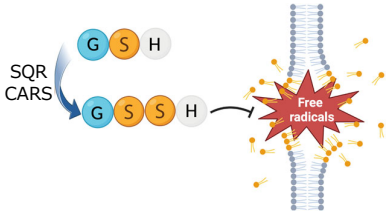




●Sulfur, a major component of life evolution

Sulfur as a key biological element is believed to have played a role in respiration once before oxygen was generated on the earth. The physiological function of sulfur, however, remains poorly understood. Recent breakthroughs made by our group is identification of the endogenous supersulfide biosynthesis enzymes like CARS that constitute a crucial pathway for energy metabolism in cells and in vivo. Supersulfides serve as electron acceptors in mitochondrial respiration, indicative of their conservation across all organisms. They modulate protein structure and function, impacting various signaling pathways. Our research also clarified remarkable radical scavenging and inhibitory activities of supersulfides against lipid peroxidation and ferroptosis (Fig. 3).

Fig. 3. Regulation of lipid radical by supersulfides



G, glutathione; S, sulfur; H, proton; SQR, sulfide:quinone oxidoreductase; CARS, cysteinyl-tRNA synthetase.

●Physiological relevance of supersulfides formed in vivo

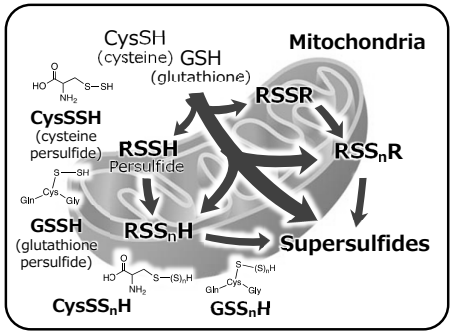
Our group discovered enzymatic sulfur catenation of sulfur-containing molecules like cysteine and GSH, leading to formation of diverse supersulfide species. It includes various R-S_n-R' compounds with varied sulfur chain lengths and structure (Fig. 1). Surprisingly, supersulfides are found to be abundantly biosynthesized in mitochondria, playing a vital role in redox regulation and antioxidant responses. Supersulfides, rich in electrons, contribute to fundamental biological processes and disease models. Manipulating supersulfide levels in vivo may warrant disease control and prevention.

Expected Research Achievements

●Research Plans and Methods

[Key questions or issues of this research and methodologies to be capitalized on]

Fig. 4. Formation of supersulfides in mitochondria



1. **Understanding the biochemical property of supersulfides (Fig. 4)**: How are the supersulfides generated in cells?; where do the supersulfides go?; and what is physiological relevance in terms of its interaction with other canonical redox molecules such as ROS and free radicals? To address these issues, we will explore (1) the molecular mechanism of CARS-mediated supersulfide generation in vivo; (2) a novel supersulfide synthesis pathway; (3) the electron flux mediated by supersulfides.
2. **MS and Raman imaging of the supersulfides and other related redox molecules**: Through the highly sophisticated technologies, we will properly and precisely localize (visualize) and quantify the supersulfides in the cells and tissues/organs.
3. **Exploring rigorously the exact functions of supersulfides**: By understanding the physiological functions of supersulfides in oxidative stress and redox signaling, the impact of supersulfides in health and diseases will be greatly enhanced accordingly.

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