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

Broad Section H

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

Takaaki Akaike
(Tohoku University, Graduate School of Medicine, Professor)

Research Project Number : 18H05277 Researcher Number : 20231798
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.

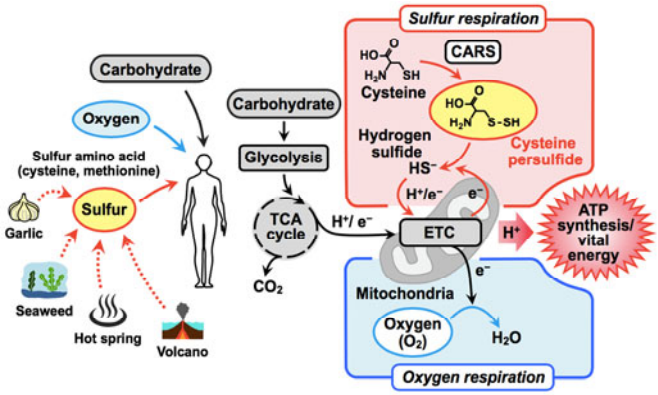


Figure 1. Sulfur respiration

【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.

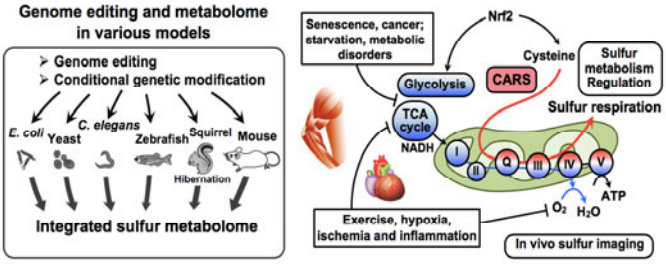


Figure 2. Research plans

【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

Title of Project : Analysis of immune regulatory mechanisms mediated by mRNA metabolism

Osamu Takeuchi
(Kyoto University, Institute for Frontier Life and Medical Sciences, Professor)

Research Project Number : 18H05278 Researcher Number : 10379092
Keyword : immune reaction, cytokine, mRNA decay

【Purpose and Background of the Research】

Immune cells eliminate pathogens by evoking immune responses by recognizing pathogens via a set of receptors such as Toll-like receptors and antigen-receptors. Cytokines are mediators of immune responses, although their production is tightly controlled to prevent inflammatory diseases. We previously identified Regnase-1 as an RNase essential for the suppression of excess immune responses. Regnase-1 post-transcriptionally controls abundance of mRNAs related with immune responses by directly degrading them. Furthermore, the studies on Regnase-1 and Roquin revealed that immune responses are fine-tuned by spatiotemporally-regulated decay of mRNAs in cells. The immune-related mRNAs are controlled not only by 3' untranslated regions (UTR) recognized by Regnase-1, but also via the coding regions and the modification of mRNAs. Although the abundance of immune-related mRNAs is determined by highly complex mRNA metabolism, the mechanism of regulation is not understood yet. In this research, we aim to elucidate the dynamic network of mRNA metabolism in immune regulation.

【Research Methods】

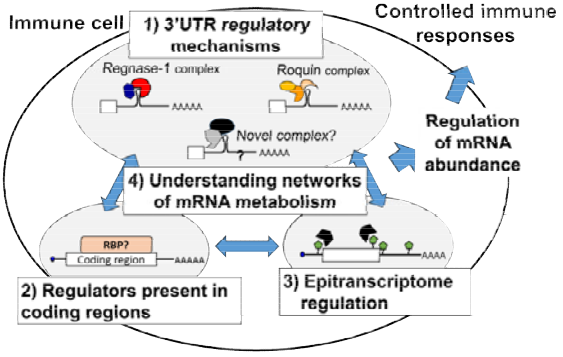


Fig. 1. Scheme of this research

In this research, we will analyze mechanisms of mRNA regulation in immune responses via following points of view.

1) Analysis of spatiotemporal regulation of immune-related mRNAs via 3' UTR.
2) Analysis of molecular mechanisms of immune-related mRNAs hidden in protein coding regions.
3) Roles of mRNA epitranscriptome in the regulation of immune reactions.

Then, the networks between immune regulatory systems studied in 1) ~3) will be integrated by in silico analysis such as machine learning.

【Expected Research Achievements and Scientific Significance】

We will try to understand dynamic mRNA metabolism networks in the control of immune responses. Further integration between mRNA regulation and transcription networks, complete understanding of gene expression networks of immune reactions will be achieved. In addition, our study will lead to the precise prediction of immune responses, which might be leading to the development of novel therapies targeting mRNA metabolisms.

【Publications Relevant to the Project】

・Yoshinaga M, Nakatsuka Y, Vandenbon A, Ori D, Uehata T, Tsujimura T, Suzuki Y, Mino T, Takeuchi O. Regnase-1 Maintains Iron Homeostasis via the Degradation of Transferrin Receptor 1 and Prolyl-Hydroxylase-Domain-Containing Protein 3 mRNAs. ***Cell Rep.*** 19:1614-1630. 2017
・Mino T, Murakawa Y, Fukao A, Vandenbon A, Wessels HH, Ori D, Uehata T, Tartey S, Akira S, Suzuki Y, Vinuesa CG, Ohler U, Standley DM, Landthaler M, Fujiwara T, Takeuchi O. Regnase-1 and Roquin Regulate a Common Element in Inflammatory mRNAs by Spatiotemporally Distinct Mechanisms. ***Cell***. 161:1058-73. 2015

【Term of Project】 FY2018-2022

【Budget Allocation】 148,900 Thousand Yen

【Homepage Address and Other Contact Information】

https://www2.infront.kyoto-u.ac.jp/Takeuchi_HP/

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

Broad Section H

Title of Project : Studies on the regulation of infection and immunity via paired receptors

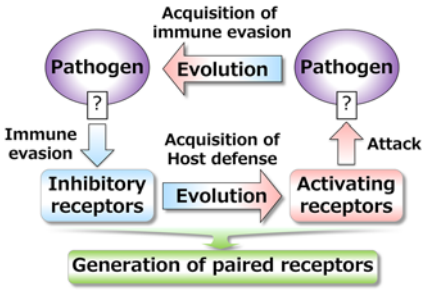
Hisashi Arase
(Osaka University, Research Institute for Microbial Diseases, Professor)

Research Project Number : 18H05279 Researcher Number : 10261900
Keyword : Paired receptors, Host-pathogen interaction, Immune evasion

【Purpose and Background of the Research】

Immune system express a series of paired receptors that consist of inhibitory and activating receptors. We have elucidated the function of various paired receptors based on our original hypothesis that the paired receptors have evolved with viruses (***Cell*** 2008; ***Nat. Immunol.*** 2012). Furthermore, we have shown that paired receptors are involved in not only virus infection but also in bacterial and malaria infection (***Nat. Microbiol.*** 2016, ***Nature*** 2017 Fig. 1). In this study, we would like to elucidate how pathogens are using inhibitory paired receptors for immune evasion. In addition, we will elucidate the function of paired receptors in host defense mechanism. Based on the studies on host-pathogen interaction, function of paired receptors in autoimmune diseases and allergic diseases will be elucidated.

Fig. 1 Coevolution of paired receptors with pathogens



【Research Methods】

We will perform the following studies. 1. We will identify the pathogen ligands for paired receptors. 2. We will study the role of paired receptors in severe infection, persistent infection or latent infection. 3. We will study the contribution of in paired receptors in autoimmunity or allergic diseases.

- **Studies on the function of paired receptors in infectious diseases.**

We will elucidate the interactions of various paired receptors with malaria molecules like FIRINs Furthermore, association of RIFIN expression and severe malaria will be elucidated. Furthermore, function of paired receptors in persistent and latent infection of virus as well as viral reactivation will be analyzed.

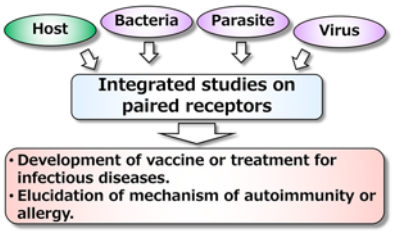
- **Studies on relationship between polymorphisms of paired receptors and diseases.**

By analyzing polymorphism of paired receptors from both host and pathogen side, we will elucidate the mechanism of autoimmunity or allergy.

【Expected Research Achievements and Scientific Significance】

Total function of paired receptors in host-pathogen interaction will be elucidated in this study. In addition, involvement of paired receptors in immune homeostasis will be elucidated. This study will be important to develop a method for prevention or treatment of infectious and immune diseases as well as vaccines (Fig. 2).

Fig. 2 Studies on regulation of infection and immunity via paired receptors



【Publications Relevant to the Project】

- Saito F, 17 others, Arase H. Immune evasion of *Plasmodium falciparum* by RIFIN via inhibitory receptors. ***Nature*** 552: 101-105, 2017.
- Hirayasu K, 14 others, Arase H. Microbially cleaved immunoglobulins are sensed by the innate immune receptor LILRA2. ***Nature Microbiology*** 25: 16054, 2016.
- Wang J, 3 others, Arase H. Neutrophil infiltration during inflammation is regulated by PILRα via modulation of integrin activation. ***Nature Immunology*** 14: 34-40, 2013.

【Term of Project】 FY2018-2022

【Budget Allocation】 148,800 Thousand Yen

【Homepage Address and Other Contact Information】

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