

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

Broad Section H



Title of Project : Comprehensive understanding of Regnase-1-mediated mRNA surveillance system

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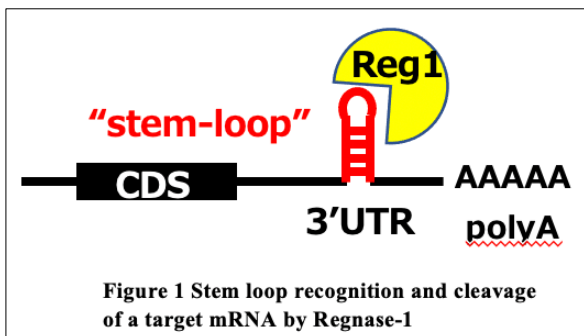
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Research Project Number: 20H05693 Researcher Number : 50192919

Keyword : Regnase-1, mRNA stability, metabolic regulation, tissue homeostasis

【Purpose and Background of the Research】

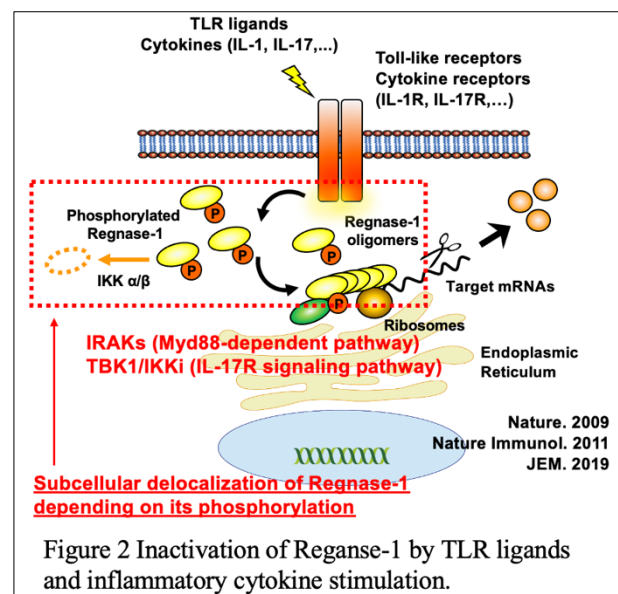
The discovery of microRNAs and non-coding RNAs has led to increase in the study of mRNA regulatory mechanisms. We identified an endoribonuclease, named Regnase-1, which binds to the 3'UTR of *IL-6* mRNA and degrades its mRNA (Figure 1). So far, RNA-binding proteins that reported to be involved in mRNA stability have no own endoribonuclease activity, but instead promote the degradation by recruiting to exosomes via interactions with target mRNAs. Besides those involved in microRNA biogenesis, Regnase family is the only RNA-binding protein possessing endoribonuclease activity in mammals. Subsequent studies have shown that Regnase-1 regulates the production of not only IL-6 but also many other mRNAs associated with inflammatory and immune responses and plays essential roles in immune system. Furthermore, it is becoming clear that Regnase-1 is involved in the regulation of various metabolic processes other than inflammatory and immune responses, suggesting that Regnase-1 participates in various biological processes. However, it is not yet known how Regnase-1 discriminates the target specificity of mRNAs. In this study, we investigate whether Regnase-1 is involved in the regulation of homeostasis and cell activation in various organs, based on the accumulated knowledge of Regnase-1. The purpose of this project is to gain a comprehensive understanding of Regnase-1-mediated mechanism of mRNA regulation.



【Research Methods】

We generate cell-type and tissue-specific knockout and various mutation knock-in mice to elucidate the *in vivo* roles of Regnase-1, a novel mechanism for the regulation of immune and inflammatory responses. We will examine

the role of Regnase-1 by using these mice-derived immune analyze the Regnase-1-mediated regulatory mechanisms, including its role in metabolism. In addition, we will search for novel molecules and small compounds that inhibit the endonuclease activity of Regnase-1, examine their effects, and explore their potential application in drug discovery.



【Expected Research Achievements and Scientific Significance】

By understanding the regulation of immune and inflammatory responses by Regnase-1 as well as its metabolic regulation, we hope to explore new areas of RNA biology. Furthermore, it is important to explore and develop small compounds that regulate immune function via Regnase-1 for the conquest of diseases.

【Publications Relevant to the Project】

- Tanaka H et al, J. Exp. Med. (2019)
- Nagahama Y et al, PNAS (2018)

【Term of Project】 FY2020-2024

【Budget Allocation】 152,400 Thousand Yen

【Homepage Address and Other Contact Information】

<http://hostdefense.ifrec.osaka-u.ac.jp/en/index.html>