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

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : The study on the molecular and cellular bases underlying the crosstalks between innate immunity and cell metabolism in lysosomes

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Research Project Number : 16H06388　Researcher Number : 60229812
Research Area : Immunology
Keyword : Innate Immunity

【Purpose and Background of the Research】

Toll-like receptors (TLRs) sense microbial products and induces defense responses. Nucleic acid (NA) is a principal ligand. Self-derived NA activates TLRs and induces a variety of autoimmune diseases. NA-sensing TLRs are localized in lysosomes.

NAs are continuously degraded in lysosomes and TLR responses to self NAs are therefore prevented in unperturbed condition. DNA degradation by DNase II, however, is required for DNA sensing by DNA-sensing TLR9. Furthermore, RNA-sensing TLR7 and TLR8 respond to ribonucleosides such as uridine and guanosine, suggesting requirement of RNA processing from RNA into ribonucleosides in RNA sensing by TLR7 and TLR8.

The mammalian target of rapamycin (mTOR) is a metabolic sensor. Although TLRs and mTOR are both localized in lysosomes, little is known about their relationship.

The present study focuses on the relationship between NA sensing by TLRs and NA metabolism in lysosomes and the relationship between TLRs and mTOR.

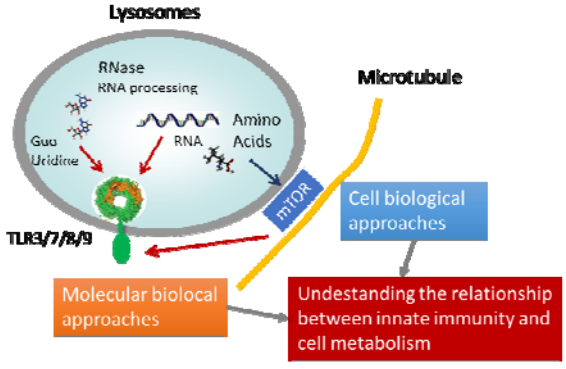

Figure 1: Understanding the crosstalks between innate immunity and cell metabolism in lysosomes

【Research Methods】

To study the relationship between NA metabolism and NA sensing, molecules involved in RNA degradation and processing will be studied with particular focus on RNases. Diseases caused by loss of function of those molecules are also to be studied.

To understand the crosstalks between NA-sensing TLRs and mTOR, molecular mechanism underlying type I IFN production by TLRs is to be studied with particular focus on TLR trafficking.

【Expected Research Achievements and Scientific Significance】

The present study aims to reveal the relationship between NA metabolism and NA sensing by TLRs in lysosomes. The finding from the present study would contribute to our understanding on the pathophysiological mechanism underlying a variety of autoimmune diseases.

After sensing NAs, TLRs activate innate immune responses. This decision needs to be made under the permission from cell metabolism. The present study would reveal the mechanism by which metabolic cues are integrated into innate immune responses. In this mechanism, we believe that TLR trafficking plays an important role. Our results would have an impact on not only immunology but also cell biology.

【Publications Relevant to the Project】

・Chan MP, Onji M, Fukui R, Kawane K, Shibata T, Saitoh SI, Ohto U, Shimizu T, Barber GN, Miyake K. DNase II-dependent DNA digestion is required for DNA sensing by TLR9. ***Nat Commun***. 2015 6:5853.

・Shibata T, Ohto U, Nomura S, Kibata K, Motoi Y, Zhang Y, Murakami Y, Fukui R, Ishimoto T, Sano S, Ito T, Shimizu T, Miyake K. Guanosine and its modified derivatives are endogenous ligands for TLR7. ***Int Immunol***. 2016 28:211-222.

【Term of Project】 FY2016-2020

【Budget Allocation】 140,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.ims.u-tokyo.ac.jp/kanseniden/index.html