

FUNDING PROGRAM FOR NEXT GENERATION WORLD-LEADING RESEARCHERS

Project Title: Induction of Autophagy and its Function in Tissue Homeostasis in Innate Immunity

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1. Background of research

Intracellular bacteria, such as *Shigella* or *Listeria*, invade into human cells for the infection, which causes the therapeutic difficulty using antibiotics. Therefore, it is indispensable for the therapy to find out how to manipulate the infection of invasive pathogens. "Autophagy", the intracellular catabolic system for the degradation of proteins and cellular components, functions to eliminate the invaded pathogens, by its specific induction *via* the recognition of pathogens. Autophagy also involved in the inflammation, since the misregulation of autophagy or pathogen recognition causes inflammation in intestine, such as Crohn's disease.

2. Research objectives

The purpose of this project is to clarify the mechanism of the induction and the function of autophagy at the infection of intracellular pathogens or inflammation, and propose the possible therapeutic targets. In this project, we propose the approaches in three research plan.

Plan 1: Analyses the pathogen recognition-mediated induction of autophagy

(Plan1-1: Identification of factors involved in the autophagy induction

Plan 1-2: Identification of microRNAs that regulate the autophagosome formation)

Plan 2: Analyses of the functions of autophagy against invasive pathogens in gut

Plan 3: Analyses of the mechanism of Crohn's disease caused by defects in autophagy or pathogen recognition

3. Research characteristics (incl. originality and creativity)

Autophagy functions at the front line of innate immunity. *Drosophila* (fruit fly) is an ideal model organism for studying innate immunity, since it does not have adaptive immunity and combats against pathogens only with innate immunity. The analogousness of the whole system of innate immunity between flies and mammals, and excellent methods of fly genetics that already established, enable us to understand the mechanism of autophagy-related immune responses, including inflammatory bowel disease.

4. Anticipated effects and future applications of research

The identification of factors for autophagy induction *via* pathogen recognition will present the new targets for chemicals against invasive pathogens. Also, the understanding the functions of autophagy in innate immunity, especially in inflammation will open the door to novel, fundamental, and complete therapeutic methods to Crohn's disease.

Project plan

innate immunity

pathogen recognition

Autophagy as
innate immune response

plan 1

Analyses of the mechanism of
autophagy induction
Analyses of the spacial regulation of
autophagosome via microRNA

plan 2

Analyses of function of
autophagy in gut
immunity

plan3

Analyses of the
mechanism of Crohn's
disease

Identification of the novel therapeutic
targets against invasive pathogens

Clarification of the cause of inflammatory
bowl disease for the proposal to the novel
therapeutic methods to Crohn's disease

Frontier studies using *Drosophila*, with its excellent genetic
and molecular techniques *in vitro* to *in vivo*

Quick and easy application to human