

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

### Biological Sciences (Medicine, Dentistry, and Pharmacy)



Title of Project : Extensive analyses of the LUBAC ubiquitin ligase

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Research Project Number : 17H06174 Researcher Number : 60252459

Research Area : General Medical Chemistry

Keyword : ubiquitin, regulation of inflammation, B cell lymphomas, LUBAC ligase, myopathy

#### 【Purpose and Background of the Research】

The ubiquitin conjugation system has been identified as a part of protein degradation system. Then, the ubiquitin research has been developed in tight relationship with proteolysis. However, linear ubiquitin chains and the LUBAC ligase (composed of three subunits) generating the chain specifically, which we discovered, are now world-widely recognized as a reversible post-translational system that is involved in signaling leading to NF- $\kappa$ B activation and protection from cell death.

Moreover, aberrant activation or impairment of the LUBAC ligase activity is shown to be involved in some form of B cell lymphomas or immunodeficiency and autoinflammation, respectively. Thus, LUBAC and the linear ubiquitin chain also attract attentions of clinicians. The leader of this research project discovered LUBAC and the linear ubiquitin chain and we have already generated transgenic and conditional knockout mice of the subunits of LUBAC. In this research project, we intend to develop LUBAC research further and to build the basis for the translational research to cure lymphomas and autoinflammatory diseases by manipulating LUBAC.

#### 【Research Methods】

Using multidisciplinary techniques including structural biology, biochemistry and mouse genetics, we intend to perform research from the following four points.

1. Structural and functional analyses of regulation and activation mechanisms of the LUBAC ubiquitin ligase
2. Dissection of the roles LUBAC and the linear ubiquitin chains played in inflammation and immune-regulation
3. Dissection of new pathophysiological function of LUBAC using genetically engineered mice
4. Dissection of the roles of LUBAC in lymphomagenesis and development of LUBAC

inhibitors

#### 【Expected Research Achievements and Scientific Significance】

The following achievement will be expected.

1. Elucidation of regulatory mechanism of the LUBAC ligase
2. Elucidation of pathogenesis mechanisms of LUBAC-related disorders
3. Elucidation of activation mechanism of inflammasomes in which LUBAC and autophagy are involved
4. Roles of LUBAC played in immune-regulation mediated by regulatory T cells

Our research project might lead to the development of the followings.

1. Development of drug modulating LUBAC activity as an anti-cancer drug
2. Provide new aspects in the research of autoimmune and autoinflammatory diseases

#### 【Publications Relevant to the Project】

1. Iwai, K., Fujita, H., and Sasaki, Y. Linear ubiquitin chains: NF- $\kappa$ B signalling, cell death, and beyond. **Nature Rev. Mol. Cell Biol.** 15(8):503-508, 2014.
2. Tokunaga, F., Nakagawa, T., Nakahara, M., Saeki, Y., Taniguchi, M., Sataka, S.-I., Tanaka, K., Nakano, H., and Iwai, K. SHARPIN is a component of the NF- $\kappa$ B activating linear ubiquitin chain assembly complex. **Nature** 471:633-636, 2011.

【Term of Project】 FY2017-2021

【Budget Allocation】 157,100 Thousand Yen

#### 【Homepage Address and Other Contact Information】

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