



Principal Investigator	Kyoto University, Graduate School of Medicine, Professor	
	IWAI Kazuhiro	Researcher Number:60252459
Project Information	Project Number : 22H04988	Project Period (FY) : 2022-2026
	Keywords : ubiquitin, inflammation, autoimmunity, cancer	

Purpose and Background of the Research

●Outline of the Research

The ubiquitin system plays an important role in the regulation of numerous functions in our bodies by degrading proteins and the Nobel Prize was awarded to its discoverers in 2004. However, the principal investigator found that linear ubiquitin chains are not involved in protein degradation, but are involved in regulation of inflammatory responses. It has been shown that linear ubiquitin chains are specifically generated by the LUBAC ligase, and that genetic mutations of LUBAC cause diseases. We have also discovered that augmented LUBAC function, which is provoked even in the absence of mutations, is involved in cancer and autoimmunity. We initiated this research to pave a road to the development of new treatments for the diseases.

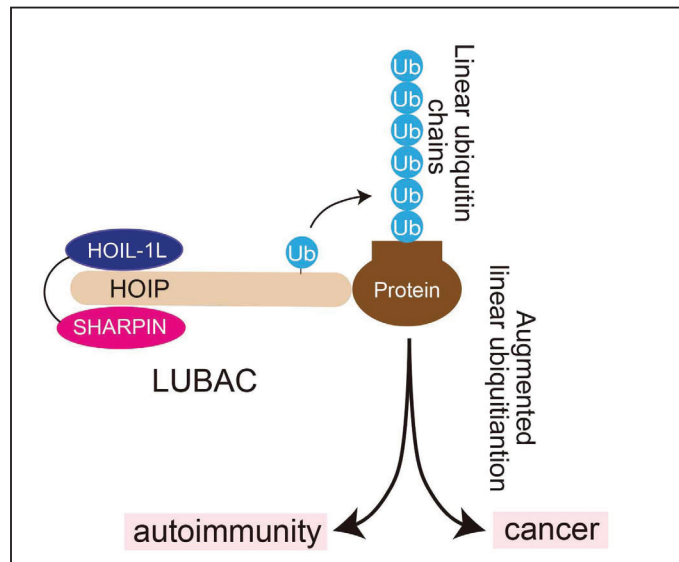


Figure 1. Analysis of the role of LUBAC-specific linear ubiquitin chains in autoimmunity and cancer

●Role of linear ubiquitin chains in autoimmunity

Loss of function of ABIN1, which selectively recognizes linear ubiquitin chains, is causative to systemic lupus erythematosus, a representative systemic autoimmune disease. Since linear ubiquitination is involved in the function of variety of cells in the immune system, we dissected the roles hyperactivity of linear ubiquitination played in the development of systemic lupus erythematosus. In addition, we will challenge the development of functional inhibitors of linear ubiquitination.

● Analysis of the role of linear ubiquitination in cancer tumorigenesis

The principal investigator has found that some cancer cells failed to form tumors in mice in case that they lost LUBAC function. Therefore, in this study, we try to elucidate the role of linear ubiquitin chains in cancer tumorigenesis.

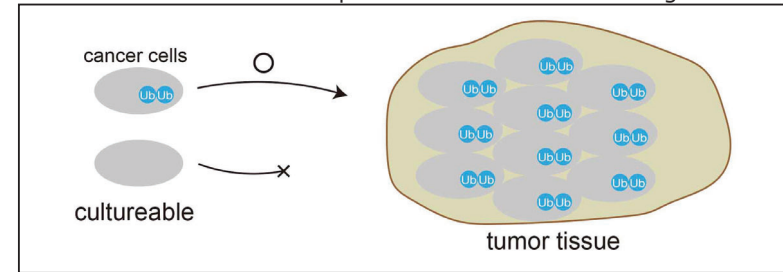


Figure 2. Cancer cells that can generate linear ubiquitin chains can form tumors

Expected Research Achievements

●Elucidation of the role of linear ubiquitin chains generated by LUBAC in the development and pathogenesis of autoimmunity and cancer

Autoimmune diseases are caused by the recognition of self antigens by the immune cells. Linear ubiquitination plays crucial roles in the functions of the immune cells, and we will elucidate the detailed mechanism that the enhanced linear ubiquitination is involved in the development of autoimmune diseases.

On the other hand, the immune cells also infiltrate into tumor tissues and causes chronic inflammation in tumors. The principal investigator has observed that cancer cells cannot form tumors if they are defective in linear ubiquitination. Since linear ubiquitination can suppress cell death induced by various stimuli, it is conceivable that linear ubiquitination enables cancer cells to evade from the attack by the immune cells.

We will vigorously promote research to show that suppression of linear ubiquitination will be a target for the development of new treatments for cancer and autoimmune diseases.

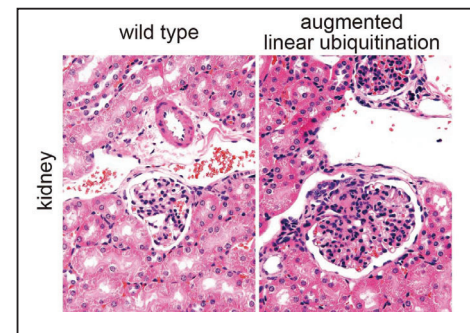


Figure 3. Systemic lupus erythematosus-like nephropathy

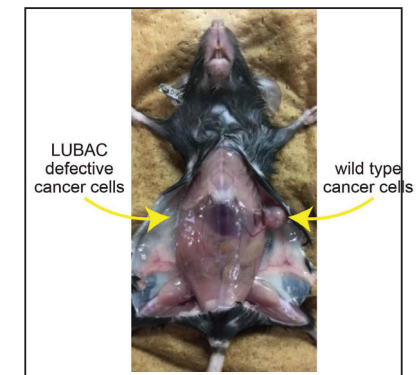


Figure 4. TumORIZATION of cancer cells transplanted into mice