Japan Academy Prize to:

Kazuhiro Iwai
Dean and Professor, Graduate School of Medicine,
Kyoto University

for "Discovery of Linear Ubiquitin Chains and Analyses of their Roles in Inflammatory Responses"

Outline of the work:

The ubiquitin system is a post-translational modification system discovered as a part of the energy-dependent protein degradation pathway. In this pathway, ubiquitin is conjugated to proteins as ubiquitin chains, polymers of ubiquitin, leading to conjugated protein degradation. The ubiquitin-proteolytic research flourished in the 1990s, and in 2004, its discoverers were awarded a Nobel Prize in Chemistry. However, the ubiquitin research further expanded in different directions in the 2000s because of the discovery of its non-proteolytic functions and multiple types of ubiquitin chains. It has also been indicated that the type of ubiquitin chain determines the conjugated protein mode of regulation.

Until the early 2000s, it has been believed that ubiquitin chains are generated via one of the seven Lys residues in ubiquitin. The prevailing hypothesis for the ubiquitin chain at that time was that the chains were elongated by individually adding ubiquitin onto the distal moiety of ubiquitin chains via the repetitive functions of three enzymes. However, Prof. Kazuhiro Iwai realized that the hypothesis for chain elongation contradicts enzymology concepts, and he started analyzing the mechanism of ubiquitin chain elongation. During the analyses, he discovered a brand-new type of ubiquitin chain that is generated via N-terminal Met of ubiquitin and named it the linear ubiquitin chain.

Since the ubiquitin system is distributed throughout eukaryotic kingdoms, the ubiquitin research was enormously conducted using yeast genetics, and seven Lys-linked ubiquitin chains exist even in unicellular budding yeast. However, the linear ubiquitin chain is found only in animal kingdoms. Thus, Prof. Iwai's identification of linear chains using biochemical methods provided a paradigm shift in ubiquitin research. He also found the sole enzyme complex, which exclusively generates linear chains, and named it the linear ubiquitin chain assembly complex (LUBAC). LUBAC is now world-renowned, and Prof. Iwai is highly reputed as the discoverer of LUBAC.

Considering that linear ubiquitin chains emerged during animal evolution, Prof. Iwai hypothesized that LUBAC-mediated linear ubiquitination is involved in regulating integrated cellular functions. He then found that linear ubiquitination plays crucial roles in activating NF-κB, a critical signal molecule involved in several important biological phenomena, including inflammatory responses and cell survival, and suppression of programmed cell death. His discovery regarding the involvement of linear chains in NF-κB activation was contradictory to the prevailed

theory that the K63-linked ubiquitin chain contributed to NF-κB activation, which caused many controversies. However, it is now clarified that recognition of linear ubiquitin chains conjugated to NEMO by another NEMO plays a predominant role in IKK activation and subsequent activation of NF-κB. His discovery showing crucial roles of linear ubiquitination in regulating inflammatory responses via NF-κB activation and cell death suppression is highly evaluated because it provides a new paradigm in NF-κB and cell death studies.

Prof. Iwai also contributed to elucidating the roles played by LUBAC-mediated linear ubiquitination in human diseases. Prof. Iwai found that in mice, severe attenuation of LUBAC function provokes immunodeficiency and autoinflammatory disease by impaired NF-κB activation and augmented programmed cell death, respectively. His report led to identifying congenital diseases in that LUBAC subunit mutations are causative autoinflammatory disease with immunodeficiency. Moreover, he identified that augmented production of linear ubiquitin chains is involved in B cell lymphomas' pathogenesis, and LUBAC inhibition suppresses the growth of B lymphoma cells. Moreover, Prof. Iwai, for the first time, identified that some pathogens secrete toxins that inhibit LUBAC and infect their hosts.

Recently, it has been reported that augmented LUBAC activity underlies resistance to widely used anti-cancer drugs, cis-platinum, and immune checkpoint therapy. It has also been shown that inappropriate suppression of linear ubiquitin signals is involved in the pathogenesis of systemic lupus erythematosus. Moreover, Prof. Iwai established the strategies to augment and suppress LUBAC-mediated linear ubiquitination.

These achievements regarding LUBAC-mediated linear ubiquitination described above, originated from Prof. Iwai's simple biochemical question "How are ubiquitin chains generated?" He elucidated its pathophysiological functions and brought up LUBAC-mediated linear ubiquitination as a world-renowned research. Therefore, Prof. Iwai's discovery of LUBAC and linear ubiquitin chains is genuinely one of the most ingenious research achievements that have originated from Japan.

List of Main Publications

1. Iwai, K, Klausner, RD, and Rouault, TA: Requirements for iron-regulated degradation of the RNA binding protein, iron regulatory protein 2. **EMBO J.**, 14; 5350–5357, 1995.
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10. Iwai, K: Diverse ubiquitin signaling in NF-κB activation. **Trends Cell Biol.**, 22; 355–364, 2012.
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