【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Agricultural sciences)

Title of Project： The molecular mechanism of ER stress response and the pathophysiology of ER stress disorders

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Research Area：Applied Biochemistry
Keyword：Cell response, Signal transduction

【Purpose and Background of the Research】

The endoplasmic reticulum (ER) is protein synthesis machineries in the cell. The newly synthesized proteins are correctly folded and assembled by the assistance of ER molecular chaperones, and finally gain of protein function. When cells are exposed to various environmental or intracellular stresses, unfolded or misfolded proteins accumulate in the ER. This state is called ER stress. Upon ER stress, cells activate unfolded protein response (UPR) pathway to upregulate the genes encoding ER chaperones and the components of ERAD (ER associated degradation), leading to alleviate the ER stress. UPR has a unique system, which contains unconventional splicing of *XBP1* mRNA by ER stress sensor IRE1 and the regulated intramembrane proteolysis of ATF6. Further ER stress has been related to neurodegenerative disease, some diabetes, and inflammatory bowel disease, but their precise molecular mechanisms have remained unclear.

In this research, we focus on physiological ER stresses observed in pancreatic islet or caused by parasitic infection, and would elucidate the role of ER stress response to maintain cellular homeostasis under physiological ER stress condition by using ER stress sensor-KO mice.

【Research Methods】

We are interested in physiological ER stress observed in islet or caused by parasitic infection. In this analysis, we will use ER stress sensor-deficient mice (IRE1α, ATF6α, IRE1α/ATF6α, and IRE1β KO mice, respectively). To analyze the symptom of diabetes mellitus, serum glucose, insulin synthesis, and glucose tolerance test are performed. In parasitic infection, we perform histochemical and electron microscopic analyses of goblet cells in small intestine after parasitic infection or IL33 administration, and also analyze the characteristics of mucin (Muc2) by immunofluorescence and SDS-PAGE. In addition to analysis of whole body level, synthesis and secretion of insulin or mucin are studied in pancreatic islet β cells and goblet cells, respectively, using biochemical and genetic engineering techniques.

【Expected Research Achievements and Scientific Significance】

Since ER stress response pathway is constitutively activated in pancreatic islet, we speculate that activation of ER stress response is quite important for insulin production and/or the survival of β cells. To address this question, we would like to demonstrate whether the disruption of IRE1α pathway would develop diabetes. Further, we would like to know the role of IRE1α in insulin synthesis, maturation, secretion or β-cell survival. Another ER stress sensor IRE1β would play an important role in proliferation and maturation of goblet cells, which secrete mucin and other factors to protect intestinal epithelial cells from various invaders. From these studies, we would provide the direct evidence that ER stress response is quite important for protecting and maintaining specific cells and tissues from physiological ER stress.

【Publications Relevant to the Project】

・Iwawaki, T., Akai, R., Yamanaka, S., & Kohno, K. Function of IRE1alpha in the placenta is essential for placental development and embryonic viability. Proc Natl Acad Sci USA, 106, 16657-16662 (2009)
・Yanagitani, K., Kimata, Y., Kadokura, H., & Kohno, K. Translational pausing ensures membrane targeting and cytoplasmic splicing of *XBP1u* mRNA. Science, 331, 387-399 (2011)

【Term of Project】

FY2012-2016

【Budget Allocation】

159,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://bsw3.naist.jp/kouno/kouno.html