【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy)

Title of Project : Homeostasis Regulation via Stress Signaling and its Molecular Basis for Drug Development

Hidenori Ichijo
(The University of Tokyo, Graduate school of Farmaceutical Sciences, Professor)

Research Area : Biochemistry, Molecular Biology
Keyword : stress, signal transduction, drug development

【Purpose and Background of the Research】

The stress response is one of the most fundamental biological processes, and its disruption results in a wide variety of human diseases, such as cancer, neurodegenerative diseases, inflammatory diseases and metabolic diseases. However, the molecular mechanism of stress sensors or receptors that recognize physico-chemical stress, such as oxidative stress, osmotic stress, endoplasmic reticulum (ER) stress and mitochondrial stress, and the molecular dynamics of the stress signaling that is activated by stress sensors remain elusive. In this project, we aim at elucidating the mechanisms of homeostasis regulation via stress signaling and its molecular basis.

【Research Methods】

We have already succeeded in identifying the key molecules in four fundamental stress responses: 1) ASK1 and ASK2 for oxidative stress; 2) ASK3 for osmotic stress; 3) SOD1 and Derlin-1 for ER stress (and zinc deficiency) and 4) PGAM5 for mitochondrial stress. In this project, we set four goals based on our previous findings.

Goal 1: Elucidation of the mechanism of the oxidative stress-dependent activation of the ASK1 complex and regulation of oxidative stress responses.

Goal 2: Elucidation of the mechanism of the osmotic stress-dependent bi-directional regulation of ASK3 activity and regulation of osmotic stress responses.

Goal 3: Elucidation of the mechanism of the SOD1-Derlin-1 interaction-dependent induction of ER stress and regulation of zinc homeostasis.

Goal 4: Elucidation of the mechanism of the mitochondrial membrane potential loss-dependent cleavage of PGAM5 and regulation of mitochondrial stress responses.

【Expected Research Achievements and Scientific Significance】

To accomplish these four goals, we will take advantage of four approaches. 1) A biochemical and molecular biological approach using cultured mammalian cells. We have already established genome-wide RNAi screening system using cellular immunostaining and high-throughput image analysis, which is applicable in the research for the four goals described above to explore novel regulators of the target molecules. 2) Mouse models for human diseases using knockout mice. We have already generated knockout mice for ASK1, ASK2, ASK3 and PGAM5. 3) A chemical compound screen for the development of chemical inhibitors of target molecules or interactions. 4) X-ray crystal structure analysis in collaboration with RIKEN and SGC Oxford. From these analyses, we will uncover the detailed molecular mechanisms of stress signaling, from stress sensing to cellular responses, and their involvement in human disease and provide new therapeutic strategies for the diseases.

【Publications Relevant to the Project】

- Naguro, I., Umeda, T., Kobayashi, Y., Maruyama, J., Hattori, K., Shimizu, Y., Kataoka, K., Kim-Mitsuyama, S., Uchida, S., Vandewalle, A., Noguchi, T., Nishitoh, H., Matsuzawa, A., Takeda, K. and **Ichijo, H**. ASK3 responds to osmotic stress and regulates blood pressure by suppressing WNK1-SPAK/OSR1 signaling in the kidney. ***Nat. Commun.***, 2012; 3:1285 (2012).
- Sekine, Y., Hatanaka, R., Watanabe, T., Sono, N., Iemura, S., Natsume, T., Kuranaga, E., Miura, M., Takeda, K. and **Ichijo, H.** The kelch repeat protein KLHDC10 regulates oxidative stress- induced ASK1 activation by suppressing PP5. ***Mol. Cell***, 48, 692-704, (2012).

【Term of Project】

FY2013-2017

【Budget Allocation】

164,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.f.u-tokyo.ac.jp/~toxicol/index.html