

**Establishment of the basis for drug development by the analysis of molecular mechanisms of stress signaling**

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**【Outline of survey】**

Stress response is one of the most fundamental cellular functions. Abrogation of the mechanisms of stress response leads to various human diseases including inflammation, cancer, neurodegeneration and autoimmunity. However, structural and spacio-temporal information of stress sensors as well as direct stress sensing mechanisms by proteins are largely unknown. In this study, we aim at elucidating the signaling mechanisms of stressors such as oxidative stress, Endoplasmic Reticulum stress and osmotic stress by focusing on the analysis of stress-activated ASK family kinases and their regulatory proteins. We would like to understand the mechanisms by which those physico-chemical and biological stressors are sensed by cells and converted to phosphorylation-dependent signals. The notable scientific features of this study are that we have been the front runner in the field of ASK family kinases and their regulatory proteins in stress responses and that we will perform these studies by using the forefront analytical techniques of stress signaling.

**【Expected results】**

We expect through this study to understand the molecular basis of stress signaling, especially sensing, recognition and conversion of cellular stressors. Our goal is also expected to lead to the development of lead chemical compounds of drugs based on our understandings of the molecular mechanisms of stress regulation of ASK family kinases. We hope accomplishment of our studies will produce fruitful results with novel principles in biology, pharmaceutical sciences and medicine.

**【References by the principal researcher】**

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- Ichijo, H., Nishida, E., Irie, K., ten Dijke, P., Saitoh, M., Moriguchi, T., Takagi, M., Matsumoto, K., Miyazono, K. and Gotoh, Y. Induction of apoptosis by ASK1, a mammalian MAPKKK that activates SAPK/JNK and p38 signaling pathways. *Science*, 275, 90-94 (1997).

**【Term of project】** FY2008—2012

**【Budget allocation】**

**160,400,000 yen** (direct cost)

**【Homepage address】**

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