Japan Academy Prize to:

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for "Elucidation of the Stress Response Mechanism based on the ASK Family"

Outline of the work:

Living organisms maintain homeostasis by responding appropriately to endogenous or exogenous stress at the cellular level. The stress response controls various cellular functions, such as proliferation, differentiation and death. Its perturbation causes various pathological conditions, such as inflammation, cancer, neurodegeneration, and diabetes. Elucidating the molecular mechanisms of stress recognition and response in cells is an important research question not only for the advancement of basic life sciences but also for the creation of new drug discovery platforms and therapeutic strategies. Since the discovery of Apoptosis Signal-regulating Kinase 1 (ASK1) as a protein kinase that induces cell death, Prof. Hidenori Ichijo has been engaged in research on stress signaling, focusing on the ASK family (ASK1, ASK2, and ASK3). He has also contributed to the foundation of innovative drug discovery, and medical science and technology by expanding his basic research findings into applied drug discovery.

1. Discovery of ASK1 as a cell death (apoptosis) inducing signal molecule

In 1997, Prof. Ichijo cloned the cDNA of the ASK1 gene, the first MAP3K that specifically activates the JNK and p38 pathways but not the ERK pathway. ASK1 is a MAP3K that is activated by TNFα and oxidative stress inducing cell death. In mammals, ASK1 forms the ASK family with ASK2 and ASK3. Prof. Ichijo identified the primary structures of all the ASK family members and analyzed the ASK family to elucidate the molecular entities and mechanisms of cellular responses to various stresses.

2. Discovery of a general molecular mechanism for sensing oxidative stress

In the late 1990s, when the basic mechanisms of the signaling pathways of major cytokines and growth factors were almost fully elucidated, the question of how cells perceive and recognize physicochemical stresses, such as oxidative stress, remained a major question in cell biology.

Prof. Ichijo hypothesized that ASK1 binds to another protein that serves as a receptor for oxidative stress and identified the redox protein thioredoxin (Trx) as a binding partner of ASK1 by using a yeast two-hybrid screen. Trx has two redox states: an oxidized form, in which two cysteine residues essential for its redox activity are disulfide bonded, and a reduced form, in which the residues are thiols. Prof. Ichijo found that only the reduced form of Trx binds to ASK1, and when

Trx is converted to the oxidized form by oxidative stress, such as reactive oxygen species, it dissociates from ASK1. In the steady state, Trx binds to the N-terminal region of ASK1 and inactivates the kinase activity of ASK1. Furthermore, he found that dissociation of Trx reciprocally allows TNF receptor-associated factor (TRAF) family molecules to bind to and activate ASK1.

In other words, the Trx-ASK1 complex is a molecular complex that senses oxidative stress and functions as a molecular switch that converts oxidative stress into protein phosphorylation signals. This finding is the first example where the concept of "signal transduction via regulation of molecular interactions by cysteine oxidation" has been proposed as a general molecular mechanism for sensing and transmitting oxidative stress.

3. Elucidation of new stress signals and development of drug discovery research

Prof. Ichijo has also pioneered the analysis of many key molecules involved in cellular stress responses, including the discovery of ASK3, which enables the osmotic stress response, and endoplasmic reticulum stress response through the interaction of SOD1 and Derlin-1.

In ALS, a neurodegenerative disease in which motor neurons are selectively damaged, Prof. Ichijo has focused on SOD1 gene mutations as a cause of ALS. He found that more than 100 mutant forms of SOD1 share a common higher-order structure that differs from normal SOD1. Furthermore, he found that mutant SOD1 induces endoplasmic reticulum stress by binding to Derlin-1 protein in the endoplasmic reticulum through the common structure. He also found that mutant SOD1 induces endoplasmic reticulum stress-dependent activation of ASK1, which ultimately leads to neurodegeneration. In addition, he explored small-molecule compounds and found that optimized ASK1 inhibitors and SOD1–Derlin-1 binding inhibitors were effective in ameliorating ALS pathology.

As described above, Prof. Ichijo, as one of the world's leading researchers in the field of biochemistry and molecular biology, has contributed to our understanding of the stress response and its application in drug discovery and medicine and has made a significant impact in this field of research. For these achievements, Prof. Ichijo has received the JCA-Mauvernay Award of the Japanese Cancer Association, the Academic Award of the Mochida Memorial Foundation, the Takamine Memorial Daiichi Sankyo Prize, the Uehara Prize, the Medal with Purple Ribbon, and the Takeda Prize for Medical Science.

List of Main Publications

1. **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).
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10. Matsuzawa, A., Saegusa, K., Noguchi, T., Sadamitsu, C., Nishitoh, H., Nagai, S., Koyasu, S., Matsumoto, K., Takeda, K. and **Ichijo, H.** ROS-dependent activation of TRAF6-ASK1-p38 pathway is selectively required for TLR-4 mediated innate immunity. ***Nat. Immunol.***, 6, 587–592 (2005).
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12. Osaka, N., Takahashi, T., Murakami, S., Matsuzawa, A., Noguchi, T., Fujiwara, T., Aburatani, H., Moriyama, K., Takeda, K. and **Ichijo, H.** ASK1-dependent recruitment and activation of macrophages induce hair growth in skin wounds. ***J. Cell Biol.***, 176, 903–909 (2007).
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