Japan Academy Prize to:

Keiji TANAKA
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for "Studies on Structure and Functions of Proteasomes (Protein-degrading Enzyme Complexes)"

Outline of the work:

Over the past 25 years, Dr. Keiji Tanaka has been engaged in first-class medical research aimed at elucidating the divergent roles of proteolysis in the cells, with a special focus on the proteasome, a eukaryotic ATP-dependent protease complex. He has made many break-through discoveries and world-renowned contributions to the structure, function, and physiology of the proteasome. Summarized below are his contributions.

1. Structural and functional characterizations of the proteasome, a eukaryotic ATP-dependent protease complex

Protein degradation plays a prominent role in the control of a diverse array of basic cellular activities by rapid and unidirectional catalysis of biological reactions. In mid-1980's, Dr. Tanaka was the first scientist to discover and characterize in detail the unusually large multi-protease complex designated the 'proteasome'. His success was in part due to the use of various up-to-date biochemical, physicochemical, and molecular biological techniques, which led to characterization of the structures of eukaryotic proteasomes, specifically in mammals. Subsequent studies found that the proteasome is a highly sophisticated protein complex that comprises approximately 50 different subunits designed to carry out selective, efficient, and processive hydrolysis of client proteins in an ATP-dependent fashion. Dr. Tanaka added another milestone in his career when he recently discovered various proteasome assembling chaperones. This discovery is important as it defines the possible mechanisms of proteasome assembly. He also introduced new technology to analyze the mouse genome in order to define the biological functions of the proteasome. His research addressed the importance of the proteasome, in conjunction with the ubiquitin system (representing a posttranslational modifier serving as a degradation signal) in selective degradation of short-lived regulatory proteins as well as abnormal proteins that must be eliminated from the cells.

2. Discovery and characterization of immunoproteasome and thymoproteasome

In 1994, the pioneer work of Dr. Tanaka led to the discovery of the "immunoproteasome" whose β1, β2, and β5 catalytic subunits are replaced by the structurally related and γ-interferon-induced β1i, β2i, and β5i, respectively. The discovery was an important landmark in the understanding of the specialized functions of the immunoproteasomes in immune responses as it defined their function as professional antigen processing enzymes. The discoveries did not end there. He also identified recently another unique "thymoproteasome", which contains a novel catalytic subunit, designated β5t, which is expressed exclusively in the thymus. More recently, he found that β5t-deficient mice displayed severe impairment in $CD8^+$ T cell development, thus highlighting the importance of the thymoproteasome in the thymic positive selection of the acquired immune system.

3. In depth analysis of the ubiquitin and autophagy systems

On another front, Dr. Tanaka has continued his first-class research work in cell biology and mouse genetics to define the role of familial Parkinson's disease gene product, parkin as a ubiquitin-protein ligase, sugar-recognizing ubiquitin ligase SCF^{Fbs1} involved in the endoplasmic reticulum-associated degradation (ERAD) pathway, and autophagy (a self-eating pathway). These studies will contribute to the creation of new bioscientific field and the development of new therapies for many intractable diseases, such as cancers, infectious diseases, and neurodegenerative diseases. The importance of such work can only be appreciated by realizing the ever increasing rates of these conditions in recent years, especially in the elderly.

References

Tanaka, K., Waxman, L., and Goldberg, A. L. (1983) ATP serves two distinct roles in protein degradation in reticulocytes. One requiring and one independent of ubiquitin. **J. Cell Biol**. 96, 1580–1585.

Tanaka, K., Yoshimura, T., Kumatori, A., Ichihara, A., Ikai, A., Nishigai, M., Kameyama, K., and Takagi, T. (1988) Proteasomes (multi-protease complexes) as 20S ring-shaped particles in a variety of eukaryotic cells. **J. Biol. Chem**. 263, 16209–16217.

Fujiwara, T., Tanaka, K., Orino, E., Yoshimura, T., Kumatori, A., Tamura, T., Chung, C. H., Nakai, T., Yamaguchi, K., Shin, S., Kakizuka, A., Nakanishi, S., and Ichihara, A. (1990) Proteasomes are essential for yeast proliferation: cDNA cloning and gene disruption of two major subunits. **J. Biol. Chem**. 265, 16604–16613.

Murakami, Y., Matsufuji, S., Kameji, T., Hayashi, S., Igarashi, K., Tamura, T., Tanaka, K., and Ichihara, A. (1992) Ornithine decarboxylase is degraded by the 26S proteasome without ubiquitination. **Nature** 360, 597–599.

Akiyama, K., Yokota, K., Kagawa, S., Shimbara, N., Tamura, T., Akioka, A., Nothwang, H. G., Noda, C., Tanaka, K., and Ichihara, A. (1994) cDNA cloning and interferon-γ down-regulation of proteasomal subunits X and Y. **Science** 265, 1231–1234.

Coux, O., Tanaka, K., and Goldberg, A. L. (1996) Structure and functions of the 20S and 26S proteasomes. **Annu. Rev. Biochem**. 65, 801–847.

Tanaka, K., and Kasahara, M. (1998) The MHC class I ligand generating system: Roles of immunoproteasomes and INF-γ inducible PA28. **Immunol. Rev**. 163, 161–176.

Imai, J., Maruya, M., Yashiroda, H., Yahara, I., and Tanaka, K. (2003) The molecular chaperone Hsp90 interacts with 26S proteasomes and regulates their assembly. **EMBO J**. 22, 3557–3567.

Mizushima, T., Hirao, T., Yoshida, Y., Lee, S. J., Chiba, T., Iwai, K., Yamaguchi, Y., Kato, K., Tsukihara, T., and Tanaka, K. (2004) Structural basis of sugar-recognizing ubiquitin ligase. **Nat. Struct. Mol. Biol**. 11, 365–370.

Hirano, Y., Hendil, K.B., Yashiroda, H., Iemura, S., Nagane, R., Hioki, Y., Natsume, T., Tanaka, K., and Murata, S. (2005) A heterodimeric complex that promotes the assembly of mammalian 20S proteasomes. **Nature** 437, 1381–1385.

Komatsu, M., Waguri, S., Chiba, T., Murata, S., Iwata, J., Ueno, T., Koike, M., Uchiyama, Y., Kominami, E., and Tanaka, K. (2006) Loss of autophagy in the central nervous system causes neurodegeneration. **Nature** 441, 880–884.

Murata, S., Sasaki, K., Kishimoto, T., Niwa, S., Hayashi, H., Takahama, Y., and Tanaka, K. (2007) Regulation of $CD8^+$ T cell development by thymus-specific proteasomes. **Science** 316, 1349–1353.

Komatsu, M., Waguri, S., Koike, M., Sou, Y., Ueno, T., Hara, T., Mizushima, N., Iwata, J., Ezaki, J., Murata, S., Hamazaki, J., Nishito, Y., Iemura, S., Natsume, N., Yanagawa, T., Uwayama, J., Warabi, E., Yoshida, H., Ishii, T., Kobayashi, A., Yamamoto, M., Yue, Z., Uchiyama, Y., Kominami, E., and Tanaka, K. (2007) Homeostatic levels of p62 control cytoplasmic inclusion body formation in autophagy-deficient mice. **Cell** 131, 1149–1163.

Saeki, Y., and Tanaka, K. (2007) Unlocking the proteasome door. **Mol. Cell** 27, 865–867.

Yashiroda, H., Mizushima, T., Okamoto, K., Kameyama, T., Hayashi, H., Kishimoto, T., Kasahara, M., Kurimoto, E.,

Sakata, E., Suzuki, A., Hirano, Y., Murata, S., Kato, K., Yamane, T., and Tanaka, K. (2008) Crystal structure of a chaperone complex that contributes to the assembly of yeast 20S proteasomes. **Nat. Struct. Mol. Biol**. 15, 228–236.

Saeki, Y., and Tanaka, K. (2008) Two hands for degradation. **Nature** 453, 460–461.

Kimura, Y., Yashiroda, H., Kudo, T., Koitabashi, S., Murata, S., Kakizuka, A., and Tanaka, K. (2009) An inhibitor of deubiquitinating enzyme regulates ubiquitin homeostasis. **Cell** 137, 549–559.

Saeki, Y., Toh-e, A., Kudo, T., Kawamura, H., and Tanaka, K. (2009) Multiple proteasome-interacting proteins assist the assembly of the yeast 19S regulatory particle. **Cell** 137, 900–913.

Kaneko, T., Hamazaki, J., Iemura, S., Sasaki, K., Furuyama, K., Natsume, T., Tanaka, K., and Murata, S. (2009) Assembly pathway of the mammalian proteasome base subcomplex is mediated by multiple specific chaperones. **Cell** 137, 914–925.

Murata, S., Yashiroda, H., and Tanaka, K. (2009) Molecular mechanisms of proteasome assembly. **Nat. Rev. Mol. Cell Biol**. 10, 104–115.

Tanaka, K. (2009) The proteasome: Overview of structure and functions. **Proc. Jpn. Acad. Ser. B** 85, 12–36.

Nitta, T., Murata, S., Sasaki, K., Fujii, H., Ishimaru, N., Koyasu, S., Tanaka, K., and Takahama, Y. (2010) Thymoproteasome shapes immunocompetent repertoire of CD8 T cells. **Immunity** 32, 29–40.

Komatsu, M., Kurokawa, H., Waguri, S., Taguchi, K., Kobayashi, A., Ichimura, Y., Sou, Y-S., Ueno, I., Sakamoto, A., Tong, K. I., Kim, M., Iemura, S., Natsume, T., Ueno, T., Kominami, E., Motohashi, H., Tanaka, K., and Yamamoto, M. (2010) The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through Keap1-inactivation. **Nat. Cell Biol**. 12, 213–223.

Matsuda, N., Sato, S., Shiba, K., Okatsu, K., Saisho, K., Gautier, C.A., Sou, Y., Saiki, S., Kawajiri, S., Sato, F., Kimura, M., Komatsu, M., Hattori, N., and Tanaka, K. (2010) PINK1 stabilized by depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. **J. Cell Biol**. 189, 211–221.