

Japan Academy Prize to:

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For “Study on Cell Signaling and Its Regulation in
Cancer”

***Outline of the work:***

Dr. Kohei Miyazono has been engaged in signaling mechanisms in cancer cells during the past 25 years, with a special focus on transforming growth factor- β (TGF- β) family signaling. TGF- β is the prototype member of the TGF- β family, which is now known to exhibit both pro-oncogenic and anti-oncogenic functions, and plays pivotal roles in progression of cancer. The TGF- β family includes 33 proteins in mammals. Among them, bone morphogenetic proteins (BMPs) are known to show broad spectra of functions, including bone and cartilage formation, during development and in adult tissues. Dr. Miyazono has identified some of the key receptors for the TGF- β family proteins, and elucidated their signaling mechanisms and biological functions.

1. Characterization of the latent forms of TGF- β

TGF- β is synthesized as latent high molecular weight complexes and requires activation steps to exhibit their biological activities. In 1988, Dr. Miyazono was the first researcher to purify the latent form of TGF- β from human platelets, and demonstrated that the latent TGF- β complex contains three components, i.e. mature TGF- β , the N-terminal remnant of the TGF- β precursor termed latency associated peptide (LAP), and a novel protein now known as the latent TGF- β binding protein 1 (LTBP-1). Dr. Miyazono has also shown that LTBP-1 plays critical roles in association of the latent TGF- β complex with the extracellular matrix, secretion from the producer cells, and activation of the latent TGF- β complex.

2. Identification of the signaling receptors for the TGF- β family proteins

Members of the TGF- β family transduce signals through two different types of serine/threonine kinase receptors, termed type I and type II receptors. In 1993, Dr. Miyazono and his colleagues succeeded in cDNA cloning of six different serine/threonine kinase receptors, termed ALK-1 through 6, and found that ALK-5 is the type I receptor for TGF- β . They have also shown that other ALKs function as type I receptors for members of the TGF- β family, including BMPs and activins. His group has furthermore identified type II receptors for BMPs, and thus, he elucidated the receptor system of the TGF- β family proteins.

3. Signaling pathways mediated by the TGF- β family proteins

TGF- β family proteins transduce intracellular signals mainly through Smad proteins. There are eight Smad proteins in mammals. In 1997, Dr. Miyazono and his colleagues characterized the function of one of the Smad proteins, Smad6, and demonstrated that Smads can be classified into three subtypes, i.e. R-Smads, Co-Smad, and I-Smads. R-Smads form complexes with Co-Smad upon activation by the type I receptors, and translocate into the nucleus where they regulate transcription of target genes through interaction with various transcription factors and transcriptional co-activators or co-repressors. I-Smads physically interact with activated type I receptors, and interfere with the activation of R-

Smads by them. Since expression of I-Smads is induced by the TGF- β family signals, they constitute a negative feedback loop to regulate TGF- β family signaling.

4. Roles of TGF- β in epithelial-mesenchymal transition (EMT) and cancer-initiating cells

Through the studies on signaling mechanisms of TGF- β , Dr. Miyazono has elucidated the roles of TGF- β in progression of cancer. TGF- β acts on epithelial cells and induces EMT. He has shown that cooperative action of TGF- β and oncogenic Ras signaling is crucial for the induction of Snail, a key transcription factor for EMT. He furthermore demonstrated that metastasis of breast cancer in mice can be effectively prevented by inhibition of TGF- β signaling through inhibition of EMT.

Cancer-initiating cells are tumor cells characterized by their ability to induce tumorigenesis and to self-renew. Dr. Miyazono has discovered that TGF- β induces the expression of Sox4, followed by the induction of Sox2 to maintain the stemness of cancer-initiating cells obtained from patients with glioblastoma. His finding thus will open a new strategy to treat cancer by targeting cancer-initiating cells using TGF- β inhibitors.

References

Research Articles

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