

6th International Conference on

Structural Biology

August 22-23, 2016 New Orleans, USA

Discovery of a GTP sensor using a structural reverse genetic approach

Toshiya Senda

High Energy Accelerator Research Organization (KEK), Japan

GTP is an energy molecule in the cell and required in protein synthesis. Reduction of GTP concentration results in slow cell growth; inversely, rapidly growing cells have elevated GTP concentration. Because of its vital roles in cell growth, GTP concentration should be monitored and homeostatically regulated in the cell. However, a sensing mechanism of cellular GTP concentration remains elusive. Here, we show that a lipid kinase, PI5P4K β , serves as a GTP sensor and GTP concentration functions as a metabolic cue *via* PI5P4K β . Our proteomics and biochemical study revealed that PI5P4K β binds GTP and its enzyme activity is significantly higher with GTP than with ATP; PI5P4K β mainly utilizes GTP for phosphorylation of PI5P. Furthermore, the kinetic characters of PI5P4K β are suitable to detect the change of cellular GTP concentration. These biochemical characteristics suggested that PI5P4K β is a GTP sensor in the cell. However, since PI5P4K β can utilize not only GTP but also ATP for the enzyme reaction in the cell, a simple knockout/down experiment is insufficient to analyze the biological function of the GTP-sensing activity of PI5P4K β . We therefore took a structural reverse genetic approach. First, we determined crystal structures of PI5P4K β -ATP/GTP complexes and used the crystal structures to prepare a PI5P4K β mutant that lacks GTP-sensing activity without changing ATP-dependent activity. We then performed biological and metabolomic analyses with the PI5P4K β mutant, revealing that PI5P4K β serves as a GTP-sensor. The GTP-sensing activity of PI5P4K β is critical for metabolic adaptation and tumorigenesis.

Biography

Toshiya Senda has completed his PhD from Nagaoka University of Technology, Niigata, Japan in 1995. He was a Research Associate in Nagaoka University of Technology (1995-2001) and a Senior Researcher in Institute of Advanced Industrial Science and Technology (2001-2012). Currently, he is the Director/Professor of Structural Biology Research Center of High Energy Accelerator Research Organization in Japan. He was awarded the CrSJ (Crystallographic Society of Japan) Award in 2014.

toshiya.senda@kek.jp

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