Elucidation of Structure of PTPN3-p38γ Complex Points to New Cancer Drug Design Strategy

A research team led by Academician Andrew H.-J. Wang, a Distinguished Research Fellow and Dr. Tzu-Ching Meng, a Research Fellow from the Institute of Biological Chemistry, has determined the architecture of the protein tyrosine phosphatase N3 (PTPN3) in complex with mitogen-activated protein kinase 12 (MAPK12/p38γ) using a hybrid method. The structure demonstrated the formation of an active-state complex and the unique regulatory role of the PDZ domain of PTPN3. The findings may enable the development of novel therapeutic intervention strategy to target cancers, particularly colorectal cancer (CRC) in which PTPN3 is highly expressed and expected to promote Ras oncogenic signaling through dephosphorylation of fully activated p38γ. The research was published in *Science Signaling* on October 14, 2014 as the cover article of the issue. In addition, the research team has been invited to conduct a *Science Signaling* podcast interview.

The Ras signaling cascade has long been considered to be an attractive therapeutic target for CRC. Among the modules in this signaling pathway, p38γ and its specific phosphatase PTPN3 are known to be the key regulators responsible for Ras-mediated oncogenic activity. Research Fellow Dr. Tzu-Ching Meng explained that recent attention has been drawn to the PDZ-mediated PTPN3-p38γ complex, which is known to be a novel target for Ras-dependent cancers. However, the dynamic nature of the phosphatase-kinase interactions has so far resisted structural biologists' attempts to explore the detailed molecular structure of this important group of drug targets.

In the study, the first author of the research team, Dr. Kai-En Chen used X-ray crystallography to solve the structure of the PTP catalytic domain of human PTPN3 in complex with a synthetic peptide that corresponds to the activation loop of p38γ. The crystal structure shows a unique feature; a glutamic acid-containing loop that defines the substrate specificity of PTPN3 towards fully activated p38γ. Small-angle x-ray scattering (SAX) and cross-linking/mass spectrometry were applied to probe the solution structure of PTPN3-p38γ active state complex. The research team further discovered that PTPN3 could form an intrinsic inhibitory conformation regulated by its PDZ domain in the absence of an appropriate substrate. The findings of this study suggest two new directions for a rational drug design to target Ras transformation. First, an allosteric inhibitor can be designed to lock the PDZ and PTP domain so that PTPN3 may stay in its inhibitory conformation.

Second, the novel inhibitory can be designed to suppress the interaction between the PDZ domain of PTPN3 and the PDZ binding motif of p38γ.

Academician Wang indicated that the cutting-edge research method applied in this study also demonstrated the strength of Taiwan's structural biology community. In particular, the resources from Academia Sinica and the National Synchrotron Radiation Research Center (NSRRC) can be integrated to tackle the extremely challenging tasks, he said.

The complete article entitled: "Reciprocal allosteric regulation of p38γ and PTPN3 involves a PDZ domain-modulated complex formation" can be found at the Science Signaling journal website at: http://stke.sciencemag.org/content/sigtrans/7/347/ra98.full.pdf

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