Tzu Ching Meng, J Proteomics Bioinform 2017, 10:8(Suppl)
DOI: 10.4172/0974-276X-C1-0100

Structural basis for PTPN3 - p38gamma complex involved in colon cancer progression

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The Ras signaling cascade acts as a key driver in human colon cancer progression. Among the modules in this pathway, p38gamma (MAPK12) and its specific protein tyrosine phosphatase PTPN3 (PTPH1) are critical regulators responsible for Ras oncogenic activity. However, the molecular basis for their interaction is completely unknown. Here we report the unique architecture of the PTPN3-p38gamma complex by employing an advanced hybrid method integrating X-ray crystallography, small-angle X-ray scattering (SAXS) and chemical cross-linking/mass spectrometry (CX-MS). Our crystal structure of PTPN3 in complex with the p38gamma phosphopeptide presented a unique feature of the E-loop that defines the substrate specificity of PTPN3 towards fully activated p38gamma. The low-resolution structure demonstrated the formation of an active-state or a resting-state complex of PTPN3-p38gamma. We showed a regulatory function of PTPN3's PDZ domain, which stabilizes the active-state complex through interaction with the PDZ-binding motif of p38gamma. Using SAXS and CX-MS approaches, we found that binding of the PDZ domain to the PDZ-binding motif lifts the atypical auto-inhibitory constraint of PTPN3, enabling efficient tyrosine dephosphorylation of p38gamma to occur. Our findings emphasize the potential of structural approach for PTPN3-p38gamma complex that may deliver new therapeutic strategies against Ras-mediated oncogenesis in colon cancer.

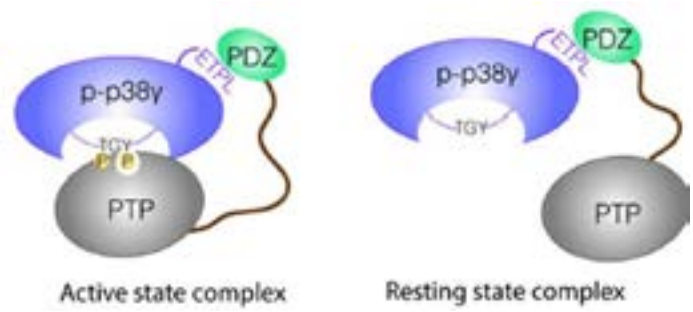

Figure1: *Our structural data suggest the presence of the active state complex (left) and the resting state complex (right) between PTPN3 and p38gamma. The interaction of PDZ domain in PTPN3 and the ETPL motif in p38gamma drives the complex formation. We show that the resting state complex may promote oncogenic signaling involved in colon cancer progression.*

Biography

Tzu Ching Meng has completed his PhD from University of Nebraska Medical Center in 1999 and Post-doctoral studies from Cold Spring Harbor Laboratory in 2003. Since then, he has been working at Academia Sinica, the premier government-funded institution in Taiwan. He is currently a Research Fellow with Professorship jointly appointed by National Taiwan University. He has published more than 40 papers in reputed journals and has been serving as an Advisory Board Member of competitive journals.

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