

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

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Abstract

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 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.