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Structural analysis of PTPN3-p38γ interactions by chemical cross-linking coupled with mass spectrometry

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Purpose: Protein tyrosine phosphatase N3 (PTPN3) and mitogen-activated protein kinase p38γ coordinate to promote Ras-induced oncogenesis. Structural analysis of PTPN3-p38γ complex is a challenging task by using traditional X-ray crystallography. Therefore, chemical cross-linking coupled with mass spectrometry (CX-MS) has been developed as an alternative method to solve this obstacle.

Experimental Description: Through covalent linkage of two spatially proximate residues within a single or between two polypeptide chains, the CX-MS approach provides structural insights into the flexible regions of proteins under any circumstances amenable to analysis. Conventionally, mapping of the protein-protein interaction sites relies on the coupling of lysine residues on the surface. Together with the distance restraint of the selected cross-linker, the segments of interaction surface can be determined.

Results: Employing this method, we have mapped the contact interfaces of the PTPN3-p38γ complex. Our finding of the solution structure indicated that the catalytic domain of PTPN3 interacts with the activation loop of phosphorylated p38γ, illustrating how PTPN3-mediated dephosphorylation of p38γ takes place. The CX-MS approach further demonstrated that the PDZ domain of PTPN3 recruits the PDZ-binding motif of p38γ, thus stabilizing the active-state complex of PTPN3-p38γ. Moreover, the CX-MS analysis defined the autoinhibitory characteristic of the PDZ domain in PTPN3 in the absence of p38γ.

Conclusions: By combining other approaches such as small-angle X-ray scattering (SAXA) and crystal structure of PTPN3-phospho-p38γ peptide, the CX-MS method generates considerable insights into the architecture of the phosphatase-kinase complex assembly.

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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