REGIONAL CENTRE FOR BIOTECHNOLOGY
Seminar series

Structural basis for conformational coupling across the plasma membrane in activation of EGFR

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Abstract

One of the fundamental problems in cell biology is to understand how extracellular signals are transmitted across the membrane through cell surface receptors. The epidermal growth factor receptor (EGFR) has served as a model system to study the mechanism of such cellular signaling processes. EGFR is a single pass transmembrane glycoprotein comprised of extracellular ligand binding domain, a transmembrane domain, juxtamembrane segment, and a tyrosine kinase domain (KD) flanked by C-terminal tail. Allosteric activation of EGFR involves homodimerization of the extracellular domain that activates the kinase domain by reorienting it into a cyclin/CDK-like asymmetric dimer. This rearrangement of the kinase domain and the extracellular domain are tightly coupled through the oligomeric states of the transmembrane and juxtamembrane region. The current mechanism of allosteric activation of EGFR kinase domain proposed by our lab requires the formation of an antiparallel helical dimer by the N-terminal juxtamembrane region. We reported earlier that the juxtamembrane interaction is sufficient to stabilize the active kinase dimer. It is possible that the transmembrane domain rotation and its dimerization could strongly affect the conformation of the adjacent juxtamembrane region. The details of this cross-talk between the juxtamembrane and the transmembrane regions are unknown. Therefore we have focused on further understanding the function of the transmembrane domain in activation of the EGFR kinase, and I will present our current results from the biophysical and biochemical characterization of transmembrane-juxtamembrane segment. We conclude that EGF binding removes steric constraints in the extracellular domain, promoting activation through N-terminal association of the transmembrane helices.