[S5-2] [4/18/2003(Fri) 14:10-14:50/Maple Hall]

Multiple Roles of Phospholipase D in Growth Factor Signaling

Sung Ho Ryu

Division of Molecular and Life Sciences, Pohang University of Science & Technology, Pohang, 790-784, Korea

The epidermal growth factor (EGF) is an important signaling ligand for the mitogenesis of many cells. The EGF receptors use signaling molecule multicomplexes and dynamic protein networks for the transmission and amplification of the signals as well as for the regulation of the cellular responses. EGF signaling has been reported to be enhanced in various tumors by the overexpressed EGF receptor and/or the mediators such as phospholipasc C-γ1(PLCγ1). The EGF receptors are mainly localized in the membrane raft region, such as the caveolae, in many cells.

The signaling networks for the EGF receptor have been established by various proteomics approaches. One of the key signaling molecules for the EGF responses, Phospholipase D (PLD), has been considered to be an important and multifunctional component of the cellular responses involved in proliferation, vesicular trafficking and cellular movement.

This study used the PLD as a key molecule for establishing the EGF signaling network. More than twenty PLD binding proteins were identified using affinity chromatography and co-immunoprecipitation with MALDI-TOF mass fingerprinting in order to understand the role of the 'EGFR-PLD machine' in the EGF-induced cellular responses. The functional roles of the interaction in EGF signaling were demonstrated in various cells using the interaction-site-specific mutants.

In this presentation, the functional role and molecular mechanism of the PLD complex in EGF signaling would be mainly focused with the binding proteins to the phox homology (PX) domain of PLD. The PLD-PX domain is a tightly folded small domain containing ~120 amino acids. This study identified many molecules that interact with the PLD PX-domain including some activators (PKC, dynamin, phosphoinositdes), inhibitors (actinin, Munc-18) and effectors

(dynamin, phospholipase C-γ1). The binding site mapped for each molecule in the PX-domain was different suggesting that the PX-domain might evolve into a multi-functional module as a core of the dynamic signaling complex. The interactions were characterized according to the functional role of these interactions in EGF signaling such as Ca^{2+} mobilization and MAP kinase activation. Some novel signal flows from the EGF through PLD such as EGF receptor-phosphatidylinositol-3-kinase-phosphyatidylinositol 3,4,5-trisphosphate-PLD1, EGF receptor-dynamin-PLD2-ERK and EGF receptor-PLD2-PLCγ1-IP_3-Ca^{2+} are suggested along with experimental evidence. In conclusion, PLD may play a multifunctional role in EGF signaling such as (1) the amplification of the signal by generating the 2nd messenger PA through several activator molecules, (2) the regulation of other signal pathways by interacting with the effecter enzymes, and (3) the reception of other signal from the regulating proteins in cells. This model may be applied to many enzymes which mediate receptor signaling.

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