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Competition for Grb2 recruitment between EphA2 and EGFR during ligand activation

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Activation of EphA2 and EGFR receptor tyrosine kinases (RTKs) is initiated immediately after binding of their respective ligands, recruiting a variety of downstream signaling proteins and ultimately triggering a diverse range of biological outcomes. Although EphA2 and EGFR respond to distinct ligands (ephrinA1 and EGF, respectively) and trigger distinct responses, they also share key proximal signaling molecules. One such molecule is Grb2, which is an adaptor protein recruited to phosphorylated tyrosine residues and responsible for the recruitment of the Ras activator, SOS. How such receptor triggered signaling activities retain the identity of the triggering receptor and how (or if) different receptors may synergize or compete remains largely unknown. Here, we monitor Grb2 recruitment to ligand-activated receptors in a live cell system in which EphA2 and EGFR are spatially segregated, thus allowing unambiguous distinction of which receptor signaling complex each Grb2 molecule is binding. Results reveal a competitive effect by which, one receptor type can influence the signaling activity of the other remotely. Detailed analysis of Grb2 membrane recruitment kinetics reveals distinct differences between Grb2 recruitment to activated EphA2 clusters and clusters of activated EGFR. Consequences of this type of molecular competition for adaptor proteins in the overall context of signal transduction will be discussed.

Recent Publications

1. Joshua A, Dongmyung Oh, et al. (2016) Time-resolved multimodal analysis of Src Homology 2 (SH2) domain binding in signaling by receptor tyrosine kinases. eLife 5: e1183.

2. Dongmyung Oh, et al. (2012) Fast rebinding increases dwell time of Src homology 2 (SH2)-containing proteins near the plasma membrane. PNAS; 109: 14024-9.

References

1. Kabir H, et al. (2016) A microbead supported membrane-based fluorescence imaging assay revels intermembrane receptor-ligand complex dimension with nanaometer precision. Langmuir; 32: 6775-6780.

Biography

Dongmyung Oh has expertise in single molecule biophysics in live cell imaging. In a recent study of receptor tyrosine singling, he found that the rebinding mechanism by which a cytosolic signaling molecules bind/unbind and rebind to receptor.

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