14a Signal Transduction at Point-Blank Range: a Brownian Dynamics Study

Michael Monine and Jason Haugh

Nearly all signal transduction pathways involve at least one critical step in which an enzyme, recruited into a complex with an activated receptor, acts upon substrate molecules associated with the plasma membrane. Prominent examples include the recruitment of Grb2-Sos and RasGAP enzymes, which perform opposing functions by accelerating the formation of the GTP-bound (active) and GDP-bound (active) forms of the membrane-anchored Ras GTPases, and recruitment of phosphoinositide (PI) 3-kinase, which phosphorylates $PI(4,5)P_2$ to produce the lipid second messenger $PI(3,4,5)P_3$. In signaling through platelet-derived growth factor (PDGF) receptors and other receptor tyrosine kinases, the phosphorylated receptors engage Grb2-Sos, RasGAP, and PI 3-kinase in a site-specific manner. As a prime example of pathway crosstalk, Ras-GTP also binds PI 3-kinase, and previous work from our laboratory indicated that receptor- and Ras-mediated activation of PI 3-kinase is consistent with the cooperative assembly of a receptor/PI 3-kinase/Ras complex. The same concept presumably applies to Grb2-Sos and RasGAP as well. We have developed a computational model of this system, implemented in stochastic, Brownian dynamics simulations, to investigate the spatial coupling between activities associated with individual receptor molecules, which spontaneously form complexes with Grb2-Sos, RasGAP, and PI 3-kinase. Specifically, we investigate the hypothesis that diffusion-limited modulation of local Ras-GTP and -GDP densities by receptor-bound Grb2-Sos and RasGAP might influence the stability of such complexes and the recruitment of additional effectors such as PI 3-kinase.