Promiscuity quantitatively and qualitatively impacts early growth factor receptor signaling

Edward C. Stites[1], Daniel D. Von Hoff[1], William S. Hlavacek[1,2,3], and Richard G. Posner[1,4]

***Short Abstract* —To study promiscuity in biochemical networks, we formulated a rule-based model for early events in IGF1R signaling. The model accounts for over 70 interactions between seven IGF1R phosphotyrosines and 45 SH2 and PTB domain-containing proteins. Model parameters are based in large part on multiplex proteomic binding assays. In the IGF1R network there is variation in promiscuity at the level of phosphotyrosines (i.e. the number of SH2/PTB proteins with which a phosphotyrosine can interact) and at the level of SH2/PTB proteins (i.e. the number of distinct phosphotyrosines with which a protein interacts). We find that promiscuity can affect cell-signaling kinetics both quantitatively and qualitatively. Neglecting promiscuity in a mass-action kinetic model may limit the predictive value of the model.**

***Keywords* — Cell signaling, mechanistic modeling, rule-based modeling, promiscuity.**

I. Purpose

PROMISCUITY, or the ability of one protein to have multiple interaction partners, is a common feature of cell signaling networks [1]. Many phosphotyrosines are capable of interacting with multiple SH2 or PTB domains [2, 3]. Similarly, many SH2 and PTB containing proteins can bind to multiple phosphotyrosine sites. Mechanistic models often explicitly consider only one or two direct interaction partners for each modeled protein. Alternatively, a modeler may impose nonphysiological complexity by lumping distinct phosphotyrosines of a protein together as a single virtual phosphotyrosine and thereby require the different interaction partners to compete with each other for binding. The impact of these common simplifications on the predictive value of a model, and the significance of physiological promiscuity on cell signaling are both unknown. We therefore developed a model that accounts for the promiscuity observed in multiplex proteomic assays characterizing SH2/PTB interactions with receptor tyrosine kinases [3]. We used the model to investigate the potential impact of promiscuity on cell signaling and the practice of modeling cell signaling.

II. Model

Our rule-based model focuses on IGF1R, its seven tyrosine residues that are phosphorylated to serve as docking sites for 55 different SH2 and PTB domains in 45 different proteins. The reported interactions describe a network with varying levels of promiscuity at the level of individual phosphotyrosines as well as varying levels of promiscuity at the level of individual SH2 and PTB domain-containing proteins [3]. We specified our model in the BioNetGen language [4] and simulated the model with NFsim [5].

III. Results

We find that the intensity and duration of total phosphorylation for an individual receptor tyrosine increases with increasing promiscuity. In contrast, the maximum intensity of the interaction between the phosphotyrosine and a specific SH2 domain decreases while the duration of the total interaction signal increases with increasing promiscuity. SH2/PTB promiscuity allowed proteins to produce kinetic behaviors that differed qualitatively from the different, individual receptor phosphotyrosine kinetics. Variation in promiscuity among phosphotyrosines and SH2/PTB domains in a receptor network can therefore result in a spectrum of distinct signaling kinetics for the proteins in the network. Despite the competition between proteins for shared phosphotyrosine binding sites, the kinetics of each protein appear robust to changes in the promiscuity and abundance of other proteins.

Promiscuity is a common feature of signaling networks that has often been neglected in mechanism-based models. The predictive abilities of models that utilize measured biochemical properties may be limited if they do not account for these promiscuous interactions. Moreover, efforts to fit a mass-action model to experimental data may struggle if qualitative features of a signal are dependent upon non-accounted for promiscuity.

References

[1] Nobeli I, Favia AD, Thornton JM. (2009) Protein promiscuity and its implications for biotechnology. *Nat Biotechnol* 27, 157-167.

[2] Jones RB, et al. (2006) A quantitative protein interaction network for the ErbB receptors using protein microarrays. *Nature* 439, 168-74.

[3] Kaushansky A, et al. (2008). A quantitative study of the recruitment potential of all intracellular tyrosine residues on EGFR, FGFR1 and IGF1R. *Mol. BioSyst.* 4, 643-653.

[4] Blinov ML, et al. (2004) BioNetGen: software for rule-based modeling of signal transduction based on the interactions of molecular domains. *Bioinformatics* 20, 3289-91.

[5] Sneddon MW, Faeder JR, Emonet T. (2011) Efficient modeling, simulation and coarse-graining of biological complexity with NFsim. *Nat Methods* 8, 177-83.

[1]Clinical Translational Research Division, The Translational Genomics Research Institute, Scottsdale, AZ 85259. E-mail: estites@tgen.org

[2]Theoretical Division, Los Alamos National Laboratory

[3]Department of Biology, University of New Mexico

[4]Department of Biology, Northern Arizona University