



BIOLOGICAL INSIGHTS FROM QUANTITATIVE ANALYSIS OF RECEPTOR TYROSINE KINASE SIGNALING NETWORKS

Forest M. White

Massachusetts Institute of Technology, USA

To effectively monitor protein phosphorylation events governing signaling cascades, we have developed a mass spectrometry-based methodology enabling the simultaneous quantification of tyrosine phosphorylation of specific residues on dozens of key proteins at multiple time points under a variety of perturbations. We have recently applied this technique to identify key signaling nodes regulating EGFR, Insulin Receptor, and T Cell Receptor signaling network response to stimulation.

We have also performed an in-depth characterization of the network-wide effects of single-point mutations on the oncogenic, constitutively active, EGFRvIII receptor tyrosine kinase. This study quantifies the adaptive capacity of cellular signaling networks and the pleiotropic effects of knocking out individual phosphorylation sites with the network. Computational analysis of the phosphorylation data relative to phenotypic data highlights the role of selected protein phosphorylation sites in regulating biological outcome. We also demonstrate the utility of a data-driven computational model that is capable of fully describing glioblastoma cell growth based on just 13 phosphoproteins. Overall, we have now demonstrated that the combination of mass spectrometry-based analysis of protein phosphorylation with phenotypic measurements and computational modeling yields novel insights into the regulation of cellular signaling on a network scale.