Adaptor-Layer Integration of RTK Signaling: Basic Understanding and Application to Prediction of Targeted Drug Resistance

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Receptor tyrosine kinases (RTKs) play a central role in regulation of cell response during development and homeostasis, and dysregulation contributes to diseases such as cancer. RTK-targeted therapies have been applied successfully in cancer treatment, though with limited effectiveness as activity of non-targeted RTKs can enable cells to become resistant. While redundant signaling is now appreciated as a common mechanism of acquired and innate resistance, the exact signaling that is essential to resistance, and whether it is conserved or varies across cancer contexts, has not been addressed. RTKs lead to a common set of downstream signals, but in vastly different quantitative combinations, and differ in their ability to confer resistance in a context-dependent manner. A fundamental, rigorous understanding of resistance is necessary if we are to develop better therapies to overcome this redundancy. TAM receptors (Tyro3, AXL, MerTK) are a family of RTKs that have attracted interest for their widespread roles in tumor resistance and metastasis. However, while the ligands for these receptors have been identified, we lack even a basic understanding of the contexts that lead to activation of these receptors.

RTKs work by auto- and trans-phosphorylation, recruiting adapter proteins, and then phosphorylating those adapters and other associated proteins. Systems biology has concentrated on easily measurable factors such as phosphorylation, but comparisons of signaling between receptors are not easily accomplished, as phosphosites between receptors do not readily equate. The amount of receptor-bound adapter molecules is one quantity that should be directly comparable however. Thus, I plan to develop techniques to measure RTK interaction quantitatively and across the multiple potential interactions within a cell simultaneously with the intention of more completely capturing signaling from these receptors. I will use these techniques combined with quantitative modeling to examine interactions during receptor activation and understand how different RTKs can provide redundant signaling leading to targeted cancer treatment resistance. These resistance and interaction models will then be applied to more specifically understand resistance conferred by the TAM family of RTKs. Through development of mechanistic models for ligand-dependent and independent signaling, linked to adapter interaction, downstream signaling, and tumor cell resistance, I plan to develop an integrative understanding of resistance. This will provide necessary information to develop therapies bypassing this problem.