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RECONSTRACTING SIGNALING NETWORKS BY INTEGRATING QUANTITATIVE PROTEOMIC AND GENOMIC DATA

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Epithelial cells respond to changes in their environment by altering their proliferation, migration and state of differentiation. The coordinated control of these complex processes is necessary to maintain tissue homeostasis in the face of injury, and their dysregulation can result in cancer and other diseases. Epithelial cells also have multiple autocrine networks in which cells respond to the same growth factors that they produce. These recursive autocrine networks, especially those that utilize the epidermal growth factor receptor (EGFR), are central regulators of epithelial cell homeostasis and are frequently altered in disease. As a foundation for understanding how signaling networks become dysregulated in cancer, we have begun a comprehensive reconstruction of the basic signaling networks of human mammary epithelial cells using a combination of quantitative MS-based proteomics, gene expression profiles and protein interaction data. To follow the flow of information through the reconstructed networks, we have used a combination of phosphoproteomics, gene expression analysis and quantitative cell imaging in combination with mathematical modeling. This multidimensional approach to reconstructing signaling networks has resulted in some intriguing findings regarding their architecture. First, there are numerous feedback loops, both positive and negative, that operate over a wide range of different temporal scales and are sensitive to different levels of stimulation. The regulation of these feedback loops appears to be central to specifying the response of cells to a given stimulus. Second, different adaptor proteins are shared between multiple signaling pathways, but are present at relatively low stoichiometries relative to receptors. This suggests that there is a signaling hierarchy between different pathways based on both receptor-ligand abundance and receptor affinity for adaptor proteins. Our results shows how quantitative proteomics data can be used to reconstruct signaling networks and indicates the usefulness of mathematical models for understanding their dynamic behavior.