

Surveying Signaling Pathway Activity in Cancer

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Genetic analysis of human tumors indicate a sobering diversity of mutations, highlighting the many different ways to generate cancer. However one simplifying theme emerges, it appears that many different genetic alterations act to deregulate a small number of key signalling pathways that control cell function. As a result, viewing cancer in the context of signalling pathways can simplify and help integrate the complex landscape of genetic alterations into a functional framework.

Technologies to monitor the activation-state of key signalling pathways important in cancer will not only help guide identification of genetic drivers but also predict drug therapies based upon blocking pathway activity. Until recently, signaling molecules and pathways have been analyzed one at a time, making it difficult to survey across the different pathways to identify those selectively altered in disease. In this talk I will describe the development of technologies needed to survey across many different signalling networks to identify activated pathways and molecules driving disease.

Using antibodies specific for different classes of protein modifications we investigate different signaling spaces using a combination of immunoprecipitation and tandem mass spectrometry. This talk will illustrate how the approach can be applied to several problems in cancer biology. First, by monitoring the activation status of different classes of protein modifications using IHC we identified aberrant phosphotyrosine signaling in about 30% of non small cell lung cancer (NSCLC) patients. A large scale analysis of phosphotyrosine signaling in over 50 NSCLC cell lines and 150 NSCLC tumor samples identified 4 new disease drivers; ALK, ROS, PDGFRA, and c-Met which account for approximately 10% of NSCLC patients. Second, signaling networks assembled by oncogenic EGFR and c-Met will be discussed and novel actions of EGFR and c-Met inhibitors will be presented. Finally, I will briefly describe applications to other signalling spaces and protein modifications including protein acetylation, methylation and ubiquitination.