

Systems analysis of intracellular signaling networks in cancer: from tissue microarrays to clinical outcomes

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Characterizing the intracellular signaling networks in an individual patient's cancer may elucidate molecular and functional sub-types of cancer, and will advance the goal of developing effective, personalized medicine. A systems level analysis of such networks has applications in clinical diagnostics and therapeutics, as well as the ability to direct further bench research.

Systems biology has already recognized the utility of studying protein networks, as such a description may possess the ability to embody cell function to a greater degree than does genomic information. While proteomic techniques such as mass spectrometry and two-dimensional gel electrophoresis have been widely implemented, there are few examples of applying other proteomic procedures to a large-scale analysis. We recognize a need to develop methods that can reconstruct protein networks from materials more readily accessible to the clinical laboratory, such as formalin-fixed paraffin-embedded tissues. As such, we have pursued strategies to reconstruct intracellular signaling networks from tissue microarray and immunohistochemistry data.

Tissue microarrays from biopsy specimens of several dozen human malignant gliomas were created. The specimens were then probed with a panel of activation state-specific antibodies in order to characterize the activation states of multiple intracellular signaling pathways. It is important to consider the phosphorylation status of the individual proteins, as the activation state of the signaling pathways has been shown to be critical in the pathogenesis of cancer.

Molecular profiles of protein expression were able to segregate the glioma samples into sub-types of cancer, and correlated with both histomorphological diagnoses and clinical outcomes. Interestingly, some samples separated into groups distinct from their pathological diagnoses, suggesting distinct molecular mechanisms may be present that are unidentifiable in current diagnostic protocols. Patient response to treatment, overall survival, and other clinical measures were carefully studied in order to extract further correlations between molecular networks and clinical outcome.

Furthermore, this large-scale approach to the study of cancer was able to elucidate molecular relationships that had not been previously identified, and as such, directed further reductionist biology research. For example, we have uncovered an association with EGFRvIII expression and β -arrestin phosphorylation. Future work involves a comparative analysis of intracellular signaling networks and identification of appropriate combinatorial therapeutic targets.