

Analysis of Large-Scale Signaling Networks in Therapeutics

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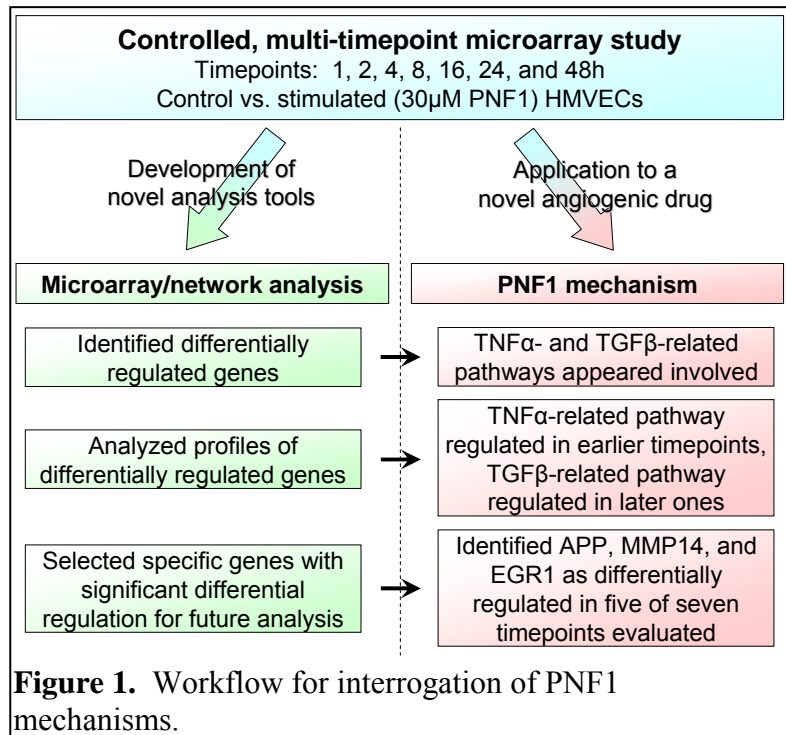
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Methods for analyzing large-scale cellular networks have been developed in the past. Specifically, techniques for reconstructing intracellular signaling, metabolic, and regulatory networks *in silico* have been employed, and systems analysis of these reconstructions have offered novel insights into their structure and function (Papin et al 2005; Papin et al 2003; Gianchandani et al 2006). For example, the JAK-STAT signaling network in human B-cells was reconstructed, and key properties of crosstalk and redundancy were characterized (Papin et al 2004). A central remaining challenge in the post-genomics era is incorporating high-throughput data into meaningful large-scale network reconstructions and identifying therapeutic avenues based on these reconstructions and the associated analyses.

Here we describe a signaling network analysis platform for therapeutic discovery from experimental assays. We utilize two diseases and two assay technologies. First, cDNA microarray expression profiles were measured for human microvascular endothelial cells (HMVEC) treated with phthalimide neovascular factor 1 (PNF1), a novel synthetic small molecule proposed for therapeutic induction of angiogenesis. Significant differential gene regulation between treated (30 μ M PNF1) and untreated (control) HMVEC was identified at 1, 2, 4, 8, 16, 24, and 48 hours post-stimulation. Bayesian inference tools were applied to the resultant data to infer the associated signaling networks for the treated and control states, and to elucidate differences between these networks/states. Affected angiogenic components, reactions, and pathways were identified as descriptors of the mechanisms underlying PNF1 activity and function (see Figure 1).



Second, publicly available immunohistochemical data from protein antibodies for normal and cancerous tissue were obtained (Uhlen et al 2005). This data set included 1,349 antibodies stained in 432 cancer tissue samples spanning 20 different types of cancers; including breast, cervical, colorectal, lung, ovarian, prostate, and skin cancers. In addition, this data set included a control of 82 normal samples taken from different tissues throughout the body. Again, a Bayesian inference tool was applied to the data set to infer the associated signaling networks for normal and cancerous states, and to characterize perturbations between these conditions. Signaling network components and pathways that deviated between normal and cancerous tissue were identified, and specific markers of individual cancer subtypes were pinpointed.

Ultimately, this approach constituted the incorporation of high-throughput data into large-scale reconstructions of cellular signaling networks. It facilitated the analysis of these networks in the context of disease and therapeutics, and yielded novel mechanistic detail in two instances of fundamental disease processes.

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