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Systems Biology Makes It Personal

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Systems biology promises to personalize medicine via network-based biomarkers that predict therapeutic effectiveness. Toward this goal, Chang et al. (2009) recently introduced a systems-based approach to break down oncogenic signaling networks into modules that predict the effectiveness of pathway-specific therapeutics.

Cancer patients may someday visit their oncologist, have their tumor biopsied, and receive customized drug cocktails based on the molecular circuitry of their tumor. This is one of the promises of systems biology—to take the guesswork out of cancer therapy through a priori identification of network-based biomarkers that predict therapeutic effectiveness in individual patients. Cancer is complex and rears its ugly head through what seems to be countless mechanisms, frustrating modern medicine and leaving patients at the mercy of trial and error for most treatments. Systems biology enables one to embrace this complexity through the use of network-based approaches (Barabasi and Oltvai, 2004; Bild et al., 2006; Ergün et al., 2007), and it has the potential to make medicine personal.

Much effort has been put toward the identification of biomarkers that predict the efficacy of cancer drugs. Although this has led to significant strides in our predicative capability, most biomarkers have been identified using methods that do not account for the important role that cellular networks play in cancer (Desmedt et al., 2008; Paik et al., 2004). In a recent issue of *Molecular Cell*, Chang et al. (2009) use a systems biology approach to break down complex oncogenic signaling networks into basic units, or modules, of signaling activity (e.g., a protein phosphorylating another protein to activate its kinase activity) and demonstrate that gene expression signatures based on these modules can predict the effectiveness of pathway-specific therapeutics.

Signal transduction cascades carry information from sensor to effector proteins and are often perturbed in cancer. These networks consist of proteins that modulate the activity of downstream targets through mechanisms such as phosphorylation. Commonly, signaling cascades are conceptualized as linear chains of events. In reality, these pathways are branched with proteins influencing multiple downstream targets and are extremely complex due to a high degree of overlap and crosstalk among pathways. This complexity is critical in defining cancer phenotypes but extremely hard to dissect and analyze. To address this challenge, Chang and colleagues devised a method to dissect signal transduction pathways into individual signaling modules, based on gene expression profiles.

The authors first identified a set of genes likely impacted by alterations to a given signaling pathway. These genes were selected using a protein-protein interaction network or gene expression data from experiments in which the pathway of interest was active. Factor analysis was then used in conjunction with a compendium of cancer data (NCI-60) to decompose expression profiles of these genes into a number of underlying signatures, which were taken to represent individual signaling modules in the pathway. Each signature was defined by a set of weighted genes, and the expression levels of these genes were weighted and averaged to create a signature score. These scores were hypothesized to represent the activity of the individual signaling modules.

Factor analysis is a statistical technique used to uncover hidden variables within complex data sets, and it has been previously used to study biomolecular networks (Brynildsen et al., 2007; di Bernardo et al., 2005; Yeung et al., 2002). The main challenge with using factor analysis is in identifying and assessing the biological meaning of the results. Chang and colleagues determined the functional identity of the deduced signaling modules by using genetic and drug sensitivity data available in the NCI-60 compendium. The authors reasoned that activation of a particular signaling module should create sensitivity to therapeutics that selectively target that module, and an association should exist between the activity of a module and mutations of genes involved in that module. In this way, modules could be assigned an identity or functional association, provided the cancer compendium included relevant mutations or therapeutics.

Chang and colleagues performed this analysis on the Ras core pathway, generating 20 module signatures. They then collected gene expression data from Ras mutant cell lines that selectively activate downstream effectors in the Ras pathway (e.g., Raf) and used these data to calculate scores for each of the 20 signatures. The module signatures associated with the downstream effectors could successfully identify cells expressing the relevant downstream branch of the Ras pathway. For example, the module linked to Raf could distinguish the cells with activated Raf signaling from other Ras mutant cell lines. These experiments demonstrate that the deduced modules accurately represent signaling activity in the pathway and that the authors' method is able to achieve branch-specific resolution of signaling cascades.

The authors also applied their analysis to the E2F and EGFR pathways, with the

goal of assessing the ability of E2F and EGFR module signatures to predict drug efficacy. E2F is a transcription factor that regulates genes involved in the G1→S and G2→M transitions of the cell cycle. From the E2F analysis, eight module signatures were generated—one associated with the S phase of the cell cycle and two with mitosis. Cell lines with high scores for the S phase module signature demonstrated sensitivity to three different S phase-targeted drugs (cisplatin, topotecan, and guanazole) but were insensitive to drugs that target mitosis (taxol and colchicine), whereas cell lines with high scores for the mitosis module signatures exhibited sensitivity to mitotic drugs but not to S phase drugs (Figure 1).

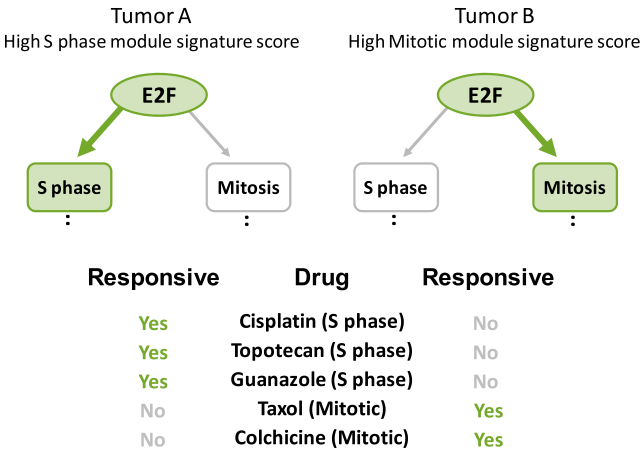

Figure 1. E2F Pathway Modules Predict Tumor Cell Line Responsiveness to Phase-Specific Therapeutics

Tumor cell lines with a high S phase module signature score demonstrate sensitivity to S phase-targeted drugs and not mitotic drugs; conversely, tumor cell lines with a high mitotic module signature score demonstrate sensitivity to mitotic drugs and not S phase-targeted drugs. Green color reflects increased activity of the designated pathway module.

Chang and colleagues also examined the responsiveness of colon cancers to cetuximab, an EGFR-targeted therapeutic. The EGFR analysis generated 20 module signatures, one of which was able to distinguish between cetuximab responders and nonresponders. These findings, together with those from the E2F analysis, demonstrate that the authors' method can be used to successfully predict the outcome of targeted cancer therapeutics.

The work of Chang and colleagues raises interesting questions regarding the impact of complex cellular networks on cancer. It is well established that perturbations to signaling cascades play a role in cancer and that this role is magnified by the influence that these regulators have on downstream targets. However, all perturbations to a signaling pathway are not the same; different downstream targets will be affected depending on the mutation. Indeed, different mutations within the same pathway can produce dramatic differences in responsiveness to targeted therapeutics (Solit et al., 2006). Chang and colleagues achieved branch-specific resolution with their method, as demonstrated with their Ras mutant validation. A key next step would be to achieve reaction-specific resolution, such as the phosphorylation of one protein by another on a specific residue, in order to further enhance the ability of the method to predict therapeutic outcomes.

An interesting outcome from the analysis of Chang and colleagues is that, of the many pathway module signatures that were deduced, only a handful could be assigned a functional identity or association. It is unclear what aspects of the signal transduction pathways are reflected in the remaining signatures; however, they may represent uncharted pathway branches and provide novel targets for drug design. As the number of compounds tested against the cancer compendium increases, the resolution and predictive power of this method will improve.

Future studies are needed to assess the ability of this method to predict disease progression, identify effective drug cocktails, and provide clinically meaningful insights into other complex diseases such as diabetes. Nonetheless, by breaking down signaling networks into fundamental modules and developing drug-sensitive biomarkers based on these modules, Chang and colleagues have taken us one step closer to making the business of treating cancer personal.

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