The network prognosis

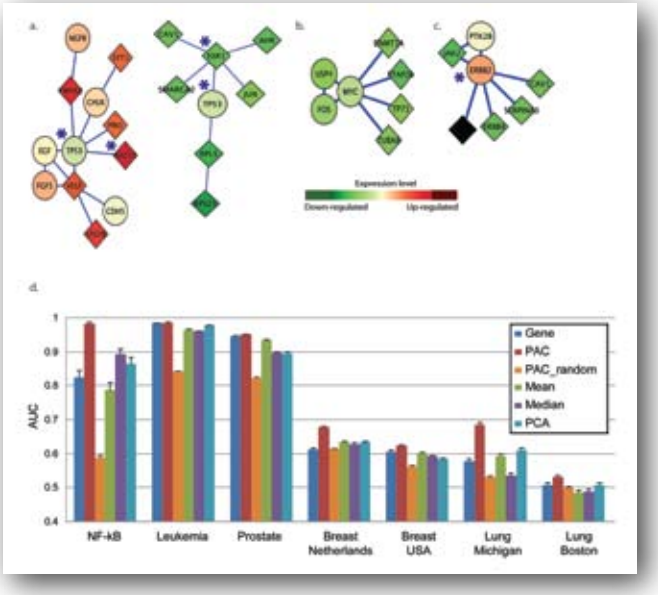
Crunching microarray profiles and protein pathways sorts out cancers by the numbers

Cancer is a disease of cells, not organs, although many still cling grimly to the old vocabulary of "lung cancer" or "breast cancer." Yet the advent of rapid microarray technology has made it possible to classify diseases on the basis of extensive gene expression patterns so that diagnosis can go beyond, say, estrogen-responsive breast cancer to a particular subtype of estrogen-responsive breast cancer with poor prognosis. But disease classification by gene expression remains a tricky business in patients. Cells taken from one tumor sample can be heterogeneous; genes switched on in cells from one part of the tumor may not be expressed elsewhere. Expression profiles compiled from a range of patients with the same type and grade of tumor can differ substantially.

But instead of looking only at gene expression, what if you could take gene expression profiles from many breast cancer patients and match them up with the known networks of signaling pathways and protein complexes in human cells? Could you identify subgroups in which gene expression changes would allow you to make predictions about disease progression—sorting out, for example, metastatic from nonmetastatic breast cancers?

Using bioinformatic algorithms to crunch through mountains of data, Trey Ideker and Han-Yu Chuang at the University of California, San Diego, working with Eunjung Lee and Doheon Lee of the Korea Advanced Institute of Science and Technology in Daejeon, South Korea, did just that. They took expression profiles from large cohorts of women with metastatic or nonmetastatic breast cancers and mapped them to an extensive human protein interaction network assembled from previously published studies. Ideker and colleagues then searched for "subnetworks" in which aggregate gene expression patterns distinguished one patient group from another. These new prognostic markers represented not individual genes but rather sets of cofunctional genes. According to Ideker, the subnetworks predicted the risk of metastasis more accurately than previous approaches based on gene expression alone. They also included many genes that genetic studies had associated with breast cancer but that previous gene expression studies had not uncovered.

Currently the researchers are extending their new integrated analysis to other cancers, including leukemia, prostate cancer, and lung cancer. They are identifying "condition-responsive" genes within signaling and transcriptional pathways that could be used to measure activation levels, another useful tool for diagnosis and prognosis.



Pathway-based cancer diagnostics: Example p53 (TP53), Myc (MYC), and Her2 (ERBB)-related protein subnetworks from the expression profiles of breast cancer patients are shown in (a-c). Each subnetwork is indicative of the cancer metastasis potential. Nodes and links represent human proteins and protein interactions, respectively. The color of each node scales with the change in expression of the corresponding gene for metastatic versus nonmetastatic cancer. The shape of each node indicates whether its gene is significantly differentially expressed (diamond) or not (circle). A blue asterisk marks known breast cancer susceptibility genes. (d) Charts the area under the curve (AUC) classification performance of our pathway markers (PAC), conventional pathway markers (Mean, Median, and PCA), and individual genes (Gene).

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Network-based Diagnosis and Modelling of Cancer Development and Progression

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