Defining cancer's genetic 'support network'

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Researchers at Duke University's Institute for Genome Sciences & Policy (IGSP) have developed a new method that essentially does for the genetic pathways underlying cancer what social networking web sites can do for people: It finds the connections among them.

The team reported its findings in *PLoS Computational Biology* on Feb. 15, 2008.

"Our major innovation is the use of gene sets in modeling tumor progression rather than single genes," said Sayan Mukherjee, an IGSP investigator and assistant professor in the department of statistical science at Duke.

The researchers first identified familiar sets of genes that work together to support the development of cancer by allowing uncontrolled growth or encouraging the development of blood vessels, for example. Then they used their new statistical techniques to look for relationships, or dependencies, that tie those separate gene sets together.

Their modeling method also enabled them to characterize gene networks as they evolve over the course of tumor progression, from normal tissue to the beginnings of cancer and on to that cancer's spread, or metastasis.

"We'd like to know why cancer goes metastatic," Mukherjee said. "Primary cancer can often be dealt with fairly well, so the real goal is to understand what happens when it spreads. My hope is that we could give these maps to a clinician and be able to tell them 'This is what it looks

like.'"

That intuitive understanding of how each pathway fits into the broader context might allow physicians to more strategically select drug targets. For instance, they might target a pathway that serves as a kind of central hub, holding the rest of the network together. Or, Mukherjee said, if the genes in a particular cancer type were found to fall into isolated clusters, they might develop a combination treatment designed to hit each one.

The researchers grouped gene pathways according to the six major hallmarks of cancer: 1) self-sufficiency in growth signals, 2) insensitivity to anti-growth signals, 3) evasion of cell death, 4) limitless ability to proliferate, 5) sustained ability to grow new blood vessels and 6) the ability to invade tissues and spread. Then they developed an analytical framework for discovering which pathways are relevant throughout a particular form of the disease and which are only active in certain stages.

The networks of genes in prostate cancer and melanoma that came out of their analysis fit well with earlier findings. "It was a surprise that we were able to recapitulate a lot of what was known," while making these broader connections, he added.

Their method can now be applied to develop models of other cancers and Mukherjee said his team is already working to unravel the pathway connections underlying colon cancer. It could also be applied in other realms, such as the study of embryonic development, he added.

Source: Duke University