Scientists identify molecular powerbrokers involved in cancer's spread

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You know the guy -- he's your Facebook friend. The one who knows everyone. Secure at the center of a dense web of relationships, he suggests causes and reconnects old friends like a skilled matchmaker. Scientists have known for some time that biological molecules interact with one another in a similarly complex pattern. Now researchers at the Stanford University School of Medicine have determined that hamstringing these molecular powerbrokers is a good way to derail processes such as cancer development.

"It's like social networking," said Paul Khavari, MD, PhD, professor of dermatology at the medical school. "If you take the most highly interconnected person and somehow hinder his access to a computer, the network may fall apart." Although the Stanford researchers were focusing on tumor invasion and metastasis, their expectation is that a similar approach could be used to identify potential targets for many different diseases.

Khavari, who is also a member of Stanford's Cancer Center and Bio-X, is the senior author of the research, which will be published in the June issue of *Cancer Cell*. He is also the clinical chief of the dermatology service at the Veterans Affairs Palo Alto Health Care System.

Khavari and genetics graduate student Jason Reuter used the concept of biological networks to investigate how cancers progress from a growing lump of unruly cells to an invasive, potentially deadly tumor. They found that inhibiting a molecule called beta-1 integrin blocked the ability of the

cells to grow and invade surrounding tissue.

"Ninety percent of all human tumors, including breast, lung, prostate, colon, pancreatic and skin cancers, arise in the epithelial tissue that lines body surfaces," said Khavari. "None of these tumors become highly dangerous to a person unless they invade through the underlying basement membrane and begin to spread to other tissue."

To conduct the research, Khavari and Reuter devised the first-ever three-dimensional model of inducible human tissue tumor development by grafting genetically engineered human skin tissue onto mice with compromised immune systems. They then treated the mice with a compound that activated an introduced cancer-causing gene in the modified human tissue, and monitored gene expression in the tumor and the surrounding tissue as the skin cancer developed and began to invade.

"This approach has been able to recapitulate in real time the progression from normal epithelial tissue to invasive cancer," said Khavari, "and now this model is being used to systematically identify the key genes in this process." He and Reuter identified more than 700 genes whose expression patterns deviated from normal during cancer development. They used an existing database to map the genes into functional networks, which varied as the tumor developed.

"A specific set of genes emerged during early tumor development," said Khavari, "which gave way to others as the tumor began to invade surrounding tissue." During early growth, for example, the researchers identified networks in the cancer cells that were involved in cell division and in the surrounding tissue that were involved in the formation of blood vessels to feed the growing tumor. As the cancer progressed, they saw the emergence of networks involved in cell movement and attachment and in remodeling of the extracellular matrix.

As in the Facebook example, the researches focused on those gene products in the networks that were the most highly connected. Sixteen of the top 25 molecules are found either on the surface or between the tumor cells, indicating that the tumor is actively involved in remodeling its surrounding environment. Beta-1 integrin, a member of a family of proteins involved in mediating attachments between cells, was the third-most well-connected. Khavari and Reuter found that blocking the activity of beta-1, which has been implicated in the growth of several human cancer cell lines, slowed the growth of both established and newly developing tumors in their model and seemed to lead to a more clearly defined border between the tumor cells and the surrounding normal tissue.

"Beta-1 integrin proved important in the co-evolution of the tumor and its supporting framework, the stroma, toward malignancy," said Khavari. He and his lab members plan to continue their analysis of other genes in the network, and to try to optimize their model for other types of cells and cancers. "We are working to build models like this for many other epithelial tissues so we can begin to identify the underlying global mediators of cancer progression."

Source: Stanford University Medical Center (news : web)