Medical Xpress

Wistar researchers show targeting 'normal' cells in tumors slows growth

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Targeting the normal cells that surround cancer cells within and around a tumor is a strategy that could greatly increase the effectiveness of traditional anti-cancer treatments, say researchers at The Wistar Institute.

In the Journal of Clinical Investigation published online November 16, they demonstrate the critical role for fibroblast activation protein (FAP), expressed by one type of these so-called "stromal" cells, in promoting tumor growth in mice. Genetically deleting or therapeutically targeting FAP significantly reduced the rate of tumor growth in mice by interrupting or blocking important signaling pathways and biological processes required for tumor growth, the Wistar team found.

"It's like taking away the soil from a seed that wants to grow," says senior author Ellen Puré, Ph.D., a professor in the Molecular and Cellular Oncogenesis Program at Wistar. "These results provide a proof-of-principle that targeting and modifying a tumor's microenvironment may be an effective approach to treating solid tumors."

Tumors are a complex mix of neoplastic cancer cells and normal cells - inflammatory and immune cells, endothelial cells, fibroblasts, pericytes, and others, collectively known as stromal cells. In addition, a web-like extracellular matrix is created by the stromal cells, and its structure is important for supporting and nurturing tumor growth through molecular signaling pathways.

The Wistar team focused on fibroblasts and pericytes. In addition to synthesizing components of the extracellular matrix, fibroblasts associated with tumors also express FAP, a particular protease that cuts up other proteins while pericytes are important to the function of the new blood vessels that develop in tumors. FAP is expressed in 90 percent of all human epithelial (solid) cancers, and FAP expression is recognized as a marker for and is thought to play a role in cancer growth, but the mechanisms through which this occurs had been previously unknown.

"Our data clearly demonstrate that FAP indeed promotes the growth of colon cancer as well as lung cancer in animal models, and provide insight into how FAP works," says Puré. To explore how FAP promotes tumor growth, lead author Angélica Santos, Ph.D., and colleagues took two approaches - genetic deletion and pharmacologic targeting of FAP to determine the effects of deactivating FAP in mouse models of lung and colon cancer.

First, they examined the genetic deletion of FAP. In collaboration with Wistar assistant professor and co-author Joseph Kissil, Ph.D., they mated mice engineered to spontaneously develop lung cancer when their K-Ras gene is activated with mice whose FAP gene had been deleted to develop a new strain of mice with a genetic deletion of FAP and expressing an activated K-Ras gene.

The Wistar team found that lung tumor growth was substantially inhibited in these mice. In another experiment the investigators transplanted colon cancer cells into FAP-deficient mice and saw a similarly marked inhibition of tumor growth.

"We found that FAP inactivation disrupts the organization of the collagen fibers which are a key component of matrix and that could be critical for many things, including cell to cell communication, cell-

matrix interactions and development of new blood vessels to feed the tumors," Puré says. "The organization or architecture of the matrix is important to supporting both stromal and cancer cells within a tumor. If stromal cells depend on this matrix for structural support and to communicate with the cancer, they can't do that properly if it is drastically modified as we observed in the absence of FAP activity. "

To explore the potential for a therapeutic approach, the investigators used a novel peptide agent, PT630, to shut down FAP activation in the lung and colon cancer mice. Again, they found a significant reduction in tumor growth by inhibiting the enzymatic activity of FAP with this candidate drug agent.

"This proof of concept is the first step toward the clinic," Puré says. "We need more drugs that target the non-cancer cells in tumors, which can then be combined with specific chemotherapies and biologic drugs to attack both the tumor and its supporting cells."

One of the benefits of such a strategy, Puré adds, is that a limited number of agents would likely be required to treat many different cancers, because stromal cells tend to have common properties and share expression of the FAP protein in most tumor types. Comparatively, targeted therapies designed for specific tumor types - such as breast or colon - will likely require a wide variety of different drugs.

The only agents currently used to treat cancer by targeting the tumor microenvironment are anti-angiogenesis drugs, like Avastin, which disrupt blood vessel formation to tumors.

Source: The Wistar Institute