Gene mutation makes tumors tense, worsens patient prognosis

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UC San Francisco researchers have discovered that the chances of survival for patients with pancreatic adenocarcinoma (PDAC)—the most common type of pancreatic cancer—may depend in part on how tense their tumors are. The researchers provide the first evidence linking tumor aggressiveness and patient survival rates to underlying genetic mutations that cause tumors to stiffen up and produce a dangerous thickening and scarring of the tissue around them.

Researchers have begun to recognize in recent years that such so-called fibrotic scarring around tumors is a bad sign for patients – in extreme cases, it can exert such pressure that blood vessels in the tissue collapse, impeding drug delivery and preventing immune cells from accessing the tissue to demolish the tumor. Oxygen-starved tumors also tend to become increasingly aggressive and liable to metastasize to other parts of the body.

"Not surprisingly, there has been a huge effort to prevent this buildup and stiffening of the connective tissue in cancer patients," says Valerie M. Weaver, PhD, a professor of surgery, anatomy and bioengineering and therapeutic sciences at UCSF and the senior author of the new paper. "However, several high-profile efforts to treat cancers with drugs that try to untangle strangling fibrotic tissue have unfortunately crashed and burned, failing to show significant efficacy in phase 2 clinical trials."

Weaver, who also directs the Center for Bioengineering and Tissue Regeneration in Surgery at UCSF and is a member of the Helen Diller

Family Comprehensive Cancer Center, believes these failures stem in part from the assumption by many researchers that fibrosis is just a matter of plumbing. Fibrotic "stiff" tissue also exerts physical forces on the tumor it surrounds, she says, like a web of rubber bands, and the tumor exerts its own physical forces in response.

The new research— published online April 18 in the journal *Nature Medicine*—demonstrates that the violence of the tug-of-war between PDAC tumors and surrounding tissue can have a major impact on how aggressive the cancer becomes. The study also suggests that the tumors of people with particular cancer-causing gene mutations may engage in this tug-of-war like players on steroids, becoming so tight and sinewy that they can roil the tissue around them into advanced states of fibrosis even in the presence of fibrosis-melting drugs.

"We found that individuals with these 'Schwarzenegger tumors' have a particularly poor prognosis and will require a different approach to treatment, one that should begin as early as possible," Weaver said. "We're hopeful that these patients' highly contractile tumor cells may be detectable with non-invasive imaging – making it easer to identify them and guide their treatment without costly genetic tests."

SMAD4 Mutations Produce Aggressive "Schwarzenegger Tumors"

Previous research had identified mutations in genes such as SMAD4 as potential risk factors for highly aggressive and invasive PDAC tumors, likely because these mutations weaken TGF-β signaling – an important molecular communication pathway in many cells in the body. Other studies had shown that lower TGF-β signaling also could result in denser, more fibrotic tumors. Weaver and her collaborators had long viewed fibrosis as an underappreciated risk factor determining cancer

progression, and they decided to investigate this possible link.

Using samples of dozens of human PDAC tumors, they found that tumors showing molecular signs of heightened aggressiveness as well as those from patients whose disease had progressed particularly quickly showed significantly worse signs of fibrosis and were surrounded by considerably thicker connective tissue than less-deadly tumors. In addition, tumors with genetic mutations that weaken TGF-β signaling were both more deadly and more likely to show signs of stiffness and fibrosis.

To understand how such mutations could lead to both stiffer tumor tissue and lower patient survival rates, the researchers turned to mouse models of PDAC, where they confirmed that a weakening of TGF-b signaling could ratchet up tissue tension and increase the amount of fibrosis surrounding the pancreas. Further experiments showed that weakened TGF-b signaling boosts the activity of a gene called Stat3, which is involved in producing molecules that affect the stiffness of the connective tissue surrounding the pancreas. This heightened tissue tension also caused the mouse PDAC tumors to tighten up like wound springs, which in turn activates genes that induce inflammation and more aggressive forms of cancer.

The researchers turned back to pancreatic tumor samples from human patients to confirm their findings, and demonstrated that tumors from patients with SMAD4 mutations and short survival times indeed had elevated levels of Stat3, high local tissue tension, altered connective tissue and molecular signs of a more aggressive status.

Understanding of Tissue Mechanics Could Change Cancer Treatment

These experiments suggest that not all tumor fibrosis is created equally: For patients with SMAD4 mutations—which Weaver estimates could be 15 to 20 percent of PDAC patients—high-tension tumors grow aggressive and trigger more inflammation, significantly increasing mortality risk. Furthermore, standard approaches to reduce fibrosis simply will not work: "You can melt the fibrosis all you want, but these tumors are so tightly wound that they'll just stir up more," she said.

Instead, approaches that crank down the tension in PDAC tumors, perhaps by reducing Stat3 signaling, could provide a unique opportunity to reduce patient mortality—particularly in patients with SMAD4 mutations—by interrupting the positive feedback loop of tissue tension and significantly improve the prognosis for these patients. It's even possible, Weaver says, that failed anti-fibrosis trials could be revisited: with these patients excluded, trials might show better results.

"The problem is that no one's been looking at these physical factors at all," Weaver said. "Tissue mechanics change how tumors behave, and cancer genes impact the mechanics. It's a really important concept to have in our arsenal."

More information: Hanane Laklai et al. Genotype tunes pancreatic ductal adenocarcinoma tissue tension to induce matricellular fibrosis and tumor progression, *Nature Medicine* (2016). DOI: 10.1038/nm.4082

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