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Tissue tension regulates tumor progression

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(PhysOrg.com) -- UCSF scientists have shown for the first time that the rigidity of a tissue can induce cancer. The research team identified an enzyme that is crucial for regulating tissue stiffness and demonstrated that the enzyme can turn abnormal but non-malignant breast tissue into tumors, according to a study published in *Cell* online.

Blocking the enzyme lysyl oxidase (LOX) decreased tissue stiffness and reduced the chance a tumor would form. It also caused tumors that did develop to be smaller and less aggressive, said senior author Valerie Weaver, PhD, associate professor and director of the Center for Bioengineering and Tissue Regeneration in the Department of Surgery at the University of California, San Francisco.

“Our study shows how stiffening of the breast tissue that is controlled by enzymes such as LOX is a key process that regulates cancer development,” said Weaver. “These findings suggest that any factor that increases the stiffness in a tissue could promote cancer. The most compelling finding of the study is that the research team identified enzymes that regulate tissue stiffening—opening up the possibility for the development of targeted therapies. The enzyme triggers a clear physical change in breast tissue and, if we could stop this happening, we expect it would prevent cancers from progressing and hopefully also prevent tumor metastasis which is the leading cause of patient mortality.”

The supportive tissue surrounding cancer cells is shaped differently than healthy tissue and is stiffer and more fibrous. These properties help

doctors detect breast cancers, but until now scientists have not appreciated that these physical changes actually control tumor development and no one has yet identified factors that regulate these modifications, according to Weaver, who is affiliated with the UCSF Helen Diller Family Comprehensive Cancer Center and the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF. She is also an associate professor in the Department of Anatomy and the new Department of Bioengineering and Therapeutic Sciences at UCSF.

In the current study, the team found that the enzyme LOX caused many of the structural changes in collagen, the major component of the supportive tissue, to change in a process known as cross-linking. In experimental models, higher levels of LOX increased the amount of collagen cross-linking in the mammary glands, made the tissue stiffer and correlated with a higher frequency of tumors invading the breast tissue.

When the team used chemicals or an antibody to block LOX, they found collagen in the mammary glands contained fewer cross-links and the tissue was less fibrous and softer, said Weaver. Most important, they found fewer and smaller tumors had formed in breast tissue and the tumors that did form were of a lower grade (less aggressive).

The study results clearly demonstrate that LOX activity increases collagen cross-linking to stiffen the tissue, and that it is the stiffness that drives the pre-cancerous cells to turn into invasive tumors, Weaver emphasized.

The work explains earlier observations by Amato Giaccia, of Stanford University, and Janine Erler, of the Institute of Cancer Research in the United Kingdom, that implicated LOX in tumor metastasis, said Weaver. In contrast to those earlier studies, however, the current work

emphasizes the critical role of early changes in the tissue microenvironment induced by LOX. The current study results reported in “Cell” build upon earlier work conducted by Weaver and colleagues that implicated integrins (receptors that help mediate attachment between a cell and surrounding tissue) as signaling molecules that play an important role in directing the cancerous behavior of a tissue. The findings also suggest why human tumors that are typically stiffer than normal tissue so often have high integrin activity.

Although the tests were carried out in breast cancer, Weaver said there is compelling evidence from her group and others that suggest a similar mechanism likely operates in many other cancers. For instance, pancreatic tumors are notoriously very rigid and highly aggressive. Weaver and colleagues recently found that pancreatic tumors have high levels of LOX in their connective tissue (stroma).

The unique perspective of the UCSF study is that until recently, most investigators have focused only on the tumor cells themselves, whereas in the current study the investigators showed that it is the cells within the connective tissue surrounding the growing tumors that express the LOX enzyme, said Weaver. These cells induce the tissue stiffening and fibrosis that then, through mechanical forces, promote the tumor cells to become invasive. These observations are significant because they emphasize the need to treat tumors early and to focus on the tissue microenvironment - not just the tumor but the surrounding area too.

The findings also suggest that cross-linking and stiffness in supporting tissue in general is important in tumor progression. Further, the findings imply that other enzymes and molecules that support this process could also promote cancer formation.

“This study may also help explain why the rate of breast cancer increases dramatically with age - aged tissues are stiffer and contain higher levels

of abnormal collagen cross-links," said Weaver. "I'm cautiously optimistic. We still have a lot more work to do, but this is certainly exciting."

Further testing established other factors that could be acting in combination with LOX, including cancer genes such as ErbB2 and other molecules including PI3kinase. Weaver said the study shows that cancer is best viewed as a complex process of changes in tissue remodeling that is tightly controlled by many biochemical and mechanical factors.

More information: Study findings appear online at www.cell.com/abstract/S0092-8674(09)01353-1

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