MedicalXpress

Dense tissue promotes aggressive cancers

August 22 2008

New research may explain why breast cancer tends to be more aggressive in women with denser breast tissue. Breast cancer cells grown in dense, rigid surroundings step up their invasive activities, Vanderbilt-Ingram Cancer Center investigators report in the Sept. 9 issue of Current *Biology*.

The findings suggest a cellular mechanism for the correlation between human breast tissue density and tumor aggressiveness. Women with increased breast density on mammograms have an increased risk for both developing breast cancer and having breast cancers with invasive characteristics.

This connection between breast density and cancer aggressiveness has begged the question of which comes first. Is the tissue denser because the tumor is more aggressive (and recruits cells that "lay down" more matrix), or is the tumor more aggressive because the tissue is denser?

"Our study shows that if you have a dense, rigid matrix, the cells will be more aggressive and invasive; it's a direct effect," said Alissa Weaver, M.D., Ph.D., assistant professor of Cancer Biology and lead author of the study.

Weaver and colleagues were interested in invadopodia – the finger-like protrusions that a cancer cell uses to drill holes in the extracellular matrix (matrix-degrading enzymes are associated with invadopodia). These structures are believed to be important for cancer invasion.

"If you have enough invadopodia, over time they'll make large holes that cells can move through to invade and metastasize," Weaver said.

Despite the intimate connection between invadopodia and the matrix, very little was known about what role the matrix might play in regulating invadopodia function. Weaver and colleagues started probing this question as part of computational math modeling project through the Vanderbilt Integrative Cancer Biology Center.

They were surprised to find that breast cancer cells cultured on a denser – and thus, more rigid – matrix had a greater number of active invadopodia than breast cancer cells cultured on a less dense matrix.

"We thought that more 'stuff' for the cells to get through was going to make it harder, so we expected to see less matrix degradation, but instead we found this interesting effect where cells actually sense the rigidity and degrade more," Weaver said.

The team examined how cells convert a sense of matrix rigidity into intracellular signals, a process called mechanotransduction.

Proteins that generate contractile forces, such as myosin "motors," are important players in mechanotransduction. Weaver and colleagues confirmed that myosin motors are involved in sparking more degradation by invadopodia in response to a rigid matrix, though the motors themselves are not present in the drilling structures.

The investigators also implicated the activities of two signaling proteins called FAK and p130Cas in the rigidity-induced invadopodia activity. These signaling proteins were present in an activated state in the invadopodia, suggesting that they are important players in this response and may represent targets for anti-invasive therapies.

Weaver said that it's exciting to find a cellular mechanism that could explain why denser breast tissue is correlated with more aggressive tumors and a poorer prognosis for patients.

"The idea that tissue rigidity leads to a more aggressive phenotype had been out there for a while," she said, "but it hadn't actually been tied to matrix degradation, which is thought to be important for metastasis and spread of cells through the body."

Because metastasis is often what makes cancers deadly, new leads on how to block it are critical, she added.

Source: Vanderbilt University Medical Center