Tissue stiffness linked to aggressive type of breast cancer

April 16 2014, by Erin Vollick

Assistant Professor Penney Gilbert. Credit: Erin Vollick

(Medical Xpress)—A new study has linked the stiffness of breast tissue to the progression of a particularly aggressive form of breast cancer. Published in *Nature Medicine* this month, the study may help clinicians differentiate between aggressive forms of the disease, which tend to have a poor prognosis, and less deadly forms.

University of Toronto Assistant Professor Penney Gilbert, a core faculty member at the University of Toronto's Institute of Biomaterials & Biomedical Engineering and the Donnelly Centre for Cellular & Biomolecular Research was involved in the two studies that led to this discovery.

Back in 2010, Gilbert and fellow researchers of Professor Valerie Weaver's laboratory at the University of California San Francisco (UCSF) discovered a vital link between the presence of a particular protein, HOXA9 and production of the BRCA1 protein. When mutated, the BRCA1 protein malfunctions and can trigger particularly deadly forms of breast cancer.

"BRCA1 mutation is one of a handful of known heritable genetic mutations that greatly increase the risk of developing breast cancer. In recent news, when Angelina Jolie learned that she was a carrier of this mutation, she underwent a double mastectomy as a preventative measure to ward off the aggressive breast cancer," says Gilbert.

The researchers, though, found that HOXA9 plays a vital role in the suppression of the disease.

"HOXA9 makes more BRCA1, which [in its non-mutated state] is a tumor suppressor," Gilbert says, "and that allowed us to understand why a population of women who didn't have BRCA1 mutation could have breast tumors that very much resembled those with a BRCA1 mutation. Low levels of HOXA9 were most commonly observed in these types of breast tumors."

The study concluded that low HOXA9 levels correlated with higher likelihood of metastasis as well as a significantly higher incidence of relapse.

"So the question is," adds Gilbert, "why do they lose HOXA9 expression?"

As it turns out, the mechanical properties of the tissue environment – in particular, its stiffness – may play a major role in the progression of the disease.

Following the 2010 study, Gilbert worked together with Janna Mouw, an associate specialist in the Weaver lab and first author of the *Nature Medicine* study, to show that HOXA9 protein expression – the protein that leads to tumor suppressing BRCA1 expression – was lost in stiff tissue environments.

"A specific microRNA (miR-18a), which is neither a protein nor a hormone but another type of small molecule, appears to dial down the levels of several breast tumor suppressors, including HOXA9," Gilbert explains, which in turn blocks production of BRCA1.

The findings are of particular clinical interest, as it may lead to quicker identification of the difficult-to-treat and aggressive breast cancer subtypes.

"This discovery of the molecular chain of events between tissue stiffening and breast cancer progression may lead to new and more effective treatment strategies that target structural changes in breast cancers and other tumors," says Valerie Weaver, professor of surgery and director of UCSF's Center for Bioengineering and Tissue Regeneration, in a statement.

"Our study indicates that it isn't enough to treat the genetic defects," Gilbert argues. "We need to look at how to return the environment surrounding the tumor to its normal softness. It's important for us to consider both the genetic and the biomechanical aspects of tumor

initiation."

Provided by University of Toronto