# 'Second hit' pushes noninvasive breast cancer towards deadly metastasis

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A new study identifies a molecule that acts cooperatively with a well known oncoprotein to drive progression of noninvasive breast cancer to metastatic, life-threatening disease. The research findings, published by Cell Press in the September issue of the journal *Cancer Cell*, could have a significant impact on therapeutic decisions by facilitating identification of high risk patients.

Elevated ErbB2, a well known invasion and metastasis promoting protein, is found in about one quarter of invasive breast cancers (IBC) and is associated with poor patient survival. However, ErbB2 is also overexpressed in more than half of noninvasive ductal carcinomas in situ (DCIS). DCIS, which is characterized by proliferation of malignant cells within mammary ducts with no invasion into surrounding tissues, is a precursor of IBC.

It is not clear why ErbB2 is more frequently overexpressed in noninvasive DCIS than in IBC or what drives the progression of DCIS to IBC. "For effective reduction of cancer mortality, it is extremely important to predict the risk of, and to intervene in, the critical transition from noninvasive DCIS to life-threatening IBC," offers senior study author Dr. Dihua Yu from the Department of Molecular and Cellular Oncology at the University of Texas, M. D. Anderson Center in Houston, Texas.

Previous research has led to the suggestion that additional risk factors may be needed for the ErbB2-overexpressing DCIS to transition into

IBC. Dr. Yu and colleagues examined whether overexpression of 14-3-3? a protein that belongs to a family of evolutionally conserved proteins involved in cancer progression, could serve as a risk factor or "second hit" and cooperate with ErbB2 to drive progression of DCIS to IBC.

The researchers observed that overexpression of both 14-3-3? and ErbB2 in DCIS was associated with a higher risk of progressing to IBC. Elevated ErbB2 increased cell migration while elevated 14-3-3? decreased cell adhesion, making it more likely that the malignant cells could escape from the tissue structure. "Importantly, patients whose breast tumors overexpressed both ErbB2 and 14-3-3? had higher rates of metastatic recurrence and death than those whose tumors overexpressed only one," says Dr. Yu. The researchers went on to identify pathways downstream of 14-3-3?, such as the TGF-?/Smads pathway, that may be amenable to therapeutic intervention.

"Our findings shed more light on the mechanism of the deadly transition from non-invasive DCIS to the life-threatening invasive breast cancer, in addition to solving a long time puzzle regarding breast cancers that overexpress ErbB2. This study also identified biomarkers that allow selection of high-risk DCIS patients for more aggressive treatments at early stages of cancer development, while saving low-risk patients from ablative clinical procedures," offers Dr. Yu. "Moreover, it provided promising targets for future intervention strategies to prevent DCIS progression to IBC."

Source: Cell Press (news : web)

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