Scientists show protein accelerates breast cancer progression in animal models

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Until this study, the significance of pleiotrophin (PTN) expression in breast cancer had not been clearly established. These new findings could lead to a better understanding of the molecular pathogenesis of breast cancer and focus attention on PTN and its signaling pathway as possible targets for new cancer therapies.

The study also found that the expression of pleiotrophin activated surrounding cells to remodel the tumor microenvironment, induced tumor angiogenesis, and increased the number of receptors for different markers of aggressive breast cancers.

“Breast cancers progress through stages of increasing malignancy triggered by mutations that promote their growth,” said Thomas Deuel, the Scripps Research scientist whose laboratory made the discovery. “The major finding of our study demonstrates both in vivo and in vitro that inappropriate expression of PTN not only promotes breast cancer progression but that by itself PTN secretion from human breast cancer cells may be sufficient to shift that progression to a more aggressive form of breast cancer.”

In the study, three models were tested to determine if inappropriate expression of PTN alone was sufficient to induce breast cancer or whether the cytokine cooperates with different pathogenic mechanisms to stimulate breast cancer progression.

The new study identified PTN as one factor that activates stromal cells-cells found in the loose connective tissue-and induces several features of aggressive breast cancer. While the importance of these cancer cell-stromal cell interactions is well established, only limited progress has been made in identifying the factors that cause stromal cells to initiate tumor progression.

“Our breakthrough findings demonstrate that PTN-activated stromal cells are responsible for the ultimate remodeling of extracellular matrix proteins, as well as the release of factors that stimulate the growth of malignant cancer cells,” Deuel said. “We’ve shown that PTN secreted from breast cancer cells is the key mechanism of stromal cell activation, and that PTN alone is sufficient to stimulate many of the critical signaling pathways that aggressively promote breast cancer progression.”

Using genetically modified mouse models, the study found that the inappropriate expression of PTN produced breast cancers of a more aggressive subtype. In those same mouse models, highly malignant cells of scirrhous carcinoma-a hard, fibrous tumor-were found to express very high levels of the mouse mammary tumor virus (MMTV)-Ptn transgene along with increases in collagen, elastin, tumor angiogenesis, and increased size of new blood vessels within the breast cancers-all markers for breast cancer.

“Our study suggests the possibility that PTN expression may account for many of the features of scirrhous carcinoma seen in the breast cancers of these mice,” Deuel said. “Pleiotrophin stimulates new collagen of different subtypes and new elastin synthesis. Collagen fragments are known to stimulate growth of carcinoma cells and to stimulate anti-apoptotic pathways, favoring growth of the carcinoma cells.”

Source: Scripps Research Institute