Gene signature helps predict breast cancer prognosis

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Vanderbilt-Ingram Cancer Center researchers have uncovered a gene signature that may help predict clinical outcomes in certain types of breast cancer.

In the Journal of Clinical Investigation, Harold (Hal) Moses, M.D., and colleagues report that this gene signature - which is associated with the transforming growth factor-beta (TGF-β) signaling pathway - correlates with reduced relapse-free survival in patients with breast cancer, especially in those with estrogen receptor (ER) positive tumors.

The results suggest that assessing TGF-β signaling may be a useful aid in determining breast cancer prognosis and in guiding treatment. The work also sheds light on how TGF-β affects tumor growth and progression.

TGF-β is a well-known regulator of tumor growth and metastasis. In the early stages of cancer, TGF-β signaling inhibits tumor growth. But for unclear reasons, most tumors eventually lose their sensitivity to TGF-β, and the once-beneficial protein begins promoting tumor growth and metastasis during later cancer stages. Loss of TGF-β signaling has been linked to tumor progression in human breast cancer.

To identify mechanisms by which TGF-β regulates tumor progression and metastasis, Brian Bierie, Ph.D., a former graduate student in the Moses lab, developed mammary cancer cell lines from mice lacking the TGF-β type II receptor (TβRII), an important component of the TGF-β signaling pathway.

Bierie examined gene expression in these cell lines and found that TGF-β signaling regulates the expression of chemokines, inflammation-associated chemical signals that direct the migration of cells - particularly, the expression of chemokines CXCL1 and CXCL5.

To determine the clinical relevance of this gene expression profile, Moses and Bierie collaborated with Christine Chung, M.D., and biostatistician Yu Shyr, Ph.D., to probe human breast cancer gene expression profiles available in public databases.

They found that the gene signature representing a complete elimination of TGF-β signaling correlated with significantly reduced relapse-free survival in all patients. This association was even stronger in patients with estrogen receptor (ER) positive tumors, a subtype of breast cancer that responds well to anti-estrogen therapies like tamoxifen.

The results suggest that testing for this gene signature could aid in the prognosis and treatment of breast cancer, especially in ER positive tumors.

The signature also points to chemokines as important mediators of TGF-β's effects on tumor growth.

"I think one of the most significant aspects of this is that it is the first real demonstration that a major function of TGF-β signaling is to suppress chemokine expression," said Moses, the Hortense B. Ingram Professor of Molecular Oncology, professor of Cancer Biology, and director of the Frances Williams Preston Laboratories.

The results also point to several potential therapeutic approaches, including the inhibition of chemokines or their receptors, Moses said.

Moses and colleagues previously found that inhibiting certain

chemokines in a mouse model of breast cancer significantly decreased the number of lung metastases by decreasing the migration of myeloid cells - a type of immune cell involved in tumor progression - into the tumor.

Targeting these myeloid cells would be a new kind of approach because it focuses on targeting normal cells outside of the tumor, or in the "stroma."

"We've had decades of treatment targeted to the cancer cell, but very little in treatment of the stromal component," Moses said.

Previous genetic signatures have been used to segregate patients that might benefit from chemotherapy from those that would derive little or no benefit - a step toward personalized cancer therapy. Moses suspects the TGF-β associated signature could provide additional guidance in individualizing cancer treatment.

"Gene profiling and biomarkers are the current directions of research to select treatments likely to benefit a given patient," Moses noted. "That's the way the field is moving. That's what we have to do."

Source: Vanderbilt University Medical Center (news : web)