Gene expression predicts chemotherapy sensitivity of triple-negative breast cancer

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German researchers have identified an unexpected molecular marker that predicts how sensitive hard-to-treat triple-negative breast cancers are to chemotherapy.

Triple-negative breast cancers --which do not express the genes for estrogen receptor, or progesterone receptor and do not have Her2/neu overexpression or amplification-- are more aggressive than other forms of the disease and cannot be treated with endocrine or Her2 targeted therapies.

At the IMPAKT Breast Cancer Conference in Brussels, PhD student Carolin Huelsewig and Dr Cornelia Liedtke from Uniklinikum Muenster report that the molecule sFRP1 is much more highly expressed in these cancers, and that levels of the molecule in an individual tumor correlate with its sensitivity to chemotherapy.

The researchers undertook their study in three steps. First they conducted a gene expression analysis in breast cancer tissue samples, looking specifically for genes whose expression level differed between triple-negative cancers and non-triple negative cancers.

That analysis revealed that sFRP1 was the most highly overexpressed gene in triple-negative cancers relative to others. "The degree of difference was up to 4.7-fold in triple-negative vs. non-triple negative cancers," Ms Huelsewig said.

The results were a surprise, as sFRP1 is known to inhibit a signaling pathway within cells that is associated with the development of cancers. "The results of the differential gene expression analysis were initially astounding as sFRP1 has so far been understood as an antagonist within the wnt signaling cascade."

The researchers then tested genes for an association with relapse-free survival and response to neoadjuvant chemotherapy, finding that while sFRP1 expression was not associated with recurrence-free survival, it was significantly correlated with an increased sensitivity to chemotherapy.

Finally, the researchers conducted 'knockdown' experiments in cell culture, using the triple-negative breast cancer cell line MDA-MB 468. These experiments involved using short segments of RNA, known as siRNA, designed to block the expression of sFRP1. In breast cancer cells where sFRP1 expression was knocked down, there was significantly decreased sensitivity to paclitaxel, doxorubicin and cisplatinum, they found.

"It is increasingly recognized that molecular subtypes of breast cancer may be examined and characterized individually --including the revealing of a potentially very distinct set of biomarkers and therapeutic tools. Our results suggest sFRP1 signaling as a biomarker tailored to the triple-negative breast cancer subtype," Ms Huelsewig said.

"It is important to recognize that our results are not ready to be transferred into the clinic just yet," she said. "However, our approach provides proof-of-principle that identification, validation and functional analysis of biomarkers for specific disease subtypes is feasible through translational research incorporating both in-silico analyses such as gene expression profiling and basic science including functional analyses."

Commenting on the study, which he was not involved in, Dr Stephen Johnston, from Royal Marsden NHS Foundation Trust & Institute of Cancer Research, highlighted that Triple Negative Breast Cancer (TNBC) is a sub-type that despite its response to chemotherapy, carries a bad prognosis.

"Understanding the molecular profile which drives this disease is crucial to allow us to use existing drugs better, as well as find more effective treatments. In both clinical and laboratory experiments these researchers have identified a gene called sFRP1 involved in the wnt signalling cascade that is frequently over-expressed in TNBC, and may predict who responds best to chemotherapy – this could help select patients for treatment in the future."

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