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Stroma genomic signature predicts resistance to anthracyclin-based chemotherapy in breast cancer

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Researchers at the Swiss Institute of Bioinformatics and the Swiss National Center of Competence in Research in Molecular Oncology in Lausanne have developed a new test to predict how breast cancer patients respond to chemotherapy, which could help change how treatment is delivered in the future. In an article, 'A stroma-related gene signature predicts resistance to neoadjuvant chemotherapy in breast cancer' i, published in *Nature Medicine*, Dr Pierre Farmer and colleagues showed the potential of the reactive stroma to modulate tumor phenotype and the clinical response to treatment. This is a major step forward in the field as identifying factors that influence response to cancer chemotherapy is crucial for improving its efficacy.

The study first started when a team of clinicians, cancer biologists and computational biologists combined their effort to address a very puzzling question: Why breast tumors that have very similar conditions in terms of aggressiveness (grade), invasiveness (node status) and hormone dependency (ER status), respond differently to the same kind of chemotherapy treatment.

"Two breast cancer patients might respond very differently to the same type of chemotherapy although their respective tumors are very similar from a clinical point of view," said Dr Pierre Farmer. "The reasons for these different responses are unknown."

To help find an answer to this question, a collaborative study was set-up within the framework of a large randomized clinical trial that involved more than 40 different hospitals throughout Europe, including those in the UK, France, Belgium, Netherlands, Poland, Sweden and Switzerland. It was led by Professor Hervé Bonnefoi of the European Organization for Research and Treatment of Cancer (EORTC) in collaboration with the Swedish Breast Cancer Group (SBCG), the Swiss Cancer Group (SAKK) and the Angloceltic group (ACOG).

In this trial, biopsies were taken from each patient and sent to Professor Richard Iggo's laboratory which was at the Swiss Institute for Experimental Cancer Research (ISREC) in Lausanne at the time of the study, which was to a large part sponsored by the National Center of Competence in Research (NCCR) in Molecular Oncology. In Lausanne, the genomic material (mRNA) of tumor samples were extracted and profiled on microarrays in order to measure the expression activity pattern of thousands of individual genes.

Meanwhile, all patients included in the said study had a tumor biopsy prior to receiving an anthracyclin-based chemotherapy followed by surgical excision of the tumour - a protocol that clinicians call neo-adjuvant chemotherapy. After the surgical intervention, pathologists analysed the surgical specimen and determined if tumor cells were still present. This is a way to measure the efficacy of the chemotherapy.

If no tumor cells were found, the patient was considered to be fully responsive to the treatment (defined as "complete pathological response"). The aim of the study was to test if genomic analysis of the tumor taken before chemotherapy treatment could allow the identification a signature which permits the prediction of the patients who would respond to the chemotherapy.

To achieve this task, Drs Farmer, Mauro Delorenzi, and Pratyaksha

Wirapati from the Swiss Institute of Bioinformatics developed new computational methods to extract relevant gene patterns from the vast quantity of data generated by the microarray experiment. "In this study, we have mined the gene expression data in order to find a particular gene activity pattern, or gene signature, that would be associated with how patients respond to chemotherapy," Dr Farmer said.

Results showed that a signature measuring the biological activity of tumor's microenvironment, also known as reactive stroma, predicted how patients would respond to the treatment.

Researchers found that it is precisely the magnitude of this stroma reaction that was predictive of a response to chemotherapy. "It was a surprise to us to find that it was not the tumor itself but rather how surrounding non-tumorous tissue reacts to the presence of the tumor that was our best clue in predicting resistance to treatment," Dr Farmer continued. "Patients who had a strong stroma reaction characterized by an increased quantity of fibroblasts surrounding the tumor were more likely to have a bad response to this particular chemotherapy."

"What this means is that success in treatment, having tumors shrink or disappear altogether, is in part due to molecular differences in tumors and their immediate surroundings," Dr Farmer continued.

Researchers hope that one day this discovery will contribute to changing how breast cancer patients are treated. Indeed, in the future, if a clinician learns with a simplified test that a particular woman has a high probability of not responding to an anthracyclin-based therapy, this clinician may consider prescribing an alternative chemotherapeutic regimen. Moreover, this study suggests that predicting how individual patients might respond to chemotherapy could be possible, which raises hopes that one day, personalized medicine in the treatment of breast cancer may become a reality.

Source: Swiss Institute of Bioinoformatics