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Protein snapshots reveal clues to breast cancer outcomes

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Measuring the transfer of tiny amounts of energy from one protein to another on breast cancer cells has given scientists a detailed view of molecular interactions that could help predict how breast cancer patients will respond to particular therapies.

At the IMPAKT Breast Cancer Conference in Brussels, Dr Gargi Patel from the Richard Dimbleby Department, King's College London, described cutting-edge research in which she and colleagues captured detailed information about protein interactions on cancer cells, and correlated that with established genetic markers for cancer spread.

Dr Patel's group used a microscope technique known as Foerster resonance energy transfer (FRET) imaging, which allows them to measure the interactions between two proteins.

In this technique, each of the proteins is labeled with a fluorescent tag --one might be labeled green and the other red, for example. A laser is used to excite one of these labels, which becomes excited and then decays back to its rest state in a specific lifetime, which the researchers define as its fluorescent lifetime.

When this label comes within a nanometer of the second label, exciting by the laser causes some of its energy to be donated to the other label, and the fluorescent lifetime of the first label becomes shorter. "In the context of our work, this process only occurs when two proteins are close enough to be interacting, and hence we can quantitate protein-

protein interactions," Dr Patel explains.

In earlier work, Dr Patel's group used this technique on breast cancer cells in the lab to describe in detail the interaction between the cell-surface molecules Her2 and Her3 that is known to determine whether a cancer will respond to the drug lapatinib.

"We aim to establish a 'signature' representing functional molecular biology, by examining protein-protein interactions, and to correlate this signature with established prognostic gene signatures and clinical and radiological data to predict patient outcome in terms of likelihood of recurrence and response to treatment such as lapatinib," Dr Patel explains. "The results we present at IMPAKT are the start of this work."

"The work I am doing captures images of the molecular state of Her2-Her3 receptors as a dimer, and shows us the results of lapatinib treatment. We have also identified a specific mutation in Her2, which reduces dimerization and the lapatinib effect. We can test tumor samples for this Her2 mutation, which would confer resistance to treatment."

This technology could have a significant clinical impact, the researchers say, by improving the accuracy of predictions about a cancer's risk of spread or response to treatment.

"Currently our methods of prognosis estimation depend on clinical data such as tumor size and lymph node status, or upon correlation with genetic signatures which may delineate tumors with higher metastatic potential. However the accuracy of any single method is far from 100%. We aim to add to the tools available by introducing a signature reflecting the functional state of cancer cells, by assessing protein-protein interactions. We could integrate this information with genetic and clinical data to more accurately predict outcome," Dr Patel said.

Commenting on the study, which he was not involved in, Dr Stephen Johnston, from Royal Marsden NHS Foundation Trust & Institute of Cancer Research, noted: "Lapatinib is a novel drug to target Her2 positive breast cancer, and works in a different way to the established monoclonal antibody trastuzumab."

"It is recognized that other growth factor receptors in breast cancer such as Her3 can modulate how Her2 positive tumors respond, often making them resistant to trastuzumab. In contrast, these researchers have developed as assay to measure Her2/Her3 heterodimers and the molecular pathways that they activate in human tumors, and suggest that in future this assay could be used to predict for response to lapatinib in the clinic."

Provided by European Society for Medical Oncology

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