Scientists uncover gene associated with an aggressive breast cancer

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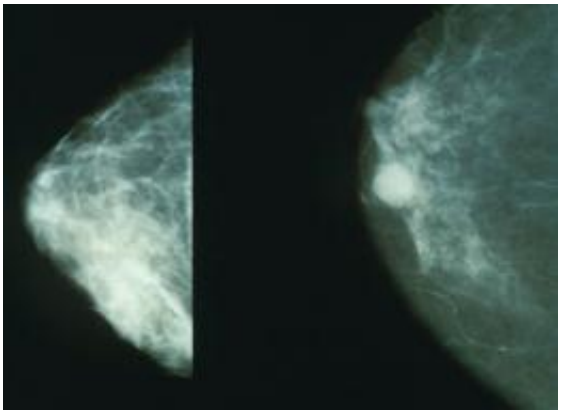

Mammograms showing a normal breast (left) and a cancerous breast (right). Credit: Wikipedia.

Scientists at A*STAR's Genome Institute of Singapore (GIS), in collaboration with local clinicians and colleagues in the USA, have identified a biomarker which is strongly associated with triple negative breast cancer (TNBC), a highly aggressive carcinoma that often has early relapse and metastasis following chemotherapy. The newly identified biomarker, a gene called RASAL2, provides a target for developing new therapeutics designed to treat this often deadly disease.

TNBC is deadly because, unlike other types of breast cancers such as estrogen receptor (ER) positive or HER2 amplified breast tumours which have effective targeted therapy, TNBC tumours do not respond to

targeted therapy.

Breast cancer has many subtypes, each with its own genetic makeup. As such, different subtypes behave differently in invasion and metastasis. Using breast cancer cell lines and genomic data from patient samples, molecular biologist Min Feng and her colleagues at the GIS adopted an integrated approach to search for genes whose deregulation may help explain the high metastatic potential of TNBC cells.

Dr Feng found that a small RNA, often called microRNA, is lost in highly metastatic TNBC cells but not in luminal breast cancer. As a result, RASAL2, which is negatively regulated by this microRNA, is up-regulated in a set of TNBC tumours. The study showed that TNBC patients whose tumours have high expression of RASAL2 tend to have a lower survival rate as compared to patients whose tumours have low levels of this gene. Additionally, the study showed that genetic knockdown of RASAL2 gene can lead to reduced metastasis in breast cancer mouse model.

The findings were published recently in the *Journal of Clinical Investigation* (*JCI*).

Intriguingly, previous research found that RASAL2 was lost in some of the luminal type of breast tumours, where it acts as a tumour suppressor.

Project leader of the study, Prof Qiang Yu, Senior Group Leader of Cancer Therapeutics and Stratified Oncology Programme at the GIS, said, "Cancer is an extremely heterogeneous disease, where many molecular processes have gone wrong in their own ways. Rather than a tumour suppressor, we show here that RASAL2 actually acts as a cancer promoting molecule in TNBC. This reminds us that the same molecule can function very differently in different subtypes of cancers, a phenomenon which has often been seen before."

The study is the result of intensive collaboration with both local and international colleagues, including Dr Ern Yu Tan at Tan Tock Seng Hospital, Singapore, and Dr Dave Hoon at the John Wayne Cancer Institute in Santa Monica, California.

Dr Tan, a breast cancer doctor, said, "Therapeutic options remain limited and women with TNBC have a higher risk of disease relapse, with prognosis being generally poor after a relapse. With this finding, RASAL2 could be a new potential biomarker that is associated with the high risk of TNBC, rather than all types of breast tumours. This illustrates an important aspect of breast cancer biology. With a better understanding of the genetic makeup of tumours, it is now recognized that breast cancer comprises a diverse mix of tumours. This explains why not everyone with tumours of the same disease stage responds the same way to similar treatment."

GIS Executive Director Prof Huck Hui Ng, said, "The study is a reflection of an adaptation of our efforts towards translational research. We are working hard to build up an ecosystem to allow close collaborations between researchers and clinicians. Because the laboratory findings do not always replicate the 'real world' of human tumours, validation with samples derived from actual human tumours remains the 'final proof' of whether novel laboratory findings can be applied to clinical practice."

Prof Yu emphasised the necessity of further clinical validation for the study. He is also seeking industrial collaboration to develop diagnostic assays for high risk TNBC patients.

More information: *Journal of Clinical Investigation*, "RASAL2 activates RAC1 to promote triple negative breast cancer progression" (2014)