New therapeutic strategy for treating a very aggressive form of breast cancer

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Scientists have identified a new therapeutic strategy for treating a very aggressive form of breast cancer.

Triple-negative breast cancer (TNBC) is one of the most aggressive and lethal types of breast cancer. It accounts for about 15 percent of all

breast cancers diagnosed and occurs more frequently in younger women. Interest in finding new medications that can treat TNBC has intensified due to the lack of targeted therapies available for this disease.

A study, partially supported by the EU-funded TRAIN-ERS and INSPIRED projects, has shown that targeting a stress response pathway known as IRE1 may improve the response to chemotherapy and reduce relapse for TNBC patients. The findings were published recently in the journal *Nature Communications*.

As summarised in a press release by the National University of Ireland (NUI) Galway, at present "chemotherapy is the mainstay treatment, and although initially successful, a large percentage of TNBC patients relapse within one to three years of treatment and have a poor long-term prognosis." The exact mechanism of tumour relapse post-chemotherapy remained unknown until recently. However, NUI Galway scientists "have shown for the first time that IRE1, which is a cellular stress sensor that normally acts to alleviate short-term stresses within cells, such as lack of nutrients or oxygen, is a central driver of treatment-related relapse."

Quoted in the same press release, first author of the study Dr. Susan Logue said IRE1 "may represent a good therapeutic target" for TNBC treatment. Prof. Afshin Samali, Director of the Apoptosis Research Centre at NUI Galway, noted the new therapeutic strategy for TNBC patients "may benefit many other cancer patients whose cancer cells rely on activated cell stress responses to survive."

Enhanced response to chemotherapy

The journal article explains that inositol-requiring enzyme 1 alpha, referred to as IRE1, but also known as ERN1, is "an endoplasmic reticulum (ER) stress sensor." Its activation is "predominantly linked to

the resolution of ER stress and, in the case of severe stress, to cell death."

The team discovered that chemotherapy can activate the IRE1 stress response in TNBC, leading to the production of survival signals that are pumped out of the cell to support the growth of new cancer cells. Their study showed that this process can be halted by inhibiting IRE1 using the small molecule drug MKC8866. According to the article, "MKC8866 is a selective IRE1 RNase inhibitor that exhibits acceptable pharmacokinetic and toxicity profiles, making it an attractive agent for pre-clinical development." Ribonuclease, abbreviated commonly as RNase, is an enzyme that catalyses the breakdown of ribonucleic acid into smaller components.

In a preclinical model, the drug increased the effectiveness of chemotherapy treatment and reduced tumour relapse. "We therefore conclude that inclusion of IRE1 RNase inhibition in therapeutic strategies can enhance the effectiveness of current chemotherapeutics."

The ongoing TRAIN-ERS (Endoplasmic Reticulum Stress in Health and Disease) project was launched to bring young researchers together with academics, clinicians and industry personnel to better understand ER stress. It also aims to develop strategies and treatments that are associated with the disruption of ER function, a common feature of diseases such as cancer, neurodegeneration, obesity and inflammation. The INSPIRED (Targeting IRE1 in disease) project, which supported the same NUI Galway study, was set up to form a network of academic and industry researchers in the field of biology and drug discovery, targeting cancer and neurodegenerative diseases.

More information: TRAIN-ERS project website: www.train-ers.eu/

INSPIRED project website: inspired-network.eu/

Susan E. Logue et al. Inhibition of IRE1 RNase activity modulates the tumor cell secretome and enhances response to chemotherapy, *Nature Communications* (2018). DOI: 10.1038/s41467-018-05763-8