

Identifying nuclear receptor disruptors as risk factors in breast cancer

A grant of £15,000 was awarded to Dr Laura Matthews, University of Leeds, to identify which nuclear receptors play a role in breast cancer and to identify chemicals which disrupt these receptors. The work was completed in April 2020.

Summary

Nuclear receptors are cellular proteins which regulate diverse functions such as reproduction, cell multiplication and metabolism. This study compared nuclear receptor activity in normal breast tissue and different types of breast cancer tissue. Seven nuclear receptors which play a role in triple negative breast cancer were identified. Using pre-existing datasets, 200 chemicals were identified that are predicted to alter nuclear receptor activity in a similar way to changes seen in triple negative breast cancer. Cell culture studies found many of these chemicals, including pesticides and disinfectants, increased breast cell multiplication, and so may increase breast cancer risk. Environmental chemicals that potentially drive breast cancer development may therefore be identified using nuclear receptor expression profiles.

Introduction

The research aimed to identify nuclear receptors that play a role in breast cancer. Nuclear receptors are cellular proteins that, when activated, bind DNA and regulate gene expression (switch genes on or off). They are activated by binding to a specific “ligand” – a hormone or cell by-product, depending on the receptor in question.

Nuclear receptors are activated in response to stress, inflammation, circadian disruption, obesity and ageing – all risk factors for developing breast cancer. Nuclear receptor expression and activity are controlled by a range of chemicals, some of which are found in the environment.

Two nuclear receptors – oestrogen and progesterone receptors – are known to be important in diagnosing and treating breast cancer. The amount of these proteins in tumours is used to assign patients to clinical

groups which can help doctors decide the best therapy. Evidence is now emerging that in some breast tumours, the level of other nuclear receptors, e.g. the androgen receptor, is altered. Understanding what causes these changes and how they might contribute to the development of breast cancer is important for identifying risk factors for breast cancer.

The research will measure the levels of all 48 nuclear receptors in normal breast tissue and breast tumour tissue samples, to help identify common nuclear receptor gene signatures. Using these results, predictions can be made to identify environmental chemicals that regulate nuclear receptor expression, and which metabolic pathways are changed following chemical exposure.

Aims

The research aimed to identify nuclear receptors that play a role in breast cancer and identify environmental chemicals which disrupt these receptors.

Summary of results

Comparison of nuclear receptor activity in healthy breast tissue and in breast cancer tissue.

Dr Matthews and colleagues used pre-existing gene expression datasets (see note 1) from breast cancer tumours to identify nuclear receptors with altered gene expression in different types of breast cancer tissues. Their results included identification of seven nuclear receptors with potential for driving triple negative breast cancer.

The nuclear receptors were associated with pathways that affect lipid (fat) metabolism. Four additional nuclear receptors that might control expression of these seven nuclear receptors were also identified.

Identification of household chemicals and pollutants that could cause similar changes in gene expression as those seen in triple negative breast cancer.

Using gene expression datasets from Enrichr (see note 2), Dr Matthews identified over 200 household chemicals and pollutants that are predicted

to cause similar changes in gene expression observed in triple negative breast cancers.

Some of the household chemicals and pollutions were found to increase multiplication of human breast cells and alter levels of nuclear receptor proteins in cells

A sub-group of chemicals was selected for laboratory-based experiments, including cell proliferation assays, which examine whether a compound increases multiplication of human breast cells grown in cell culture, and other studies which enable measurement of how much nuclear receptor protein is present in breast cells. Many of the compounds tested, which included fungicides, disinfectants, insecticides and prescription drugs, increased multiplication of breast cells and affected expression of some of the seven nuclear receptors highlighted by the initial analysis.

Results allow identification of household chemicals and pollutants that may affect breast cancer risk

The results provide preliminary evidence that chemicals in the environment can alter nuclear receptor expression and increase proliferation of breast cells. The pathways that link nuclear receptor expression to breast cancer are likely to be associated with cell growth and division and lipid metabolism. Further understanding of this nuclear receptor network and how it is controlled will help to identify risk factors for triple negative breast cancer and suggest therapeutic interventions.

Future work

Dr Matthews and colleagues will continue to explore the actions of the panel of chemicals on breast cell growth and division, using 3D breast cell models. This approach can be used to track the effects of chemical treatments over time. They will also determine if any nuclear receptors are activated directly by the chemicals. The seven nuclear receptors that were differentially expressed in TNBC and the 4 nuclear receptors that are predicted to control them will be investigated further.

Note 1: The datasets comprise RNA sequencing data from normal breast tissue and different types of breast cancer tissue. Comparison of these data show which nuclear receptors are differentially expressed between normal and cancer tissue. This enables generation of a nuclear expression profile specific to a particular type of breast cancer.

Note 2: [Enrichr](#) is a web-based analysis tool which was used to identify chemicals predicted to have a similar nuclear expression profile to that identified for triple negative breast cancer. Enrichr provides access to thousands of gene expression datasets derived from chemical and drug treatments.