Scientific abstract

THSD4 is a novel mediator of T cell exclusion and anti-PD-1 response in breast cancer

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Introduction: Emerging treatments for breast cancer include pembrolizumab, an antibody which targets the programmed cell death protein 1 (PD-1) and causes activation of T cells against cancer cells. Some breast cancers are resistant to anti-PD-1 because they have low T cell infiltration. To improve anti-PD-1 efficacy we need predictive biomarkers and therapeutic strategies that increase T cell infiltration.

Objectives: Identify novel genetic factor(s) that suppress T cells infiltration in breast cancer and assesses the genetic factor(s) as predictive biomarkers and targets to increase T cell infiltration and anti-PD-1 efficacy in breast cancer.

Methods: Transcriptome deconvolution was performed on TCGA breast cancer RNA sequencing data to estimate the proportions of T cells in tumours and identify genes negatively correlated with T cells. Marathon of Hope Nova Scotian breast cancer patient tumour RNA sequencing data and associated fixed tumour sections that were immune cell-profiled by multiplex-immunofluorescence were assessed for genes negatively correlated with T cells. The gene array data from the I-SPY2 breast cancer clinical trial was evaluated for gene expression associated with non-pathological response to pembrolizumab. The top gene from these three analyses was knocked down in the syngeneic mouse hormone receptor-positive (HR+) TS/A breast tumour model and assessed for effects on anti-PD-1 tumour growth inhibition and immune cell infiltration by flow cytometry.

Results: Thrombospondin type 1 domain containing 4 (THSD4) was the top hit associated with low T cells and pembrolizumab resistance in breast cancer patient tumours, especially in HR+ breast cancers. Knockdown of THSD4 in TS/A mouse tumours treated with anti-PD-1 significantly reduced tumor growth and increased T cell infiltration.

Conclusions and anticipated impact: Our findings indicate that breast cancer patients may be stratified for immunotherapy treatment based on THSD4 expression in their tumours and that THSD4 could be a novel therapeutic target for enhanced pembrolizumab efficacy in breast cancer.

Plain language abstract

New gene discovery could boost the immune system's cancer-fighting power in breast cancer

Introduction: Breast cancer is a major health problem for women. Doctors are trying a new treatment called pembrolizumab, which helps the body's immune system fight cancer. But this drug is not effective for all breast cancer patients, especially when there are not enough cancer-fighting immune cells (called T cells) in the tumour.

Objectives: We need to find out why some breast cancers have few T cells and determine how to predict for which patients the drug will help, and which will be resistant. This will ensure that only patients that will benefit from pembrolizumab will receive it. Importantly we also need to find ways to make the drug work better overall so more patients can be helped by pembrolizumab treatment.

Methods: We assessed all the genes of breast cancer patients looking for correlations between gene expression levels and low T cells in breast tumours and resistance to pembrolizumab. We tested this idea in mice by reducing the activity of the genes in their tumours and giving them a mouse version of pembrolizumab.

Results: Our analyses in breast cancer patients revealed that a previously unstudied gene was very active in breast tumours that had few T cells and in patients that were resistant to pembrolizumab. When we reduced this gene in mouse tumours and gave the mice the drug, the tumours grew more slowly, and more T cells entered the tumours.

Conclusions: Our data means that this new gene might be the key to making pembrolizumab work better for breast cancer patients. Doctors could potentially test this gene in breast cancer patients to see who might benefit most from the drug, and we can develop a new drug that stops this gene to make the treatment more effective.