breast cancer target identification, validation and preclinical models

Targeting the hedgehog signalling pathway in triple negative breast cancer

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Background: The improvement in breast cancer outcome to date is largely due to the use of targeted therapy - tamoxifen and aromatase inhibitors in oestrogen receptor positive disease and trastuzumab in HER2 amplified breast cancer. To further improve disease outcome, new targeted therapies are needed for triple negative breast cancer (TNBC). The hedgehog (Hh) signalling pathway is activated in the stroma of TNBC in response to Hh ligand secreted by cancer epithelial cells. We hypothesized that cancer associated fibroblasts (CAFs), known for mediating therapeutic resistance, are the primary stromal cells that respond to Hh ligand stimulation. By targeting both cancer epithelial cells (with chemotherapy, C) and stromal cells (with Hh pathway inhibitor, LDE225), we anticipate improved TNBC outcomes in primary tumour control and overall survival.

Methods: To identify the stromal cell types that respond to Hh ligand stimulation in the tumour microenvironment, Hh overexpressing mammary tumours were dissociated into epithelial and stromal single cell suspensions followed by single cell PCR studies. The efficacy of combination therapy (C and LDE225) was carried out in immunodeficient NOG mice bearing TNBC xenografts (MDA-MB-231 and patient derived xenografts, PDX). In the short term study, mice were treated with daily LDE225 and weekly C for 28 days then aged to endpoint. In the long term survival study, mice received the same treatment until endpoint.

Results: Single cell PCR confirmed that Hh ligand activates the pathway only in CAFs. Combination therapy led to significant inhibition in tumour growth and survival compared to monotherapy. At the time of reporting, median survival was not reached in the combination therapy arm in the long term study. Tumours in the monotherapy groups grew steadily despite the use of maximum tolerated doses. There was no significant toxicity observed in mice treated with combination therapy.

Conclusions: Hh ligands secreted by TNBC epithelial cells activate Hh pathway signalling in stromal CAFs which mediate therapeutic resistance. Targeting stromal CAF with Hh pathway inhibitor, LDE225 in combination with chemotherapy led to significant inhibition in primary tumour growth and improved overall survival.

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