Trial Watch

PREDICTING CHEMOTHERAPY RESISTANCE

Using pretreatment biopsies of oestrogen receptor-negative (ER^-) breast tumours, Farmer *et al.* have shown that a stromal gene signature can predict resistance to neoadjuvant chemotherapy.

Pretreatment biopsies were taken from 63 patients enrolled in the randomized Phase III European Organisation for Research and Treatment of Cancer (EORTC) 10994 trial; these patients were from the treatment arm that received 5-fluorouracil, epirubicin and cyclophosphamide (FEC) prior to surgery. The majority (84.1%) of tumours had ductal histology; 6.3% were lobular and 9.5% were not assessable. Conventional techniques were unable to predict the response of these patients to FEC, so the authors developed a new strategy examining clusters of coexpressed genes related to nine specific cell types and biological processes: stroma, T cells, B cells, adipocytes, luminal–basal cells, apocrine cells, proliferation, hypoxia and interferon signaling. A representative gene for each process or cell type was chosen, and the model was fitted using an external data set comprising 581 tumour samples from the Netherlands Cancer Institute (NKI) and Erasmus Medical Center (EMC). The authors chose 50 genes with the strongest association to each of the 9 representative genes in the NKI-EMC data set. They then averaged the expression data from the EORTC data set for the 50 genes to generate a metagene, comprising a single value, for each of the 9 processes or cell types.

Pathological complete response was predicted by only 2 of the 9 metagenes: interferon signaling and stroma. Validation in an independent cohort of ER^- breast tumour samples from a study on neoadjuvant chemotherapy with paclitaxel, 5-fluorouracil, doxorubicin and cyclophosphamide (T-FAC) confirmed that the stromal metagene was associated with response to chemotherapy ($p = 0.01$) but the interferon signaling metagene was not. Specifically, increased expression of genes within the stromal metagene was associated with resistance to both FEC and T-FAC chemotherapy. Further analysis showed that the stromal metagene was predictive of therapy response but not prognostic for survival, supporting the hypothesis that increased stromal gene expression is linked to chemotherapy resistance and not to intrinsically more aggressive tumours.

The stromal metagene was significantly associated with the amount of reactive stroma present in histological sections from the EORTC biopsies ($p = 0.009$). Microdissection of breast tumours confirmed that increased expression of stromal genes probably comes from the stroma itself rather than epithelial cells. However, epithelial–mesenchymal transition of epithelial tumour cells could account for at least some of the increase in stromal gene expression, so the observed resistance to chemotherapy might come from tumour cells that have undergone epithelial–mesenchymal transition and developed stem-cell-like properties.

This gene expression study identifies a new mechanism of resistance to FEC chemotherapy in ER^- breast cancer and suggests that targeting the stroma might circumvent resistance.

ORIGINAL RESEARCH PAPER Farmer, P. *et al.* A stroma-related gene signature predicts resistance to neoadjuvant chemotherapy in breast cancer. *Nature Med.* **15**, 68–74 (2009)