BREAST CANCER

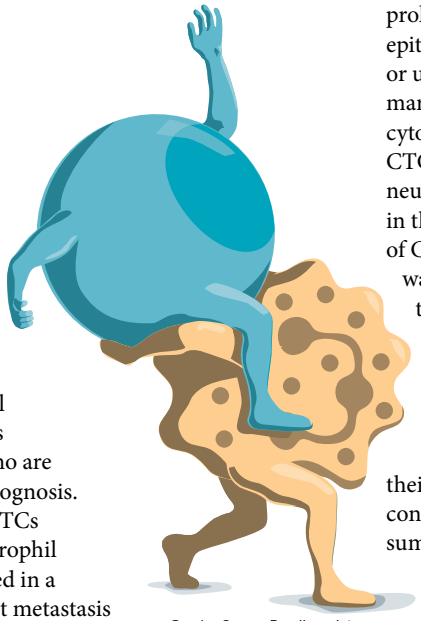
CTCs 'piggyback' off neutrophils

Circulating tumour cells (CTCs) are the 'seeds' of metastasis. Physical interactions with neutrophils have previously been shown to increase the metastatic potential of CTCs by enhancing their adhesive and migratory capacities. Results of a recent study provide new insights into these interactions and identify an additional mechanism by which neutrophils promote metastasis.

This study involved single-cell RNA sequencing or immunostaining and morphological analyses of CTCs isolated from 34 of 70 patients with breast cancer. Most CTCs were solitary or present in homogeneous clusters. However, 3.4% of CTCs were adherent to immune cells, most of a myeloid lineage (75%); ~90% of the myeloid cells were neutrophils with a pro-tumour 'N2-like' signature. Similar findings were obtained in five mouse models of breast cancer.

Notably, patients with ≥1 CTC–neutrophil cluster detected had significantly worse progression-free survival than those with ≥5 CTCs detected ($P = 0.0001$), who are known to have a poor prognosis. Moreover, injection of CTCs derived from CTC–neutrophil clusters into mice resulted in a more rapid onset of overt metastasis than injection of the solitary CTCs. Interestingly, certain recurrent mutations in CTCs (for example, affecting *MERTK* and *TLE1*) were associated with CTC–neutrophil clustering and might, therefore, have prognostic relevance.

The gene expression profiles of CTCs from CTC–neutrophil clusters indicated increased proliferative activity but not epithelial–mesenchymal transition or upregulation of stem cell markers. The data also revealed cytokine–receptor pairing between CTCs and neutrophils, implicating neutrophil-derived IL-6 and IL-1β in the enhanced proliferation of CTCs. Moreover, VCAM1 was identified as a potentially targetable protein that mediates CTC–neutrophil interactions.



Credit: Simon Bradbrook/ Springer Nature Limited

"Our data suggest that CTC–neutrophil clusters are very efficient seeds of metastases, and preventing their formation in mouse models considerably delays metastasis," summarizes Nicola Aceto, who led the study. "Preventing the formation of these clusters in patients might also markedly reduce the metastatic potential of cancer cells, and clinical studies are needed to address this point," he concludes.

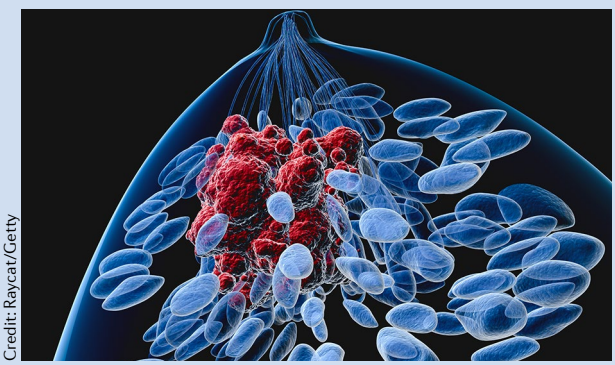
David Killock

ORIGINAL ARTICLE Szczerba, B. M. et al. Neutrophils escort circulating tumour cells to enable cell cycle progression. *Nature* https://doi.org/10.1038/s41586-019-0915-y (2019)

BREAST CANCER

Early PET response predicts complete response

The addition of pertuzumab plus trastuzumab to neoadjuvant chemotherapy has improved the outcomes of women with high-risk HER2$^+$ breast cancer, although the risk of adverse events remains problematic.



Credit: Raycat/Getty

Now, data from a phase II trial suggest that a reduction in tumour metabolic activity on PET imaging at 15 days after treatment initiation is a biomarker of pathological complete response (pCR).

In this single-arm trial, a total of 88 women with stage II/III, oestrogen receptor (ER)$^-$, HER2$^+$ breast cancer received four cycles of neoadjuvant pertuzumab plus trastuzumab and underwent ^{18}FDG-PET–CT imaging before and 15 days after the start of treatment. Determining the relationship between early changes in maximum standard uptake value corrected for lean body mass (SUL_{max}) and pCR after four cycles of therapy was the primary objective. Highlighting the motivations for this trial, lead author Roisin Connolly explains: "several clinical trials have revealed a subset of patients who have a pCR to neoadjuvant pertuzumab plus trastuzumab alone, and could thus be spared chemotherapy; however, robust biomarkers are required in order to consistently identify such patients".

A total of 28 patients (34%) had a pCR after four cycles of therapy. Patients with a pCR had a significantly greater median reduction in SUL_{max} at 15 days than those without a pCR (63.8% versus 33.5%; $P < 0.001$). Applying an exploratory cut-off value of a 40% reduction in SUL_{max} yielded an 86% level of sensitivity and a specificity of 55%. Most notably, this threshold also provides a high negative predictive value (88%). "These data suggest that patients who do not have a substantial reduction in SUL_{max} by day 15 are unlikely to have a pCR to targeted therapies alone," Connolly summarizes.

This finding suggests that the majority of patients with an initial response to targeted therapy could be safely spared chemotherapy and the associated risk of adverse events. Furthermore, because these changes occur early in the course of treatment, patients who do not have a substantial reduction in SUL_{max} could potentially be assigned to other therapies. Further clinical validation of this biomarker is necessary and eagerly awaited.

Peter Sidaway

ORIGINAL ARTICLE Connolly, R. M. et al. TBCRC026: phase II trial correlating standardized uptake value with pathologic complete response to pertuzumab and trastuzumab in breast cancer. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2018.78.7986 (2019)