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BREAST CANCER

CTC heterogeneity is dynamic

Circulating tumour cells (CTCs) from patients with hormone-receptor-positive (HR^+) and HER2-negative ($HER2^-$) breast cancer acquire HER2 expression, but how these changes affect tumour progression and response to therapy remains unclear. This question was addressed by Shyamala Maheswaran and Daniel Haber in a newly published study.

The functional importance of HER2 heterogeneity was modelled using CTCs derived from patients with metastatic HR^+ breast cancer. In ~85% of patients with HR^+HER2^- breast cancer, CTCs acquired HER2 expression during disease progression. In addition, "CTC cell lines consisted of a mixed population of $HER2^-$ and $HER2^+$ cells, a transition that is known to occur in patients but cannot be observed using ATCC breast cancer cell lines", Maheswaran explains. CTC populations spontaneously switched between the two states both in culture and in orthotopically inoculated tumours. Of note, $HER2^+$ CTCs formed tumours more rapidly than $HER2^-$ CTCs when orthotopically injected into mice. In addition, $HER2^-$ CTCs harboured differential activation of the Notch-signalling pathway. Exposure to chemotherapeutic agents and/or oxidative stress promoted transition to the $HER2^-$ phenotype, which is associated with drug resistance. Additional cues involved in this phenotype switch remain to be identified.

On the clinical implications of these findings, Maheswaran highlights: "$HER2^+$ tumour cells in patients with HR^+HER2^- metastatic breast cancer are not responsive to HER2-targeted therapies. The fact that they coexist with $HER2^-$ CTCs, and that activation of different pathways renders both populations sensitive to different drugs suggests that combination therapies might effectively eliminate these tumours".

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ORIGINAL ARTICLE Jordan, N. V. *et al.* HER2 expression identifies dynamic functional states within circulating breast cancer cells. *Nature* **537**, 102–106 (2016)