MICROENVIRONMENT

Domino effect

> a CXCR2 antagonist and chemotherapy synergistically reduced metastases

In advanced breast cancer, metastasis and resistance to chemotherapy are clinically linked. Acharyya *et al.* have identified a paracrine signalling network between tumour and stromal cells that may drive these processes.

Using syngeneic and xenograft mouse models of breast cancer, and tail-vein injection of metastatic cells, they found that depletion of the chemokines CXCL1 and CXCL2 in tumour cells inhibited tumour growth and reduced metastasis to the lungs. Tumour cells expressed low levels of the receptors for these chemokines (primarily CXCR2), indicating that paracrine signalling to other cell types in the tumour microenvironment might be involved. Indeed, they found low numbers of $CD11b^{+}GR1^{+}$ myeloid cells in tumours lacking CXCL1 and CXCL2, and identified the inflammatory proteins S100A8 and S100A9 as candidate paracrine mediators: tumour growth and metastasis were reduced in mice transplanted with *S100a9*$^{-/-}$ bone marrow. Furthermore, mouse mammary tumours that developed resistance to chemotherapy had high expression of CXCL1 and CXCL2 and increased recruitment of S100A9-expressing cells. Human breast tumour samples also showed increased levels of S100A9-expressing cells after chemotherapy.

In addition, tumour necrosis factor-α (TNFα) was secreted by endothelial and other stromal cells following chemotherapy, and stimulated CXCL1 and CXCL2 expression downstream of nuclear factor-κB activation in tumour cells, thus amplifying CXCL1 and CXCL2–S100A9 signalling. Increased TNFα levels were also evident in human tumours after chemotherapy. Importantly, treatment of mice with a CXCR2 antagonist and chemotherapy synergistically reduced metastases, highlighting the clinical potential of targeting this axis.

Sarah Seton-Rogers

ORIGINAL RESEARCH PAPER Acharyya, S. *et al.* A CXCL1 paracrine network links cancer chemoresistance and metastasis. *Cell* **150**, 165–178 (2012)