CELL SIGNALLING

Stuck in the middle of chemoresistance and metastasis

Most breast cancer-related deaths are due to metastatic disease, which is strongly associated with resistance to chemotherapy. However, not all tumour cells are able to migrate and subsequently colonize a metastatic site and, certainly, not all tumour cells can resist chemotherapy. This scenario prompted Joan Massagué and colleagues to wonder whether both processes, metastatic and chemotherapeutic, selected a cell population with a special skill set that allowed it to survive in those circumstances.

On the basis of previous results that had showed that expression of the chemokine CXCL1 was associated with breast cancer metastasis in the lung, the researchers found that the gene *CXCL1* and the related gene *CXCL2* were amplified in a subset of both primary breast tumours and metastases. To further investigate the role of these two chemokines in the metastatic process, the authors used two different mouse models. Knocking down the expression of CXCL1 and CXCL2 reduced tumour volume and lung metastasis in both models. Interestingly, the receptors for CXCL1/2 were not detected in tumour cells. As it is established that not only tumour cells participate in cancer progression but also the surrounding stromal cells and immune cells, the researchers sought to identify which cells in the tumour microenvironment responded to CXCL1/2. They found out that, in both mouse models, those tumours with low levels of expression of CXCL1/2 had a reduced population of a particular subset of myeloid cells (CD11b^{+}Gr1^{+}) in their microenvironment. This finding suggests that CXCL1/2 attracts CD11b^{+}Gr1^{+} myeloid cells, which support the survival of cancer cells. But how?

A gene expression analysis of breast tumour samples revealed expression of 43 genes associated with *CXCL1*, among which *S100A8* and *S100A9* were expressed in tumour-derived CD11b^{+}Gr1^{+} myeloid cells. Indeed, in patients with breast cancer, high levels of S100A8/9 in lung metastases correlated with poor survival.

Similarly, there was an increase in cells that were positive for S100A8/9 in breast tumours from patients who had received chemotherapy compared with those who had not. Further experiments in the mouse models showed that treatment with chemotherapy stimulated the expression of TNF-α in the epithelial cells from the lung, which in turn activated CXCL1 expression through NF-κB. Treating the mice with an antibody against TNF-α reduced recruitment of S100A8/9 positive cells, and a combination of an antagonist of CXCL1/2 receptor with chemotherapy synergistically reduced lung metastases.

These results describe a new environment-tumour pathway that mediates metastasis and resistance, opening new possibilities for cancer therapy.

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