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IMMUNOLOGY

Bad company

> “CD68^{high}–CD4^{high}–CD8^{low} expression was an independent predictor of reduced overall survival and relapse-free survival, and an independent predictor of relapse-free survival in patients with lymph node metastases at diagnosis.”

The presence or absence of different types of immune cells is known to influence outcome for cancer patients, but we are still some way from understanding the complex interaction between immune cell subsets and how they affect tumour growth and regression. A paper published in *Cancer Discovery* shows that the response of patients with breast cancer to specific chemotherapies is influenced by the subsets of leukocytes that are present in the tumour.

Building on data showing that tumour-associated macrophages (TAMs) correlate with a poor prognosis in several tumour types, that TAMs are recruited through the secretion of colony stimulating factor 1 (CSF1) and interleukin-34 (IL-34), and that, in the absence of CD8$^+$ cytotoxic T cells, CD4$^+$ T helper cells increase the pro-tumour activity of CD68$^+$ TAMs, Lisa Coussens and colleagues examined the density of the CD8$^+$, CD4$^+$ and CD68$^+$ leukocyte infiltrates in breast cancer tissue microarrays. A fully automated algorithm generated high and low staining information for each leukocyte subset of 179 chemotherapy-naive primary tumour samples that were subject to immunohistochemistry. High levels of CD4$^+$ T cells and low levels of CD8$^+$ T cells correlated with reduced overall survival in these patients, and levels of CD8$^+$ T cells were inversely correlated with the CD68$^+$ infiltrate. This cohort of samples was further used to establish immunohistochemical expression thresholds to identify tumours with CD68^{high}–CD4^{high}–CD8^{low} versus CD68^{low}–CD4^{low}–CD8^{high} leukocyte subsets. Use of these thresholds on 667 chemotherapy-naive breast cancer samples with outcome data indicated that CD68^{high}–CD4^{high}–CD8^{low} expression was an independent predictor of reduced overall survival and relapse-free survival, and was also an independent predictor of relapse-free survival in patients with lymph node metastases at diagnosis.

Coussens and colleagues also found that the treatment of human breast cancers with chemotherapy increased the numbers of TAMs in the tumour, but had no effect on the presence of CD8$^+$ T cells. Moreover, using various mouse models of breast cancer, they established that expression of CSF1 and IL-34 by mouse mammary epithelial cells was induced by chemotherapy and resulted in macrophage recruitment. Inhibition of CSF1 activity *in vivo* using a CSF1 antibody or a tyrosine kinase inhibitor, PLX3397, which targets the CSF1 receptor and KIT, reduced TAM numbers. Importantly, the treatment of mice with polyoma middle T-induced mammary tumours with paclitaxel combined with either the CSF1 antibody or PLX3397 improved survival compared with mice treated with each drug as a monotherapy. Treatment with paclitaxel and PLX3397 reduced the development of late-stage tumours and pulmonary metastases.

The reduction in the levels of TAMs within the primary tumours increased the numbers of active cytotoxic T cells, and *in vitro* data indicated that TAMs repress CD8$^+$ T cell proliferation. In addition, deletion of CD8$^+$ T cells from mouse mammary tumours prevented the chemosensitizing effect of PLX3397 combined with paclitaxel, indicating that the effect of this drug combination partly stems from enabling the activation of CD8$^+$ cytotoxic T cells owing to the reduced numbers of TAMs.

Examination of fine-needle aspirates taken from 311 patients with newly diagnosed breast cancer prior to treatment with neoadjuvant chemotherapy followed by surgery showed that patients with a high ratio of *CD68* mRNA expression to *CD8* mRNA expression had a significantly lower rate of pathological complete responses than patients with low *CD68* and high *CD8* mRNA expression. Taken together, these findings indicate that the drugs that prevent the recruitment of macrophages should be investigated further and that the ability to identify women with immune profiles that are likely to benefit from such treatment is imperative.

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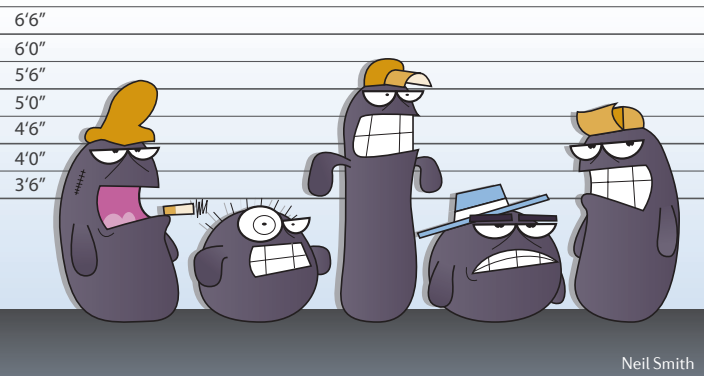

ORIGINAL RESEARCH PAPER DeNardo, D. G. *et al.* Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. *Cancer Discovery* 3 Apr 2011 (doi:10.1158/2159-8290.CD-ITI11-0)