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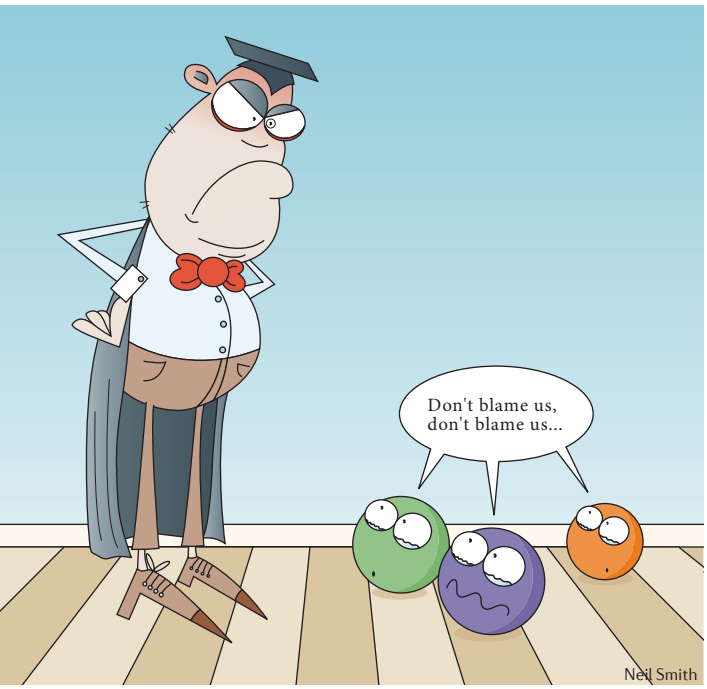
METASTASIS

Influencing bad behaviour

> “...CD4$^+$ T cells can promote metastasis in a mouse model of breast cancer through their influence on macrophages.”

Inciting antisocial behaviour is a crime and it is one that CD4$^+$ T cells stand accused of in a paper recently published in *Cancer Cell*. Lisa Coussens, David DeNardo and colleagues show that CD4$^+$ T cells can promote metastasis in a mouse model of breast cancer through their influence on macrophages.

Innate and adaptive immune cells are no strangers to tumours, but their precise effect on the tumorigenic process has not always been easy to pin down. Macrophages, which are part of the innate immune response, can mediate metastasis of malignant mammary epithelial cells (MECs) by secreting epidermal growth factor (EGF). However, adaptive immune cells, such as CD4$^+$ and CD8$^+$ T cells, which regulate the function of innate immune cells, are also present. What is the function of these cells in breast cancer? Coussens and colleagues examined the development of breast cancers driven by the polyoma middle T (PyMT) antigen under the control of the mouse mammary tumour virus (*MMTV*) promoter in mice with dysfunctional adaptive immune systems. They found that these mice showed no changes in primary tumour growth and angiogenesis, but mice lacking CD4$^+$ T cells, or mice with established tumours that were then depleted of CD4$^+$ T cells, had reduced levels of pulmonary metastases, as well as fewer circulating tumour cells.



Given the association of macrophages with breast cancer metastasis, the authors asked whether CD4$^+$ T cells can affect macrophage function in breast tumours. Although macrophages were still present in breast tumours in *MMTV–PyMT*;*Cd4*$^{-/-}$ mice, analysis of their activation status indicated that they had an M1 phenotype, whereas those in mice with CD4$^+$ T cells were of an M2 phenotype. M2 macrophages, unlike M1 macrophages, express pro-angiogenic, pro-tissue remodelling cytokines in response to T helper 2 cytokines, such as interleukin 4 (IL-4), IL-10 and IL-13. Indeed, CD4$^+$ T cells isolated from the mouse mammary tumours expressed these cytokines.

To show that CD4$^+$ T cells and the cytokines they produce are the driving force for metastasis, the authors cultured MECs from MMTV–PyMT mice in three-dimensional organoid culture and then added tumour-associated macrophages and CD4$^+$ T cells isolated from MMTV–PyMT mice. Only under these conditions did malignant MECs grow invasively. Moreover, *MMTV–PyMT*;*Il4*$^{-/-}$ mice also had reduced levels of pulmonary metastases, suggesting that this CD4$^+$ T cell-expressed cytokine is crucial. How does IL-4 affect the macrophages? IL-4 significantly increased the expression of EGF by the macrophages, and inhibition of the EGF–EGF receptor pathway suppressed the invasive growth of malignant MECs in the three-dimensional co-culture assay.

Therefore, the innate and adaptive immune responses collaborate to induce pulmonary metastases in mice with mammary tumours. These results indicate that targeting CD4$^+$ T cells and IL-4 could inhibit the formation of metastasis in patients with breast cancer.

Nicola McCarthy

ORIGINAL RESEARCH PAPER DeNardo, D. G. *et al.* CD4$^+$ T cells regulate pulmonary metastasis of mammary carcinomas by enhancing pro-tumour properties of macrophages. *Cancer Cell* **16**, 91–102 (2009)
FURTHER READING Joyce, J. A. & Pollard, J. W. Microenvironmental regulation of metastasis. *Nature Rev. Cancer* **9**, 239–252 (2009)