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TUMOUR IMMUNOLOGY

Dendritic cell switch

> Immuno-competence was lost by DCs in advanced tumours

Immune cells in the tumour microenvironment can either promote or suppress tumour progression. However, the relative contribution of different immune cell populations, and how this might vary between pre-malignant lesions and aggressive tumours, is less clear. Jose Conejo-Garcia and colleagues have analysed this process using a new, inducible mouse model of ovarian cancer.

The authors first generated a model of ovarian cancer induced by the deletion of *Trp53* (through the ovarian-specific delivery of adenoviruses that expressed the Cre recombinase) and the activation of oncogenic *Kras* in adult mice, to mimic tumorigenesis in humans. Analysis of the immune cells that infiltrated these tumours indicated that they were similar to those found in human ovarian tumours.

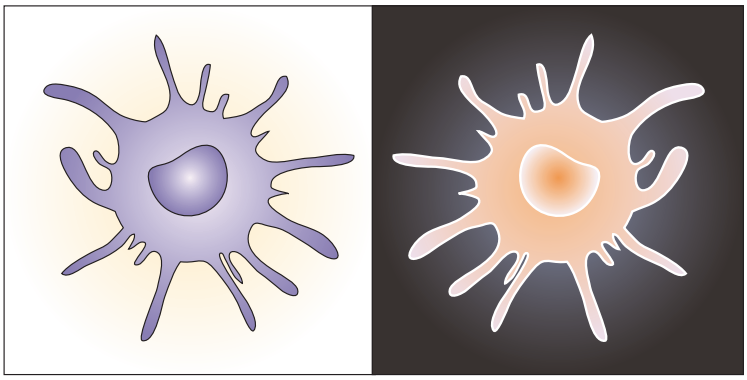
How do the infiltrating immune cell populations and functions change during tumour progression? At the point when ovarian tumours became palpable in this model, the authors noted an increase in the ratio of dendritic cells (DCs) to T cells, which was similar to the ratio found in advanced human tumours; this was followed by a period of exponential tumour expansion. Antibody-mediated depletion of $CD8^+$ T cells accelerated malignant progression in the mice. Furthermore, T cells that were isolated from mice in the early stages of tumorigenesis specifically responded to tumour antigens, and this response was blunted in T cells from mice with advanced tumours. Because the same tumour antigens, derived from advanced tumours, were used in both experiments, this suggests that these tumours remain antigenic, and that the ability of these T cells to respond to tumours decreases during tumour progression. The authors also analysed the immune-modulating effects of DCs in the tumour microenvironment at various stages during tumour progression. DCs from mice in the early stages of ovarian tumorigenesis were immunocompetent (as measured by their ability to induce expansion of tumour-reactive T cells). Immunocompetence was lost by DCs in advanced tumours, and these DCs could also suppress the T cell expansion that was induced by immunocompetent DCs from early stage tumours.

How do DCs change to become immunosuppressive? DCs from advanced mouse tumours expressed higher levels of programmed death ligand 1 (PDL1) and had strong arginase activity, both of which are immunosuppressive. High arginase activity was also observed in DCs taken from advanced human ovarian tumours, and this activity was reduced by incubation with immunostimulatory agents. Depletion of DCs early in tumorigenesis enhanced progression, which is consistent with a tumour-suppressive ability of these cells during these early stages. However, at later time points DC depletion had the opposite effect and slowed tumour progression, suggesting that the enduring, albeit decreased, activity of anti-tumour T cells could control tumour progression. Finally, to investigate signals that might promote this switch in DC function, the authors examined cytokines and chemokines secreted by cells that were derived from advanced mouse tumours, and they found high levels of prostaglandin E_2 (PGE_2) and transforming growth factor-β1 (TGFβ1). Both PGE_2 and TGFβ1 upregulated PDL1 in DCs, and inhibition of either prevented immunosuppressive DCs from blocking T cell expansion.

If similar functional changes are confirmed in DCs in human tumours, perhaps preventing this switch could be exploited therapeutically to keep tumours in check.

Sarah Seton-Rogers

ORIGINAL RESEARCH PAPER Scarlett, U. K. *et al.* Ovarian cancer progression is controlled by phenotypic changes in dendritic cells. *J. Exp. Med.* 20 Feb 2012 (doi:10.1084/jem.20111413)



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