Journal club

BACTERIA, INFLAMMATION AND CANCER

In 1863, Virchow proposed that inflammation and cancer are linked and that the “lymphoreticular infiltration” of cancer reflected its origins at sites of inflammation. This view led to the concept of ‘smoldering inflammation’ as one of the major causes of cancer (discussed in Balkwill *et al.*, 2005). At the same time, it had been proposed that the immune system continuously surveys the organism and deletes most tumours before they become clinically relevant (discussed in Dunn *et al.*, 2002).

A 2003 paper by Enzler *et al.* provides unexpected insight into the role of the immune system in promoting or inhibiting tumour development. The central message of this provocative paper has been rather overlooked and merits recognition; it suggested that the immune system, rather than deleting nascent tumour cells, keeps the microbiome in balance so that pathogenic bacteria do not become dominant and cause persistent

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cancer-causing inflammation. This paper made me re-think the origins of cancer and, given my interest in the role of macrophages in the inflammatory response, to refine the concept of cancer immunology in cancer pathogenesis.

Enzler *et al.* made the surprising observation that genetic deletion of both granulocyte-macrophage colony-stimulating factor (GM-CSF) and interferon- γ (IFN γ) in mice resulted in the formation of diverse haematological and solid neoplasias within a background of persistent infection and inflammation. More than 50% of the mice had solid tumours, many of which are rare in mice. Treatment of a cohort of these mice from birth with a broad-spectrum antibiotic inhibited the formation of all of these tumours. These data indicate that the cause of cancer formation in these mice was bacterial, presumably due to the creation of a persistent inflammatory response, rather than resulting from defective immune surveillance of tumour cells.

Once formed, tumours do engage the immune system, and it is probable that they need to undergo ‘immunoediting’ to escape immune

rejection for progression to malignancy (discussed in Dunn *et al.*, 2004). Nevertheless, the paper by Enzler *et al.* shows, in keeping with Virchow, that the function of immunosurveillance in relation to cancer initiation is mostly to restrain pathogenic organisms that otherwise create a cancer-causing inflammatory microenvironment. Such studies presaged the appreciation of the microbiome having a marked effect on cancer incidence.

Jeffrey Pollard

MRC Centre for Reproductive Health,
Queen's Medical Research Institute,
University of Edinburgh,
Edinburgh EH16 4TJ, UK.

e-mail: Jeff.Pollard@ed.ac.uk

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ORIGINAL RESEARCH PAPER Enzler, T. *et al.* Deficiencies of GM-CSF and interferon gamma link inflammation and cancer. *J. Exp. Med.* **197**, 1213–1219 (2003)

FURTHER READING Balkwill, F., Charles, K. A. & Mantovani, A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell* **7**, 211–217 (2005) | Dunn, G. P. *et al.* Cancer immunoediting: from immunosurveillance to tumor escape. *Nat. Immunol.* **3**, 991–998 (2002) | Dunn, G. P., Old, L. J. & Schreiber, R. D. The three Es of cancer immunoediting. *Annu. Rev. Immunol.* **22**, 329–360 (2004)