TUMOUR IMMUNOLOGY

IFNs boost cancer killers

The immune system can influence tumour growth, although not always successfully. However, the underlying mechanisms of priming tumour-specific T cells remain unknown. Now, two studies from the Gajewski and Schreiber laboratories (Fuertes *et al.* and Diamond *et al.*, respectively) show that early type I interferon (IFN) production, acting on CD8α$^+$ dendritic cells (DCs), is required for effective activation of tumour antigen-specific CD8$^+$ T cells.

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Previous studies by Gajewski and colleagues identified a correlation between T cell markers and IFN-induced transcripts in human melanoma metastases, and Schreiber and colleagues had identified a central role for type I IFNs in cancer immunoediting (a process whereby the interaction of tumour cells with the immune system generates tumour variants with altered immunogenicity). So, both groups set out to assess the role of type I IFNs in the initiation of antitumour immune responses.

Although the groups used different transplantable tumour models, an early increase in type I IFN production was observed following implantation of tumour cell lines in both studies. Fuertes *et al.* identified CD11c$^+$ DCs as the source of type I IFNs and found that this early type I IFN response was accompanied by tumour antigen-specific CD8$^+$ T cell priming. Furthermore, Diamond *et al.* showed that type I IFNs were required for the initiation of an antitumour response that resulted in the spontaneous rejection of immunogenic tumours.

But what are the physiological target cells for the antitumour actions of type I IFNs? By generating chimeric mice using combinations of bone marrow cells from mice lacking the type I IFN receptor (IFNAR) or its downstream signalling molecule STAT1 and from mice lacking adaptive immune cells, both groups showed that innate immune cells were the target cell types. Analysis of additional mixed bone marrow chimeric mice showed that type I IFNs must signal on CD8α$^+$ DCs, but not on granulocytes or macrophages, for optimal priming of antitumour CD8$^+$ T cell responses *in vivo*.

In vitro analysis by Diamond *et al.* suggested that type I IFN-mediated signalling in CD8α$^+$ DCs enhanced their ability to cross-present antigen. Furthermore, in mice that lacked IFNAR expression specifically on DCs, CD8α$^+$ DCs were defective in antigen cross-presentation to CD8$^+$ T cells *ex vivo*. However, using T cell receptor (TCR) tetramers, Fuertes *et al.* showed that the presentation of a tumour-derived antigen by CD11c$^+$ DCs was unaffected by the absence of type I IFN signalling *in vivo*. So, further investigation is needed to determine exactly how type I IFN signalling in CD8α$^+$ DCs results in priming of antitumour CD8$^+$ T cell responses.

These studies provide a mechanistic explanation for the involvement of type I IFNs — exogenous administration of which has shown efficacy in the treatment of patients with cancer — in antitumour immune responses.

Olive Leavy

ORIGINAL RESEARCH PAPERS Diamond, M. S. *et al.* Type I interferon is selectively required by dendritic cells for immune rejection of tumors. *J. Exp. Med.* **208**, 1989–2003 (2011) | Fuertes, M. B. *et al.* Host type I IFN signals are required for antitumor CD8$^+$ T cell responses through CD8α$^+$ dendritic cells. *J. Exp. Med.* **208**, 2005–2016 (2011)