Nature Reviews Immunology | AOP, published online 20 August 2010; doi:10.1038/nri2838

TUMOUR IMMUNOLOGY

Tumours support the T cell response

Although several studies have shown that naive CD8$^+$ T cells can become activated in the tumour-draining lymph nodes during tumour outgrowth, whether naive CD8$^+$ T cells are activated in the tumour mass itself remains to be established. Now Thompson and colleagues show that naive tumour-specific CD8$^+$ T cells can infiltrate the tumour where they are activated, acquire an effector phenotype and proliferate in response to a specific antigen.

Tumours were established in mice using B16-ovalbumin (OVA) melanoma cells (which present OVA_{257} peptide in an MHC class I-dependent manner). Following transfer of naive OT-I T cell receptor-transgenic T cells (which recognize the OVA_{257} epitope), activated OT-I T cells, which were characterized by expression of CD25 and CD69, were found in the tumours; the authors also showed this in two other tumour models and with T cells specific for an endogenous tumour antigen. To directly show that OT-I T cells were activated in the tumour and not in the draining lymph nodes, lymph node development was inhibited in mice *in utero*. Whereas only naive OT-I T cells were present in the bone marrow, liver and lungs of these mice, activated OT-I T cells were found within tumours, both in a perivascular arrangement and in the parenchyma, showing that naive T cells infiltrate tumours.

Following treatment with the inhibitor FTY720, which blocks the migration of T cells out of lymph nodes, a significant number of divided tumour-specific T cells were still present in the tumours of FTY720-treated animals. A decrease in the number of divided OT-I T cells in non-draining lymph nodes compared with untreated controls was observed. However, this decrease was significantly greater than the decrease in the tumour, suggesting that intratumoral OT-I T cells did not arise in the draining lymph node. This was confirmed in lymph node-depleted mice; the size of the OT-I T cell population in the tumours of these mice was the same as in FTY720-treated animals with lymph nodes, suggesting that tumours can, without draining lymph node support, mediate CD8$^+$ T cell activation and proliferation.

Does intratumoral activation of naive CD8$^+$ T cells correlate with the generation of functional effector CD8$^+$ T cells? Following *ex vivo* culture with OVA_{257} peptide-pulsed stimulators, a significant number of OT-I T cells purified from B16-OVA tumours of FTY720-treated mice secreted interferon-γ (IFNγ) and expressed granzyme B and CD107a, which are markers of cytotoxic activity. Furthermore, the cells retained their functionality *in vivo* despite potential exposure to suppressive factors in the tumour microenvironment.

Finally, the authors attempted to identify whether cross-presentation by antigen-presenting cells (APCs) or direct presentation by tumour cells mediates CD8$^+$ T cell activation. By using B16-F1 tumour cells, which express tyrosinase but lack the MHC class I molecule required to present the tyrosinase epitope (Tyr_{369}), it was shown that Tyr_{369}-specific CD8$^+$ T cells upregulated CD25 and CD69 and could proliferate, degranulate and secrete IFNγ, supporting a role for cross-presentation by APCs. In addition, using chimeric animals in which bone marrow-derived populations cannot present OVA_{257}, OT-I T cell activation, proliferation and acquisition of effector function was similar to that in wild-type animals, providing evidence for direct presentation by tumour cells. Thus, the data show that both APCs and tumour cells have a role in CD8$^+$ T cell activation in tumours.

So, tumours support the infiltration, activation, effector differentiation and proliferation of naive CD8$^+$ T cells and, consequently, intratumoral CD8$^+$ T cell activation may be a target for cancer immunotherapy.

Karen Irving

ORIGINAL RESEARCH PAPER Thompson, E. D., Enriquez, H. L., Fu, Y. X. & Engelhard, V. H. Tumour masses support naive T cell infiltration, activation, and differentiation into effectors. *J. Exp. Med.* **207**, 1791–1804 (2010)