TUMOUR IMMUNOLOGY

Editorial selection demystified

GETTY

> these studies emphasize the importance of key, dominant antigens in cancer immunoediting

The immune system can eliminate immunogenic tumour cells, but such immune reactivity may lead to the somatic evolution of tumours so that they are no longer recognized by the immune system. This process is known as cancer immunoediting, but the tumour antigens and immune mechanisms that underlie this remain poorly understood. Two new studies show that immunoediting can be triggered by strongly immunogenic tumour antigens and that $CD8^+$ T cell-mediated clearance of antigenic tumour cells is involved.

The studies used different approaches to dissect the details of immunoediting. Tyler Jacks and colleagues used a mouse model of sarcoma in which tumorigenesis was driven by Cre recombinase-triggered activation of the *Kras*^{G12D} oncogene and inactivation of the *Trp53* tumour suppressor gene. The authors monitored the incidence and progression of sarcomas both in wild-type mice and in immunocompromised *Rag2*$^{-/-}$ mice. To understand the contribution of antigens that induce a strong T cell response, they induced tumorigenesis using either a lentivirus that only expressed Cre (Lenti-x) or a lentivirus that expressed Cre and three immunogenic peptides (Lenti-LucOS). Fewer tumours were established in wild-type mice that were injected with Lenti-LucOS than in wild-type mice injected with Lenti-x. T cells specific for the immunogenic peptides could be isolated from the Lenti-LucOS-injected mice and, using antibody-mediated depletion of T cells, the authors showed that T cells promoted the increased tumour elimination in these mice. By contrast, almost all *Rag2*$^{-/-}$ mice that were injected with either Lenti-LucOS or Lenti-x developed similar tumour burdens.

Next, the authors examined tumour evolution by transplanting tumours from wild-type or *Rag2*$^{-/-}$ mice into naive wild-type recipients. Whereas Lenti-LucOS-induced sarcomas from *Rag2*$^{-/-}$ mice were rejected after transplantation, Lenti-LucOS sarcomas that developed in wild-type mice were not rejected. This indicates that immunoediting selects for tumour cells that no longer provoke a T cell response. Consistent with this, Lenti-LucOS-induced tumours that had developed in or were transplanted through immunocompetent mice lost expression or presentation of the immunogenic peptides.

Robert Schreiber and colleagues investigated which tumour-intrinsic antigens trigger immunoediting in a methylcholanthrene-induced mouse model of sarcoma. From an 'unedited' tumour that had developed in a *Rag2*$^{-/-}$ host, the authors generated immunoedited escape variants by transplanting the tumour through wild-type mice. They further subcloned the unedited tumour into highly immunogenic clones that were rejected when transplanted into wild-type mice and into less-immunogenic clones that survived transplantation. Reasoning that tumour-specific mutant proteins (neoantigens) might be the key immunogenic antigens, the authors used high-throughput cDNA sequencing to identify candidate neoantigens. They then used computational algorithms to focus on those neoantigens that were most likely to be presented to $CD8^+$ T cells. Expression of only ~1% of putative neoantigens was lost by tumour cells following immunoediting, and one of these putative neoantigens was an R913L mutant of spectrin-β2. As evidence for its functional relevance, R913L-peptide-specific $CD8^+$ T cells were found in wild-type mice that were transplanted with unedited tumour cells but not in wild-type mice transplanted with immunoedited tumour cells. Could this antigen alone be sufficient to trigger an antitumour immune response? In wild-type mice, but not in *Rag2*$^{-/-}$ recipients, forced expression of the R913L peptide caused the rejection of immunoedited tumours. Moreover, wild-type mice transplanted with mixed tumour cell populations became selectively depleted of R913L-peptide-expressing tumour cells.

It is noteworthy that both of these studies emphasize the importance of key, dominant antigens in cancer immunoediting. It will be interesting to see which antigens are most relevant in tumours of other tissue types, as well as in humans. Importantly, such knowledge could inform immunotherapy strategies.

Darren J. Burgess,
Assistant Editor, Nature Reviews Cancer

ORIGINAL RESEARCH PAPERS DuPage, M. *et al.* Expression of tumour-specific antigens underlies cancer immunoediting. *Nature* **482**, 405–409 (2012) | Matsushita, H. *et al.* Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. *Nature* **482**, 400–404 (2012)

This article is modified from the original in *Nature Rev. Cancer* (doi:10.1038/nrc3251).