TUMOUR IMMUNOGENICITY

Editorial selection demystified

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> immunoediting selects for tumour cells that no longer provoke a T cell-mediated immune response

Cancer immunoediting is the process by which the immune system protects the host from tumour development and guides the somatic evolution of tumours by eliminating highly immunogenic tumour cells. However, the tumour antigens and immune mechanisms that underlie this process remain poorly understood. Two new studies show that immunoediting can be triggered by strongly immunogenic tumour antigens and that it involves the $CD8^+$ T cell-mediated clearance of antigenic tumour cells.

The studies used different approaches to dissect the details of immunoediting. Tyler Jacks and colleagues monitored the incidence and progression of $Kras^{G12D}$;$Trp53^{-/-}$-driven sarcomas both in immunocompetent mice and in immunocompromised $Rag2^{-/-}$ mice. To understand the contribution of antigens that induce a strong T cell response, the authors modified a lentivirus that only expressed Cre (Lenti-x) by introducing three immunogenic peptides fused to the carboxyl terminus of luciferase (Lenti-LucOS); they injected the lentiviruses into the muscle to activate $Kras^{G12D}$ and to inactivate *Trp53*. Tumour establishment was significantly impaired in the immunocompetent mice that were injected with Lenti-LucOS.

As $Rag2^{-/-}$ mice lack both T cells and B cells, the authors used antibody depletion of T cells to show that a loss of T cells in wild-type mice enabled the growth of LucOS-expressing sarcomas. In addition, $CD8^+$ T cells that were specific for the LucOS peptides were isolated from mice injected with Lenti-LucOS, including mice that did not develop overt tumours. Only Lenti-LucOS-induced sarcomas, but not Lenti-x-induced sarcomas, from $Rag2^{-/-}$ mice were rejected after transplantation into immunocompetent mice, whereas Lenti-LucOS sarcomas that developed in immunocompetent mice and that were transplanted into immunocompetent mice were not rejected. This indicates that immunoediting selects for tumour cells that no longer provoke a T cell-mediated immune response. Consistent with this, LucOS tumours that had developed in or that were transplanted through immunocompetent mice showed a loss of LucOS peptide expression or presentation.

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 tumours by transplantation through wild-type mice; they also subcloned the unedited tumour into highly immunogenic clones that were rejected when transplanted into wild-type mice and less-immunogenic clones that survived transplantation. Reasoning that tumour-specific mutant proteins (neoantigens) might be the key tumour-rejection antigens, the authors used high-throughput cDNA sequencing to identify expressed neoantigens genome-wide in various clones and escape tumours, and they used computational algorithms to focus on those that were most likely to be presented to $CD8^+$ T cells. Expression of only ~1% of putative neoantigens was lost 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 with edited tumour cells. Could this antigen alone be sufficient to trigger an anti-tumour immune response? In wild-type but not in $Rag2^{-/-}$ recipients, forced expression of the R913L peptide caused the rejection of immunoedited tumours, and transplanted mixed-cell populations became selectively depleted of R913L-peptide-expressing cells.

Despite vastly different mutational loads, it is noteworthy that both mouse models 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 and in humans, and whether such knowledge could inform immunotherapy strategies.

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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)