ddhCTP-incorporated RNA did not support further extension of the RNA template. This ex vivo action of ddhCTP as a chain terminator was also shown for RdRps from other members of the flavivirus family, namely West Nile virus, Zika virus and hepatitis C virus. In cell-based experiments, synthetic ddhC nucleoside inhibited the replication of various strains of Zika virus in a mammalian cell line.

To the authors' knowledge, this is the first example of a human protein that produces a direct inhibitor of viral replication, although they do not rule out that viperin has other antiviral functions. Cell viability was not affected by the addition of ddhC, which shows that mammalian DNA and RNA polymerases are not susceptible to ddhC-mediated premature chain termination.

*Kirsty Minton*

**ORIGINAL ARTICLE** Gizzi, A. S. et al. A naturally occurring antiviral ribonucleotide encoded by the human genome. *Nature* https://doi.org/10.1038/s41586-018-0238-4 (2018)

exposure to CGRP and IL-33. Exposure to GABA had little effect on ILC2s. Instead, GABA was shown to target goblet cells, as mice with a defect in GABA production by PNECs did not develop goblet cell hyperplasia following OVA challenge, yet induced type 2 immune responses similar to controls.

Confirming the key roles for PNEC-derived CGRP and GABA, the authors showed that intratracheal administration of CGRP and GABA was sufficient to restore allergic responses in PNEC-deficient mice following OVA challenge. Finally, antibody staining of lung sections showed an expansion of PNECs and a greater proportion of CGRP$^+$ PNECs in patients with asthma than in controls, suggesting that the findings in mice may be relevant to humans.

So, PNECs and ILC2s establish a neuroimmunological module to respond to environmental stimuli and represent new targets for treating allergic lung diseases.

*Lucy Bird*

**ORIGINAL ARTICLE** Sui, P. et al. Pulmonary neuroendocrine cells amplify allergic asthma responses. *Science* **360**, eaan8546 (2018)

IMMUNOTHERAPY

# Tumour decides immune cell ins and outs

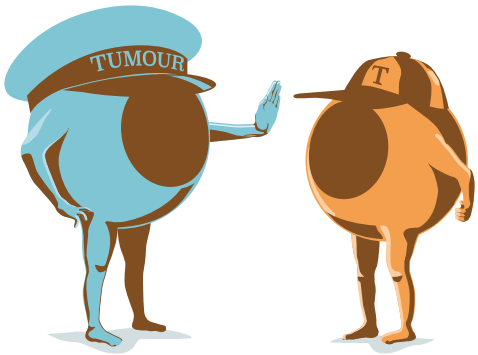
The extent to which a tumour is infiltrated with immune cells can determine the outcome of immunotherapy. Now, Li et al. report that tumour cell-intrinsic factors underlie the heterogeneity in the immune landscape of tumours as well as the response to immunotherapy of pancreatic ductal adenocarcinoma (PDA).

Quantification of CD8$^+$ T cells and total T cells in resected tumours from patients with PDA and those from a mouse model of PDA (KPC mice) showed that T cell abundance varied greatly: tumours could be categorized as 'T cell high' (T cell$^{hi}$) or 'T cell low' (T cell$^{low}$). After establishing a library of congenic tumour cell clones from a collection of mouse PDAs, individual clones were implanted into healthy mice and the tumours they formed had similar immune microenvironments to the tumours from which they were derived, indicating that the tumour immune microenvironment is transplantable. Interestingly, T cell$^{hi}$ tumours tended to have a higher number of dendritic cells (DCs) and a lower number of myeloid cells than T cell$^{low}$ tumours. Further analysis revealed that the difference in immune cell infiltration was likely not due to the mutational burden, site of injection or host microbiome.

The authors then determined whether the difference in T cell infiltration influenced the response of primary tumours to a chemotherapy–immunotherapy combination — T cell$^{low}$ tumours were minimally affected, whereas mice with T cell$^{hi}$ tumours had improved survival and their tumours showed marked regression. Most (75%) T cell$^{hi}$ tumours were cleared by combination therapy, whereas no T cell$^{low}$ tumours were cleared. Importantly, when mice cured of a T cell$^{hi}$ tumour were challenged with a different T cell$^{hi}$ clone or with a T cell$^{low}$ clone, tumour growth was reduced by combination therapy, suggesting that tumour clones have shared tumour antigens that are recognized by infiltrating T cells.

Next, the authors analysed the immune cell populations of T cell$^{hi}$ and T cell$^{low}$ tumours. CD8$^+$ T cells in T cell$^{hi}$ tumours had higher expression of markers of activated or antigen-experienced T cells, such as PD1, CD44, LAG3, CTLA4, TIM3 and NUR77, than those in T cell$^{low}$ tumours, although functional activity was not higher. For clones with similar T cell infiltration levels, the efficacy of combination therapy correlated with the proportion of PD1$^+$CD8$^+$ T cells in the tumours they formed, suggesting that this proportion determines the response to combination therapy.

Cross-presenting (CD103$^+$) DCs are crucial for tumour immunity and, indeed, their abundance




Credit: Simon Bradbrook/Springer Nature Limited

correlated with CD8$^+$ T cell number across tumour clones. Importantly, PDA tumours established in mice lacking CD103$^+$ DCs almost completely lacked CD8$^+$ T cells. Further analysis suggested that CXCR3 was necessary for bulk CD8$^+$ T cell recruitment to tumours, but PD1$^+$CD8$^+$ T cells were present and able to drive tumour responses after therapy when used in combination with CXCR3 blockade. Additionally, T cell$^{low}$ tumours promoted an increase in circulatory myeloid cells, although contralateral injection experiments established that the systemic factors presumably responsible for this expansion did not alter the tumour microenvironment (TME) of T cell$^{hi}$ tumours. By contrast, co-injection of T cell$^{hi}$ and T cell$^{low}$ clones at the same site showed that T cell$^{low}$ tumour cells acted dominantly to locally suppress T cell infiltration into the tumour.

As secreted factors seemed to mediate immune suppression, examination of chemokine expression established that *Cxcl1* was the most differentially expressed chemokine in T cell$^{hi}$ and T cell$^{low}$ tumours, which was shown by epigenomic analysis to be due to a more accessible *Cxcl1* promoter region and enrichment of an active histone mark in T cell$^{low}$ tumour cells. Further experiments suggested that tumour cell-derived CXCL1 promotes the recruitment of suppressive myeloid cells into tumours, which suppresses T cell infiltration, contributing to immunotherapy resistance.

Finally, the authors identified additional factors (for example, CSF3) that affect immune cell infiltration into the TME. Their new experimental system should prove highly useful for identifying additional mechanisms underlying tumour immune heterogeneity.

*Grant Otto*

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