
Credit: Thamrongpat Theerathammakorn/Alamy

leukaemia models with low levels of antigen expression — which is thought to be a limiting factor for CAR T cell therapy in human leukaemia — JUN overexpression also increased the antitumour efficacy of CAR T cells. Furthermore, JUN overexpression increased the proliferation of CAR T cells with two different specificities in an osteosarcoma model and increased long-term survival. Importantly, CAR T cells have not yet induced a sustained response to solid tumours in humans.

The results therefore support the clinical testing of JUN-overexpressing CAR T cells. JUN has not been described as an oncogene in mature T cells and there was no evidence of T cell transformation in this study, but the use of a JUN mutant that is defective for transcriptional activation, which is not required to overcome exhaustion, could alleviate some safety concerns.

Kirsty Minton

ORIGINAL ARTICLE Lynn, R. C. et al. c-Jun overexpression in CAR T cells induces exhaustion resistance. *Nature* **576**, 293–300 (2019)
RELATED ARTICLE Blank, C. U. et al. Defining 'T cell exhaustion'. *Nat. Rev. Immunol.* **19**, 665–674 (2019)

Credit: Simon Bradbrook/Springer Nature Limited

of glycolysis, the pentose phosphate pathway and the Krebs cycle. Most prominently, PD1-deficient myeloid cells showed an accumulation of cholesterol. Because cholesterol is required for the differentiation of inflammatory macrophages and DCs and promotes their antigen-presenting function, this may explain how metabolic reprogramming of emergency myelopoiesis by PD1 blockade promotes antitumour immunity. Consistent with this idea, myeloid cell-specific *Pdcd1* deletion did not have a quantitative effect on T cells responding to a tumour but it enhanced their anti-tumour function, including the generation of more effector memory T cells producing both interferon-γ and interleukin-17, despite preserved PD1 expression on T cells. In addition, DCs isolated from *Pdcd1*$^{-/-}$ mice bearing B16-F10 melanomas more efficiently induced antigen-specific T cell proliferation and interferon-γ production in vitro than DCs from wild-type tumour-bearing mice.

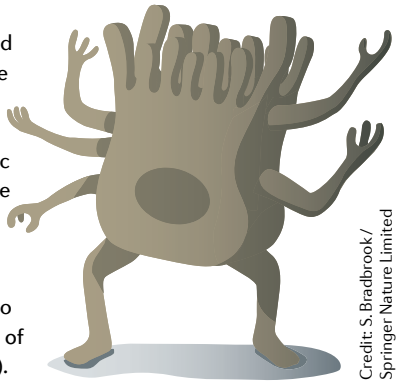
This paper highlights the importance of myeloid cell-intrinsic PD1 in regulating tumour-driven myeloid cell fate, function and metabolism and suggests that this pathway might be a key mechanism of successful immune checkpoint blockade.

Lucy Bird

ORIGINAL ARTICLE Strauss, L. et al. Targeted deletion of PD-1 in myeloid cells induces antitumor immunity. *Sci. Immunol.* **5**, eaay1863 (2020)

INFLAMMATION

Bad mutants in IBD


Credit: S. Bradbrook / Springer Nature Limited

Self-renewing cells acquire mutations and some of these provide survival advantages, leading to the emergence of somatic clones that contribute to tumorigenesis. Nanki et al. now report that such somatic evolution also occurs in the context of ulcerative colitis (UC). They show that the UC epithelium accumulates loss-of-function and gain-of-function somatic mutations in genes that provide resistance to IL-17A-mediated apoptosis.

The authors established colorectal organoids from patients with UC and healthy controls, focusing on left-sided UC in order to establish uninflamed (UC^{uninf}) and inflamed (UC^{inf}) organoids from the same donor. Notably, unlike in healthy or UC^{uninf} organoids, UC^{inf} organoids acquired recurrent truncating mutations in genes related to the IL-17–NF-κB signalling pathway. In UC^{inf} organoids, truncating mutations were identified in *NFKBIZ* and *PIGR*, which encode the NF-κB regulator IκBζ and the polymeric immunoglobulin receptor, respectively, as well as in *TRAF3IP2*, which encodes an adaptor that is essential for activation of NF-κB downstream of the IL-17 receptor. Further studies identified a *ZC3H12A*^{S438L} mutation in several UC^{inf} organoids; notably, this mutation led to gain of function in ZC3H12A, an RNA-binding protein that helps to dismantle the mRNAs of inflammatory genes, including *NFKBIZ* and *IL17RA*.

Using CRISPR-based knockout screening in colon organoids, the authors showed that the mutations identified in the UC^{inf} organoids confer resistance to IL-17A-mediated cytotoxicity. This suggests that IL-17A is detrimental to the epithelial lining and that epithelial cells that acquire resistance to IL-17A have a selective advantage in tissue affected by UC. Exploration of the cytotoxic mechanism involved indicated that IL-17A induces pro-apoptotic signals that affect the superficial layer of the epithelium via the induction of inducible nitric oxide synthase and nitric oxide.

This study shows that in patients with ulcerative colitis, the epithelium can accrue mutations affecting the IL-17 signalling pathway that are irrelevant for tumorigenesis but that enable the selective expansion of mutant clones under inflammatory conditions. Notably, some of the genetic mutations identified in this study are linked to worse colitis in mouse models; therefore, the authors suggest that extensive expansion of mutant clones may exacerbate inflammatory bowel disease.

Yvonne Bordon

ORIGINAL ARTICLE Nanki, K. et al. Somatic inflammatory gene mutations in human ulcerative colitis epithelium. *Nature* https://doi.org/10.1038/s41586-019-1844-5 (2019)