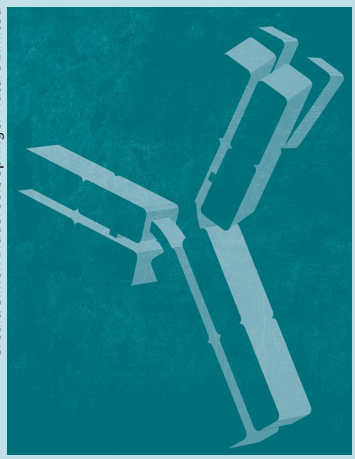
Indeed, the TOX2 target genes were overlapping with, but not the same as, the target genes of BCL-6 and other factors involved in T_{FH} cell differentiation such as IRF4 and BATF.

Further evidence of the in vivo relevance of TOX2 for T_{FH} cell differentiation was provided by *Tox2*$^{-/-}$ mice, which had decreased frequencies of T_{FH} cells and GC B cells after immunization compared with wild-type mice. Co-transfer experiments showed that this phenotype is intrinsic to TOX2-deficient CD4$^+$ T cells and could be rescued by exogenous TOX2 expression in these cells.

Thus, the results indicate that TOX2, which is induced downstream of BCL-6, can bind to and increase chromatin accessibility and gene expression at a set of T_{FH} cell-associated genes, including *Bcl6* itself. This feedforward loop drives T_{FH} cell development.

Kirsty Minton

ORIGINAL ARTICLE Xu, W. et al. The transcription factor Tox2 drives T follicular helper cell development via regulating chromatin accessibility. *Immunity* https://doi.org/10.1016/j.immuni.2019.10.006 (2019)



Credit: Simon Bradbrook/Springer Nature Limited

two signals to T cells while simultaneously directing them to cancer cells. Moreover, the flexibility of the format should allow the targeting of any cancer surface antigen or a combination of antigens, as well as the precise stimulation of immunomodulatory signals.

Alexandra Flemming

ORIGINAL ARTICLE Wu, L. et al. Trispecific antibodies enhance the therapeutic efficacy of tumour-directed T cells through T cell receptor co-stimulation. *Nat. Cancer* https://doi.org/10.1038/s43018-019-0004-z (2019)

NEUROIMMUNOLOGY

T cells with fragmented mitochondria frazzle the mind

Credit: Simon Bradbrook/Springer Nature Limited

There is a growing appreciation of the link between the immune system and mental health. Reporting in *Cell*, Fan et al. have found that mice lacking CD4$^+$ T cells are protected against stress-induced anxiety-like behaviours.

To begin with, the authors exposed mice to an electronic foot shock (ES) model of acute stress. ES induced anxiety-type behaviour in wild-type mice, as measured by their reduced exploration and locomotion, but did not have this effect on *Rag*$^{-/-}$ mice, which lack lymphocytes. Notably, antibody-mediated depletion of CD4$^+$ T cells (but not CD8$^+$ T cells) protected wild-type mice against ES-induced anxiety behaviours. Moreover, CD4$^+$ T cell depletion prevented anxiety-type behaviours in a model of chronic ES stress and in an acute restraint stress model. Adoptive transfer of CD4$^+$ T cells from ES-treated mice induced anxiety behaviour in *Rag*$^{-/-}$ mice and, surprisingly, naive CD4$^+$ T cells induced greater anxiety than effector CD4$^+$ T cells. Therefore, CD4$^+$ T cells influence the development of anxiety behaviours in various mouse models of stress, independently of their activation status.

The authors next assessed differentially expressed genes (DEGs) in naive CD4$^+$ and CD8$^+$ T cells isolated from non-treated or ES-treated mice. They identified 128 DEGs that were specific to the ES-treated CD4$^+$ T cells and a large number of these encoded mitochondrial proteins. Further analyses showed that ES-treated naive CD4$^+$ T cells showed severely reduced levels of glycolysis and oxidative phosphorylation and had short, fragmented (punctate) mitochondria. The authors examined the role of various neurotransmitters, hormones and arachidonic acid (AA) metabolites that have been previously linked to depression and anxiety; these experiments suggested that the AA metabolite leukotriene B4 (LTB4) is upregulated in response to stress and can promote anxiety-type behaviours by inducing mitochondrial fission in CD4$^+$ T cells.

To further explore a link between mitochondrial fission and anxiety behaviours, the authors generated mice lacking the mitochondrial fusion protein mitoguardin 2 (MIGA2). The mitochondria in the naive CD4$^+$ T cells of these mice were highly fragmented and, strikingly, the animals showed decreased locomotor activity, social motivation and curiosity, and increased fear. As in the ES models, depletion of CD4$^+$ T cells alleviated these anxiety-type behaviours. Moreover, mice with a T cell conditional knockout of MIGA2 (MIGA2^{TKO} mice) or that lacked mitochondrial fusion proteins mitofusin 1 (MFN1) and (MFN2) in T cells also developed anxiety-type behaviours. Thus mitochondrial fragmentation in CD4$^+$ T cells seems to be a general inducer of anxiety.

The authors found that purines and their derivatives, including adenine, hypoxanthine and xanthine, were 10–100 times more abundant in the serum of MIGA2^{TKO} mice than wild-type mice. They identified a role for excessive xanthine in particular in driving anxiety-type behaviours and found that xanthine produced by CD4$^+$ T cells can accumulate in the brain and trigger the proliferation of oligodendrocytes in the left amygdala, a region of the brain that has been linked with anxiety and stress-related psychiatric disorders.

Finally, they showed that mitochondrial fission promotes the de novo synthesis of xanthine in CD4$^+$ T cells by shifting glucose flow to the pentose phosphate pathway. Notably, treatment of MIGA2^{TKO} mice with the glucose analogue 2-deoxy-D-glucose (2-DG; which inhibits glucose catabolism and de novo purine synthesis) alleviated their anxiety-type behaviours. Mitochondrial fission was further shown to induce excessive xanthine production in T cells by promoting the accumulation of IRF1, a transcriptional activator of xanthine dehydrogenase. Indeed, MIGA2^{TKO} mice that also lacked IRF1 expression in T cells were protected against anxiety-type behaviours.

These findings suggest a model in which stress-induced LTB4 drives mitochondrial fission in CD4$^+$ T cells, leading to the upregulation of xanthine that can trigger anxiety behaviours by stimulating oligodendrocytes in the left amygdala of the brain. The mechanism by which LTB4 affects mitochondrial morphology remains to be determined, but the authors propose that this pathway could be targeted in various psychiatric and metabolic diseases.

Yvonne Bordon

ORIGINAL ARTICLE Fan, K.-Q. et al. Stress-induced metabolic disorder in peripheral CD4$^+$ T cells leads to anxiety-like behavior. *Cell* **179**, 864–879 (2019)