mutations in mature GCs. Multiple mechanisms, including lack of GLT expression and downregulation of the enzyme APE1, likely a target of the transcriptional repressor BCL-6, were proposed to contribute to the repression of CSR in GC B cells.

Interestingly, in silico analysis of CSR and SHM suggested that the determination of the isotype before the GC phase of intense B cell selection and proliferation promotes isotype diversity, whereas ongoing switching in GCs would homogenize the isotype distribution and would be incompatible with the observation of IgM-dominated GCs. The authors also point out that restricting CSR from GCs reduces the risk of GC B cells carrying pathogenic double-stranded breaks becoming long-lived. It also allows production of IgM memory B cells that can switch to protective isotypes upon encounter with antigenically related pathogens.

Alexandra Flemming

ORIGINAL ARTICLE Roco, J. A. et al. Class-switch recombination occurs infrequently in germinal centers. *Immunity* https://doi.org/10.1016/j.immuni.2019.07.001 (2019)

a PLGF–STAT3 axis favours the differentiation of disease-causing T_H17 cells at the expense of homeostasis-maintaining T_{reg} cells.

Yoo et al. used models of delayed-type hypersensitivity and experimental autoimmune encephalomyelitis in *Plgf*-transgenic and *Plgf*-knockout mice to show that this signalling axis is relevant to T_H17 cell-mediated diseases in vivo. Furthermore, they showed that human T cells also produce IL-17 in response to PLGF. In synovial fluid samples of patients with rheumatoid arthritis, levels of PLGF production by $CD4^+$ T cells correlated with levels of IL-17, particularly in patients with low levels of IL-6 in synovial fluid. This study outlines a positive feedback loop between angiogenesis and autoimmunity mediated by T_H17 cell production of PLGF, which might therefore be a new therapeutic target.

Kirsty Minton

ORIGINAL ARTICLE Yoo, S.-A. et al. Placental growth factor regulates the generation of T_H17 cells to link angiogenesis with autoimmunity. *Nat. Immunol.* https://doi.org/10.1038/s41590-019-0456-4 (2019)

REGULATORY T CELLS

A metabolic peace process

In humans, loss-of-function mutations in the key regulatory T (T_{reg}) cell transcription factor FOXP3 lead to the severe autoimmune disease IPEX (imunodysregulation, polyendocrinopathy, enteropathy, X-linked). A recent study suggests that T_{reg} cell function could be restored in such patients by targeting the mTOR pathway.

Although T_{reg} cells still develop in the thymus of FOXP3-deficient patients and mice, they show defective suppressive activity and acquire effector-like functions. Charbonnier et al. reasoned this could be linked to altered cell metabolism, as effector T cells show several metabolic changes, including an increase in aerobic glycolysis and oxidative phosphorylation (OXPHOS). The authors generated a *Foxp3*$^{\Delta EGFPiCre}$ knock-in mouse system that allowed for the co-deletion of other molecules in FOXP3-deficient T_{reg} cells. Similarly to other FOXP3-deficient strains, male mice hemizygous for the *Foxp3*$^{\Delta EGFPiCre}$ allele were runted and died early from autoimmune lymphoproliferative disease. Compared with control T_{reg} cells, the FOXP3-deficient T_{reg} cells from *Foxp3*$^{\Delta EGFPiCre}$ mice showed increased activation of the mTOR pathway, which is crucial for supporting effector T cell metabolism and function.

The mTOR kinase is the catalytic subunit of two distinct complexes; mTORC1 and mTORC2. The authors therefore generated mice in which FOXP3-deficient T_{reg} cells also lacked RAPTOR and/ or RICTOR, which are key components of mTORC1 and mTORC2, respectively. Mice with T_{reg} cells deficient in both FOXP3 and RICTOR still showed lymphoproliferation but had less tissue inflammation, increased body weight and better survival compared with mice with FOXP3-deficient T_{reg} cells. By contrast, deletion of RAPTOR or both RAPTOR and RICTOR in FOXP3-deficient T_{reg} cells did not ameliorate disease. However, mice with RAPTOR-deficient FOXP3-deficient T_{reg} cells showed a reversal of the T_{reg} cell population expansion seen in *Foxp3*$^{\Delta EGFPiCre}$ mice. Therefore, mTORC1 seems to support the population expansion of FOXP3-deficient T_{reg} cells in *Foxp3*$^{\Delta EGFPiCre}$ mice, whereas mTORC2 drives the dysregulation of FOXP3-deficient T_{reg} cells that causes inflammatory disease.

Indeed, RICTOR deficiency in FOXP3-deficient T_{reg} cells restored their suppressor functions and reversed the upregulation in T helper 1 (T_H1) cell-type effector activity. RICTOR deficiency also enhanced regulatory functions in FOXP3-sufficient T_{reg} cells but did not cause effector T cells to acquire suppressive functions.

Transcriptomics indicated that RICTOR deficiency in FOXP3-deficient T_{reg} cells is associated with the upregulation of a core set of T_{reg} cell-associated genes, including *Il10*, and with the suppression of genes linked to effector T cell function. Notably, neutralization of IL-10 abrogated the improved suppressor activity of RICTOR-deficient FOXP3-deficient T_{reg} cells. Further experiments indicated that the improved suppressor functions seen in RICTOR-deficient FOXP3-deficient T_{reg} cells were largely dependent on the activity of FOXO1, which is an important negative regulator of the T_H1 cell programme.

Metabolic analyses indicated that FOXP3-deficient T_{reg} cells had increased expression of enzymes linked with the glycolytic and pentose phosphate pathways and showed an increase in glycolysis and OXPHOS; concurrent RICTOR deficiency reversed most of these changes. Moreover, deletion of the bifunctional enzyme PFKFB3 — a potent stimulator of glycolysis — in FOXP3-deficient T_{reg} cells had a similar effect to RICTOR deletion in restoring their capacity to suppress T_H1 cell-type immune responses, although unlike RICTOR deficiency it did not restore the capacity of FOXP3-deficient T_{reg} cells to suppress effector T cell proliferation. Loss of both PFKFB3 and RICTOR from FOXP3-deficient T_{reg} cells did not have an additive effect, confirming aerobic glycolysis as a common target of both interventions; therefore, mTORC2-dependent metabolic dysregulation, including increases in glycolysis and OXPHOS, may drive distinct facets of the regulatory dysfunction in FOXP3-deficient T_{reg} cells.

> “targeting mTOR could improve T_{reg} cell functions not only in patients with IPEX but in patients with other autoimmune or inflammatory diseases”

Importantly, the authors found that T_{reg} cells from patients with IPEX also showed increased glycolytic activity. Although T_{reg} cells from these patients do not normally suppress effector T cell proliferation in vitro, pretreatment with an mTOR inhibitor enabled this suppressive capacity. Furthermore, mTOR inhibitors were found to heighten the suppressive functions of FOXP3-sufficient T_{reg} cells from control individuals. Therefore, targeting mTOR could improve T_{reg} cell functions not only in patients with IPEX but in patients with other autoimmune or inflammatory diseases not associated with FOXP3 deficiency.

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ORIGINAL ARTICLE Charbonnier, L.-M. et al. Functional reprogramming of regulatory T cells in the absence of Foxp3. *Nat. Immunol.* https://doi.org/10.1038/s41590-019-0442-x (2019)