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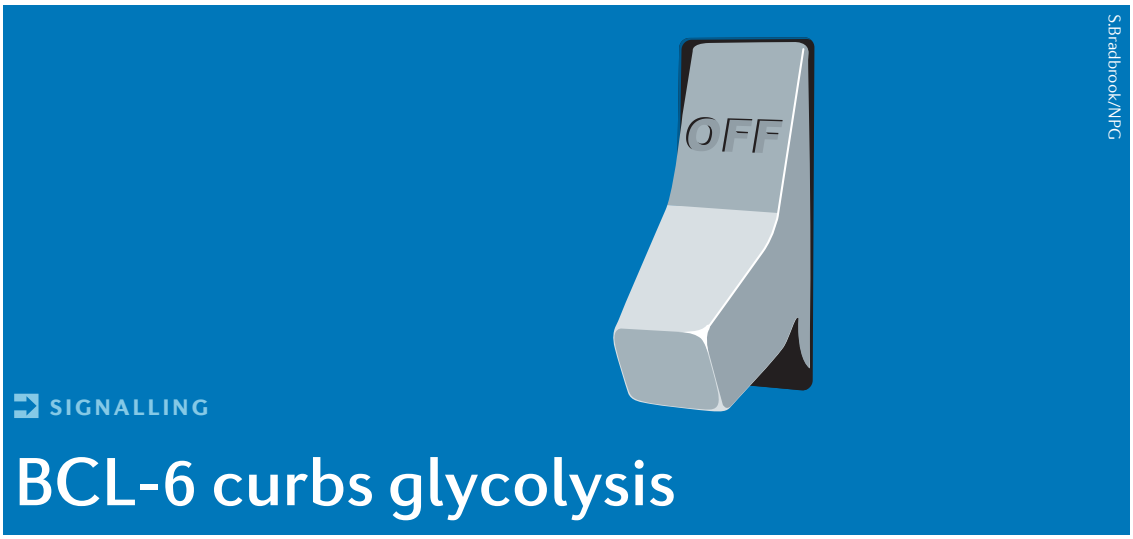

SIGNALLING

BCL-6 curbs glycolysis

The metabolic state of lymphocytes influences their function, with effector T cells using the glycolytic pathway and memory T cells switching to fatty acid oxidation. Many of the molecular events that induce glycolysis in effector T cells have been described, but less is known about the factors that repress it in memory T cells. Reporting in *Nature Immunology*, Weinmann and colleagues show that the transcription factor BCL-6 suppresses the expression of a subset of important glycolytic genes and that the molecular balance between the T helper 1 (T_H1) cell lineage-specifying factor, T-bet, and BCL-6 influences the metabolic gene programme of the cell.

> BCL-6 was shown to dominantly repress the promoter activity and expression of key glycolytic genes

One of the many roles of BCL-6 is in promoting the development of memory cells from both $CD4^+$ and $CD8^+$ effector T cells. High environmental concentrations of interleukin-2 (IL-2) reduce BCL-6 expression, whereas low concentrations of IL-2 promote BCL-6 expression. In addition, high levels of IL-2 promote the expression of genes encoding glycolytic molecules. But are these two pathways functionally linked and if so, how?

Here, the authors showed that the expression of BCL-6 was inversely correlated with the expression of a subset of IL-2-sensitive glycolytic genes in both $CD8^+$ cytotoxic T cells and $CD4^+$ T_H1 cells. Using several different experimental approaches, BCL-6 was shown to dominantly repress the promoter activity and expression of key glycolytic genes — including genes that encode glycolytic enzymes and transporters — in primary T_H1 cells in the presence of low IL-2 concentrations. Furthermore, enforced expression of BCL-6 in T cells stimulated with high levels of IL-2 repressed the expression of glycolytic genes. These data indicate that BCL-6 directly suppresses the activation of an IL-2-sensitive glycolytic transcriptional programme, which suggests that the upregulation of BCL-6 under conditions of diminishing IL-2 — as occurs near the termination of an immune response — may initiate the transition of effector T cells to memory T cells.

Previous studies have shown that in T_H1 cells, T-bet can form a complex with BCL-6, thereby repressing its activity. Here, the authors showed that the expression of many BCL-6-target genes encoding glycolytic molecules was lower in T-bet-deficient T_H1 cells than in wild-type cells. Furthermore, lactate production (a readout of glycolysis) was lower in T-bet-deficient cells than in wild-type T cells cultured in the presence of high concentrations of IL-2. These data suggest that T-bet is required to inhibit the modest amounts of BCL-6 expressed by effector T_H1 cells and thus control the dominant repressive activity of BCL-6 on the glycolytic pathway.

Together, these data show that BCL-6 is an IL-2-sensitive repressor of genes encoding molecules in the glycolysis pathway and that the ratio of T-bet to BCL-6 influences the metabolic gene programme in T cells.

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ORIGINAL RESEARCH PAPER Oestreich, K. J. *et al.* Bcl-6 directly represses the gene program of the glycolysis pathway. *Nature Immunol.* http://dx.doi.org/10.1038/ni.2985 (2014)
FURTHER READING Pollizzi, K. N. & Powell, J. D. Integrating canonical and metabolic signalling programmes in the regulation of T cell responses. *Nature Rev. Immunol.* **14**, 435–446 (2014)