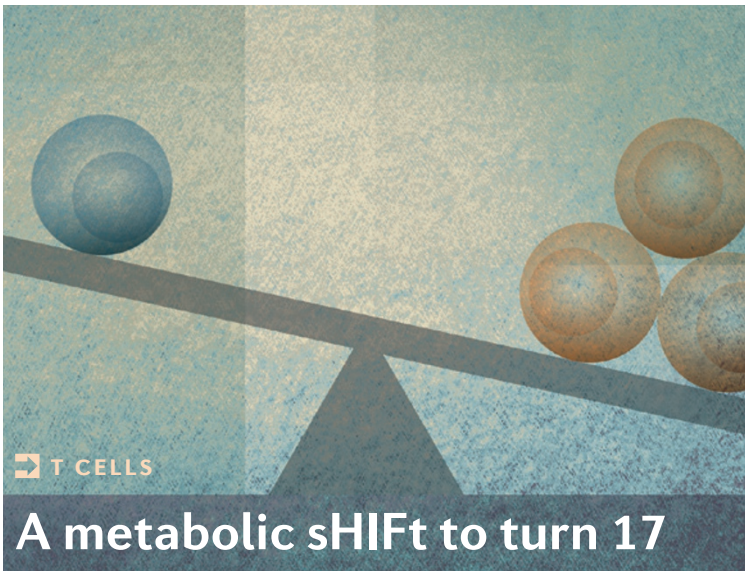

A metabolic sHIFt to turn 17

Naive T cells are known to upregulate glycolysis when they differentiate into effector T cells, and they subsequently rely on this pathway to produce ATP. By contrast, recent findings have indicated that the generation of induced regulatory T (T_{Reg}) cells does not involve this metabolic switch. However, the mechanisms that link cellular metabolism with immune signalling and cell fate have not been fully deciphered. A new study shows that the transcription factor hypoxia-inducible factor 1α (HIF1α) is required for the metabolic changes that occur in differentiating T helper 17 (T_H17) cells and thus can alter the balance between T_H17 and induced T_{Reg} cell generation.

HIF1α is a key player in the cellular response to hypoxia as it controls the switch to anaerobic respiration (in which ATP is produced by the glycolytic pathway). However, HIF1α can also be upregulated under normal oxygen conditions by mammalian target of rapamycin (mTOR), a kinase that is known to promote effector T cell differentiation. So, is this pathway responsible for the metabolic switch that occurs during the induction of T_H cells?

Shi *et al.* found that HIF1α expression was specifically increased in T_H17 cells during their development, and this increase was dependent on mTOR. They next confirmed that HIF1α was required for the modification of T_H17 cell metabolism by showing that, following activation under T_H17 cell-polarizing conditions, *Hif1a*$^{-/-}$ T cells had significantly lower rates of glycolysis than control T cells.

But can metabolic changes feed back to affect T cell fate decisions? *Hif1a*$^{-/-}$ T cells generated fewer interleukin-17 (IL-17)-expressing cells than control T cells, despite having similar proliferation rates and similar expression levels of the T_H17 cell master transcription factor retinoic acid receptor-related orphan receptor-γt (RORγt). Conversely, the number of forkhead box P3 $(FOXP3)^+$ induced T_{Reg} cells in the activated *Hif1a*$^{-/-}$ T cell population was increased. Furthermore, low-level inhibition of the glycolytic pathway had an equivalent impact to HIF1α deficiency on the metabolism and differentiation of T_H17 cells. Thus, HIF1α-dependent upregulation of glycolysis influences the balance between T_H17 and induced T_{Reg} cell differentiation.

To extend the relevance of these observations to an *in vivo* setting, the authors investigated the induction of T_H17 cells in mice. Following antigen injection, fewer antigen-specific T_H17 cells were present in the draining lymph nodes of mice treated with a glycolytic inhibitor than in those of control mice. Moreover, *Hif1a*$^{-/-}$ T cells caused less severe disease than control T cells in a T_H17 cell-dependent mouse model of neuroinflammation. So, blocking the HIF1α-dependent glycolytic pathway could minimize T_H17 cell differentiation and might thereby offer therapeutic benefits in certain autoimmune conditions.

These findings suggest that, under T_H17 cell-polarizing conditions, mTOR upregulates HIF1α, which implements a transcriptional programme in T cells to enhance the rate of glycolysis. This increase promotes T_H17 cell differentiation, whereas an insufficient metabolic response diverts cells towards a T_{Reg} cell fate. Interestingly, HIF1α levels were not increased in T_H1 or T_H2 cells, even though these populations also upregulate glycolysis during their activation, indicating that different T cell subsets use distinct pathways to control their metabolism and differentiation.

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ORIGINAL RESEARCH PAPER Shi, L. Z. *et al.* HIf1α-dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of T_H17 and T_{reg} cells. *J. Exp. Med.* **208**, 1367–1376 (2011)