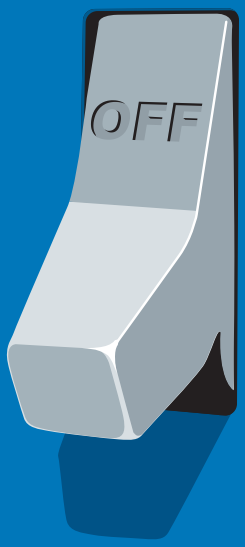
*Nature Reviews Immunology* | Published online 27 Feb 2017; doi:10.1038/nri.2017.17

IMMUNOMETABOLISM

# Powering down leukaemia






> B-lymphoid transcription factors can protect against leukaemic transformation by restricting glucose and energy usage in pre-B cells

Patients with pre-B cell acute lymphoblastic leukaemia (pre-B ALL) typically have mutations in genes that encode transcription factors involved in B cell development, but it has been unclear how these affect disease development. Chan *et al.* now show that B-lymphoid transcription factors can protect against leukaemic transformation by restricting glucose and energy usage in pre-B cells.

Initially, the authors screened leukaemia cells from 279 patients with pre-B ALL and found that 209 patients had inactivating lesions in genes encoding the B cell transcription factors PAX5, IKZF1, EBF1 and TCF3. ChIP–seq (chromatin-immunoprecipitation followed by sequencing) analyses showed that each of these transcription factors binds to the promoter regions of genes encoding proteins involved in glucose uptake and metabolism, as well as to the promoters of genes encoding negative regulators of glucose uptake, such as NR3C1 (the glucocorticoid receptor), TXNIP (a glucose feedback sensor) and cannabinoid receptor 2 (CNR2). Reconstitution of *PAX5* or *IKZF1* in pre-B ALL cells lacking functional copies of these genes induced activation of the LKB1–AMPK energy stress sensor pathway, decreased expression of glucose transporters and effectors of glucose metabolism, and increased expression of glucose-transport inhibitors. These changes were associated with reduced glucose uptake and ATP depletion and a loss of these cells in competitive-growth assays. The authors also compared glucose uptake and energy metabolism in pre-B cells from *Pax5* wild-type and haplosufficient mice in the presence of the oncogene *BCR–ABL1*. A *BCR–ABL1* transgene did not increase glucose uptake and ATP levels in *Pax5* wild-type pre-B cells, but markedly increased glucose uptake, glycolysis and ATP levels in *Pax5*-haplosufficient pre-B cells. Therefore, PAX5 is able to act as a 'gatekeeper' to restrain glucose uptake and ATP supply in pre-B cells.

Although B-lymphoid and myeloid leukaemias often carry the same oncogenes, they show distinct biological and clinical characteristics. To explore whether this is due to unique metabolic properties, the authors compared glucose and energy metabolism in *BCR–ABL1*$^+$ pre-B ALL cells and chronic myeloid leukaemia (CML) cells. Interestingly, they found that CML cells had more abundant reserves of glucose and ATP compared with pre-B ALL cells. In keeping with this, respiration and mitochondrial ATP levels were lower in pre-B ALL cells and they showed lower expression of effectors of glucose metabolism, increased expression of glucose transport inhibitors and constitutive activation of the LKB1–AMPK pathway. When pre-B ALL cells were reprogrammed to acquire a myeloid cell identity (through overexpression of CEBPα), they upregulated effector molecules of glucose metabolism, increased glucose uptake and cellular ATP levels, and decreased activation of the LKB1–AMPK pathway. Deletion of *Lkb1* or *Ampka2* in pre-B ALL cells led to rapid cell death and prevented malignant transformation; by contrast, deletion of *Lkb1* in myeloid leukaemia cells increased cellular proliferation, ATP levels and glucose uptake. The authors further showed that high expression of LKB1 and AMPK is associated with poor clinical outcome in patients with B-lymphoid leukaemia, but not in myeloid leukaemia.

As it was recently shown that deletion of *Ampka1* leads to accelerated tumour growth in mature B cell lymphoma, the authors reasoned that the LKB1–AMPK pathway may represent a stage-specific metabolic checkpoint during early B cell development. Indeed, deletion of *Lkb1* at the pre-B cell stage completely blocked B cell development, whereas loss of *Lkb1* in mature B cells had no major effect on their survival. They further showed that BML275, a small-molecule inhibitor of AMPK, can induce cell death in pre-B ALL cells but had no effect on myeloid leukaemia or mature B cell lymphoma cells. Notably, co-treatment with BML275 and the glucocorticoid prednisolone had a strong synergistic effect in inducing cell death in pre-B ALL cells. Glucocorticoids are used to treat B-lymphoid ALL but are ineffective in myeloid leukaemia; the authors found that PAX5 and IKZF1 determine the responsiveness of leukaemia cells to glucocorticoid-mediated cell death by positively regulating NR3C1 levels. CRISPR–Cas9-mediated deletion of the PAX5 targets NR3C1, TXNIP and CNR2 mitigated the tumour-suppressor effect of PAX5, and accordingly, agonists for CNR2 and TXNIP also synergized with glucocorticoids to induce pre-B ALL cell death.

These data show that B-lymphoid transcription factors exert tumour-suppressor functions by restricting the supply of glucose and ATP to prevent malignant transformation of pre-leukaemic cells. Based on these findings, the authors propose that TXNIP, CNR2 and AMPK represent novel therapeutic targets for pre-B ALL.

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**ORIGINAL ARTICLE** Chan, L. N. *et al.* Metabolic gatekeeper function of B-lymphoid transcription factors. *Nature* http://dx.doi.org/10.1038/nature21076 (2017)