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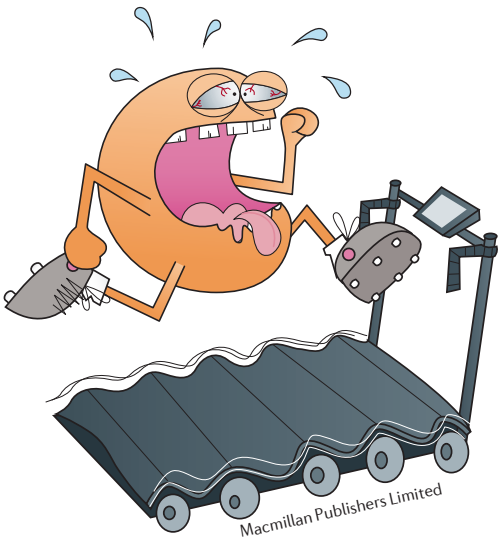
AUTOIMMUNITY

LKB1 helps T_{reg} cells battle exhaustion

> Antibodies that block PD1 or its ligands reversed the muted T_H2 cell suppression

Regulatory T (T_{reg}) cells have a crucial role in preventing autoimmune disorders owing to their ability to suppress effector T (T_{eff}) cells. A recent article in *Nature* demonstrates that the tumour suppressor liver kinase B1 (LKB1), which is known to control cell growth and metabolism, also coordinates metabolic and immunological homeostasis of T_{reg} cells to prevent functional exhaustion.

In this article, mice in which the gene encoding LKB1 was deleted in T_{reg} cells (*Foxp3*^{cre}*Stk11*$^{fl/fl}$ mice) had short lifespans, low body weight, skin ulcers and inflammatory manifestations including splenomegaly, lymphadenopathy and immune cell infiltration of multiple organs that led to a fatal autoimmune disease. This phenotype was associated with high levels of T helper 2 (T_H2) cytokines — IL-4 and IL-5 — present in the serum and secreted by T_{eff} cells.



T_{reg} cell numbers were reduced in *Foxp3*^{cre}*Stk11*$^{fl/fl}$ mice and these cells expressed high levels of apoptotic markers. Depletion of the pro-apoptotic protein BIM largely restored T_{reg} cell numbers but did not restore T_{eff} cell numbers, suggesting that LKB1 affects T_{reg} cell apoptosis and function through independent mechanisms.

Unexpectedly, the activity and phosphorylation of key molecules in the canonical LKB1 pathway downstream of T cell receptor engagement — namely, AMP-dependent kinase (AMPK) signalling — were impaired, but deletion of the genes encoding AMPKα1 and AMPKα2 did not affect immune homeostasis. From gene set enrichment analysis, they found instead that WNT signalling was induced by activation of wild-type but not LKB1-deficient T_{reg} cells.

Next the authors noted that the expression of the co-receptors PD1, GITR and OX40, which can reduce the capacity of T_{reg} cells to suppress T_H2 cell responses, was notably upregulated on T_{reg} cells from *Foxp3*^{cre}*Stk11*$^{fl/fl}$ mice. T_H2 cell responses are promoted by dendritic cells (DCs) that have been primed by cytokines such as thymic stromal lymphopoietin (TSLP), which is produced by epithelial cells and induces expression of the PD1 ligand PDL2 on DCs. TSLP levels in the lung interstitium and PDL2 levels on DCs were increased in *Foxp3*^{cre}*Stk11*$^{fl/fl}$ mice. Furthermore, wild-type but not LKB1-deficient T_{reg} cells inhibited PDL2 expression on TSLP-primed DCs, suggesting that LKB1-deficient T_{reg} cells are unable to suppress these T_H2-promoting cells. Antibodies that block PD1 or its ligands reversed the muted T_H2 cell suppression that was observed in cultures with LKB1-deficient T_{reg} cells.

The authors then examined the connection between low WNT signalling and high PD1 expression in LKB1-deficient T_{reg} cells. Expression of constitutively active β-catenin (a key WNT signalling mediator) in LKB1-deficient T_{reg} cells reversed the aberrant expression of PD1 and GITR and enabled these cells to suppress PDL2 expression on DCs and limit T_H2 cell differentiation.

These data demonstrate that LKB1 restrains the expression of PD1 and other molecules through a WNT-dependent mechanism and thus enables T_{reg} cells to control T_H2 cell responses. Whereas blocking PD1 signalling in cancer can promote an antitumour response, doing the same in autoimmune disorders could reinvigorate T_{reg} cells to control T_H2 cell-mediated inflammation.

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