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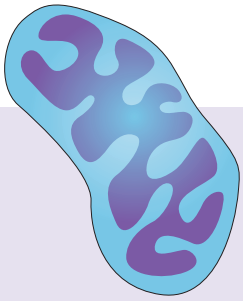
IMMUNOLOGY

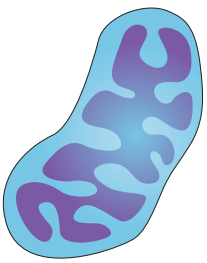
# Metabolic changes modify $T_{reg}$ cell function

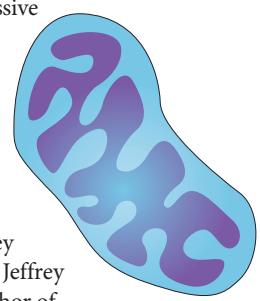


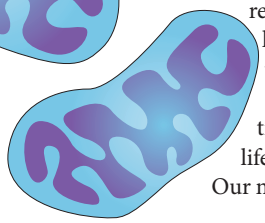
Regulatory T ($T_{reg}$) cell metabolism is controlled by a balance of signals from Toll-like receptors (TLRs) and the $T_{reg}$ transcription factor forkhead box protein P3 (FOXP3), according to a new paper published in *Nature Immunology*. Moreover, the study shows that changes in these intracellular metabolic pathways are sufficient to alter $T_{reg}$ cell proliferation and function, highlighting the importance of the metabolic balance to suppression of inflammation.

> "changes in … metabolic pathways are sufficient to alter $T_{reg}$ cell proliferation and function"

Previous work by several groups showed that effector T cells rely on glycolytic metabolic pathways that support their proliferation and inflammatory functions, whereas $T_{reg}$ cells rely primarily on mitochondrial oxidation of lipids — a mode of metabolism that provides only inefficient support for anabolic growth pathways. However, $T_{reg}$ cells have also been shown to be highly proliferative and capable of inducing glycolysis. The new findings shed light on the bioenergetic mechanisms that modulate the balance between $T_{reg}$ cell proliferation and suppressive function. "Our data show that $T_{reg}$ [cells] can actually switch between [oxidative and glycolytic] phenotypes to allow inflammation when they are glycolytic, but to suppress inflammation and promote resolution when they are more oxidative," explains Jeffrey Rathmell, corresponding author of the paper.



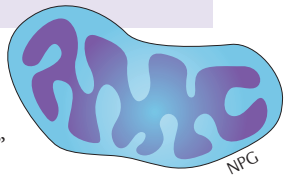




Proliferative FOXP3$^+$ thymus-derived $T_{reg}$ cells were marked by increased expression of the glucose transporter GLUT1 (also known as solute carrier family 2, facilitated glucose transporter member 1) and serine/threonine-protein kinase mTOR activity. Treatment of activated $T_{reg}$ cells with a TLR1 and TLR2 agonist further increased the expression of GLUT1, in association with increased proliferation and activation of the mTOR complex 1 (mTORC1) pathway. However, these TLR-treated cells also showed a decreased capacity to suppress the proliferation of effector CD8$^+$ T cells, an effect that was dependent on activation of mTORC1 signalling.

Conversely, expression of FOXP3 in CD4$^+$ T cells promoted the expression of genes encoding products involved in oxidative metabolic pathways, and downregulated those involved in glucose metabolism. FOXP3 expression reduced GLUT1 expression and inhibited mTORC1 signalling and glycolysis, but promoted oxidative metabolism and slowed the proliferation of $T_{reg}$ cells.

Together, the results demonstrate the counter-regulation of $T_{reg}$ cell metabolism by signals from inflammatory ligands and receptors, which promote increased mTOR activity and glycolysis, and FOXP3, which suppresses those same pathways and promotes mitochondrial pathways. "This shows a new level of dynamic regulation for $T_{reg}$ [cell] metabolism," says Rathmell. "It also fits well with work [from] the past decade showing that TLR [ligation] can increase $T_{reg}$ [cell] proliferation but reduce suppression. Our metabolic data now provides a potential mechanism for this regulation," he continues.




Frank Buttgereit, who was not involved in the study, asserts that the work underlines the importance of understanding the machinery providing the energy required for immune cell functions, and which is capable of regulation via bioenergetic mechanisms. "I think this is a brilliant example to explain in greater detail what 'immunometabolism' really means, and why this field currently represents such a modern and active research field describing the interface of immune and metabolic processes — that is, the changes in intracellular metabolic pathways in immune cells that alter their function (and vice versa)," he comments.

Rathmell thinks that this metabolic switch might aid infection clearance. "This could have … implications in inflammatory resolution, and [provide] a natural mechanism to increase $T_{reg}$ suppressive function as TLR ligands decrease (and pathogens are cleared)." He adds, "[This switch] could also be interesting in the setting of chronic autoimmunity or inflammation, where inflammatory signals persist long term and $T_{reg}$ often accumulate, but fail to control the inflammation."

*Sarah Onuora*

**ORIGINAL ARTICLE** Gerriets, V. A. *et al.* Foxp3 and Toll-like receptor signaling balance $T_{reg}$ cell anabolic metabolism for suppression. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3577 (2016)
**FURTHER READING** Newton, R. *et al.* Immunometabolism of regulatory T cells. *Nat. Immunol.* **17**, 618–625 (2016)