Nature Reviews Immunology | AOP, published online 14 January 2011; doi:10.1038/nri2920

REGULATORY T CELLS

Weight watchers

There is a growing understanding of how host metabolism can affect the immune system. Now, a study by Procaccini *et al.* has described another important link between host energy status and immune function by showing that leptin, a hormone that is mainly produced by adipocytes and that controls food intake and energy expenditure, can activate mammalian target of rapamycin (mTOR) and regulate the proliferative capacity of regulatory T (T_{Reg}) cells.

mTOR is a serine/threonine kinase that integrates signals from environmental nutrients and growth factors to control cell proliferation and differentiation. In initial experiments conducted *in vitro*, freshly isolated human T_{Reg} cells showed higher mTOR activity and an increased metabolic rate compared with purified effector T cells. Although T_{Reg} cells do not normally proliferate in response to *in vitro* T cell receptor (TCR) stimulation, transient inhibition of mTOR, through pretreatment with rapamycin, led to robust proliferation of T_{Reg} cells following culture with CD3- and CD28-specific antibodies. Extending these findings *in vivo,* the authors found that a single injection of rapamycin promoted T_{Reg} cell proliferation in mice, both in the steady state and after immunization with antigen. Additionally, in a model of experimental autoimmune encephalomyelitis (EAE), mice treated with rapamycin before EAE induction showed increased frequencies of T_{Reg} cells and decreased disease severity. Interestingly, although decreased mTOR activity seemed to be necessary for the initial phases of T_{Reg} cell proliferation, T_{Reg} cells that were actively proliferating *in vivo* expressed high levels of phosphorylated mTOR. Furthermore, continuous treatment with rapamycin or silencing of mTOR expression with short hairpin RNA failed to reverse T_{Reg} cell anergy *in vitro*. Thus, although early, transient inhibition of mTOR activity could overcome T_{Reg} cell anergy, subsequent upregulation of mTOR activity seemed to be required to sustain T_{Reg} cell proliferation, indicating that the mTOR pathway has a dynamic role in T_{Reg} cell responsiveness.

As previous work showed that leptin can be produced by, and inhibits the proliferation of, T_{Reg} cells, the authors predicted that this molecule might interact with the mTOR pathway. In support of this, addition of leptin to cultures of TCR-activated, rapamycin-treated T_{Reg} cells led to increased activation of the mTOR pathway and prevented T_{Reg} cell proliferation. In addition, neutralization of leptin markedly reduced mTOR activity in cultured T_{Reg} cells, suggesting that autocrine production of leptin by T_{Reg} cells may promote their high mTOR activity *in vitro.*

Finally, the authors examined the effects of acute starvation (which markedly reduces circulating levels of leptin and immune function) on the mTOR pathway and T_{Reg} cell function. Strikingly, starvation led to increased proportions of T_{Reg} cells in peripheral lymph nodes. Furthermore, T_{Reg} cells from starved mice showed markedly reduced mTOR activity and increased rates of proliferation *in vitro* compared with T_{Reg} cells from control animals.

Taken together, this study describes the leptin–mTOR signalling pathway as an important link between host energy status and T_{Reg} cell activity. The authors conclude that oscillating mTOR activity is necessary for T_{Reg} cell activation and suggest that this may explain why T_{Reg} cells are unresponsive to TCR stimulation *in vitro*, where high levels of leptin and nutrients may sustain mTOR activation.

CORBIS

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ORIGINAL RESEARCH PAPER Procaccini, C. *et al.* An oscillatory switch in mTOR kinase activity sets regulatory T cell responsiveness. *Immunity* **33**, 929–941 (2010)

FURTHER READING Finlay, D. & Cantrell, D. A. Metabolism, migration and memory in cytotoxic T cells. *Nature Rev. Immunol.* 14 Jan 2011 (doi:10.1038/nri2888)