stands out is the gene encoding the α-chain of the receptor for IL-4 (*Il4ra*)[4]. IL-6 directly increases *Il4ra* expression in macrophages via phosphorylation of the transcription factor STAT3 and subsequent regulation of the *Il4ra* promoter. This is of particular interest because IL-4 is secreted from T cells or eosinophils in adipose tissue and in turn promotes the M2 polarization of macrophages[10]. That is accompanied by increased expression of many genes encoding molecules (particularly IL-10) that contribute to greater sensitivity to insulin in adipocytes[5]. Together these data suggest that IL-6 may influence sensitivity to insulin in liver and fat by promoting a switch in macrophage polarization from a proinflammatory M1 phenotype to an anti-inflammatory M2 phenotype[4].

While those data further support the proposal that IL-6 serves a beneficial role in the regulation of metabolism, several questions remain about a teleological explanation for those observations. IL-6 itself is generated as a part of the inflammatory program, and its expression in myeloid cells and other cells is known to be controlled by inflammatory signals such as those from the transcription factor NF-κB[11] and by catabolic hormones and biogenic amines that increase the concentration of cAMP[12]. Since the upstream signals that increase the secretion of IL-6 generally oppose the action of insulin, it seems reasonable to conclude that IL-6 may in this case act as a feedback regulator, attenuating inflammatory and catabolic signaling to preserve the action of insulin. Such a 'counterinflammatory' role for IL-6 is consistent with other feedback signals that might serve to limit inflammation in obesity and thus promote the storage of energy in the face of the catabolic pressure of inflammation.

Another question is about the relevance of the various tissues from which IL-6 is secreted and how this influences metabolic homeostasis (**Fig. 1**). Several studies have demonstrated that IL-6 is secreted from skeletal muscle in response to exercise and from brown or white fat depots in response to sympathetic activation. Not only is IL-6 secreted from various metabolically active tissues but it also has important metabolic effects in those tissues. IL-6 can diminish the hepatic expression of genes encoding gluconeogenic molecules to decrease the concentration of sugar in the blood during the fasting state, an effect presumably independent of the innate immune system[9]. Thus, the crucial sites for the secretion and action of IL-6 remain uncertain, and the observation that this cytokine is apparently produced in response to proinflammatory and catabolic signaling to produce anti-inflammatory and anabolic effects is itself paradoxical. Thus, some of the confusion about the metabolic role of this interesting cytokine might persist for a while longer.

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1. Lumeng, C.N. & Saltiel, A.R. *J. Clin. Invest.* **121**, 2111–2117 (2011).
2. Pradhan, A.D. *et al. J. Am. Med. Assoc.* **286**, 327–334 (2001).
3. Goldfine, A.B. *et al. Ann. Intern. Med.* **152**, 346–357 (2010).
4. Mauer, J. *et al. Nat. Immunol.* **15**, 423–430 (2014).
5. Lumeng, C.N., Bodzin, J.L. & Saltiel, A.R. *J. Clin. Invest.* **117**, 175–184 (2007).
6. Schenk, S., Saberi, M. & Olefsky, J.M. *J. Clin. Invest.* **118**, 2992–3002 (2008).
7. Ueki, K. *et al. Proc. Natl. Acad. Sci. USA* **101**, 10422–10427 (2004).
8. Wallenius, V. *et al. Nat. Med.* **8**, 75–79 (2002).
9. Stanford, K.I. *et al. J. Clin. Invest.* **123**, 215–223 (2013).
10. Wu, D. *et al. Science* **332**, 243–247 (2011).
11. Cai, D. *et al. Nat. Med.* **11**, 183–190 (2005).
12. Burýsek, L. & Houstek, J. *FEBS Lett.* **411**, 83–86 (1997).

SGK1: master and commander of the fate of helper T cells

Matthew Norton & Robert A Screaton

Cytokines and other environmental cues influence polarization of CD4$^+$ helper T cells, but the signaling pathways that are involved are less clear. Recent findings show that signaling via an mTORC2-SGK1 kinase axis regulates T_H1-T_H2 cell-fate polarization.

Immunity is classified into the innate and adaptive systems, which oversee the immediate nonspecific responses to pathogens and the acquired, highly specific and long-term responses to pathogens, respectively. Naive CD4$^+$ T cells are derived from the thymus and, after being activated by antigen-specific cues in the periphery, can differentiate into the T_H1, T_H2 or T_H17 lineage of effector helper T cells. The T_H1 and T_H2 subsets define two classes of CD4$^+$ helper T cells and control cell-mediated immunity to pathogens and extracellular immunity to pathogens, respectively. Over-reactive T_H1 cells are associated with organ-specific autoimmunity, such as multiple sclerosis and type 1 diabetes mellitus, while T_H2 cells are associated with the pathology of allergic asthma[1]. While current therapy for asthma focuses on relieving symptoms, earlier therapeutic intervention to diminish skewing toward T_H2 cell–mediated immune responses may lead to better responses in patients[2]. As those conditions affect hundreds of millions of people worldwide, improved understanding of the mechanisms of T cell determination holds the promise of novel therapies for those affected. In this issue of *Nature Immunology*, Powell and colleagues report that the serum- and glucocorticoid-regulated kinase SGK1 is a critical determinant of the developmental fate of T cells that functions to promote differentiation into the T_H2 lineage while simultaneously blocking differentiation into the T_H1 lineage[3].

SGK1 belongs to the AGC family of kinases, which features the iconic members Akt and S6K; these collectively relay extracellular signals designed to elicit cellular growth, proliferation and survival responses. SGK1 is a downstream target of the metabolic checkpoint kinase complex mTORC2; it is thought to regulate the expression of sodium channels in the kidney and has garnered attention as a critical mediator of the pathogenic actions of T_H17 cells[4–6]. This new work from Powell and colleagues[3] expands the understanding of the biological roles of SGK1 to include determining the fate of CD4$^+$ helper T cells. While commitment to the T_H1 lineage or T_H2 lineage is known to be regulated by defined cytokines and transcription factors, Powell and colleagues[3] describe a signaling pathway that may

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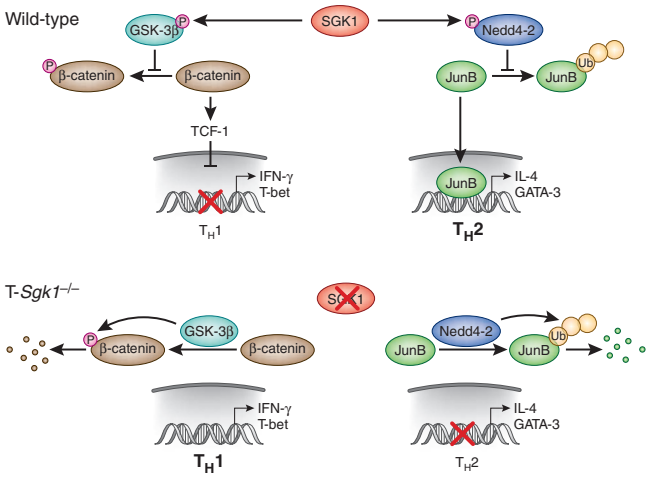

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Figure 1 Regulation of the fate of helper T cells by SGK1. In the signaling pathways downstream of SGK1 in wild-type cells (top), phosphorylation of the kinase GSK3-β blocks the degradation of β-catenin, which leads to the accumulation of TCF-1 and inhibition of downstream targets associated with the T_H1 phenotype. SGK1 also phosphorylates Nedd4-2 to block ubiquitination (Ub) of JunB and its turnover by the 26S proteasome. That stabilization of JunB facilitates a gene-expression program that involves IL-4 and GATA-3 and is required for the T_H2 cell lineage. In T cells from T-*Sgk1*$^{-/-}$ mice (bottom), active GSK3-β phosphorylates β-catenin, which triggers its degradation and, in turn, relieves the repression of the transcription of the genes encoding IFN-γ and T-bet required for the T_H1 lineage. In parallel, unphosphorylated Nedd4-2 ubiquitinates JunB and thus prevents expression of the genes encoding IL-4 and GATA-3.

determine how these lineages are affected by environmental cues. By crossing mice with *lox*P-flanked alleles encoding SGK1 with mice that express Cre recombinase under the control of the *Cd4* promoter, the authors generate 'T-*Sgk1*$^{-/-}$' progeny in which SGK1 is deleted specifically in the precursors of CD4$^+$ helper T cells. When stimulated to differentiate into the T_H2 lineage, T-*Sgk1*$^{-/-}$ cells fail to express the signature T_H2 cell–associated transcriptional regulator GATA-3 or to produce the T_H2 cell–associated cytokines interleukin 4 (IL-4), IL-5 and IL-13. That indicates that SGK1 is required for the *in vitro* differentiation of CD4$^+$ T cells into the T_H2 lineage. Unexpectedly, in that setting, T-*Sgk1*$^{-/-}$ cells inappropriately produce interferon-γ (IFN-γ) and express the transcription factor T-bet, both hallmarks of the T_H1 lineage. Such observations demonstrate a dual role for SGK1 in regulating the fate of helper T cells: to act as a positive regulator of T_H2 differentiation and to act as a negative regulator of T_H1 differentiation.

From a disease perspective, T-*Sgk1*$^{-/-}$ mice have lower concentrations of IL-4 in bronchoalveolar lavage fluid and diminished allergy-associated production of immunoglobulin E in the serum than do their wild-type counterparts and thus are resistant to T_H2 cell–mediated allergic asthma. In contrast, T-*Sgk1*$^{-/-}$ mice demonstrate superior T_H1 cell–mediated antiviral and antitumor responses than that of their wild-type counterparts, including increased production of IFN-γ following a challenge with vaccinia virus or B16 mouse melanoma cells. Consistent with the enhanced IFN-γ production associated with an expanded T_H1 cell population, T-*Sgk1*$^{-/-}$ mice have a diminished tumor burden after B16 melanoma challenge and longer survival than that of their wild-type counterparts. Thus, SGK1-dependent control of T cell fate has important implications for human disease.

The transcription factor JunB is needed to activate a T_H2 cell–specific gene-expression program[7]. JunB is ubiquitinated by the ubiquitin ligase Itch and the adaptor Ndfip1 ('Nedd4 family–interacting protein 1'); that ubiquitination triggers its degradation[8]. Because SGK1 phosphorylates and inhibits the E3 ligase and Itch homolog Nedd4-2 (ref. 4), the authors investigate whether the SGK1-Nedd4-JunB pathway has a role in T_H2 differentiation[3]. Indeed, during T_H2 differentiation, Nedd4-2 is inhibited by phosphorylation, leading to the accumulation of JunB in wild-type cells, whereas in T-*Sgk1*$^{-/-}$ cells JunB is degraded. Notably, silencing the expression of Nedd4-2 or Ndfip1 in the T-*Sgk1*$^{-/-}$ cells partially restores T_H2 differentiation by increasing the stability of JunB and the production of IL-4. This shows that the SGK1-Nedd4-JunB pathway regulates T cell differentiation by SGK1-dependent phosphorylation of Nedd4-2 to inhibit ubiquitination of JunB (**Fig. 1**). Stabilization of JunB can then promote IL-4 production and T_H2 differentiation.

Having established that the SGK1-Nedd4-JunB axis promotes T_H2 differentiation, Powell and colleagues investigate why T-*Sgk1*$^{-/-}$ cells differentiate toward the T_H1 lineage when stimulated to produce T_H2 cells[3]. Because under T_H2-skewing conditions T cells that lack long isoforms of the transcription factor TCF-1 inappropriately produce the T_H1 cell marker IFN-γ[9], Powell and colleagues express long-form TCF-1 in T-*Sgk1*$^{-/-}$ cells and observed a reduction in IFN-γ production[3]. In the absence of β-catenin, T-*Sgk1*$^{-/-}$ cells have lower expression of the long isoforms of TCF-1, which allows T_H1-like differentiation under T_H2-skewing conditions. Thus, by simultaneously activating JunB and the long isoforms of TCF-1, SGK1 acts both as an accelerator for the T_H2 fate and a brake on T_H1 differentiation.

As noted above, published reports have demonstrated a role for SGK1 in the induction of pathogenic T_H17 cells. SGK1 promotes expression of the receptor for IL-23 by deactivating the transcription factor Foxo1 and therefore sustains signaling via IL-23 that is critical for stabilizing the T_H17 lineage[6]. Interestingly, SGK1 expression is induced by extracellular salt, and loss of SGK1 diminishes the sodium-mediated stabilization of T_H17 cells. As inflammatory T_H17 cells have a large role the development of autoimmune diseases, such reports raise many questions about the role of dietary salt in autoimmune diseases and the regulation of T cells[5,6]. Consistent with that published report[6], Powell and colleagues show that SGK1 is not required for T_H17 differentiation[3]. However, further studies to determine the role that dietary salt or other environmental cues might serve in regulating T_H1 and T_H2 differentiation via SGK1 will be of interest. We speculate that SGK1-mediated effects on T cell differentiation may connect environmental conditions to signal-transduction events that ultimately influence the development of allergic asthma and antitumor immunity.

As Powell and colleagues have demonstrated a requirement for mTORC2 in the activation of SGK1 during T_H2 differentiation[3], it will also be interesting to determine the upstream signaling factors that promote the activation of SGK1 through mTORC2. While there is evidence that mTORC2 can be activated in response to insulin in a manner dependent on phosphatidylinositol-3-OH kinase and can be inactivated by S6K-dependent phosphorylation of the mTORC2 component Sin1 to suppress tumorigenesis and promote the uptake of glucose in muscle tissue[10,11], additional upstream signals (beyond growth factors) that may regulate mTORC2 have yet to be described[12]. Loss of mTORC2 activity due to deficiency in the mTORC2 adaptor Rictor in adipose tissue, pancreatic beta cells,

neurons and the heart results in deleterious effects on cell survival, organ size and whole-animal metabolism[12,13]. Although many of those phenotypes can be linked to impaired signaling via Akt, a role for SGK1 in those settings may yet be revealed. Finally, it will be interesting to determine whether small-molecule inhibitors of SGK1 (refs. 14,15) could be used to prevent T_H2 cell–mediated immune disease states or to promote T_H1 cell–mediated antitumor responses.

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1. Murphy, K.M. & Reiner, S.L. *Nat. Rev. Immunol.* **2**, 933–944 (2002).
2. Bosnjak, B., Stelzmueller, B., Erb, K.J. & Epstein, M.M. *Respir. Res.* **12**, 114 (2011).
3. Heikamp, E.B. *et al. Nat. Immunol.* **15**, 457–464 (2014).
4. Debonneville, C. *et al. EMBO J.* **20**, 7052–7059 (2001).
5. Kleinewietfeld, M. *et al. Nature* **496**, 518–522 (2013).
6. Wu, C. *et al. Nature* **496**, 513–517 (2013).
7. Li, B., Tournier, C., Davis, R.J. & Flavell, R.A. *EMBO J.* **18**, 420–432 (1999).
8. Oliver, P.M. *et al. Immunity* **25**, 929–940 (2006).
9. Yu, Q. *et al. Nat. Immunol.* **10**, 992–999 (2009).
10. Gan, X., Wang, J., Su, B. & Wu, D. *J. Biol. Chem.* **286**, 10998–11002 (2011).
11. Liu, P. *et al. Nat. Cell Biol.* **15**, 1340–1350 (2013).
12. Oh, W.J. & Jacinto, E. *Cell Cycle* **10**, 2305–2316 (2011).
13. Yano, T. *et al. Circ. Res.* doi: 10.1161/CIRCRESAHA.114.303562 (20 February 2014).
14. Ackermann, T.F., Boini, K.M., Beier, N., Scholz, W., Fuchss, T., Lang, F. *Cell. Physiol. Biochem.* **28**, 137–146 (2011).
15. Sherk, A.B. *et al. Cancer Res.* **68**, 7475–7483 (2008).