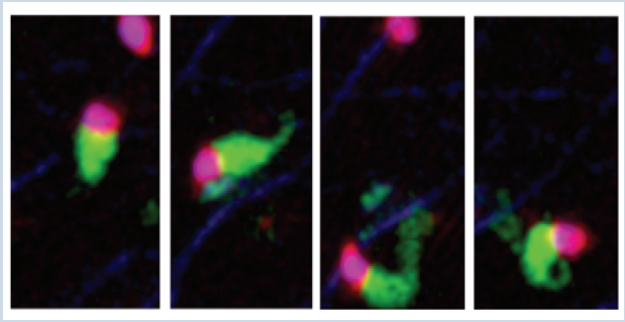
cells[13,14]. Whether the absence of TRAF6 and the reported increase in PI3K activity is due to hyperactivation of the PI3K-PKB pathway to compensate for the lack of TRAF6 remains to be examined.

Future research could also define the upstream molecular pathway that allows TRAF6 to regulate T-cell susceptibility to Treg inhibition. A separate study may provide a hint: it found that deficiency for the E3 ubiquitin ligase Cbl-b may also permit T cells to ignore Treg signals[15]. Unraveling the pathways that relay these signals between Treg and T helper cells would provide a promising approach for manipulating autoimmunity or tumor immune therapy.

1. Sakaguchi,S. *Annu. Rev. Immunol.* **22**, 531–562 (2004).
2. King, C.G. *et al. Nat. Med.* **12**, 1088–1092 (2006).
3. Akira, S., Uematsu, S. & Takeuchi, O. *Cell* **124**, 783–801 (2006).
4. Sun, L., Deng, L., Ea, C.K., Xia, Z.P. & Chen, Z.J. *Mol. Cell* **14**, 289–301 (2004).
5. Wu, H. & Arron, J.R. *Bioessays* **25**, 1096–1105 (2003).
6. Deane, J.A. & Fruman, D.A. *Annu. Rev. Immunol.* **22**, 563–598 (2004).
7. Di Cristofano, A. *et al. Science* **285**, 2122–2125 (1999).
8. Borlado, L.R. *et al. FASEB J.* **14**, 895–903 (2000).
9. Parsons, M.J. *et al. J. Immunol.* **167**, 42–48 (2001).
10. Suzuki, A. *et al. Immunity* **14**, 523–534 (2001).
11. Rathmell, J.C., Elstrom, R.L., Cinalli, R.M. & Thompson, C.B. *Eur. J. Immunol.* **33**, 2223–2232 (2003).
12. Ohashi, P.S. *Nat. Rev. Immunol.* **2**, 427–438 (2002).
13. Wong, B.R. *et al. Mol. Cell* **4**, 1041–1049 (1999).
14. Wong, F., Hull, C., *Blood* **103**, 4520–4526 (2004).
15. Wohlfert, E.A., Gorelik, L., Mittler, R., Flavell, R.A. & Clark, R.B. *J. Immunol.* **176**, 1316–1320 (2006).

Enabling the suppressors



Reprinted with permission of *Cell Press*

Despite their growing fame, very little is known about how regulatory T cells (Tregs) generate immunological tolerance. Thorsten Mempel, Mikael Pittet and colleagues examined the activity of these cells *in vivo*, using real-time imaging in mice.

The investigators reported that Tregs seem to operate by preventing cytotoxic 'killer' T cells (CTLs) from releasing the deadly contents of cytolytic granules (*Immunity* **25**, 129–141). Shown is a cytotoxic T cell (green) raised in an environment with Tregs. This CTL engaged an antigen-presenting B cell (purple) and followed it around for 14 minutes, indicating that regulated CTLs can interact with their targets. Eventually the CTL disengaged and the B cell carried on (not shown; for movies, go to http://cmir.mgh.harvard.edu/cip/cip_research_cancer_2.php?menuID_=367). The researchers found that nonregulated CTLs killed their targets 6.6 times faster than regulated CTLs—which are slow to release the contents of their granules.

Consistent with previous findings, transforming growth factor-β was found to be necessary for the suppressive activity of Tregs. Tregs themselves are an unlikely source of this cytokine, but in *Nature* (doi:10.1038/nature05010), Li-Fan Lu *et al.* speculate that mast cells might be one source. The researchers report that mast cells, best known for their proinflammatory role in allergic disorders, seem to mediate the generation of tolerance by regulatory T cells.

Charlotte Schubert