Abundance of ITAM prevents autoimmunity

For T cell receptors, more activation motifs means less autoimmunity, say Jeff Holst, Dario Vignali (St. Jude’s Children’s Research Hospital, Memphis, TN), and colleagues.

The T cell receptor’s four CD3 subunits contain a total of 10 tyrosine-based activation motifs (ITAMs). These motifs dock with tyrosine kinases inside the cell to promote signaling, but it’s unclear why the receptor needs so many ITAMs.

The authors generated mice that expressed mutant CD3 subunits with different numbers of ITAMs. Mice with seven or more ITAMs on their CD3 subunits developed normally, but with six or fewer, mice were prone to autoimmune disease. “Number was more important than ‘flavor,’” Vignali says. Although flavor—the specific ITAM type—also played some part, since two of the four strains with six ITAMs remained healthy.

Autoimmunity can be caused by loss of tolerance for self-antigens during development in the thymus. To test whether ITAM number affected self-antigen recognition, the authors created male mice in which either wild-type or mutant CD3 subunits were combined with a T cell receptor specific for a male antigen. Although wild-type mice deleted thymic T cells bearing the receptor, those with few functional ITAMs allowed the T cells to develop and enter the periphery, where they could provoke an autoimmune reaction. “Self-antigens have to be recognized in the thymus even when affinity and density is low,” Vignali says. The large number of ITAMs might therefore ensure the message isn’t lost. JCB

Holst, J., et al. 2008. Nat. Immunol. doi:10.1038/ni.1611.

Sweeter tumors with EGFR

EGFR sweetens cancer cells to keep them alive, say Zhang Weihua, Mien-Chie Hung, Isaiah Fidler, and colleagues (University of Texas, Houston, TX).

Prognosis for many epithelial tumors correlates with the expression level of epidermal growth factor receptor. “It has traditionally been thought that tumor cells with too much receptor have too much tyrosine kinase activity,” Hung says. “But therapeutic kinase blockade has been only partially successful.”

Investigating other mechanisms, the authors showed that knockdown of EGFR reduced intracellular glucose levels, and increased production of energy-scavenging autophagosomes, ultimately leading to cell death. This cell death could be prevented by providing extra glucose.

This effect on cellular glucose is due to an interaction between EGFR and the sodium/glucose cotransporter, SGLT1, the team found. EGFR knockdown reduced expression of SGLT1, and SGLT1 knockdown caused autophagosome-induced death. Transporter loss was not due to lowered transcription, suggesting that the protein became unstable in the absence of EGFR. EGFR’s stabilizing effect was dependent on its extracellular domain and remained even in the absence of its kinase activity.

“The excess stabilization of the glucose transporter allows these cells to survive in harsher conditions,” Hung says. Targeting this additional function of EGFR might therefore make for a better therapy. JCB

Weihua, Z., et al. 2008. Cancer Cell. 13:385–393.