IN BRIEF

MAST CELLS

Distal signalling in mast cell degranulation

Ligation of the high-affinity Fc receptor for IgE (FcεRI) promotes mast cell activation. Now, a role for a truncated splice variant of the FcεRI β-subunit (tFcεRIβ) in mast cell degranulation has been identified. Findings by Cruse *et al.* suggest that full-length FcεRIβ might inhibit mast cell degranulation. By contrast, tFcεRIβ promoted mast cell degranulation and the release of interleukin-8, acting downstream of calcium mobilization. Notably, mast cell activation promoted the translocation of the tFcεRIβ complex to the Golgi apparatus, where it initiated microtubule formation. Thus, tFcεRI could be targeted in the future to inhibit the microtubule-dependent degranulation of mast cells and their release of pro-inflammatory mediators in patients with allergies.

ORIGINAL RESEARCH PAPER Cruse, G. *et al.* A truncated splice-variant of the FcεRIβ receptor subunit is critical for microtubule formation and degranulation in mast cells. *Immunity* 2 May 2013 (doi:10.1016/j.immuni.2013.04.007)

TECHNIQUE

A genetically encoded T cell calcium indicator

For the first time, the genetically encoded calcium indicator TN-XXL has been used for *in vivo* imaging of T cell activation. As TN-XXL is self-replenishing, it should enable longer-term *in vivo* work to be carried out than the synthetic calcium indicator dyes that have been previously used. TN-XXL comprises a fluorophore donor attached to a fluorophore acceptor by a calcium-sensitive linker. Binding of free calcium to the linker results in energy tranfer from the donor to the acceptor. The resulting change in the fluorescence ratio is a direct indicator of a change in intracellular calcium concentration. The previously developed form of TN-XXL was optimized by the authors through codon diversification to enable the retroviral transduction of T cells. A linker with increased calcium affinity was used to increase sensitivity and to enable the measurement of physiologically relevant changes in intracellular calcium levels that occur in T cells after antigen stimulation. As a proof of principle, the resulting construct (Twitch-1^{CD}) was used to transduce myelin-specific 2D2 T cells and to assess their activation in response to antigen *in vivo*.

ORIGINAL RESEARCH PAPER Mues, M. *et al.* Real-time *in vivo* analysis of T cell activation in the central nervous system using a genetically encoded calcium indicator. *Nature Med.* 12 May 2013 (doi:10.1038/nm.3180)

MACROPHAGES

Metabolites mangle microbes

Macrophages express high levels of immunoresponsive gene 1 *(IRG1)* under inflammatory conditions but the function of this gene has been unknown. This study now identifies IRG1 as an enzyme that catalyses the production of itaconic acid by decarboxylating the Krebs cycle intermediate *cis*-aconitate. When mouse macrophages were activated with lipopolysaccharide (LPS), they upregulated *Irg1* transcripts in 2 hours and showed increased levels of itaconic acid by 6 hours. Human monocyte-derived macrophages showed a similar response to LPS. Why do activated macrophages upregulate this metabolite? Itaconic acid can inhibit the glyoxylate shunt — this metabolic process is not found in animals but it is essential for bacterial growth when fatty acids or acetate are a limiting carbon source. Notably, when *Mycobacteria* spp. or *Salmonella* spp. were cultured under such conditions, itaconic acid inhibited their growth. Finally, silencing of *Irg1* in mouse macrophages prior to infection with *Salmonella* spp. increased intracellular bacterial loads.

ORIGINAL RESEARCH PAPER Michelucci, A. *et al.* Immune-responsive gene 1 protein links metabolism to immunity by catalyzing itaconic acid production. *Proc. Natl Acad. Sci. USA* **110**, 7820–7825 (2013)