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Journal club

ITIMs: EPISODE 1 OF THE INHIBITORY SAGA

The negative regulation of lymphocyte activation has become an area of intense investigation and excitement. In particular, the use of monoclonal antibodies that block inhibitory receptors expressed by T cells — the so-called checkpoint inhibitors — has shown unprecedented clinical benefits in patients with many different types of cancer. But at the start of the 1990s, the concept that the engagement of cell surface receptors with their cognate ligands might inhibit immune cell activation was only beginning to be unveiled.

In those days, the dissection of the signalling pathways that mediate T cell activation was an extremely hot topic. In his seminal 1989 scientific correspondence to *Nature*, 'Antigen receptor tail clue', Michael Reth identified ITAMs (immunoreceptor tyrosine-based activation motifs) in the intracellular domains of the CD3 subunits that associate with the T cell receptor (TCR). My excitement at these developments was piqued by the discovery of signals that could block the activation of another group of lymphocytes, the natural killer (NK) cells, which prompted the dissection of the signalling pathways involved in this negative regulation. Such a path was enlightened by a very thorough study led by Marc Daëron and published in *Immunity* in 1995. The report focused on an Fc receptor, FcγRIIB, that is conserved across species and expressed by a variety of haematopoietic cells. Although the groups of Sebastian Amigorena and Jeffrey Ravetch had previously revealed the inhibitory function of FcγRIIB in B cells, the Daëron *et al.* paper elegantly revealed the broad inhibitory function of an amino acid motif in the cytoplasmic tail of FcγRIIB. FcγRIIB was indeed not only able to mediate B cell inhibition but was also able to inhibit T cell activation induced by the TCR and mast cell activation induced by the high-affinity IgE receptor FcεRI. The authors coined the term ITIM (immunoreceptor tyrosine-based inhibition motif) to describe this inhibitory intracellular signalling domain.

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For me, this paper was episode 1 of a vast saga in which several of us identified a large family of ITIM-bearing receptors and showed that their mode of action was through the recruitment of protein tyrosine phosphatases, such as SHP1, or lipid phosphatases, such as SHIP1. Today, there is still considerable effort being made to understand the negative regulation of immune cell activation as well as the dynamic equilibrium between activating and inhibitory receptors that controls immune cell behaviour.

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ORIGINAL RESEARCH PAPER Daëron, M. *et al.* The same tyrosine-based inhibition motif, in the intracytoplasmic domain of FcγRIIB, regulates negatively BCR-, TCR-, and FcR-dependent cell activation. *Immunity* **3**, 635–646 (1995)

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