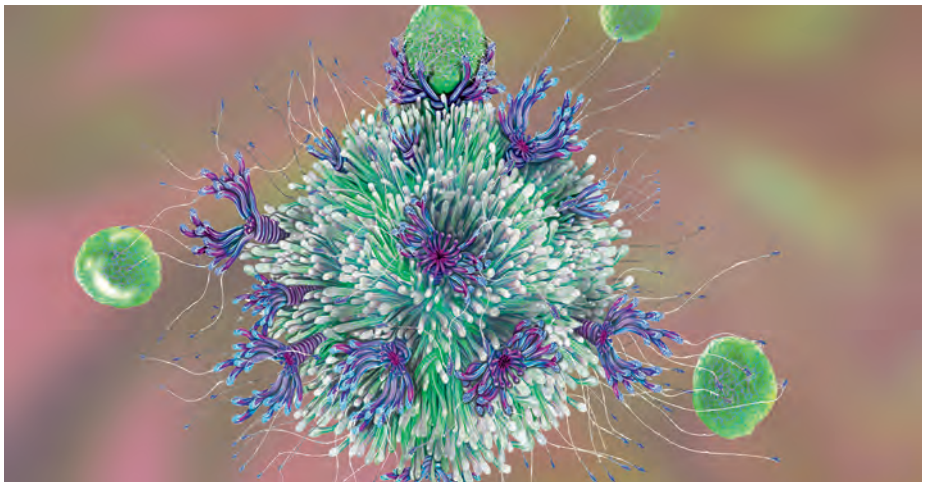
Milestone 10



T cell response to antigen is enabled by costimulation

Recognition of antigens is prompt and specific. But should a T cell initiate an unstoppable chain reaction of destruction against the intruder? Is it an intruder at all? It all depends on the circumstances. T cells have a number of sensors with which they receive information from soluble factors in their microenvironment and from other interacting cell types. Those signals are then integrated to determine the response, which could be attack but could also be tolerance.

T cell co-stimulatory receptors are monovalent molecules that do not contribute to antigen-recognition specificity; however, they receive signals from the environment and are necessary for full T cell activation.

A decade after the discovery of monoclonal antibodies in the 1970s, technology enabled the mapping of surface proteins on T cells. One of these molecules, astonishingly, showed similarity to immunoglobulins, which prompted the hypothesis that T cells recognize antigens with the same high le vel of specificity as antibodies. And indeed, T cells are equipped with an antigen-sensing surface receptor, which today is called the T cell antigen receptor (TCR) (Milestone 8).

What was puzzling for immunologists of the day was the presence of several other molecules on T cells, independent of the TCR, that responded to antagonistic stimulation by cognate antibodies with phenotypic changes, ranging from proliferation and production of the cytokine IL-2 to inhibition of T cell functions.

In 1986, two independent research groups discovered that a surface antigen, called Tp44, transmits T cell-activation signals. Martin and colleagues established, by competitive antibody-binding experiments, that epitope recognition by antibodies to Tp44 and those to the TCR invariant chain CD3 is mutually exclusive. Stimulation with antibody to Tp44 (anti-Tp44) had no effect on either expression of the IL-2 receptor (regulated by engagement of the TCR or CD3) or release of IL-2 (regulated by antigen-presenting cell–T cell interaction). However, when the T cells were stimulated by the mitogen concanavalin A or a monoclonal antibody to CD3, which provided a primary TCR signal, engagement by anti-Tp44 induced IL-2 release in the absence of monocytes.

Weiss and colleagues came to the same conclusion about cooperative signalling via engagement of the TCR or CD3 and ligation of Tp44, but went further in exploring the intracellular consequences of ligand engagement, which were hydrolysis of poly-phosphoinositides and calcium release.

These findings had arisen from T cell stimulation under non-natural conditions; thus, their relevance was debated. They are now recognized as milestones for their contribution to the concept that multiple signals are required for maximal T cell activation.

The orphan receptor Tp44, later called CD28, provides a secondary activating signal to T cells after antigen engagement. The discovery of CD28 supported the theory that co-receptors diversify lymphocyte effector function after antigen recognition, resulting in outcomes from tolerance to killing, and from clonal anergy to priming for helper T cell function.

The two milestone studies also indicated downstream signal integration and suggested the hypothesis that antigen-presenting cells express a natural ligand to stimulate the co-receptor CD28. The ligand for CD28 was eventually discovered by Linsley and colleagues 4 years later, in 1990, which proved the physiological relevance of CD28. These researchers over-expressed CD28 in Chinese hamster ovary cells. After co-culture, B cells adhered to the CD28-expressing cells. A mini-library of monoclonal antibodies that recognize molecules on the B cell surface was tested for its capacity to inhibit the CD28-mediated B cell adhesion.

The cognate antigen to the adhesion-blocking antibody was identified as the B cell–activation molecule B7 (also known then as BB-1). Following this pioneering discovery, CTLA-4 was also identified as an additional receptor that engages with B7. CTLA-4 – unlike the constitutively expressed co-stimulatory molecule CD28 – is transiently expressed after T cell activation and functions to limit CD28-dependent activation of T cells by competing for the same ligands but also transmitting inhibitory signals.

The concept of modulating T cell function via activating and inhibitory receptor engagement naturally led to the idea of therapeutic manipulation of T cell signalling via agonistic and antagonistic molecules (Milestone 13). Deborah Lenschow and colleagues demonstrated in 1992 that a soluble fusion protein of the immunoglobulin IgG1 constant region and the extracellular part of CTLA-4 could be used to block binding of B7 to CD28 for therapeutic inhibition of T cell activation in organ transplantation and, potentially, autoimmune diseases. Clinical translation of the approach became a reality in 2003, when Kremer and colleagues reported the successful application of co-stimulation blockers in the treatment of rheumatoid arthritis.

Ildiko Gyory
Senior Editor, *Nature Communications*

Milestone studies

Martin, P. J. et al. A 44 kilodalton cell surface homodimer regulates interleukin 2 production by activated human T lymphocytes. *J. Immunol.* **136**, 3282–3287 (1986) | Weiss, A. et al. Synergy between the T3/antigen receptor complex and Tp44 in the activation of human T cells. *J. Immunol.* **137**, 819–825 (1986)

Further reading

Please visit the online article for a full list of further reading.