

Viewpoint

Signal 3 and its role in autoimmunity

Ranjeny Thomas

Centre for Immunology and Cancer Research, Princess Alexandra Hospital, University of Queensland, Brisbane, Australia

Corresponding author: Ranjeny Thomas (e-mail: rthomas@cicr.uq.edu.au)

Received: 6 Nov 2003 Accepted: 21 Nov 2003 Published: 19 Jan 2004

Arthritis Res Ther 2004, **6**:26-27 (DOI 10.1186/ar1033)
© 2004 BioMed Central Ltd (Print ISSN 1478-6354; Online ISSN 1478-6362)

What is the third signal?

Dendritic cells (DCs) are the professional antigen-presenting cells (APCs) of the body, and as such play a key role in the signaling of T cells for effector responses to antigen. Various co-stimulatory and adhesive interactions between DCs and T cells are able to drive proliferative, proinflammatory cytokine and cytotoxic effector functions of T cells [1]. The effector response made to antigen presented by DCs depends on the co-stimulatory signals delivered to T cells along with the antigen signal presented in the context of MHC molecules [2]. Lafferty's concept of a second or co-stimulatory signal stands as a key model for our understanding of the generation of immunity, and also for our understanding of the basis for peripheral tolerance [3].

In recent years, through the study of interactions taking place at the immunological synapse, at which T cells are signaled by antigen-bearing APCs, several groups have studied the minimal requirements of CD4⁺ and CD8⁺ T cells for these effector functions. Mescher *et al.*, for example, have done so using a simple system of beads conjugated with MHC and antigen – whose density can be varied – (signal 1), and various membrane co-stimulatory molecules (signal 2), such as CD80/86 or CD54 (ICAM-1). In this context, they have shown for CD8⁺ T cells that signals 1 and 2 are sufficient for proliferation and cytokine production, but that a third signal, IL-12, is required for cytotoxic effector function [4]. The authors indicate that IL-12 is not the only soluble factor which can function as a third signal for CD8⁺ T cells, but that it can be substituted by other, as yet unknown, factors.

In a recent paper, Mescher *et al.* extend the concept of the third signal *in vivo* to show that the presence of signals 1 and 2 but the absence of IL-12 results in peripheral tolerance in the CD8⁺ T-cell compartment [5]. Thus, CD8⁺ T cells are able to proliferate and to produce IFN- γ *in vivo* in the absence of IL-12, but this cytokine production and cytotoxic T-lymphocyte (CTL) activity are limited. The data

are consistent with the work of others, showing the important role of IL-12 in driving IFN- γ effector function by T cells [6]. Further upstream, IL-12 production by DCs has been shown to be driven by dual TLR (toll-like receptor) and CD40 signals [7]. In this regard, it is of interest that the minimum required signals for CD154 (CD40L) expression by CD4⁺ T cells are CD80/86 and CD54, even in the absence of signal 1 [8].

The signal 3 requirements for CD4⁺ T cells are less well defined. Indeed it is more difficult to define an effector function beyond cytokine production for CD4⁺ T cells that is equivalent to the "higher order" effector function represented by CTL activity for CD8⁺ T cells. This is paradoxical, because higher order consequences of CD4⁺ T-cell helper function for B cells, CTL activity and memory are driven largely by CD154 as well as other CD40-dependent and -independent co-stimulatory interactions, including OX40, 41BB, ICOS and other members of the B7 family [1]. Nevertheless, using the readout of IFN- γ production by CD4⁺ T cells as a measure of T helper type 1 (Th1) effector function, Mescher *et al.* previously suggested that IL-1 β could act as a third signal for CD4⁺ T cells [9].

Implications for autoimmune disease pathogenesis

Although most autoimmune diseases are driven principally by autoreactivity of CD4⁺ T cells to self-antigen presented in the context of MHC class II, some – notably type 1 diabetes – show a clear association with CD8⁺ T-cell autoreactivity. IL-12 is a major driver in the pathogenesis of type 1 diabetes in NOD mice, and both IFN- γ and CTL effector function of CD8⁺ T cells in response to self-antigen are critical for disease development and progression [10].

Over the last 10 years, fascinating roles for IL-1 β in autoimmune disease pathogenesis have also emerged. As a "third signal," it appears to have profound roles in the initiation and persistence of autoimmunity beyond its better-

known roles in tissue inflammation, and damage in innate immunity. Besides its capacity to drive the production of IFN- γ and IL-2 by CD4⁺ T cells directly, IL-1 β has been shown by several groups to act on the DC to enhance the production of proinflammatory cytokines, including TNF α and more significantly IL-12, which itself has important effects on the production of IFN- γ by CD4⁺ T cells [11]. Kopf *et al.* recently showed, in a model of autoimmune myocarditis, that mice deficient in IL-1 receptor-1 were resistant to disease induction, but that this resistance could be overcome by the transfer of wild type DCs pulsed with autoantigen, since IL-1 signaling of the DCs now induced IL-12 production and effective autoantigen presentation [12]. Of interest, Sedgwick *et al.* have demonstrated that, rather than IL-12, the more recently discovered IL-23, also with the capacity to drive production of IFN- γ by CD4⁺ T cells, was essential for the pathogenesis of the autoimmune central nervous system inflammatory disease, experimental allergic encephalomyelitis [13].

Lastly, an IL-1 receptor antagonist (IL-1ra) deficiency on a BALB/c but not C57Bl/6 background leads to the spontaneous development of inflammatory arthritis [14-16]. This highlights the critical role of IL-1ra in the constitutive maintenance of peripheral tolerance, and in counterbalancing the proinflammatory effects of IL-1 and IL-17.

Conclusions

Although apparently simple, the concept of a third (cytokine) signal for T-cell responses to antigen is also powerful, in that elucidation of third signals in simple *in vitro* systems has enabled essential ingredients that drive spontaneous autoimmunity to be defined. A model for T-cell activation can be envisaged in which each T cell integrates a range of proinflammatory, stimulatory and regulatory signals to determine the effector functions activated. In this model, one can imagine that in autoimmune-prone individuals, the contributions of each signal may be altered, through polymorphisms in the genes responsible for production of, or response to, the signal. Alternatively, environmental factors, such as infectious or toxic signals, may reset the signal threshold. Together, the genetically determined settings of the T-cell response mechanism and the environmental exposure history, for each individual, govern the risk of autoimmune disease manifestation. Finally, the mandatory contribution of signals other than antigen to T-cell activation supports the current model in which interaction of the innate and adaptive immune systems determines the outcome of antigen exposure not only at sites of tissue inflammation and destruction, but also at the time of antigen presentation. This model highlights the role of innate and adaptive immune system interactions in the failure of peripheral tolerance. It will be fascinating in the future to extend this concept to understand the impact of third signals on failure of mechanisms of central tolerance in the thymus.

Competing interests

None declared.

References

1. Delon J, Stoll S, Germain RN: **Imaging of T-cell interactions with antigen presenting cells in culture and in intact lymphoid tissue.** *Immunol Rev* 2002, **189**:51-63.
2. O'Sullivan B, Thomas R: **CD40 and dendritic cell function.** *Crit Rev Immunol* 2003, **23**:83-107.
3. Gill RG, Coulombe M, Lafferty KJ: **Pancreatic islet allograft immunity and tolerance: the two-signal hypothesis revisited.** *Immunol Rev* 1996, **149**:75-96.
4. Valenzuela J, Schmidt C, Mescher M: **The Roles of IL-12 in Providing a Third Signal for Clonal Expansion of Naive CD8 T Cells.** *J Immunol* 2002, **169**:6842-6849.
- 5.* Curtsinger JM, Lins DC, Mescher MF: **Signal 3 determines tolerance versus full activation of naive CD8 T cells: dissociating proliferation and development of effector function.** *J Exp Med* 2003, **197**:1141-1151.
6. Banchereau J, Paczesny S, Blanco P, Bennett L, Pascual V, Fay J, Palucka AK: **Dendritic cells: controllers of the immune system and a new promise for immunotherapy.** *Ann N Y Acad Sci* 2003, **987**:180-187.
7. Schulz O, Edwards DA, Schito M, Aliberti J, Manickasingham S, Sher A, Reis e Sousa C: **CD40 triggering of heterodimeric IL-12 p70 production by dendritic cells in vivo requires a microbial priming signal.** *Immunity* 2000, **13**:453-462.
8. Ding L, Green JM, Thompson CB, Shevach EM: **B7/CD28-dependent and -independent induction of CD40 ligand expression.** *J Immunol* 1995, **155**:5124-5132.
9. Curtsinger JM, Schmidt CS, Mondino A, Lins DC, Kedl RM, Jenkins MK, Mescher MF: **Inflammatory cytokines provide a third signal for activation of naive CD4+ and CD8+ T cells.** *J Immunol* 1999, **162**:3256-3262.
10. Adorini L, Gregori S, Harrison LC: **Understanding autoimmune diabetes: insights from mouse models.** *Trends Mol Med* 2002, **8**:31-38.
11. Luft T, Jefford M, Luetjens P, Hochrein H, Masterman KA, Maliszewski C, Shortman K, Cebon J, Maraskovsky E: **IL-1 beta enhances CD40 ligand-mediated cytokine secretion by human dendritic cells (DC): a mechanism for T cell-independent DC activation.** *J Immunol* 2002, **168**:713-722.
12. Eriksson U, Kurrer MO, Sonderegger I, Izzi G, Tafuri A, Hunziker L, Suzuki S, Bachmaier K, Bingisser RM, Penninger JM, Kopf M: **Activation of dendritic cells through the interleukin 1 receptor 1 is critical for the induction of autoimmune myocarditis.** *J Exp Med* 2003, **197**:323-331.
- 13.* Cua, DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymour B, Lucian L, To W, Kwan S, Churakova T, Zurawski S, Wiekowski M, Lira SA, Gorman D, Kastelein DA, Sedgwick JD: **Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain.** *Nature* 2003, **421**:744-748.
14. Nakae S, Asano M, Horai R, Sakaguchi N, Iwakura Y: **IL-1 enhances T cell-dependent antibody production through induction of CD40 ligand and OX40 on T cells.** *J Immunol* 2001, **167**:90-97.
15. Horai R, Saijo S, Tanioka H, Nakae S, Sudo K, Okahara A, Ikuse T, Asano M, Iwakura Y: **Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin 1 receptor antagonist-deficient mice.** *J Exp Med* 2000, **191**:313-320.
16. Nakae S, Saijo S, Horai R, Sudo K, Mori S, Iwakura Y: **IL-17 production from activated T cells is required for the spontaneous development of destructive arthritis in mice deficient in IL-1 receptor antagonist.** *Proc Natl Acad Sci USA* 2003, **100**:5986-5990.

Note

* These papers have been highlighted by Faculty of 1000, a web-based literature awareness service. F1000 evaluations for these papers are available on our website at http://arthritis-research.com/viewpoints/reflinks6_01.asp

Correspondence

Ranjery Thomas, Centre for Immunology and Cancer Research, Princess Alexandra Hospital, University of Queensland, Brisbane, 4102, Australia. Tel: +61 7 32405365; fax: +61 7 32405946; e-mail: rthomas@cicr.uq.edu.au