Viewpoint

Signal 3 and its role in autoimmunity

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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-1β 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-1β 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-

APC = antigen presenting cell; CTL = cytotoxic T-lymphocyte; DC = dendritic cell; IFN-γ = interferon-γ; IL = interleukin; IL-1ra = IL-1 receptor antagonist; MHC = major histocompatibility complex; Th = T helper cell; TLR = Toll-like receptor; TNF = tumor necrosis factor

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-1β has been shown by several groups to act on the DC to enhance the production of proinflammatory cytokines, including TNFα 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.

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Note

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