CTLA-4 up-regulation plays a role in tolerance mediated by CD45

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Many inhibitory molecules have been described on the surface of various cells of the lymphoid system. Fecteau *et al*.[1] demonstrate the functional outcome of, and mechanism by which, CTLA-4 is responsible for graft survival induced by treatment with an antibody to CD45RB[2]. To describe and explain their findings, Fecteau *et al*. use the 'signal 1' terminology put forward by Schwartz and colleagues[3], which, in turn, was based on the original concepts of Bretscher and Cohn[4]. These first identified signals *via* the antigen-receptor, along with those described by Matzinger[5], were considered to be negative signals that costimulation[3], associative recognition (or signal 2)[4] and danger[5] reversed. None of these two-signal theories[3–5] included a mechanism that was independent of, but interacting with, antigen-receptors and second signals as essential in the negative regulation of immune responses. Negative regulation was the product of simple antigen-receptor engagement.

The observations of Fecteau *et al*.[1] are better understood if one conceptualizes a three-signal model[6] in which negative regulation is assigned to an independent molecule, such as CTLA-4, that is influenced by and influences signaling *via* the antigen-receptor. In a three-signal model, the antigen-receptor is now considered to be an activating mechanism rather than an anergy- or tolerance-inducing mechanism. Tolerance is assigned instead to many coinhibitors, including CTLA-4.

This distinction should not be thought of as a question of semantics. In two-signal thinking, one induces anergy or tolerance by avoiding costimulation, needing only the negative signal *via* the antigen receptor (signal 1) to have its negative effect. In three-signal thinking, one does what Fecteau *et al*. did[1], increase the activity of a coinhibitor (CTLA-4) to get a negative effect. One could also lower costimulation to allow a coinhibitor to express its negative effect. In addition, as suggested by Fecteau *et al*., one must be careful not to interfere with coinhibition. In terms of the three-signal model, signal 1 is not a negative signal *via* antigen receptors but, instead, a negative signal *via* coinhibitory receptors, such as CTLA-4.

Lastly, many immunoreceptor tyrosine-based inhibitory motifs (ITIMs) occur on activating pathways and a wide range of inhibitory pathways[7]. Thus, negative signaling may not be restricted to a series of specialized coinhibitory receptors so that signal 1 may be divided into at least three subgroups: those mediated by specialized coinhibitory receptors; activating pathways; and regulatory pathways not activated by coinhibitory receptors. Because ITIMs are not the exclusive mechanism for negative signaling[8], elements involved in negative signaling may extend even further. However, as elegantly shown by Fecteau *et al*., specialized coinhibitory receptors, such as CTLA-4, are functionally important.

1. Fecteau, S. *et al. Nature Immunol.* **2,** 58–63 (2001).
2. Lazarovits, A. *et al. Nature* **380,** 717–720 (1996).
3. Schwartz, R. H., Mueller, D. L. Jenkins, M. K. & Quill, H. *Cold Spring Harb. Symp. Quant. Biol.* **54,** 605–610 (1989).
4. Bretscher, P. & Cohn, M. *Science* **169,** 1042–1049 (1970).
5. Matzinger, P. *Annu. Rev. Immunol.* **12,** 991–1045 (1994).
6. Sinclair, N. R. StC. *Cell. Immunol.* **130,** 204–212 (1990).
7. Sinclair, N. R. StC. *Crit. Rev. Immunol.* **20,** 89–102 (2000).
8. Fong, D. C. *et al. J. Immunol.* **165,** 4453–4462 (2000).