CORRESPONDENCE

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 CD45RB². To describe and explain their findings, Fecteau et al. use the 'signal 1' terminology put forward by Schwartz and colleagues³, which, in turn, was based on the original concepts of Bretscher and Cohn4. These first identified signals via the antigen-receptor, along with those described by Matzinger⁵, were considered to be negative signals that costimulation3, associative recognition (or signal 2)4 and danger5 reversed. None of

these two-signal theories3-5 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 model6 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.

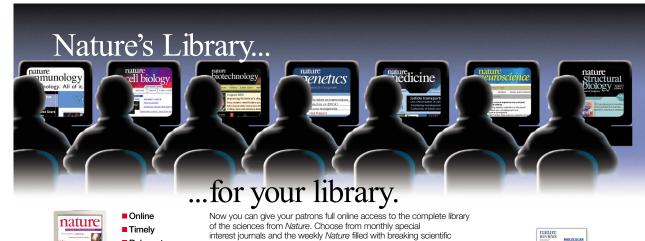
This distinction should not be thought of as a question of semantics. In two-signal thinking, one induces anergy or tolerance by avoiding costimulation, needing only the negative signal via the antigen receptor (signal 1) to have its negative effect. In three-signal thinking, one does what Fecteau et al. did1, 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 pathways7. 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 signaling8, 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.

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