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Response to Taraban, Ferdinand, and Al-Shamkhani

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Letter

We demonstrated that the TNF receptor superfamily member 25 (TNFRSF25) agonistic antibody 4C12 drives the in vivo proliferation of preexisting CD4+FoxP3+ cells (Tregs) but not that of conventional CD4 cells (Tconvs) (1). TNFRSF25-mediated Treg proliferation depends upon MHC II loaded with self-antigen and is blocked by calcineurin inhibitors. If antigen is provided to Tconvs in vitro or in vivo, TNFRSF25 signals also costimulate proliferation and effector cell activity (2–5). Thus, Treg proliferation to TNFRSF25 signals is due to the continuous presence of self-antigenic stimulation of the TCR in vivo, rather than to the level of TNFRSF25 expression. TNFRSF25-mediated Treg expansion is not unique to the agonistic 4C12 antibody, as a TL1A-Ig fusion protein mediates similar Treg expansion in vivo (unpublished observations). In support of this conclusion, the subsequent reports by Al-Shamkhani's group and Siegel's group demonstrated that in transgenic mouse models overexpressing TL1A, Tregs proliferate at high frequencies throughout the secondary lymphoid organs and have increased frequencies of Tconvs with an effector/memory phenotype systemically, resulting in mice that are prone to spontaneous inflammatory bowel disease (6, 7). Meylan et al. also demonstrate that TL1A inhibits the de novo induction of Tregs from Tconvs in vitro (7). Both of these recent reports agree that TNFRSF25 attenuates the suppressive capacity of Tregs. In a letter to the JCI, Al-Shamkhani and colleagues provide […]

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In a letter to the *JCI*, Al-Shamkhani and colleagues provide evidence that the level of expression of TNFRSF25 appears much more similar between Tregs and Tconvs than we originally reported. In recent studies, we have further explored the binding of additional anti-TNFRSF25 antibodies and TL1A-Ig fusion proteins generated in our laboratory to Tregs and Tconvs by flow cytometry. We have found clone-specific variations in the intensity of TNFRSF25 staining between Tconvs and Tregs, which suggests that, as indicated by Al-Shamkhani, the absolute expression of TNFRSF25 between Tconvs and Tregs is not a key determinant in the proliferative specificity of TNFRSF25 agonists or TL1A to Tregs. Instead, as both our and Siegel's group concluded, the determining factor of TNFRSF25 action in vivo is the availability of cognate antigen, with self-antigen continuously present for Treg expansion.

Together, these three reports agree that TNFRSF25 is a regulator of Treg proliferative responses, both with the natural ligand (TL1A) and with receptor agonistic reagents (antibodies and fusion proteins). In the transgenic systems used by Taraban and colleagues and Meylan et al., the continuous availability of TL1A stimulates both the proliferation of Tregs and activation of antigen-experienced effector/memory phenotype Tconvs systemically (6, 7). The finding by Meylan et al. with regard to inhibition of in vitro iTreg generation by TL1A is consistent with the possibility of a role for TL1A in inflammatory bowel disease, in which tolerance to endogenous microbial antigens may have been disrupted by transgenic overexpression of TL1A (7). The balance of TNFRSF25 triggering regulatory or effector immunity is likely dependent upon the availability of cognate antigen to Tregs or Tconvs and not on absolute differences in the expression of the receptor between each subset.

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Conflict of interest: Eckhard R. Podack and Taylor H. Schreiber have patent applications relevant to material described in this manuscript. Any potential conflicts of interest are managed by the University of Miami Miller School of Medicine.

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