

TGF β 1 Prevents Autoimmune Disease by Maintaining [Ca²⁺]_i Homeostasis in T Cells

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Transforming growth factor *beta*1 (TGF β 1) is a polypeptide growth modulatory and differentiation factor involved in many biological processes including immune homeostasis and self-tolerance. *Tgfb1* knockout mice die around weaning age due to severe inflammation in most major organ systems. In *Tgfb1*^{-/-} mice immature thymic T lymphocytes are hyper-responsive to mitogenic stimulation whereas mature splenic T cells are hypo-responsive to receptor-mediated mitogenic stimulation. Our results demonstrate that immature DP, and SP thymocytes exhibit elevated [Ca²⁺]_i levels. In *Tgfb1*^{-/-} thymocytes Ca²⁺ flux, in response to anti-CD3, is either not affected (CD4⁺CD8⁺DP thymocytes) or is increased (CD4⁺CD8⁻SP thymocytes). In *Tgfb1*^{-/-} mice mature splenic T cells are already activated *in vivo* as evidenced by elevated basal [Ca²⁺]_i levels, reduced Ca²⁺ flux upon stimulation, decreased CD3 expression, increased LFA-1 expression, and increased cell size. Our data demonstrate that the hypo-responsiveness of *Tgfb1*^{-/-} splenocytes is due to prior activation of T cells resulting from deregulated [Ca²⁺]_i levels. The present findings suggest that TGF β 1 functions to inhibit aberrant T-cell expansion and autoimmunity by maintaining [Ca²⁺]_i levels low enough to prevent a mitogenic response in the absence of optimal stimulation.