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**Peripheral Immune Tolerance Abrogation in Lupus erythematosus-
Intrinsic Threshold Defects of T cell Activation in the MRL Mouse Strain**

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In systemic lupus erythematosus (SLE), T and B cell interactions result in the generation of autoantibodies and immune complexes, which, along with autoreactive T cells, cause pathology in multiple target organs. Disease is the result of a cascade of events that occur on the background of an appropriate genetic predisposition. The final disease phenotype is most likely the result of many interactions arising from an initial loss of peripheral tolerance followed by the amplification of specific autoimmune responses.

Polyclonal T cell activation is a consistent feature of murine lupus. However, the precise mechanism of such activation remains elusive. I hypothesized that naïve $CD4^+$ T cells in lupus have a lower threshold of activation through their (TCR-CD3)- complex that renders them more susceptible to stimulation with self-antigens.

To test this hypothesis, I compared population based and single cell proliferation, apoptosis and cell death, early and late activation and effector marker up-regulation and IL-2 production of naïve $CD4^+$ T cells isolated from Fas-intact MRL/+$^{Fas\text{-}lpr}$ and H-2^k matched B10.BR and CBA/CaJ controls, following anti-CD3 stimulation in the presence or absence of co-stimulatory CD28. I also assessed the responsiveness of naive $CD4^+$ T cells isolated from Fas-intact MRL and control mice bearing a rearranged TCR specific for amino acids 88-104 of pigeon cytochrome C (PCC) to cognate and low affinity peptide antigens presented by CH27 B lymphoblastoid and bone marrow-matured dendritic cells.

TCR transgenic and wild type $CD4^+$ T cells from MRL mice were found to display a lower threshold of activation than control cells, a response that was shown to be class II MHC dependent. Unlike previously suggested, DC from the lupus-prone MRL mice did not display any abrogations in their stimulatory potential compared to control DC. Thus, this data suggests that peripheral immune tolerance abrogation in lupus is due to polyclonal activation of $\alpha\beta$ T cells as a result of a heightened response to peptide antigens, especially to those of

low affinity, independent of the nature of the antigen presenting cell and degree of co-stimulation.

In order to investigate the biochemical mechanisms underlying this newly defined hyper-excitable T cell phenotype the method of single cell Ca^{2+} imaging of T cells was established in the laboratory. Rise in intracellular Ca^{2+} in MRL versus controls was enhanced and prolonged following anti-CD3 triggering, suggestive of proximal defects in TCR-engendered signaling as the mechanism for the observed hyperactivity. These findings were observed as early as 1-2 months post-weaning, and based upon analysis of F_1 T cells, appeared to be dominantly expressed.

This genetically altered threshold for activation of MRL T cells, a consequence of a proximal defect in CD3-mediated signal transduction, may contribute to the abrogation of T cell tolerance to self-antigens in lupus.