

Dendritic cells from lupus-prone mice are defective in repressing immunoglobulin secretion

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Systemic Lupus Erythematosus (SLE) is a multiorgan autoimmune disease characterized by the production of autoantibodies to nuclear components. Autoimmunity results from a breakdown in tolerance mechanisms that regulate autoreactive lymphocytes. Understanding the mechanisms that regulate autoreactive B cells could lead to more specific therapies that re-establish tolerance in SLE patients. Recently, we identified a novel mechanism of tolerance wherein dendritic cells (DCs) and macrophages (MΦs) repressed immunoglobulin (Ig) secretion by autoreactive B cells. Our data showed that DCs and MΦs secreted IL-6 that repressed Ig secretion during innate immune responses. Significantly, IL-6 selectively repressed autoreactive, but not naïve B cells. Therefore, the lack of repressive soluble factors, like IL-6, or the inability to differentially respond to these factors on the part of the autoreactive B cell, could lead to a breakdown in tolerance, resulting in autoantibody secretion during innate immune responses.

We hypothesize that DC and/or MΦ-mediated tolerance mechanisms are dysfunctional in murine models of lupus disease. Here, we describe that TLR4-activated DCs from lupus-prone, MRL/*lpr*, mice are defective in repressing autoantibody secretion, coincident with diminished IL-6 secretion. Reduced production of IL-6 by MRL/*lpr* DCs reflected the failure to sustain IL-6 mRNA synthesis, coincident with lack of NF-κB translocation, and failure to sustain IκBα phosphorylation. Analysis of individual mice showed that some animals partially repressed Ig secretion despite reduced levels of IL-6. This suggests that, in addition to IL-6, DCs secrete other soluble factor(s) that regulate autoreactive B cells. Collectively, the data show that MRL/*lpr* mice are defective in DC/IL-6-mediated tolerance, but that some individuals maintain the ability to repress autoantibody secretion by alternative mechanisms.