#50: Mechanisms of apoptotic cell-mediated dysregulation of germinal center tolerance checkpoint: Implications in autoimmunity

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High-affinity antibody-secreting B cells are generated through somatic hypermutations (SHM) in their immunoglobulin genes. SHM occurs in B cells within germinal centers (GCs), in secondary lymphoid organs. Owing to its random nature, SHM generates autoreactive B cells as by-products, which are deleted by GC-specific peripheral tolerance mechanisms. Loss of GC tolerance leads to positive selection and expansion of autoreactive B cells causing autoantibody production, as in systemic lupus erythematosus (SLE). One contributing factor in murine and human SLE is inefficient clearance of apoptotic cells. Patients with SLE usually show a deficiency in clearing apoptotic cells. TAM (Tyro-3, Axl and Mer) receptor tyrosine kinases (TAM-RTKs) along with their ligands PROS-1 and/ Gas6 are involved in the efficient clearance of ACs in mice and humans and signal to inhibit innate immune responses. TAM-RTKs are expressed on myeloid cells. Their deficiency or aberrant function can lead to autoimmunity. Polymorphisms in Mer tyrosine kinase (MerTK) gene are associated with human SLE and multiple sclerosis. In previous studies form our lab we demonstrated that (MerTK) deficiency results in apoptotic cell accumulation in GCs, loss of B cell tolerance, Th1 cytokine induction, and autoimmunity in mice. To delineate the mechanism(s) of MerTK-dependent dysregulation of germinal center responses, we reasoned that MerTK signaling could directly affect antigen-presentation by macrophages and other APCs; possibly also resulting in increased self-antigen presentation. To test the hypothesis, we analyzed OT-II T cell proliferation in MerTK deficient (Mer-/-) vs WT mice after OVA-immunization. We observed increased proliferation of OT-II T cells in Mer-/- mice compared to WT mice. To further delineate which APCs in the GC environment could contribute to increased Ag-presentation we used in-vitro OVA antigen-presentation system. B cells, bone marrow derived DCs (BMDCs) or bone marrow derived macrophages (BMM) from Mer-/- or WT mice were used as APCs. We observed more proliferation of OT-II T cells when cultured with B-APC and DC-APC from Mer-/- mice compared to WT mice. However, very interestingly, MHC-II dependent antigen-presentation by BMM only occurred in the presence of apoptotic cells.

We propose that defective MerTK signaling causes enhanced antigen presentation by APCs especially in the presence of apoptotic cells, which promotes activation of T cells even with low affinity for self-antigens. Therefore, in the presence of ACs, even low affinity activated autoreactive BCRs find help from T cells to get positively selected in the GCs leading to autoantibody production. Further studies are underway to confirm these observations.