Patients with auto-immune disorders have low HDL levels. Mice deficient in genes regulating cholesterol homeostasis, such as liver X receptor (LXR) or apolipoprotein A1 (apoA1), show an autoimmune phenotype. LXR regulates the expression of ATP Binding Cassette A1 and G1 (ABCA1 and ABCG1) that mediate cholesterol efflux to apoA1 and HDL. ABCG1 is highly expressed in dendritic cells (DCs). We hypothesized that ABCA1 and ABCG1 regulate autoimmunity.

On a chow diet, 40 weeks old Abca1-/-Abcg1-/- mice showed enlarged lymph nodes (LNs), increased plasma auto-antibodies to dsDNA, and glomerulonephritis, with characteristics typical for lupus nephritis. Using the Cre loxP system, we investigated whether these effects were due to Abca1/g1 deficiency in T-cells, macrophages, or DCs. Only Abca1/g1 deficiency in DCs in CD11cCreAbca1fl/flAbcg1fl/fl mice replicated the auto-immune phenotype found in Abca1-/-Abcg1-/- mice. This suggests a major role for DC cholesterol homeostasis in autoimmunity.

DCs present antigens to T-cells, leading to their activation. CD11cCreAbca1fl/flAbcg1fl/fl mice showed increased T-cell activation in blood, spleen, and LNs. After immunization, DCs from CD11cCreAbca1fl/flAbcg1fl/fl mice showed increased antigen presentation to T-cells in vitro and in vivo. CD11cCreAbca1fl/flAbcg1fl/fl mice had increased CD80+ DCs. CD80 is a co-stimulatory molecule required for antigen presentation. Abca1/g1 deficiency in DCs increased endosomal cholesterol accumulation in vitro. Ligands for Toll like receptor (TLR) 3 and 4 increased CD80 mRNA in CD11cCreAbca1fl/flAbcg1fl/fl compared to Abca1fl/flAbcg1fl/fl DCs, where the effect of ligands for TLR3>TLR4. Cholesterol depletion by cyclodextrin decreased CD80 mRNA and antigen presentation in CD11cCreAbca1fl/flAbcg1fl/fl DCs in vitro. The increased CD80 mRNA in CD11cCreAbca1fl/flAbcg1fl/fl DCs was also reversed by a type I interferon (IFN) antibody, suggesting excessive signaling by the known TLR3-IFN-CD80 axis. These studies show for the first time a role for cholesterol efflux pathways in DCs in maintaining immune tolerance.