

Control of autoimmune T cell responses by hypercholesterolemia

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Patients with systemic autoimmune diseases show increased incidence of atherosclerosis. However, the contribution of proatherogenic factors to autoimmunity remains unclear. The atherosclerosis-associated autoimmune diseases include psoriasis, rheumatoid arthritis, and systemic erythematosus lupus. Since these immune disorders are known to be mediated by aberrant autoimmune T cell responses, we hypothesize that proatherogenic factors impact the differentiation and/or effector function of autoreactive T cells. We found that atherogenic mice (herein referred to as LDb mice) exhibited increased serum interleukin-17, which was associated with increased numbers of T helper 17 (Th17) cells in secondary lymphoid organs. The environment within LDb mice was substantially favorable for Th17 cell polarization of autoreactive T cells during homeostatic proliferation, which was considerably inhibited by antibodies directed against oxidized low-density lipoprotein (oxLDL). The uptake of oxLDL induced dendritic-cell-mediated Th17 cell polarization by triggering IL-6 production in a process dependent on TLR4, CD36, and MyD88. Self-reactive CD4⁺ T cells that expanded in the presence of oxLDL induced more profound experimental autoimmune encephalomyelitis, and LDb mice treated with anti-oxLDL exhibited reduced autoreactive Th17 cell responses *in vivo*. In addition, ApoE-deficient mice fed on high-fat diet exhibited exaggerated germinal center reactions associated with enhanced follicular T helper (Tfh) cell population and decreased follicular regulatory T (Tfr) cell population. ApoE-deficient recipients of lupus-prone BXD2 bone marrow had remarkably elevated amounts of autoantibodies to dsDNA and histone, particularly IgG2c isotype. The atherogenic mice exhibited increased level of IL-27 in circulation. T cells stimulated with IL-27 induced increased production of IgG2c from B cells. Furthermore Ebi3xapoE-doubly deficient mice showed significantly diminished germinal center reactions in comparison to ApoE-deficient mice *in vivo*. These findings together demonstrate that proatherogenic factors promote the polarization and inflammatory function of autoimmune Th17 cells and Tfh cells, which could be critical for the pathogenesis of atherosclerosis and other related autoimmune diseases.