A Natural Repertoire of T Cells Recognizing ApoB-100 is Generated Early in Life and is Progressively Depleted During Atherosclerotic Disease

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Background: A large body of evidence implicates a role for T cell driven auto-immunity in atherosclerosis. T cells in the atherosclerotic plaque specifically respond to auto-antigens, including ApoB-100, the main protein in low-density lipoprotein (LDL). However, existence, function, and location of auto-reactive T cells in mice have not been demonstrated.

Methods and Results: We have previously identified several peptides derived from mouse ApoB-100 that bind with high affinity to the I-A^b MHC class II molecule of C57BL/6 mice. Immunization with these peptides conferred atheroprotection. We designed a novel fluorochrome-labeled P6:I-A^b multimer to detect T cells specifically recognizing this complex by flow cytometry. Surprisingly, we detected small numbers of P6:I-A^{b+} $CD4^+$ T cells in young C57Bl/6 mice that reside in peripheral lymph nodes, indicating the existence of a small natural repertoire of P6:I-A^b auto-reactive T cells. This repertoire of T cells was increased in atherosclerosis-prone A*poe*$^{-/-}$ and *Ldlr*$^{-/-}$ mice and showed signs of previous antigen-exposure in 4 week old animals. T cells recognizing P6:I-A^b were undetectable directly after birth, but expanded rapidly within the first 28 days in lymph nodes. The majority of P6:I-A^{b+} T cells expressed the defining transcription factors of T_H1, T-bet, T_H17, ROR-gamma T, or of T-regulatory cells, FoxP3. Feeding of Apoe$^{-/-}$ mice with a western diet induced a further skew towards the T_H1 and T_H17 lineage, but also resulted in a progressive loss of antigen-specific cells over time. In Apoe$^{-/-}$ mice fed with a western diet for 1 year, but not in Apoe$^{-/-}$ mice fed with a standard chow diet, auto-reactive T cells disappeared. Mechanistically, we found enhanced expression of exhaustion markers like ICOS-1 or PD-1 in antigen-specific T cells likely due to persisting antigen-exposure in this model.

Conclusion: Our findings indicate that T cells specifically recognizing a peptide derived from ApoB-100 do not expand during the natural course of disease, but instead exist in atherosclerosis-prone animals in early life. Chronic exposure to antigen induces a progressive loss of auto-reactive T cells.

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