Programmed cell death-1 deficiency exacerbates T cell activation and atherogenesis despite expansion of regulatory T cells in atherosclerosis-prone mice.

T cell activation represents a double-edged sword in atherogenesis, as it promotes both pro-inflammatory T cell activation and atheroprotective Foxp3(+) regulatory T cell (Treg) responses. Here, we investigated the role of the co-inhibitory receptor programmed cell death-1 (PD-1) in T cell activation and CD4(+) T cell polarization towards pro-atherogenic or atheroprotective responses in mice. Mice deficient for both low density lipoprotein receptor and PD-1 (Ldlr(-/-)Pd1(-/-)) displayed striking increases in systemic CD4(+) and CD8(+) T cell activation after 9 weeks of high fat diet feeding, associated with an expansion of both pro-atherogenic IFN?-secreting T helper 1 cells and atheroprotective Foxp3+ Tregs. Importantly, PD-1 deficiency did not affect Treg suppressive function in vitro. Notably, PD-1 deficiency exacerbated atherosclerotic lesion growth and entailed a massive infiltration of T cells in atherosclerotic lesions. In addition, aggravated hypercholesterolemia was observed in Ldlr(-/-)Pd1(-/-) mice. In conclusion, we here demonstrate that although disruption of PD-1 signaling enhances both pro- and anti-atherogenic T cell responses in Ldlr(-/-) mice, pro-inflammatory T cell activation prevails and enhances dyslipidemia, vascular inflammation and atherosclerosis.