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PI3-kinase delta protects against atherosclerosis progression by governing regulatory T-cell biology

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Introduction and Purpose: Atherosclerosis is a chronic inflammatory disease of arteries and represents the main underlying cause of death worldwide. Macrophages are major drivers of atherosclerosis by ingestion of lipoproteins, foam cell formation, and secretion of pro-inflammatory mediators. Although macrophages outnumber other leukocytes in atherosclerotic plaques, T and B lymphocytes can shape the course of disease by promoting or mitigating inflammatory responses. Leukocytes highly express the phosphoinositide 3-kinase isoform delta (PI3Kδ), exerting a key role in the regulation of immune responses including the activation, proliferation, differentiation, and effector function of lymphocytes. Since macrophages and lymphocytes are all major effectors of atherosclerosis, we aimed to understand the role of PI3Kδ in these leukocytes during atherogenesis.

Methods and Results: To investigate the role of haematopoietic PI3Kδ in atherosclerosis, bone marrow from PI3Kδ−/− or PI3Kδ+/+ mice was transplanted into LDLR−/− mice. After 6 weeks of feeding on an atherogenic diet, PI3Kδ−/− recipient LDLR−/− mice displayed significantly impaired CD4+ and CD8+ T-cell numbers, CD4+ T-cell activation, CD4+ effector T cells, and proatherogenic CD4+ T helper (Th) 1 responses in para-aortic lymph nodes and spleen compared with PI3Kδ+/+ transplanted controls. Surprisingly, the net effect of PI3Kδ deficiency was a substantial increase of aortic inflammation and atherosclerosis in LDLR−/− mice. Moreover, haematopoietic PI3Kδ deficiency augmented macrophage accumulation in atherosclerotic plaques of LDLR−/− mice, whereas major macrophage functions including foam cell formation, effecytosis, and cytokine secretion were unaffected by PI3Kδ inactivation in these phagocytes. However, haematopoietic PI3Kδ deficiency led to depletion of atheroprotective B-1 cells and reduction of proatherogenic B-2 cells in LDLR−/− mice. Moreover, haematopoietic PI3Kδ deficiency caused a significant reduction of regulatory CD4+ T cells (Tregs) in plaques, para-aortic lymph nodes, and spleen of LDLR−/− mice. Furthermore, PI3Kδ−/− Tregs exhibited reduced secretion of anti-inflammatory cytokines IL-10 and TGF-β as well as impaired suppression of CD4+ T-cell proliferation. Consequently, adoptive transfer of PI3Kδ+/+ Tregs fully constrains the atherosclerotic burden in PI3Kδ−/− transplanted LDLR−/− mice without affecting B cell numbers.

Conclusions: We demonstrate that PI3Kδ plays a crucial role in B lymphocytes, Th1 cells, and Tregs during atherogenesis. Lack of PI3Kδ signalling in atheroprotective Treg responses outplays its impact on proatherogenic Th1 responses, thus leading to aggravated atherosclerosis. Hence, PI3Kδ is a key regulator of Treg biology and thereby protects against atherosclerosis progression.