Inhibition of pro-inflammatory cytokine Interleukin-17 reduces atherosclerotic lesion development in ApoE−/− mice

Atherosclerotic plaque typically contains infiltrates of activated macrophages and T cells. In human carotid artery plaques, we previously showed the presence of IL-17 producing T cells (Th17) and IL-23. Effects of inhibition of the pro-inflammatory cytokine IL-17 on atherosclerosis development was studied in a rodent model. 15 female ApoE−/− mice fed a normal diet were treated with a specific blocking antibody against IL-17 for 12 weeks (100µg intraperitoneally once per week). For analysis, aortic root was embedded in OCT and serially cryosectioned in 5µm intervals; distal aorta was snap frozen for mRNA analysis. Sections every 75µm were stained with Oil RedO, the lesion area was quantified using PC-based image analysis. In IL-17 mAb treated mice no changes in serum total cholesterol and triglyceride levels was seen. Inhibition of IL-17 markedly reduced atherosclerotic plaque volume by 65%\((p=0.004)\) and fractional stenosis by 52%\((p=0.01)\),and promoted a more stable phenotype of atherosclerotic lesions with the conglomeration of SMCs and higher amount of collagen in the region of the fibrous cap compared to control ApoE−/− mice. Immunohistochemistry revealed significant reduction of T cell \((p=0.002)\) and macrophage \((p=0.015)\) infiltration, and VCAM expression \((p=0.02)\) in atherosclerotic lesions. By quantitative RT-PCR, significantly reduced expression was shown for
CD3e ($p<0.01$), LCK ($p=0.01$), Foxp3 ($p=0.006$) and VCAM ($p<0.001$), but IL-4 expression ($p=0.01$) was upregulated. Using FACS, systemic immunologic changes were shown by the reduction of activated T cells ($p=0.01$), NKT cells ($p=0.002$), regulatory T cells ($p=0.008$) and IFN-$\gamma$ positive cells ($p<0.05$) in the spleens from IL-17 mAb treated mice. In line with the results in vivo, the effects of IL-17 on endothelial cells and macrophages in vitro showed that IL-17 induced NF-$\kappa$B activation and increased the expression of NF-$\kappa$B target genes, including inflammatory cytokines (TNF-a, IL-1$\beta$, IL-6), chemokines (IL-8, MCP-1) and adhesion molecules (ICAM-1, VCAM-1, Eselectin). Our findings suggest a relevant role for IL17-producing T cells in atherosclerosis warranting further study of pathogenic mechanisms and therapeutic potential.