Lili Chen

Dr. med.

Inhibition of pro-inflammatory cytokine Interleukin-17 reduces atherosclerotic lesion development in ApoE$^{-/-}$ mice

Geboren am 08 May, 1974 in Xingshan county, Hubei Province, P. R. China

Examen am Juli 1996, an der Tongji Universität, P.R. China

Promotionsfach: Innere Medizin

Doktorvater: Prof. Dr. med. Thomas J. Dengler

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 contol 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-γ 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-κB activation and increased the expression of NF-κB target genes, including inflammatory cytokines (TNF-a, IL-1β, 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.