ENGINEERED REGULATORY T CELL ADOPTIVE THERAPY AS A NOVEL TOOL FOR THE TREATMENT OF ATHEROSCLEROSIS

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Aim: Loss of anti-inflammatory activity of Tregs has been associated to immunoinflammatory diseases, including atherosclerosis. Therefore, the use of Treg-Adoptive Cell Therapy(ACT) is emerging as a therapeutic strategy to specifically modulate impaired immune responses. Although ACT has produced encouraging results in animal models, a main limitation remains the possibility to target a selected tissue. Our aim was to develop a plaque-homing selective Treg-ACT in models of atherosclerosis.

Methods: Treg were retrovirally (IRES-EGFP vector) transfected with chemokine receptors or an empty vector and i.v. injected ($2x10^5$GFP+ cells/mouse) in male 8-week WTD LDLR-KO. Homing of transfected Treg to atherosclerotic plaque, its progression and composition was analysed by flow-cytometry and histology.

Results: The chemokine CX3CL1is selectively expressed in the aorta, but not in other tissues (lymph nodes, spleen and liver) of 8-week WTD LDLR-KO, contrary to CCL2, usually associated with inflammation during atherosclerosis. Therefore, we compared homing of CCR2- and CX3CR1-transfected Treg to the aorta. While migration of CCR2-Treg was not selective, CX3CR1-Treg showed a specific homing to atherosclerotic plaque ($p<0.05$) with similar homing in lymph nodes and spleen. Next, we investigated whether CX3CR1-Treg reduce atherosclerosis by performing plaque analysis 4weeks after ACT. Altough levels of plasma cholesterol were similar, CX3CR1- vs control-Treg treated mice showed decreased plaque area and macrophage infiltration and increased stability($p<0.05$).

Conclusion: CX3CL1/CX3CR1axis targets selective migration to the atherosclerotic plaque. Overexpressing CX3CR1appears a promising ACT to promote selective homing of Treg into the plaque thus limiting atherosclerosis progression.