Title: ***Marcophage proliferation during plaque regression in response to cholesterol lowering***

Introduction: Guidelines recommend cholesterol lowering for primary and secondary prevention of cardiovascular disease. While lipid lowering has been reported to induce plaque regression, the underlying mechanisms have remained speculative. We hypothesized that lipid uptake triggers local macrophage proliferation in the plaque, and conversely, statin treatment inhibits local macrophage proliferation leading to plaque regression.

Medthods: APOE*3-Leiden.huCETP mice with established atherosclerosis were randomized to three groups: Continued cholesterol diet, cholesterol diet supplemented with 0.01% atorvastatin, and cholesterol free diet for 4 weeks to study mechanisms of plaque regression. Mixed bone marrow chimeras were generated in LDLR-/- mice reconstituted with wild type and scavenger receptor deficient, cholesterol exporter or NLRP3 deficient bone marrow cells to study cell autonomous effects on macrophage proliferation.

Results: Proliferation of scavenger receptor deficient macrophages with impaired lipid uptake was reduced by 30-50% in the plaque, while ABCA1/ABCG1 exporter deficiency resulted in cholesterol overloading and apoptosis. Triggering of macrophage proliferation is partially mediated by NLRP3. Oral atorvastatin treatment decreased total plasma cholesterol levels by 50% to the same extend as cholesterol free diet feeding in APOE*3-Leiden.huCETP. Cholesterol lowering resulted in a 50% reduction in local macrophage proliferation and plaque regression with reduced macrophage and lipid contents and increased collagen. The phenotype was independent of pleiotropic statin effects. GFP bone marrow reconstitution of APOE*3-Leiden.huCETP mice in which the aortas were shielded from irradiation showed infiltrating monocytes to contribute only 11% to the plaque macrophage pool during plaque progression, thereby underscoring the relevance of targeting macrophage proliferation for plaque regression. Finally, rates of macrophage proliferation in human carotid artery plaques correlated with serum LDL-cholesterol levels, in line with our experimental studies.

Conclusion: Our study identifies macrophage proliferation as the predominant turnover determinant and an attractive target for inducing plaque regression.

References: Härdtner C et al. Curr Opin Lipidol. 2021; Härdtner C et al. Basic Res Cardiol. 2020; Robbins CS et al. Nat Med. 2013.