# Integrative single cell RNA-sequencing descrambles a substantial divergence of adaptive immune cell identities and transcriptional programs in mouse and human atherosclerosis

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**Aims:** The distinct function of immune cells in human atherosclerosis has been mostly defined by preclinical mouse studies. Contrastingly, the immune cell composition of human atherosclerotic plaques and their contribution to disease progression is only poorly understood. It remains uncertain whether genetic animal models allow for valuable translational approaches.
**Methods and results:** We performed single cell RNA-sequencing (scRNAseq) to define the immune cell landscape in human carotid atherosclerotic plaques. The human immune cell repertoire was dominated by T cells with a considerable inter-patient variability and an unexpected heterogeneity. We performed bioinformatical integration with 7 mouse data sets and discovered a total of 38 cellular identities, of which some were not conserved between species and exclusively found in mice or humans. Locations, frequencies, and transcriptional programs of immune cells in preclinical mouse models did not resemble the immune cell landscape in human atherosclerosis. In contrast to mice, human plaques were not myeloid- and B cell-dominated and instead contained several T cell phenotypes with hallmarks of T cell memory, dysregulation, exhaustion, and activation. Human immune cells were predominantly enriched for transcriptional programs of hypoxia, glucose, and autoimmunity. In a validation cohort of 43 patients activated immune cell subsets defined by multi-colour flow cytometry associated with cerebral ischemia and coronary artery disease.
**Conclusion:** Here, we uncover yet undefined immune cell types associating with clinical disease. This leukocyte atlas of human atherosclerosis builds the conceptual basis for subsequent identification of cellular targets for clinical immunomodulatory therapies and risk prediction.