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Human atherosclerotic plaque macrophages associate with clinical presentation and follow diverse lineage differentiation routes

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Atherosclerosis is characterized by inflammation and lipid accumulation, leading to complications such as stroke and myocardial infarction. Various macrophage subsets are present in human atherosclerotic plaques. However, it is unclear how subsets are interrelated and contribute to the disease process and its clinical outcomes.

Here, we employed single-cell RNA-seq (scRNA-seq) on blood and plaque material from carotid endarterectomy patients enrolled in the AtheroExpress (AE) cohort to define regulatory pathways of macrophage recruitment, differentiation, and development. Additionally, we used these scRNA-seq data to deconvolute a large AE bulk RNA-seq cohort to allow correlating cellular subsets in plaques with clinical traits.

Interestingly, we found that macrophages and their subsets are the only cell population significantly associated with major adverse cardiac events (MACE) during a 3-year follow-up period. Subsequently, we could divide plaque macrophages into 3 populations: inflammatory, tissue-resident / lipid-associated (TREM2 high), and foamy macrophages (TREM1 high). While the latter two are correlated with MACE, the inflammatory macrophages are inversely correlated with statin use.

Cellular fate analyses revealed two major paths of macrophage development in the plaque. First, non-classical monocytes entering the plaque, turning into inflammatory cells before becoming foamy and eventually dying. Second, resident-like macrophages that turn into either inflammatory- or lipid-associated macrophages, before meeting their foamy demise.

Together, these findings provide important insights on macrophages in atherosclerosis and suggest new leads to discover therapeutic targets for this disease.