Lipid-associated macrophages transition to an inflammatory state in human atherosclerosis, increasing the risk of cerebrovascular complications

Dib L, Koneva LA, Edsfeldt A, Zurke Y-X, Sun J, Nitulescu M, Attar M, Lutgens E, Schmidt S, Lindholm MW, Choudhury RP, Cassimjee I, Lee R, Handa A, Goncalves I, Sansom SN, Monaco C.

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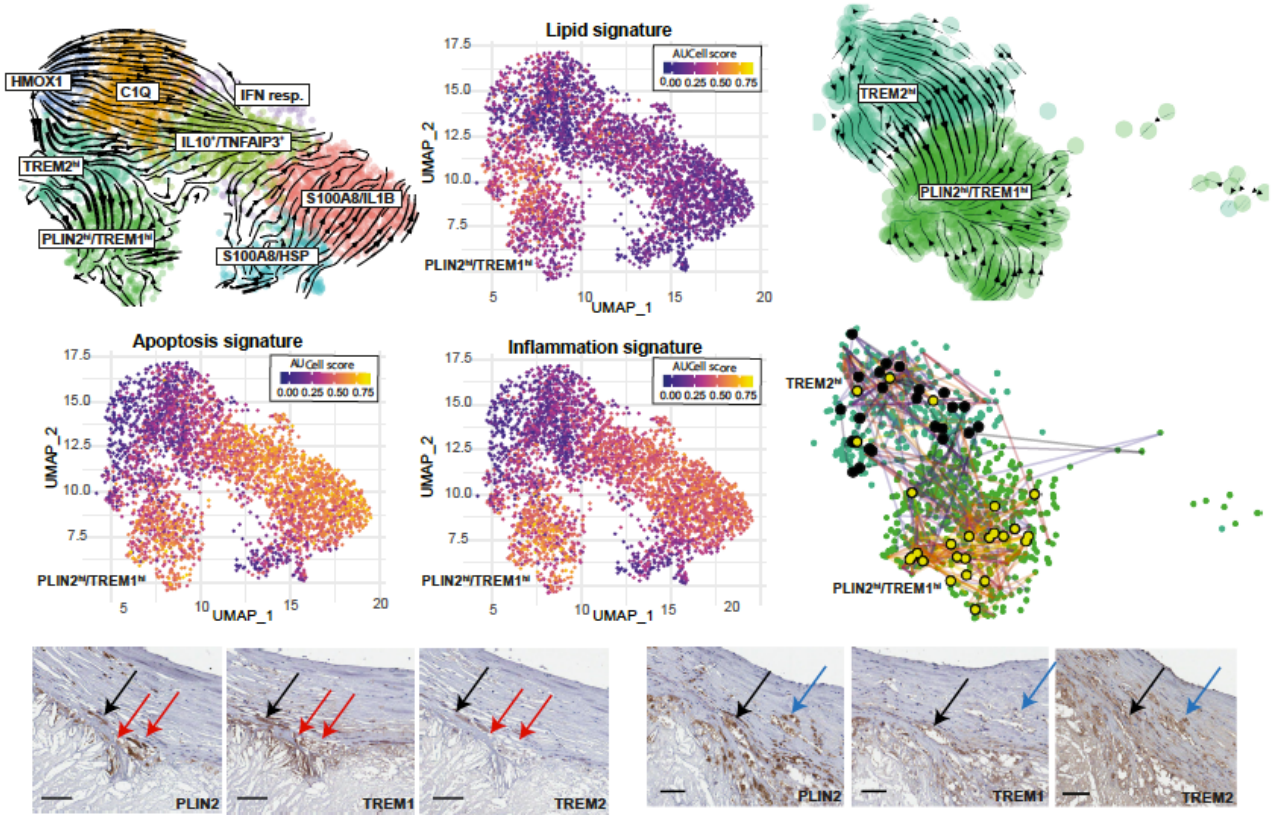

Key findings:

- A new human atherosclerosis immune single-cell atlas reveals two subsets of lipid-associated macrophages (LAMs) in human carotid plaques: the well-recognized TREM2^{hi} homeostatic LAMs and a previously unidentified pro-inflammatory LAMs PLIN2^{hi}/TREM1^{hi}.
- PLIN2^{hi}/TREM1^{hi} cells are the only subset of myeloid cells in human plaque to simultaneously exhibit inflammatory, lipid handling and apoptosis signatures suggesting a terminal inflammatory LAM state.
- Functional evidence shows that lipid-associated macrophages progress from homeostatic TREM2^{hi} to the pathogenic pro-inflammatory PLIN2^{hi}/TREM1^{hi} state under toll-like receptor 2 activation.
- The two LAM subsets are transcriptionally and spatially distinct and occupy different topographical niches within the atherosclerotic plaques as shown with immunohistochemical evidence.
- PLIN2^{hi}/TREM1^{hi} signature shows a significant association with symptomatic disease (including stroke and transient ischaemic attack) in a large and independent validation cohort (the Carotid Plaque Imaging Project Cohort).