ATHEROSCLEROSIS

Distinct immune microenvironments in atherosclerotic plaques

Although immune mechanisms are known to drive progression of atherosclerosis, the immune responses that occur in the plaque are poorly understood. A new study now shows that T cells are the predominant immune cell type in carotid artery plaques from patients with cerebrovascular disease and that plaque macrophages have differentially activated phenotypes. “Plaque cells display not just distinct enrichments compared with blood of the same patient, but they show a functional specialization to the plaque niche,” explains Chiara Giannarelli, lead investigator of the study.

Credit: V. Summersby/Springer Nature Limited

Vascular inflammation is a well-established driver of plaque erosion and rupture, but the immune microenvironment of atherosclerotic lesions and the immune responses driving plaque progression are unclear. “Understanding human atherosclerotic lesion composition has been challenging as the tissue is particularly difficult to work with due to the complexity of human plaques and the lack of methods to analyse them,” says Giannarelli. “However, the advancement of single-cell studies now allows unprecedented high dimensionality and granularity, and can advance our understanding of the disease.”

The research team mapped and assessed the immune composition of atherosclerotic plaques from 46 patients undergoing carotid endarterectomy. Mass cytometry (CyTOF) analyses showed that T cells were the most abundant immune cells in the plaques. Plaque T cells were highly heterogeneous and had a chronically activated and differentiated phenotype compared with T cells in blood samples from the same patient. Furthermore, some plaque T cell subsets had markers of T cell exhaustion. T cell subsets were also analysed with cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq), a technique that incorporates proteomic and transcriptomic data into a single readout. Consistent with the CyTOF results, T cells were found to be the predominant immune cell type in the plaque, and CD8⁺ T cells were enriched in the plaque compared with blood. Furthermore, plaque T cells had transcriptional profiles associated with T cell activation, exhaustion and cytotoxicity compared with blood T cells, which expressed genes associated with inhibition of T cell function.

CITE-seq analysis identified five plaque macrophage subsets with distinct transcriptional signatures, including states linked to pro-inflammatory, foam cell and anti-inflammatory functions. Single-cell RNA sequencing was performed to assess differences in T cell and macrophage phenotypes.

Together, these data derived from single-cell immune mapping of atherosclerotic plaques have uncovered specific features of innate and adaptive immune cells associated with cerebrovascular events. “These data could help guide the design of new therapeutic approaches, and are imperative for understanding the risk associated with the development of immune treatments for other diseases such as cancer,” highlights Giannarelli.

Karina Huynh

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“therapeutic targeting of platelet–myeloid interactions is likely to suppress atherogenesis”

demonstrate the immune effector function of platelets during hypercholesterolaemia and suggest that therapeutic targeting of platelet–myeloid interactions is likely to suppress atherogenesis.”

Gregory B. Lim

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towards an abnormal, osteogenic phenotype that promotes calcification. Finally, in vivo assays in a mouse model of vascular calcification caused by deficiency in matrix Gla protein showed that HDAC9 deficiency led to a 40% reduction in aortic calcification and improved survival.

“Our work points to an important mechanistic role for HDAC9 in the development of vascular calcification and cardiovascular disease, and identifies a new, potentially modifiable pathway for intervention,” highlight Malhotra and O'Donnell. “The next step would be to determine if HDAC9 is a suitable target for pharmacological therapy,” they add, and explain that several factors have to be considered when developing new medicines, such as selectivity to the target and the potential off-target and adverse effects.

Irene Fernández-Ruiz

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