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LINKING IMMUNE ACTIVATION AND CEREBROVASCULAR PATHOLOGY IN MOYAMOYA DISEASE THROUGH SPATIAL AND SINGLE-CELL TRANSCRIPTOMICS

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Background and aims: Moyamoya disease (MMD) is a rare cerebrovascular disease causing ischemic and hemorrhagic stroke through progressive arterial occlusion and formation of fragile collateral vessels. The East-Asian p.R4810K founder mutation in RNF213, a key antimicrobial protein that directly counteracts Salmonella and other intracellular bacteria, suggests a role for immune dysfunction in MMD pathogenesis. We investigate immune–vascular mechanisms in MMD using multi-omics approaches and here describe a single-cell transcriptomics analysis on patient-derived PBMCs as well as spatial transcriptomics analysis on an affected artery retrieved post-mortem.

Methods: PBMCs from four genetically diagnosed MMD patients and matched controls were stimulated with LPS or infected with Salmonella and analyzed by single-cell RNA sequencing using the Chromium platform. Post-mortem arterial tissue was processed for spatial transcriptomics using the Visium HD technology.

Results: Single-cell analysis of 113562 cells revealed condition-specific differences between patients and controls, and between untreated and immune-stimulated/infected cells. Spatial mapping of mRNA expression showed clear differences between occluded and non-occluded artery sections, with variations in proliferative and immune pathways across the intima and media. Our integrated approach demonstrates that immune activation is closely linked to cerebrovascular pathology in MMD. PBMCs exhibit altered bacterial responses consistent with RNF213-related immune dysregulation, while arteries show localized

proliferative and immune alterations. These findings highlight immune–vascular interactions as important contributors to MMD pathogenesis.

Further downstream analysis is needed to identify in depth cell population differences and altered immunological pathways.

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