Abstract citation ID: aakag023.447

ABSTRACT NUMBER: ESOC2026A842

TEMPORO-SPATIAL ANALYSIS OF THE IMMUNE RESPONSE IN HUMAN ISCHEMIC STROKE

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Background and aims: Immune responses are central but incompletely understood drivers of human ischemic stroke pathology. Limited access to human tissue and reliance on rodent models have constrained the identification of human-specific cellular programs.

Methods: We generated an integrated spatiotemporal atlas of the post-stroke immune response using postmortem human brain tissue, combining immunohistochemistry, single-nucleus RNA sequencing, and spatial transcriptomics, with validation in the murine MCAO model.

Results: The immune response followed a stereotyped sequence, characterized by rapid neutrophil infiltration into the infarct core, delayed T cell entry, and progressive accumulation of activated microglia/macrophages, defining an “inflammatory penumbra” at the infarct border. Single-nucleus profiling resolved 19 transcriptionally distinct cell populations and revealed a temporal cascade of early neuronal loss, subsequent oligodendrocyte and astrocyte decline, and late dominance of infiltrating myeloid cells. Stroke-associated myeloid cells (SAMCs) expanded between days 5–15, exhibited proliferative and lipid-clearance signatures, localized to degenerating neurons and oligodendrocytes, and were activated via APP-CD74 signaling. Fibroblasts dynamically reprogrammed toward wound-healing and matrix-remodeling states, while endothelial cells underwent endothelial-to-mesenchymal transition (EndMT), which was modulated by neutrophils and T cells in the MCAO model.

Conclusions: SAMCs and EndMT represent conserved, temporally regulated hallmarks of the human post-stroke response. This study establishes a translational framework for dissecting human-specific immune mechanisms in stroke and highlights potential cellular targets for therapeutic intervention.

Conflict of interest: nothing to disclose