Abstract citation ID: aakag023.1429

ABSTRACT NUMBER: ESOC2026A846

THE ROLE AND MECHANISM OF AHR-MEDIATED MICROGLIAL PHAGOCYTIC FUNCTION IN REGULATING NEURONAL SYNAPTIC PLASTICITY IN POST-STROKE COGNITIVE IMPAIRMENT

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Background and aims: Stroke is a leading global cause of death and disability, with post-stroke cognitive impairment (PSCI) as its most common complication. Our prior single-cell sequencing of stroke patient brains revealed significant upregulation of the aryl hydrocarbon receptor (Ahr), which correlated with cognitive outcomes. Although Ahr is known to function in microglia, its role in stroke and PSCI remains unclear.

Methods: We constructed Ahr+/+ and Ahr-/- transgenic mice and induced ischemic stroke via the dMCAO model. Cognitive behavior, infarct volume (TTC staining), and histopathology were assessed. A microglia-neuron co-culture model under oxygen-glucose deprivation (OGD) was used to examine the effect of microglial Ahr on neuronal morphology and synaptic spines. Transcriptomic analysis of Ahr-modulated microglia identified synaptic regulatory pathways, which were validated in vivo and in vitro.

Results: Ahr-/- mice showed larger cerebral infarcts and significant cognitive decline at 24 weeks post-stroke, whereas Ahr+/+ mice had smaller infarcts and improved cognitive function. Inhibiting Ahr in microglia alleviated OGD-induced synaptic spine loss and neuronal damage. Transcriptomics revealed Ahr-associated synaptic pathways in microglia.

Conclusions: Ahr in microglia improves infarct size and cognitive recovery after stroke by regulating synaptic function, highlighting its protective role in PSCI.
Conflict of interest: Name of author: nothing to disclose