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Senolytic-Induced Clearance of Senescent Astrocytes Mitigates Neurovascular Unit Deterioration in Post-COVID-19 Cognitive Impairment

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Abstract

Post-acute sequelae of SARS-CoV-2 infection (PASC) frequently manifest as persistent cognitive deficits, yet underlying neurobiological mechanisms remain elusive. We demonstrate that SARS-CoV-2 spike protein induces cellular senescence in cortical astrocytes through p16INK4a/p21Cip1 pathway activation, triggering blood-brain barrier breakdown and synaptic pruning. Administration of the senolytic combination dasatinib plus quercetin (D+Q) in a hamster model of long COVID selectively eliminated senescent astrocytes, restored pericyte coverage, and improved spatial memory performance. Transcriptomic analysis revealed dampened interferon-stimulated gene expression and normalized vascular endothelial growth factor signaling. These findings position astrocytic senescence as a targetable node in post-viral neurodegeneration.

Keywords: cellular senescence, senolytics, long COVID, astrocytes, neurovascular unit, dasatinib-quercetin