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Disrupted Muscle–Brain Crosstalk through Apelin–APJ Signaling in Post-ICU Syndrome

Post-Intensive Care Syndrome (PICS) is characterized by physical weakness, depression, and cognitive impairment that persist after an ICU stay, particularly in patients with ARDS and severe COVID-19. However, the molecular mechanisms remain poorly understood.

Here, we identify impaired Apelin–APJ signaling as a key contributor to PICS pathogenesis through disruption of muscle–brain crosstalk. In a mouse model combining acute lung injury with hindlimb immobilization, we observed muscle atrophy, lung inflammation, and neurobehavioral abnormalities. Single-cell RNA sequencing of brain tissue revealed activation of gene programs associated with Alzheimer's disease and depression, particularly in endothelial cells and microglia. At the same time, Apelin–APJ signaling was downregulated in skeletal muscle, suggesting impaired myokine-mediated communication with the brain. These alterations were aggravated in Apelin-deficient mice and ameliorated by muscle-specific Apelin overexpression, which also reduced systemic IL-6 and restored circulating Apelin.

In ARDS survivors with severe COVID-19, ICU-acquired weakness was associated with reduced plasma Apelin and elevated IL-6. Transcriptomic profiling of patient PBMCs revealed gene expression signatures linked to depression and neurodegeneration, paralleling the murine findings.

Together, these results indicate that impaired Apelin–APJ signaling disrupts muscle–brain crosstalk and contributes to PICS pathophysiology. Targeting this pathway may provide a novel therapeutic strategy to improve long-term outcomes in ICU survivors.

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