HIV Infection Orchestrates Modality-Specific Spliceosome Stress Across Acute Microglial, Chronic CNS, and Peripheral Immune Compartments: A Multi-Dataset Convergence Study

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HIV persists in the central nervous system despite antiretroviral therapy, contributing to chronic inflammation and HIV-associated neurocognitive disorders (HAND). While transcriptomic studies have identified inflammatory gene-expression signatures, alternative pre-mRNA splicing, a key regulator of protein function and cellular stress responses, remains poorly characterized in HIV-driven neuroimmune dysfunction. We analyzed three independent bulk RNA-sequencing datasets representing acute HIV infection in iPSC-derived human microglia, chronic HIV-associated changes in post-mortem brain tissue, and circulating peripheral blood mononuclear cells. Using a unified framework, we examined alternative splicing, differential transcript usage, and differential gene expression across these compartments. Despite major differences in cell type, tissue source, and disease phase, all datasets showed a conserved pattern of selective, modality-specific “graded spliceosome stress.” Splicing alterations affected fewer than 1% of detectable splice sites, were primarily characterized by exon skipping, and largely occurred independently of transcriptional changes. Affected genes were enriched in pathways regulating mitochondrial homeostasis, autophagy/lysosomal function, chromatin regulation, innate immune sensing, and RNA processing. Eleven genes, including LY6E, MDM2, and RANGAP1, demonstrated convergent dysregulation across splicing, transcript usage, and gene expression, identifying high-priority candidates for functional validation. These findings identify alternative splicing as a previously underrecognized, post-transcriptional mechanism of HIV-associated neuroimmune dysfunction and highlight potential biomarkers and therapeutic targets for HAND.