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Multiomics approach to unravel signaling modulation in neurodegeneration

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Brain health is guaranteed through adaptive changes provided by combinations of biological processes in response to external and internal stimuli. These dynamic processes are orchestrated by synchronous activity of various signaling pathways, initiated and regulated at multiple levels. Understanding these signaling pathways, both by themselves and as parts of an integrated network, is instrumental in elucidating the molecular mechanisms underlying complex and heterogeneous disorders such as neurodegenerative disease.
The multiomics approach provides an integrated perspective to power discovery across multiple levels of biology.
Kainic Acid (KA) has been extensively used in rodents for exploring the pathogenesis of excitotoxicity, characteristic of many neurodegenerative disorders.
Hence, the use of the KA mouse model of neurodegeneration combined with different genetic backgrounds, conditions and experimental methods has the potential for decoding the molecular cascade from excitatory/inhibitory imbalance to neuronal demise.
Notch1/Rbpjk loss of function in hippocampal pyramidal neurons upon KA injury has been explored using a previously optimized Chromatin Immunoprecipitation (ChIP) protocol and RNA sequencing. This investigation led to the conclusion that Notch/Rbpjk signaling in neurons has direct and indirect targets instrumental for synaptic plasticity and qualifies Notch as a promising signaling cascade to fine-tune in order to ameliorate synaptic transmission and memory deficits occurring in early phases of Alzheimer's Disease.
The analysis of the KA mouse model was extended to single cell resolution, using single nucleus RNA sequencing of hippocampal tissue. The study explored gene expression alterations upon KA insult to the level of individual cellular subtypes, at the 12hr time point of neuronal damage and at the 24hr time point of initial neuronal recovery, providing a powerful resource to explore the transcriptomes of diverse cell types/subtypes of the hippocampus, and to investigate cell type-specific regulatory mechanisms in response to excitotoxic injury.

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