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Novel Approach for Cell-Type Specific Profiling of Histone Post-Translational Modifications and Corresponding Gene Expression

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Recent evidence suggests that histone post-translational modifications (HPTMs) regulate neuronal gene expression via chromatin accessibility and transcription factor recruitment. Yet, the functional relevance of HPTMs in specific cell types remains elusive. In the nucleus accumbens, a hub region within the mesocorticolimbic reward pathway, transcription differs between the two distinct subtypes of GABAergic medium spiny neurons (MSNs). MSNs generally express either D1 dopamine receptor (Drd1) or adenosine 2A receptor (A2a). Drd1 and A2a MSNs have differential efferent pathways, which define the direct and indirect motor output pathways, respectively, and express distinct genes in response to rewarding stimuli, such as drugs of abuse. Here, we employed novel techniques to establish a methodology for transcriptional and epigenetic profiling of specific neuronal cell types, MSNs, in mouse brain. We produced transgenic mouse lines that express an affinity tagged nuclear receptor (GFP- Sun1 fusion) in dopamine Drd1- or A2a-containing MSNs. The bilateral caudate/striatum of male and female mice from these mouse lines were subjected to affinity isolation of nuclei tagged in specific cell types (INTACT) protocol. Cell-type specific nuclei were then subjected to cleavage under targets and release using nuclease (CUT&RUN) or quantitative PCR (qPCR). Using this approach, we were able to bioinformatically profile multiple HPTMs and gene expression in specific cell-types of a single bilateral mouse striatum. Here, we present data from our INTACT into CUT&RUN and qPCR protocols, unveiling a robust method of cell-type specific quantification of HPTMs and corresponding gene expression.