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Multi-omic single nuclei data provide insight into the cellular origin of whole brain coexpression patterns related to *Oprm1*

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Systems genetics analysis of model organisms is an effective way to understand complex molecular and environmental interactions that contribute to the predisposition to opioid use disorder (OUD). We developed a pipeline for linking RNA coexpression modules in bulk brain tissue to physiological/behavioral traits in the Hybrid Rat Diversity Panel. However, the relationship of candidate coexpression modules to the cellular elements of brain remained unresolved. We have identified cell types in rat prefrontal cortex using single nuclei data on RNA expression and methylation patterns (snmCT-seq) and used this data to integrate cell type information with an existing rat whole brain coexpression module that includes the *Oprm1* (mu opiate receptor) transcript. The highest level of *Oprm1* RNA expression in the snmCT-seq data was in the cluster representing short projection excitatory neurons originating in frontal cortical layer 6 (NP-L6). All other transcripts but one in this coexpression module were also expressed in NP-L6 nuclei. The transcript not expressed in the NP-L6 cluster (*Erbb4*) codes for the receptor for neuregulin 1, which is localized in terminals of GABA interneurons. We postulate a trans-synaptic relationship between excitatory neuron function and control of this function by *Erbb4* expressed in GABA interneurons. These initial results illustrate how gene expression networks generated from bulk brain data can be integrated with single-cell technologies to provide insight into cell types and intercellular communication pathways that may predispose to OUD and to also define networks associated with intrinsic brain function.

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