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Single-cell characterization of epigenomic remodeling in cocaine self-administration in mice

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Relapse to drug use is the major challenge in combating addiction. Central to this problem is the post-withdrawal long-lasting changes in the brain that can persist for an extended period. This long-lasting impact on brain function and behavior is associated with long-term changes in gene expressions, suggesting alterations in the epigenome. Indeed, drug-induced epigenomic changes in bulk preparations of mouse and human brain samples have been reported. However, these studies lack the necessary resolution as to in which cell types and which neural projections the epigenomic remodeling occurs and how different aspects of the epigenome cooperatively regulate the gene expression. We hypothesize that the epigenomic regulations are cell type- and projection-specific in the brain's reward circuitry and are dynamic in response to drug consumption and abstinence. To test the hypothesis, we use an interdisciplinary approach that combines the mouse model of intravenous self-administration (IVSA) of cocaine with single-cell epigenomics and multi-omics assays. In the pilot study, we analyzed the dynamic landscapes of chromatin accessibility and DNA methylation in nucleus accumbens (NAc) after cocaine IVSA and abstinence. We observed genome-wide epigenomic changes, the majority of which were cell-type specific. To investigate the epigenomic remodeling in different projections in the brain's reward circuitry, we will apply a novel single-cell epigenomics method that I have developed, which combines retrograde tracing for circuitry dissection with single-cell epigenomics sequencing. These ongoing studies will for the first time illustrate the cell-type and projection-specific epigenomic remodeling in drug self-administration and abstinence, and provide the crucial knowledge for follow-up targeted functional studies of the role of epigenomic regulations in addiction.