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Re-engineering brain transcription factors connects transposable elements and neuroimmune response to drug-use and social behaviors

Zfp189, which encodes a Krüppel-associated box zinc finger protein (KZFP) transcription factor (TF), differentially accumulates in rodent cortical and limbic brain regions in response to social stress- or drug-use experience. Here, we aimed to illuminate the brain cell-type specific molecular mechanisms through which this and other KZFP TFs produce cocaine-related brain changes, with emphasis on investigating transposable elements (TEs), since KZFPs like ZFP189 are known regulators of TEs. To investigate this, we quantified TE transcripts in existing single nuclei and bulk RNA-sequencing datasets of rodents exposed to cocaine. TE transcripts often go unanalyzed in transcriptomic data due to multi-mapping reads. We identified dynamic TE transcript expression across cocaine exposure, especially in nucleus accumbens (NAc) medium spiny neuron (MSN) subtypes. To directly regulate brain TEs, we created novel synthetic ZFP189 TFs and synthetic KZFP-interacting TRIM28, each capable of exerting distinct forms of transcriptional control at KZFP-regulated genes, including TEs. These KZFP TFs were virally delivered to targeted regions of mouse brain, including the prefrontal cortex for social-related behavioral interrogation and the NAc for cocaine-related interrogations. In the NAc, including conditional delivery to MSNs, we characterized the consequences on cocaine-related behaviors, including intravenous self-administration, and transcriptional response, by bulk and snRNAseq. We discovered that normal KZFP function in brain is critical to produce cocaine-induced NAc transcription and an escalation of cocaine-taking behaviors, and this can be impeded with synthetic KZFP TFs. Our synthetic KZFPs release TEs that form cis-regulatory contacts with down-regulated, predominantly immune-related genes. Collectively this work points to the KZFP-mediated transcriptional repression of brain TEs as an important mechanistic step in cocaine-induced gene expression and behavioral changes.

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