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A zinc finger transcription factor in the nucleus accumbens regulates cocaine-induced transcription and behaviors in a cell type specific manner

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Our lab has demonstrated that that *Zfp189* expression in *Drd2*+ medium spiny neurons (MSNs) of the nucleus accumbens (NAc) is a molecular signature of chronic cocaine exposure. The *Zfp189* gene product is a Krüppel associated box zinc finger transcription factor (TF) of poorly understood function. To interrogate the transcriptional function and gene targets of ZFP189, we reprogrammed the endogenous ZFP189^{WT} by replacing the repressive KRAB domain with a transcriptional activation domain (VP64-p65-Rta (ZFP189^{VPR}) or by removing the functional moiety entirely (ZFP189^{NFD}). These synthetic ZFP189 TFs exert divergent transcriptional regulation at a *luciferase* target gene, *in vitro*. We investigated the NAc cell type specific contribution of our ZFP189 variants to cocaine-induced locomotor behavior. Utilizing transgenic mice that express Cre recombinase under the *Drd1*- or *Drd2*- promoter in combination with Cre-dependent expression vectors, we see that ZFP189^{VPR} in *Drd1*+ MSNs and ZFP189^{WT} in *Drd2*+ MSNs cause an increase in cocaine-induced locomotor behavior. We next investigated the consequences of altered ZFP189-mediated transcription on dendritic spine morphology in *Drd1*+ or *Drd2*+ MSNs. ZFP189^{VPR} within *Drd1*+ MSNs and ZFP189^{WT} within *Drd2*+ MSNs both elicit a similar change in spine morphology. To understand the NAc cell-type specific correlates of this result, we performed single nuclei RNA sequencing on infected NAc tissues. ZFP189^{VPR} within *Drd1*+ MSNs elicits a possible protective mechanism through neuroimmune pathways not produced by ZFP189^{WT} within *Drd2*+ MSNs. Collectively, this work highlights a possible cell type specific immune-related mechanism that could be targeted to help alleviate ZFP189-mediated chronic cocaine maladaptations.