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**The Role of Δ FosB in the Development of Drug Addiction:
Identifying Δ FosB Transcriptional Targets in Nucleus Accumbens**

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Drug addiction exacts a devastating impact on drug users, their family members, and the nation's public health. Although different in chemical structures and initial mechanisms affecting the brain, all classes of drugs of abuse induce the expression of the transcription factor Δ FosB in nucleus accumbens (NAc), the central node of the reward circuitry. Studies with Δ FosB genetic manipulation in mouse suggest that Δ FosB in NAc neurons is involved in the development of addiction. However, the molecular mechanisms of Δ FosB remain incompletely understood. Here, we extend earlier work on revealing Δ FosB's transcriptional targets, which interrogated promoter regions only, by leveraging the CUT&RUN (cleavage under targets and release using nuclease) method to pinpoint Δ FosB coverage genome-wide upon chronic cocaine exposure. Thousands of Δ FosB peaks were revealed; interestingly, one third of the loci are positioned at distal intergenic enhancers while only ~15 percent of the peaks occur within known promoter areas, suggesting that a primary function of Δ FosB is coordinating distal regulatory elements with the transcription machinery. In addition, we identified Δ FosB peaks specific to medium spiny neurons (MSNs) expressing either dopamine receptor D1 or D2 – the two major neuronal types in NAc, which adds to the early discovery that Δ FosB directs differential molecular and synaptic plasticity in D1- versus D2-type MSNs. Further extension of this CUT&RUN approach to other chromatin regulatory mechanisms in D1- and D2-type MSNs within NAc will set the groundwork for understanding distinct roles of these MSN subtypes, and their adaptations to chronic drug exposure, in drug addiction.

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