MACMILLAN AUSTRALIA

PSYCHIATRIC DISORDERS

A feat of epigenetic engineering

“single epigenetic modifications can modulate both *Fosb* expression and its behavioural effects.”

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Chronic exposure to stress or drugs of abuse causes widespread changes in the activity of chromatin remodelling enzymes. However, it has been difficult to determine the relative functional importance of drug- or stress-induced epigenetic modifications of individual genes. Nestler and colleagues have now employed gene- and brain-region-specific chromatin remodelling to examine the role of one particular gene, *Fosb*, in addiction- and depression-related changes in the brain and behaviour.

Changes in *Fosb* expression in the nucleus accumbens (NAc) via epigenetic remodelling have been connected to addiction- and depression-related behaviour. To examine this link more precisely the authors generated engineered transcription factors comprised of zinc-finger proteins (ZFPs) or transcription-activator-like effectors (TALEs) that were targeted selectively to the *Fosb* promoter and were fused to domains that promote transcriptional activation or repression via histone modification.

The authors showed that expression of constructs that promote transcriptional activation (*Fosb*-ZFP-p65

and *Fosb*-TALE-VP64) in the mouse NAc increased levels of *Fosb* as well as the level of H3K9 acetylation (an activating histone modification) at the *Fosb* promoter. Conversely, expression of a construct containing a transcriptionally repressive domain (*Fosb*-ZFP-G9a) decreased *Fosb* expression and increased the level of the repressive histone modification H3K9me2. Thus, the engineered transcription factors induced specific histone modifications and regulated *Fosb* expression *in vivo*.

Cocaine exposure induces *Fosb* expression in the NAc, and the authors showed that expression of *Fosb*-ZFP-G9a blocked this induction. Furthermore, *Fosb*-ZFP-G9a expression blocked the cocaine-induced enrichment of phosphorylated CREB at the *Fosb* promoter. H3K9me2 therefore regulates cocaine-induced *Fosb* expression by inhibiting transcription factor binding.

Next, the authors examined the role of histone modification at *Fosb* on the behavioural effects of exposure to cocaine or stress. They found that *Fosb*-ZFP-G9a

expression blocked cocaine-induced locomotor sensitization, whereas *Fosb*-ZFP-p65 and *Fosb*-TALE-VP64 enhanced this response. Susceptibility to depression has been linked to reduced FOXB levels in humans and animal models. The authors showed here that expression of *Fosb*-ZFP-G9a increased depression-like behaviour in a chronic social defeat stress model, indicating that the H3K9me2 modification mediates this effect.

This study shows that single epigenetic modifications can modulate both *Fosb* expression and its behavioural effects. A similar approach may be used to target other genes of interest and elucidate further the changes in molecular pathways that underlie psychiatric disorders.

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ORIGINAL RESEARCH PAPER Heller, E. A. *et al.* Locus-specific epigenetic remodeling controls addiction- and depression-related behaviors. *Nature Neurosci.* <http://dx.doi.org/10.1038/nn.3871> (2014)
FURTHER READING Robison, A. J. & Nestler, E. J. Transcriptional and epigenetic mechanisms of addiction. *Nature Rev. Neurosci.* **12**, 623–637 (2011)