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DEPRESSION

In pursuit of happiness

Major depressive disorder (MDD) is associated with structural alterations to the hippocampus that are thought to underlie some symptoms of the disease, such as impaired cognition and depressed mood. However, the molecular changes that cause the pathophysiology are largely unknown. Duric *et al.* now identify a key role for dual specificity protein phosphatase 1 (DUSP1; also known as MKP1), a negative regulator of the neurotrophic factor–mitogen-activated protein kinase (MAPK) cascade.

The authors conducted a genome-wide microarray analysis of post-mortem human hippocampal tissue samples. They found that DUSP1, which dephosphorylates MAPK1 and MAPK3, was upregulated in the dentate gyrus and area CA1 in samples from depressed human subjects compared with matched control samples. Furthermore, the expression of kinases in the DUSP1-regulated cascade and numerous downstream targets was downregulated in depressed subjects.

The role of DUSP1 in pathology was then pursued in a rat model of depression involving chronic unpredictable stress (CUS), which recapitulates the key features of MDD. Exposure to CUS increased the levels of *Dusp1* mRNA in the dentate gyrus and area CA1, and this was partially attenuated by treatment with fluoxetine (Prozac).

To demonstrate a direct involvement of DUSP1 in the pathophysiology of depression, the authors used a viral vector to deliver the *Dusp1* gene to the dentate gyrus in rats. Subsequently, these rats showed numerous depression-related behavioural responses, such as a decreased preference for sucrose over water.

Complementing these overexpression studies, the authors examined the effect of CUS on *Dusp1* knockout mice, which show no abnormalities under baseline conditions. Whereas CUS caused wild-type mice to consume significantly less sucrose, it had no effect on sucrose consumption in *Dusp1*$^{-/-}$ mice. Similarly, *Dusp1*$^{-/-}$ mice exposed to CUS spent more time in the open arm of the elevated plus maze than did wild-type mice exposed to CUS. Together, these findings indicate resilience to stress-induced depressive behaviours in the knockout mice.

Consistent with the proposed upregulation of DUSP1 in depression, Western blot analysis revealed that phosphorylation levels of MAPK1 and MAPK3 were reduced in wild-type mice, but not in *Dusp1*$^{-/-}$ mice, following CUS.

Changes in neurotrophin signalling have previously been implicated in depression and antidepressant-like responses in animal studies. Beginning with 'hit' identification in patients followed by validation in animal models, Duric *et al.* highlight a key downstream regulator of these signalling pathways that could be an important therapeutic target.

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ORIGINAL RESEARCH PAPER Duric, V. *et al.* A negative regulator of MAP kinase causes depressive behaviour. *Nature Med.* **16**, 1328 –1332 (2010)