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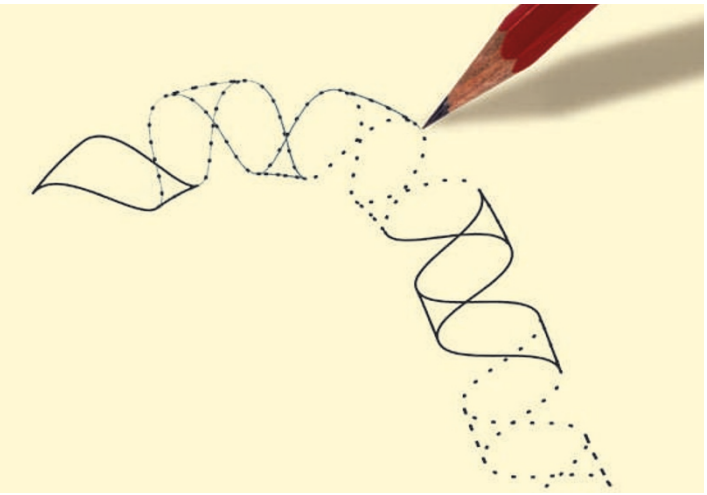
NEURODEGENERATIVE DISEASE

# Joining the dots



There are signs that postmitotic neurons initiate cell cycle re-entry in several neurodegenerative disorders; however, the mechanisms by which this occurs are unclear. Similarly, although DNA damage is thought to contribute to neuronal death in many conditions, the factors that underlie this damage are poorly understood. In their new paper, Tsai and colleagues provide a mechanistic link between cell cycle re-entry, DNA damage and neuronal cell death.

Cyclin-dependent kinase 5 (CDK5) and its activator p25 have been linked to both the repression of cell cycle re-entry and neurodegeneration. Here the authors used mice in which p25 activity can be induced in the postnatal forebrain by the removal of doxycycline (CK-p25 mice), leading to neurodegeneration, cell death and cognitive impairment, to investigate the neurodegenerative processes connected to CDK5 and p25 activity.

Analysis of gene and protein expression two weeks after p25 induction revealed an upregulation of several cell cycle proteins in cells expressing p25. Interestingly, the authors also observed an upregulation of genes that are associated with DNA repair, as well as high levels of DNA double strand breaks (DSBs), suggesting a link between p25 expression, aberrant cell cycle re-entry and DNA damage.

Reasoning that chromatin remodelling could provide a connection between the changes in gene transcription and an increased sensitivity to DNA damage, the authors investigated the effect of p25 induction on histone deacetylase 1 (HDAC1), an enzyme that has been linked to the repression of the transcription of genes that encode cell cycle proteins. They showed that p25 interacts with the catalytic domain of HDAC1 in the brains of CK-p25 mice, inhibiting HDAC1 activity. Furthermore, *in vitro* experiments indicated that p25 also decreases HDAC1's ability to bind to and repress the promoters of genes that encode cell cycle proteins.

These results suggested that p25 induces cell cycle re-entry and DNA strand breaks (and hence neurodegeneration) by repressing HDAC1 activity. Indeed, reducing HDAC1 activity using small interfering RNA or a specific inhibitor in cultured cortical neurons or *in vivo* resulted in increased numbers of DSBs, the expression of cell cycle proteins and cell death. Increasing HDAC1 function by overexpressing it had the opposite effect, protecting cells against DSBs and neurotoxicity. Finally, the authors showed that overexpression of HDAC1 could protect rats against neuronal degeneration following a subsequent transient forebrain ischaemia.

These findings demonstrate a functional link between CDK5 and p25 activation, aberrant re-entry into the cell cycle, DNA damage and neurodegeneration and highlight the importance of HDAC activity for neuronal function. It remains to be seen whether the protective effects of HDAC1 against ischaemia can be reproduced in delayed-treatment paradigms or in models of other neurodegenerative diseases; nevertheless, this study reinforces the potential of chromatin-remodelling enzymes as therapeutic targets.

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**ORIGINAL RESEARCH PAPER** Kim, D. *et al.* Deregulation of HDAC1 by p25/Cdk5 in neurotoxicity. *Neuron* **60**, 803–817 (2008)
**FURTHER READING** Herrup, K. & Yang, Y. Cell cycle regulation in the postmitotic neuron: oxymoron or new biology? *Nature Rev. Neurosci.* **8**, 368–378 (2007)