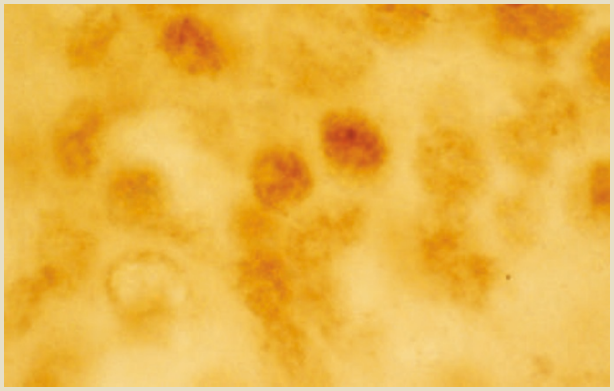
T.D. *Cancer Res.* **63,** 8586–8591 (2003).
8. Difilippantonio, S. *et al. Nature Cell Biol.* **7,** 675–685 (2005).
9. Bakkenist, C.J. & Kastan, M.B. *Nature* **421,** 499–506 (2003).
10. Lee, J.H. & Paull, T.T. *Science* **308,** 551–554 (2005).
11. Nakada, D., Matsumoto, K. & Sugimoto, K. *Genes Dev.* **17,** 1957–1962 (2003).
12. Falck, J., Coates, J. & Jackson, S.P. *Nature* **434,** 605–611 (2005).
13. Huyen, Y. *et al. Nature* **432,** 406–411 (2004).
14. Kobayashi, J. *et al. Curr. Biol.* **12,** 1846–1851 (2002).
15. Fernandez-Capetillo, O. *et al. Nature Cell Biol.* **4,** 993–997 (2002).

Huntingtin and the vicious circle

Huntington's disease is a neurodegenerative disorder, caused by mutations in the huntingtin (htt) protein that result in expanded amino-terminal polyglutamine tracts. Recent data from genetic studies and transgenic mouse models suggest that N-terminal fragments of the expanded protein — released by proteolytic cleavage — may be the toxic species responsible for neuronal death and disease pathology. A new study from David Rubinsztein and colleagues, published in the 23 May issue of the *Journal of Cell Biology* (**169,** 647–656; 2005), shows that the action of Cdk5 kinase decreases the proteolytic processing of htt by caspases and so reduces production of the toxic fragments. They further find a positive feedback loop between the htt fragments and Cdk5, which could be key to the pathological mechanism of Huntington's disease.

Cdk5 was a good candidate for being a potential regulator of htt: there are several Cdk5 consensus phosphorylation sites in htt, and Cdk5 activity was known to be most prominent in neural tissue where it is activated by p35. These authors now show that Cdk5 and htt interact *in vivo*, and that Cdk5 phosphorylates htt at Ser 434. Phosphorylation at this site leads to decreased cleavage by caspase — one of the three classes of proteases that cleaves htt — and so reduces release of the toxic N-terminal fragment. Thus, Cdk5 activity is predicted to protect against mutant htt-mediated neurodegeneration.

In a mouse model for Huntington's disease that expresses the expanded htt protein, Cdk5 activity and phosphorylation of endogenous htt in neural tissue were lower than in wild-type mice. The authors show that this is probably because the N-terminal fragment of htt disrupts the interaction between Cdk5 and its activator p35. This predicts a positive feedback loop by which production of the toxic fragments leads to decreased Cdk5 activity and decreased htt phosphorylation; this in turn increases caspase-mediated cleavage of htt, and thereby increases release of toxic fragments. Such a positive feedback mechanism has been postulated to be important for the pathology of Huntington's disease, given that neurodegeneration is seen to be much faster after disease onset than before. The key, then, is to find a way to intercept this positive feedback loop and so say to Huntington's disease, once and for all, goodbye!



Transgenic mouse model of Huntington's disease, overexpressing the expanded form of the mutant huntingtin protein. Aggregated mutant huntingtin can be seen in the neuron on the right. Image courtesy of David Rubinsztein, Cambridge Institute for Medical Research.

JACK HORNE