IN THE NEWS

Cheerful treatment

Amphetamine derivatives, such as the 'party' drug ecstasy and the antidepressant Prozac, could potentially help treat lymphoma, according to a new study from the University of Birmingham (Meredith, E. J. *et al*. *FASEB J*. 3 May 2005 (doi:10.1096/fj.04-3477fje)).

After finding that the serotonin receptor was involved in mediating apoptosis in lymphoma cells, John Gordon and his team tested the effects of several antidepressants that target this receptor on various lymphoma-derived B-cell lines. They found that these drugs had significant antiproliferative and pro-apoptotic effects on the tumour cells. "This is quite a breakthrough in medical research into the treatment of lymphoma cancers, including some types of leukemia," said Professor Gordon, "The success of anti-depressants on slowing down the cancer is very exciting." (*Washington Times*, 12 May 2005.) At present, the doses of these drugs that would be required to block cancer growth would be fatal, but, referring to ecstasy, a member of the team, Nick Barnes, is hopeful: "Perhaps by breaking down the actions of this designer drug we can extract its cancer-killing properties from the more general toxic effects that are associated with its use." (http://news.bbc.co.uk/, 10 May 2005). David Grant, of the Leukaemia Research Fund, who funded the study, said: "The possibility some patients can be treated with anti-depressants that have cancer-killing properties is truly remarkable." (http://www.mirror.co.uk/, 11 May 2005).

Lesley Cunliffe

CELL CYCLE

Checking in

Cell-cycle checkpoints are activated to ensure that a cell progresses through DNA replication and mitosis with its genetic information intact. The phosphorylation of protein substrates triggers these checkpoints and so dephosphorylation is required for cells to resume normality. Lawrence Donehower and colleagues show that the p53-regulated serine/threonine phosphatase PPM1D is important for checking cells back into the cell cycle.

DNA-damage-induced activation of the kinases ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3 related (ATR) is crucial for stimulating downstream checkpoint-associated proteins, including p53 and the checkpoint kinases CHK1 and CHK2. The question of how cells turn off this response remains largely unexplored. PPM1D is activated in response to a range of DNA-damage stimuli, including ionizing radiation (IR) and ultraviolet (UV) light. Given that several other phosphatases have been implicated in regulating checkpoint proteins, Donehower and co-workers asked if PPM1D also has a similar function.

Initially the authors used *in vivo* co-immunoprecipitation assays to identify PPM1D substrates. They found that PPM1D binds CHK1 and dephosphorylates Ser345, which inhibits the capacity of CHK1 to phosphorylate and activate downstream checkpoint proteins. In addition, short interfering RNAs (siRNAs) that target PPM1D increased the levels of phosphorylated CHK1 protein after exposure to UV light. CHK1 regulates the G2/M checkpoint and these data indicate that PPM1D could also be involved.

Previous results from the author's laboratory indicated that PPM1D might also regulate phosphorylation of Ser15 on p53. *In vitro* and *in vivo* kinase assays reported in this paper confirm that PPM1D can dephosphorylate Ser15, possibly reducing the function of p53. Ser15 is phosphorylated by ATM or ATR in response to IR or UV light, but the authors show that PPM1D does not function at the level of these kinases.

p38 MAP kinase, a PPM1D substrate, can also regulate the G2/M checkpoint under certain conditions, so the authors investigated whether p38 was involved in the activity of PPM1D. They found that inhibition of p38 did not reduce the capacity of overexpressed PPM1D to impair the function of CHK1. The authors also found that PPM1D suppresses the intra S-phase and G2/M checkpoints in response to IR or UV light.

Is PPM1D implicated in tumorigenesis? Previous experiments have indicated that overexpression of PPM1D enhances oncogenic transformation of cells and loss of PPM1D confers resistance to transformation. PPM1D is also overexpressed in several human tumour types, including 15% of breast cancers. Donehower and colleagues investigated the levels of phosphorylated Ser345 on CHK1 in three breast cancer cell lines that have increased expression of PPM1D. Treatment with UV light resulted in high levels of Ser345 phosphorylation in control cell lines, but only a modest induction in the breast tumour lines. By abrogating cell-cycle checkpoints, upregulated expression of PPM1D could result in increased proliferation and chromosomal instability, and, because of its effect on the DNA-damage response, increased PPM1D levels could also enhance the accumulation of mutations. All of these aspects merit further investigation.

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References and links

ORIGINAL RESEARCH PAPER Lu, X. *et al*. PPM1D dephosphorylates chk1 and p53 and abrogates cell cycle checkpoints. *Genes Dev.* 3 May 2005 (doi:10.1101/gad.1291305)