bipolar patients, and in the pattern formation that *D. discoideum* shows when it is exposed to stress. When *D. discoideum* is starved, for instance, the single-celled organisms aggregate to form a multicellular colony, before forming so-called 'fruiting bodies' composed of specialized disc and spore cells.

When a member of Harwood's group, Melanie Keim, exposed slime mould colonies to 7 μM concentrations of lithium chloride solution, she found this fruiting body formation was disrupted, while aggregation was preserved. But when the concentrations were raised to 10 μM, it was the aggregation that was disrupted, while some cells were still able to produce fruiting bodies.

While the formation of the fruiting bodies requires the Wnt pathway, aggregation requires the inositide pathway. 'It looks like the inositide pathway may be related to the drug's therapeutic effects, while the Wnt-signalling pathway is involved in the teratogenic abnormalities,' says Keim.

Keim then went on to use her slime mould model to identify mutants that aggregated normally, even when exposed to 10 mM lithium ion concentrations-believing that the mutated genes in those cases might be closely related to the human genes responsible for lithium resistance.

### Reversing the effects

One such mutant, dubbed LisA by the researchers, lacks the enzyme prolyl oligopeptidase (PO), which reverses the inositol depletion triggered by lithium. According to Harwood, new research in bipolar patients suggests that they are significantly deficient in PO compared with schizophrenic controls.

When they tested the effect of PO in their *in vitro* neuronal growth cone system, they found that it could reverse the cone-collapsing effects of both lithium and valproic acid, in a similar manner to that achieved with the addition of inositol.

Their latest findings add more detail to the picture, indicating that lithium and valproic acid exert their effects at different stages of the inositide-signalling pathway. '*Dictyostelium* is a wonderful system in which to study this pathway because you can manipulate it with mutants and study each step, which is impossible in humans,' said neurogeneticist James Kennedy of the University of Toronto, Canada (http://www.utoronto.ca), who describes the findings as 'impressive'. He added: 'This model may help in designing and testing new medications [for bipolar disorder].'

The British researchers have also discovered some mutants that only affect the Wnt pathway, from which they hope to learn about lithium's side-effects and, potentially, how to avoid them.

They presented their research at the beginning of July 2003 at the International Congress of Genetics in Melbourne, Australia (http://www.geneticscongress2003.com/index.php).

# Cell cycle that rewrites the text books

**Helen Dell**, h.dell@elsevier.com

Research into an unusual and specialized cell cycle has uncovered a new protein kinase complex that directs key cell-division regulators called cyclins and researchers are now using a functional genomics approach to look for substrates for the complex.

### The cell cycle

In several non-mammalian organisms, including insects and amphibians, a modified cell cycle occurs immediately after fertilization, which enables a period of rapid embryogenesis. This modified cycle is a stripped down

version of the archetypal cell cycle, explains Terry Orr-Weaver, principal investigator at the Whitehead Institute in Cambridge, MA, USA (http://www.wi.mit.edu). It has the standard DNA replication phase (S) and mitotic cell division phase (M), but unlike the normal cell cycle, there are no discernible gap (G) phases when growth and transcription usually occur.

In a normal cell cycle, the key transition points at the onset of S phase and of M phase are controlled by regulatory proteins called cyclins. Cyclins are crucial for throwing the switches in the cell cycle, says Orr-Weaver, and in the normal cell cycle that switch is thrown by accumulating transcripts. The minimal embryonic cycle, however, does not allow time for transcription, suggesting

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that there must be a different method of regulation. Now Orr-Weaver and colleagues have found a protein complex that might be involved in this regulation.

### Underlying the defects

They began by looking at *Drosophila melanogaster* mutants that show a defective rapid embryonic cell cycle, and identified the genes that underlie the defects. These genes encode a protein complex containing a kinase and two activating subunits.

Importantly, the complex specifically regulates the level of mitotic cyclins, says Orr-Weaver, who presented her findings at the International Congress of Genetics in Melbourne, Australia at the beginning of July 2003 (http://www.geneticscongress2003.com/index.php). This is not a localization phenomenon, she adds, the protein kinase complex is controlling the amount of cyclin by regulating either translation or protein degradation.

The findings are unexpected, says Todd Stukenberg, Assistant Professor of Biochemistry and Molecular Genetics at the University of Virginia (http://www.virginia.edu). 'It is quite surprising that this [protein complex] is a regulator of cyclins,' said Stukenberg, who also studies the early embryonic cell cycle. 'There are paradigms [of how cyclins are regulated] that are models in text books that seemed worked out, so if there is a new player, that is important.'

### Functional genomics

The researchers are now using a functional genomics approach to search for substrates of the complex. They have already scanned 42% of the *Drosophila* genome and found six candidates. The next step is to find out how these are involved, to try to work out whether the new complex is involved in translation control or protein degradation, they say.

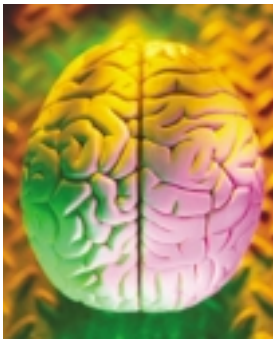
Although mammalian embryos do not have a period of rapid embryogenesis equivalent to that seen in *Drosophila*, understanding the different ways in which cyclins are regulated after transcription will be useful in the study of the normal cell cycle in all organisms, says Orr-Weaver. It might also provide clues to how the cell cycle is coordinated with other developmental events, for instance how it restarts after fertilization, she says.

Stukenberg agrees that understanding the regulation of the modified embryonic cell cycle will be important. The cell cycle has an 'oscillator' signal that regulates the switch from S phase to M phase and back again, he explains. In addition, there are regulatory checkpoints at the entry to each phase. 'You can not study the oscillator in somatic cells because the checkpoints are always a part of it,' he said. 'So, if you want to look at the core oscillator, the early embryonic system is really the only place to look at it. And you can not do that sort of experiment in mammalian cells, because you can not get the cells to be in the same synchronized state.'

# News in brief

## Targets and Mechanisms

### Untangling the AD tangle



The two main molecular events that are characteristic of Alzheimer's disease (AD) brain cells, extracellular amyloid plaques and intracellular neurofibrillary tangles (composed of tau protein), have recently been linked by researchers at the Feinberg School of Medicine, Northwestern University (http://www.feinberg.northwester.edu) [1]. The new findings reveal a novel mechanism involving proteolysing caspases.

Previous investigations, into which of the two pathological entities is the primary cause of AD, already hinted at amyloid promoting assembly of tau into tangles; however, the exact mechanism was not clear. Caspases provided a strong candidate for this 'missing link' as they are known to be activated in degenerating neurons in AD and to occasionally cleave tau.

In experiments exposing neurons to amyloid-β, caspases were activated, which in turn, rapidly (within 2 h) cleaved tau at a conserved aspartate residue ($Asp^{421}$) in its C terminus. This truncated form of tau (lacking its C-terminal 20 amino acids) was more likely to form tangled filaments than wild-type tau. Indeed, further studies using a specific monoclonal antibody established that the tau protein in the AD tangles was commonly cleaved at the $Asp^{421}$ site. Researchers still have to determine the timing of tau cleavage in AD brains in relation to other events.

This work 'points to the need to consider both of these interrelated pathological events in future studies and therapies' say Lester I. Binder and Vincent L. Cryns, the co-senior authors of the report.

1 Gamblin, C.T. *et al.* (2003) Caspase cleavage of tau: Linking amyloid and neurofibrillary tangles in Alzheimer's disease. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.1630428100 (http://www.pnas.org)

### New insight into diabetes

A new system has been designed that could enable the much-needed elucidation of the stages of normal pancreatic

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