IN THE NEWS

Banking on ES cells

The first embryonic stem (ES) cells to be grown in the United Kingdom hit the headlines in mid-August. The new stem-cell lines — to be deposited at the United Kingdom Stem Cell Bank — will allow much easier access to ES cells for European researchers in particular (*BBC News*).

The Stem Cell Bank, which will open in autumn 2003 (*Financial Times*), will be a world first. This Medical Research Council initiative should be a source of quality-controlled stem cells for researchers worldwide. Having ES cells maintained in a centralized resource will also reduce the number of surplus embryos that are required by individual research teams.

The *Financial Times* reported that the ES cell lines produced by teams at King's College London and Newcastle University were generated from surplus *in vitro* fertilization embryos. Peter Braude from King's College said: "We are proud of the particular way that our lines have been generated".

The King's College group is targeting Parkinson disease and type 1 diabetes as disorders that could benefit from ES cell research: "We already know that putting cells into patients with those diseases works but there is a significant shortage of transplantable material", said Stephen Minger (*BBC News*).

Predictably, pro-life groups saw things differently: "It's forbidden fruit, playing with human life", said Jack Scarisbrook, chair of the group Life (*The Guardian*).

Media coverage elsewhere was muted, which is unsurprising given that many other countries including the United States, Australia, India and Sweden have already successfully grown ES cell lines (*New Scientist*). Despite this, the breakthrough, coupled with the imminent opening of the United Kingdom Stem Cell Bank, should provide a significant spur to geneticists who are interested in using ES cells for their research.

Nick Campbell

HUMAN DISEASE

Fragile X: a class of its own

Just over a decade ago, fragile X syndrome — a common form of hereditary mental retardation — rose to notoriety by being the first disorder to be caused by the expansion of a trinucleotide repeat. Fragile X sufferers have more than 200 CGG repeats in the 5′ untranslated region of the fragile X mental retardation 1 (*FMR1*) gene, compared with 60 or fewer in normal individuals. As in other similarly inherited conditions, the expanded disease alleles derive from phenotypically normal individuals that carry an intermediate number of unstable repeats, which in the case of fragile X ranges from 60 to 200.

Although this inheritance model has held true for years, some of these so-called 'premutation' carriers have now been found to develop a new form of progressive neurodegeneration — a phenotype that is unrelated to fragile X. This observation provided the starting point for the study by Peng Jin and colleagues. By modelling the condition in *Drosophila* they show that human premutation repeats alone can lead to neurodegeneration, and that the effect depends on the abundance and length of the repeat. This is also the first time that neurodegeneration has been attributed to RNA alone.

To test whether the neurodegeneration phenotype could be pinned down to changes in CGG-repeat size, Jin and colleagues looked at the effect of expressing human repeats of different length in several *Drosophila* tissues. What they found was clear cut — moderate expression of 60 CGG repeats ($rCGG_{60}$) had no effect, but moderate expression of the longer premutation $rCGG_{90}$, or overexpression of either $rCGG_{60}$ or $rCGG_{90}$, causes progressive degeneration specifically in neuronal tissue. This tells us that longer repeats are more toxic than shorter (normal length) ones and that toxicity increases with transcript abundance. The result also tallies nicely with what is seen in premutation patients, who have high levels of *FMR1* mRNA.

Fragile X patients lack any *FMR1* message, so the mechanism that underlies the progressive neurodegeneration must be distinct from that which causes fragile X. Instead, it could resemble that of other neurodegenerative disorders, such as some forms of spinocerebellar ataxia, which are caused by repeat expansions in noncoding regions and have been blamed on RNA.

But are we any closer to understanding what these repeat RNAs do? In both the experimental flies and human premutation patients, nuclear aggregates are seen that also contain ubiquitin and so it is possible that here the RNA repeats sequester vital proteins from their normal functions. The fact that the formation of these clumps can be reversed by overexpressing the chaperone heat shock protein 70 (Hsp70), which normally unravels or destroys badly folded proteins, is intriguing: the involvement of the protein-degradation machinery could link these RNA-mediated defects to the larger class of protein-based neurodegenerative disorders, many of which are also reversed by Hsp70.

The creation of a *Drosophila* model for this disease has already paved the way for targeted genetic studies. Meanwhile, it looks like fragile X is back where it started — in a class of its own.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPER Jin, P. *et al.* RNA-mediated neurodegeneration caused by the fragile X premutation rCGG repeats in *Drosophila*. *Neuron* **39**, 739–747 (2003)

WEB SITE

Stephen Warren's laboratory:
http://www.emory.edu/WHSC/MED/GENETICS/visitors/warren.html