

In the news SYSTEMS BIOLOGY
WITH A VIEW

Imagine a cutting-edge systems biology unit in a state-of-the-art research park with a community of top scientists, all within a stone's throw of the sand and waves of the sunny Mediterranean coast. Well, there is no longer a need to daydream — in September 2006, the European Molecular Biology Laboratory (EMBL) and the Centre for Genomic Regulation (CRG) launched the EMBL/CRG Research Unit for Systems Biology in Barcelona, Spain.

"Systems biology is the future of biomedicine," says Luis Serrano, the coordinator of the unit, "and in this new partnership we will combine theoretical and experimental approaches to better understand some of the key aspects of human health" (EMBL press release, 7 September 2006). In support, the Spanish ministry for Education and Science has pledged €12.7 million over the next nine years to the new unit.

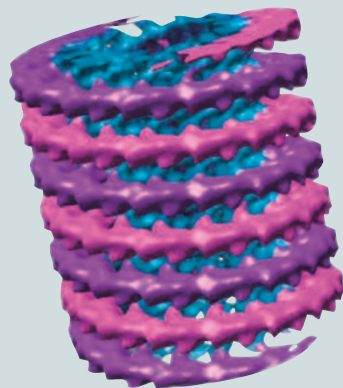
Miguel Beato, Director of the CRG, hopes that through "adopting EMBL's system of fostering young talents and regular staff turnover we will ensure a continuous flow of ideas" (EMBL press release, 7 September 2006). Serrano intends to develop "a spirit of rotation and the removal of the 'position for life' philosophy" (*Science*, 2 June 2006). To this end, researchers at the unit will receive 5-year contracts that can be extended for 4 years.

The unit will be in the beachfront Barcelona Biomedical Research Park, which can house up to 80 research groups and includes other units, such as Barcelona's Municipal Institute of Medical Research, a Centre for Regenerative Medicine, an Institute of Advanced Technology and a 400-bed hospital. Primary researchers are currently being recruited, so if this sounds like the ideal place for you then prepare your *curriculum vitae*, and don't forget to pack your towel.

Asher Mullard

 MOLECULAR MOTORS

Run rings around



Three-dimensional reconstruction of kinesin-13 spirals. Image courtesy of H. Sosa, Albert Einstein College of Medicine, Bronx, New York, USA.

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Most kinesins use energy from ATP hydrolysis to move and generate force along microtubules; however, exceptions exist. Rather than moving along microtubules, kinesin-13 proteins (kinesin-13s) actively depolymerize microtubules, which is important for chromosome segregation during mitosis. What is the structural basis of this unusual behaviour by kinesin-13s? And what is the mechanism that is used to depolymerize microtubules? Tan *et al.* now provide some answers.

The authors used electron microscopy to investigate the structure of the complex that is formed between microtubules and *Drosophila melanogaster* or hamster kinesin-13s. They found that kinesin-13s form rings and spirals around microtubules — rings only formed in the presence of both microtubules and kinesin-13s, and

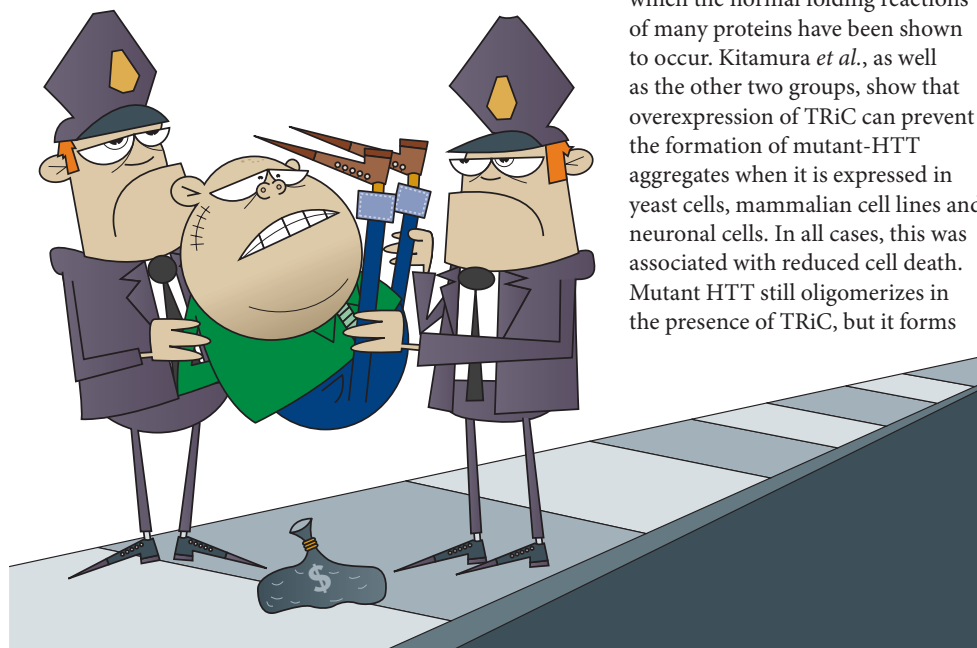
 MECHANISMS OF DISEASE

Folding away the bad guys

The correct folding of newly synthesized proteins is regulated by a pathway that involves heat-shock proteins and chaperonins, such as TRiC (also known as CCT). Three groups have identified a new substrate for TRiC — Huntingtin (HTT) — and show that TRiC can

direct HTT away from forming the toxic aggregates that characterize the devastating pathology of Huntington's disease.

TRiC is a cytoplasmic protein that is made up of two rings of eight homologous subunits, stacked back-to-back, that form a cage in which the normal folding reactions of many proteins have been shown to occur. Kitamura *et al.*, as well as the other two groups, show that overexpression of TRiC can prevent the formation of mutant-HTT aggregates when it is expressed in yeast cells, mammalian cell lines and neuronal cells. In all cases, this was associated with reduced cell death. Mutant HTT still oligomerizes in the presence of TRiC, but it forms



were favoured specifically by the ATP-bound forms of these kinesins.

To gain further insights into the structure of the ring, Tan *et al.* created a three-dimensional reconstruction of the spirals that are formed on microtubules with 15 protofilaments. The molecular model showed that contacts along a tubulin protofilament in the outside ring must stabilize the spiral and that the innermost part of the ring is a kinesin motor domain that interacts with the microtubule wall. In addition, interactions between two kinesin motor domains bridged the inner and outer ring regions, which implies that the interactions between the kinesin molecules are part of the mechanism that leads to ring and spiral formation.

So, what could be the function of these rings? *In vivo* analysis showed that the *D. melanogaster* kinesin-13

KLP59C specifically accumulates at the depolymerizing microtubule end and slides along the tubule lattice as the depolymerizing end advances. Based on their findings, the authors proposed that kinesin-13s in higher eukaryotes have a dual function during mitosis — they control microtubule depolymerization and they form a loose sleeve, or ring, that can slide along the microtubule lattice and keeps kinesin-13s associated with the microtubule ends.

Ekaterini Kritikou

ORIGINAL RESEARCH PAPER Tan, D. *et al.* Kinesin-13s form rings around microtubules. *J. Cell Biol.* 2 Oct 2006 (doi:10.1083/jcb.200605194)

WEB SITE

Hernando Sosa's laboratory:
<http://www.aecom.yu.edu/home/faculty/profile.asp?id=23660=1>

aggregates with different properties that do not seem detrimental to cell survival.

Behrends and colleagues investigated a possible cooperative function of TRiC with a second protein that is involved in regulating protein folding — heat-shock protein-70 (HSP70). They found that the protective function of TRiC depended on the presence of HSP70, and that TRiC could only act on HTT after it had been processed by HSP70. This fits with the well known role of these proteins in normal protein regulation: HSP70 interacts first at the point of translation to prevent premature folding events, whereas TRiC functions downstream to regulate the correct folding and aggregation of proteins.

Previous work has shown that TRiC specifically prevents the aggregation of newly synthesized proteins by recognizing hydrophobic β -strands. Interestingly, toxic conformations of mutant HTT adopt a β -sheet structure, thereby providing a glimpse of how TRiC might recognize and regulate the conformation of HTT.

Tam *et al.* investigated the effect of overexpressing each of the eight subunits of TRiC. Whereas most subunits did not prevent the formation of cellular inclusions, subunit-1 strongly inhibited toxic HTT aggregation and increased

neuron viability. This protective activity was found to reside in the apical domain of the protein, which has been recently shown to contain the protein's polypeptide-binding site. However, RNA knockdown of just one of the other eight subunits was enough to stimulate HTT aggregation and neuronal toxicity, which, instead, indicates that only the fully assembled TRiC chaperonin complex can provide neuroprotection against mutant HTT.

So, it seems that mutant HTT can oligomerize by mechanisms that can lead to the formation of either toxic or benign aggregates. If the findings of Tam *et al.* — that part of subunit-1 is sufficient to promote a non-toxic HTT-aggregation pathway — can be verified, then small peptide inhibitors, modelled on the TRiC binding site, might serve as effective therapies against Huntington's disease.

James Pickett

ORIGINAL RESEARCH PAPERS Kitamura, A. *et al.* Cytosolic chaperonin prevents polyglutamine toxicity with altering the aggregation state. *Nature Cell Biol.* 8, 1163–1169 (2006) | Behrends, C. *et al.* Chaperonin TRiC promotes the assembly of polyQ expansion proteins into nontoxic oligomers. *Mol. Cell* 23, 887–897 (2006) | Tam, S. *et al.* The chaperonin TRiC controls polyglutamine aggregation and toxicity through subunit-specific interactions. *Nature Cell Biol.* 8, 1155–1162 (2006)

FURTHER READING Young, J. C. *et al.* Pathways of chaperone-mediated protein folding in the cytosol. *Nature Rev. Mol. Cell Biol.* 5, 781–791 (2004)



CYTOSKELETON

Modelling moves on

Previously developed models for the cytoskeletal network in stationary cells (that is, ignoring cell spreading and motility) have been based on the assumption that the cytoskeleton is a structure of passive filaments. However, such models ignore the biochemical reactions within the cell that generate, support and respond to mechanical forces. Deshpande *et al.* now present a biochemically inspired model for the dynamic rearrangement of the cytoskeleton that addresses important challenges in the field of cell biomechanics.

The authors considered recent observations of the forces that are exerted by mammalian cells on a compliant substrate — for example, spatial correlations have been observed between the force vectors that operate on the substrate and the organization of the stress fibres. A model was then developed to capture the reorganization of the cytoskeleton in response to mechanical perturbations.

Experiments, for example, measure the forces that are exerted by cells on a bed of microneedles, with the stress fibres revealed by actin staining. So, how can one model such experiments? The model is based on three important biological processes: an activation signal that triggers actin polymerization and myosin phosphorylation; the tension-dependent assembly of actin and myosin into stress fibres; and the cycling between actin and myosin filaments that generates the tension. Because the precise details of these biochemical processes are still unclear, the authors have developed a model that does not depend on the details and serves as a framework that can be appropriately modified when these biochemical processes are better understood.

Deshpande *et al.* propose that simple relationships simulate these coupled phenomena and show that their model can be used to predict experimentally verified data, such as the influence of cell shape and boundary conditions, on the orientations of the fibres as well as the high concentration of the stress fibres at the focal adhesions. Most importantly, this model can measure the mechanical characteristics of living cells that react to the measurement tools and, therefore, can be used as a framework to design and interpret experiments.

Ekaterini Kritikou

ORIGINAL RESEARCH PAPER Deshpande, V. S. *et al.* A bio-chemo-mechanical model for cell contractility. *Proc. Natl Acad. Sci. USA* 103, 14015–14020 (2006)

WEB SITE

Anthony G. Evans's laboratory:
http://www.me.ucsb.edu/dept_site/people/evans_page.html