WEB WATCH

The A–Z of cell migration

• www.cellmigration.org

The web site for the Cell Migration Consortium, which is "…dedicated to accelerating progress in migration-related research … comprised of a number of investigators and collaborators from over 10 institutions…" is a site that's really going places.

The available information falls into three sections: 'Cell Migration Science', 'The Consortium' and 'Research Resources'. For the more hands-on among you, the first and last sections will probably be most appealing, but the additional information about the Consortium is well worth a read too.

Within the Cell Migration Science section, click on 'Migration 101' — here you'll find a nice overview of cell migration (complete with an animated schematic of a migrating cell!), where you can brush up on the basics of migration mechanics and read about the pivotal role of cell migration throughout life. For 'proteinophiles', a really useful link is 'Molecules', which provides a comprehensive list of proteins — from α-Actinin to Zyxin. Another nice feature is the movies, although, at present, the collection's rather sparse.

Although the 'News' section is not very current, the rest of the site provides reasonably up-to-date information, such as PubMed links to abstracts of relevant primary papers and reviews within the Cell Migration Science category. There are further links and job postings, too.

Another useful resource is the links to relevant meetings, which currently extends into May 2003, and for those of you who are interested in 'migrating' down the slopes, the Cell Migration Consortium will be meeting up at the Keystone Cell Migration and Invasion meeting in Breckenridge next January.

Katrin Bussell

PROTEIN METABOLISM

A deadly detour

The mammalian prion protein (PrP) is a cell-surface glycoprotein that has been linked to various neurodegenerative diseases. Transmissible prion diseases involve an infectious agent that is thought to be an altered conformation of PrP — PrP^{Sc}. But what initiates the formation of PrP^{Sc}, and which forms of PrP are toxic? Ma and Lindquist showed previously that PrP can accumulate in the cytosol by retrograde transport from the endoplasmic reticulum (ER) when proteasome activity is inhibited. Now, in two papers in *Science Express*, Lindquist and colleagues show that PrP that accumulates in the cytosol can convert to a self-perpetuating form of PrP^{Sc}, and that another cytosolic form of PrP is neurotoxic.

In the first study, Ma and Lindquist began by assessing the conformational state of cytosolic PrP that accumulates by retrograde transport. They did this using various inhibitors to block proteasome activity in several cell types that had been transfected with the mouse *PrP* gene. They found that most cytosolic PrP had formed amorphous aggregates, but that some had converted to a PrP^{Sc}-like form. They noted, however, that the fraction of PrP that converted to PrP^{Sc} varied greatly with the experimental set-up used, and showed that increased conversion to PrP^{Sc} correlates with an increased initial rate of PrP accumulation.

So, can the PrP-to-PrP^{Sc} conversion that occurred because of a loss of proteasome activity be sustained after the restoration of proteasomal activity? The authors studied the effect of restoring proteasome activity in COS cells that were expressing both PrP and the cystic fibrosis transmembrane conductance regulator (CFTR) — another protein that forms cytosolic aggregates in response to proteasome inhibitors. On restoration of proteasome activity, Ma and Lindquist saw no further increase in the amount of cytosolic aggregated CFTR, whereas the amount of aggregated PrP continued to increase, with a fraction of it converting to PrP^{Sc} as well as to other misfolded forms. This shows that "…PrP has an inherent capacity to promote its own conformational conversion in mammalian cells."

In the second study, Lindquist and colleagues studied the relationship between cytosolic PrP and neurotoxicity by looking at the effect of proteasome inhibitors on neuroblastoma (N2A) cells expressing PrP or presenilin-1. (Like PrP, presenilin-1 traffics through the ER and is subject to retrograde transport). On proteasome inhibition, the authors found that PrP and presenilin-1 accumulated in the cytosol of N2A cells. However, whereas N2A cells containing cytosolic presenilin-1 died at the same rate as wild-type cells, cells containing cytosolic PrP died more rapidly. In addition, the toxicity of cytosolic PrP seems to be cell-type specific, as the authors found

that NIH3T3 fibroblasts did not die on accumulation of cytosolic PrP.

Is the toxicity of cytosolic PrP relevant to whole-animal disease states? Lindquist and colleagues made transgenic mice that express a cytosolic form of PrP, and showed that, although the mice developed normally, they all acquired severe neurodegenerative disease, including cerebellar atrophy and gliosis. On dissection, the authors found that the disease pathology related to transgene expression.

These papers have enabled Lindquist and colleagues to propose a unifying model for PrP-associated diseases. PrP is normally present on the cell surface. However, a portion of PrP misfolds in the ER (this misfolding might be increased by disease-causing PrP mutations) and is retrogradely transported to the cytosol for proteasomal degradation. If cytosolic PrP accumulates (for example, if proteasomal activity is compromised, which can occur with stress or age), it can be neurotoxic. In addition, this accumulation might nucleate conversion to the infectious, non-toxic PrP^{Sc} conformation, which can then propagate the disease state.

Rachel Smallridge

References and links

ORIGINAL RESEARCH PAPERS Ma, J. & Lindquist, S. Conversion of PrP to a self-perpetuating PrP^{Sc}-like conformation in the cytosol. *Science Express* 2002 October 17 (DOI: 10.1126/science.1073619) | Ma, J., Wollmann, R. & Lindquist, S. Neurotoxicity and neurodegeneration when PrP accumulates in the cytosol. *Science Express* 2002 October 17 (DOI: 10.1126/science.1073725)

FURTHER READING Aguzzi, A. *et al.* Prions: health scare and biological challenge. *Nature Rev. Mol. Cell Biol.* **2**, 118–126 (2001)

WEB SITES

Susan Lindquist's laboratory: http://www.wi.mit.edu/far/far_lindquist_bio.html

Encyclopedia of Life Sciences: http://www.els.net/ Prions | Prion diseases