WEB WATCH

A forum for all

Sorting the wheat from the chaff when it comes to web sites is always tricky, especially in fields of public interest. But for anybody seeking to learn more about Alzheimer's disease, the Alzheimer Research Forum is a good place to start. Although the site has been around for some years (indeed, the archive goes back to February 1996), it is regularly updated and contains an impressive variety of sections and links.

First, though, the visitor must identify themself — layperson, physician or researcher? After logging in the layperson is directed to an 'Alzheimer general information directory' containing basic information about the latest research, and links to Alzheimer associations and support groups around the world. As a physician or researcher, however, you are directed to a different home page.

Here you'll find the expected lists of relevant papers, some of which have links through to PubMed, and 'Abstracts in Advance' from *The Journal of Alzheimer's Disease*. There's also a directory listing "genes that have been studied in relation to their role in Alzheimer's disease" — again with useful links to public databases. Other features that catch the eye are the 'Forum Interviews' with well-known researchers such as Dennis Selkoe and Bruce Yankner, the various mutations directories (APP, presenilins and tau), and the 'Virtual Conferences', where you can listen to recordings of the speakers.

There are a few glitches in this otherwise excellent site. For example, many of the newest 'Papers of the Week' do not yet contain PubMed links, and the 'Milestone Papers' section needs updating (for instance, there is no mention of the recent γ-secretase studies). But overall this is an easily navigable, useful site.

Alison Mitchell

CYTOSKELETON

Subunits 1: Polymers 0

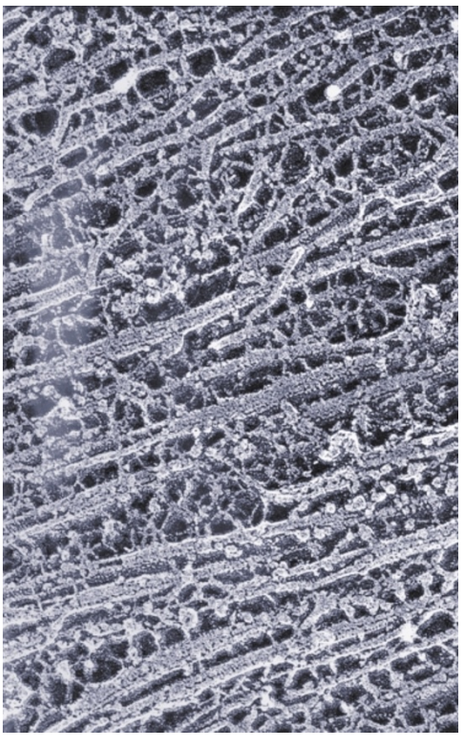
The field of slow axonal transport is divided between those who believe that cytoskeletal subunits are transported along the axon (the subunit model) and those who believe that entire filaments move (the polymer model). What both camps have in common is ignorance of the precise transport mechanism, whatever the cargo might be. Reporting in *Cell*, Hirokawa and colleagues now provide evidence that slow axonal movement requires kinesin motors and microtubule tracks.

The visualization of slow axonal transport is not trivial (see Anthony Brown's article on page 153 of this issue), and finding an appropriate model system is half the job. Hirokawa and colleagues used the squid giant axon in their studies because it has two advantages: it is translucent and it is big. They injected fluorescent tubulin into the axon and measured the speed at which it moved away from the cell body. The values obtained with this experimental set-up were similar to those reported for mammalian axons.

In a series of pharmacological studies, the speed of movement was considerably reduced when microtubules were depolymerized, but remained constant in the absence of polymerized actin microfilaments. Similarly, transport was slowed down when kinesin's motor activity was inhibited, but myosin seemed to be dispensable for this process.

Hirokawa and colleagues also observed that the diffusion rate of the transported tubulin is lower than the diffusion rate of creatine kinase (another cargo for slow axonal transport), but higher than the diffusion rate of taxol-stabilized microtubules. The authors interpret this finding as an indication that tubulin is transported in a complex that is large but different from a fully polymerized microtubule. This would tilt the balance in favour of the subunit model again, at least for the transport of tubulin. Figuring out the polymerization state of tubulin transported in this complex will hopefully clarify this issue.

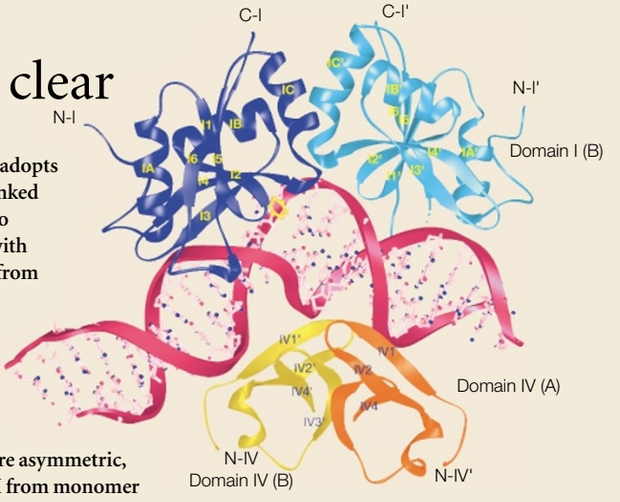
Raluca Gagescu



The axonal cytoskeleton. Courtesy of N. Hirokawa, University of Tokyo, Japan.

DNA REPAIR

Recognition is crystal clear



DNA polymerases are not infallible — they make mistakes while replicating DNA. Sometimes these errors are deliberate (see, for example, the review by Goodman and Tippin on page 101 of this issue). But often they are not, and that's when mismatch repair kicks in to protect against mutation. This system identifies DNA bases that have been incorrectly paired up, and allows the correct base to be reinserted. But how does it recognize the mismatches? Two groups, reporting in the 12 October issue of *Nature*, have studied the bacterial mismatch-repair protein MutS to address this question.

In the first paper, Obmolova *et al.* present the crystal structures of a *Thermus aquaticus* MutS homodimer, both alone and as a complex with DNA containing a single unpaired thymidine. The authors show that the DNA adopts an unusual kinked shape owing to interactions with two domains from each MutS monomer (domains I and IV). However, these interactions are asymmetric, with domain I from monomer A in the diagram donating the phenylalanine residue (yellow ring) that interacts specifically with the unpaired base.

This message — that the MutS homodimer is actually a heterodimer at the structural level — also emerges from the second paper by Lamers and colleagues. These authors report the crystal structure of *Escherichia coli* MutS binding to a G•T mismatch. Mismatch binding is known to induce the uptake of ATP, and both groups show that the ATPase domains also differ between the two MutS monomers. This asymmetry between the monomers in DNA and ATP binding could explain the specificity of MutS for