The riddle of slow transport – an introduction

Dennis Bray

You could say that microtubules are the ringmasters of the eukaryotic cytoplasm. They point organelles to their correct locations and then control their movements, in so doing determining the overall shape of the cell. But, if this is the case, who directs the ringmaster? How are microtubules themselves controlled? The usual answer to this question is 'by dynamic instability' – that is, by the nucleated growth of microtubules from rings of gamma tubulin in the centrosome followed by the selective capture and stabilization of their plus-ends. But, far-reaching though this important concept is, it just does not account for all the arrangements of microtubules found in eukaryotic cells. In particular, it does not explain the many examples in which stable microtubules lie in precisely oriented positions in the cytoplasm without any visible attachment to the centrosome or to other conspicuous structures. At present, we have only the vaguest idea where these 'unadopted' microtubules are made and how they are delivered to their correct locations in the cytoplasm.

The puzzle is dramatically illustrated in nerve axons. All developing nerve cells contain bundles of microtubules in their axons as they grow and most retain them throughout life. Individual microtubules in axons do not extend all the way from the cell centre to the synaptic endings (just as well, if you think of the recurrent laryngeal nerve of a giraffe!) but exist instead as independent structures, typically 10 to 100 μm in length, with both ends free in the cytoplasm. Alongside the microtubules, in most axons, are multiple neurofilaments and microfilaments, which present a similar problem of where they are made and how they get where they are.

In the past, two diametrically opposite theories have been proposed to explain how these axonal microtubules and filaments are put in place. The first (Fig. 1a) opines that these polymeric structures grow, as normal, in the nerve cell body and then break away and travel into the axon like logs in a sluice. The second theory (Fig. 1b) is that molecules of tubulin, actin or neurofilament protein are transported in some unassembled (although possibly oligomeric) form in the axon and are then added where necessary to the exposed ends of the protein polymer.

The subtlety and complexity of these issues, and the ingenuity of experimenters who try to resolve them, are laid out in the following two articles. Each represents one of the two opposing viewpoints, either assembly in the cell body followed by transport of the polymer down the axon, or transport of a subunit or oligomer followed by assembly at a suitable location in the axon. You are invited to read the evidence and make your own assessment of which is the most plausible judgement. It is a fascinating riddle and very difficult to solve. But the answer, when it comes, will be of great importance – not just for slow axonal transport but for cell morphogenesis in general.

Dennis Bray is in the Dept of Zoology, Downing Street, Cambridge, UK CB2 3EJ.

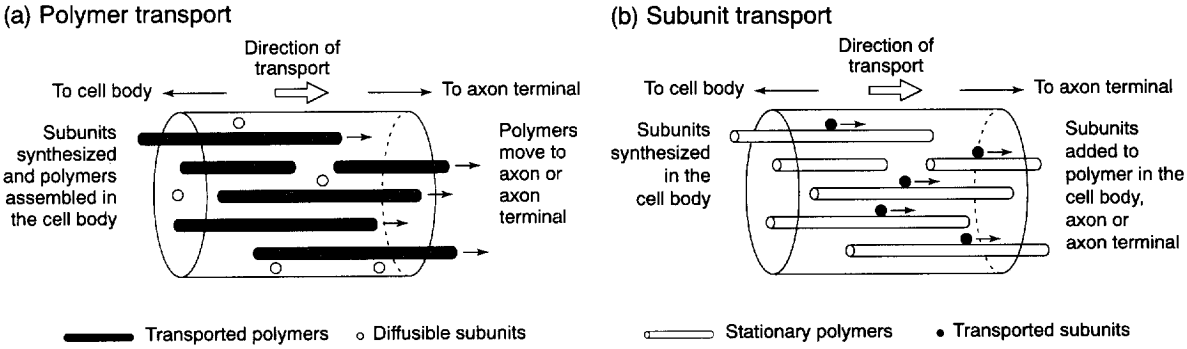

FIGURE 1

Illustration of the main features of the polymer and subunit models for a generic cytoskeletal protein. Both models assume that the polymers are dynamic and can undergo substantial length changes within the axon. In the polymer transport model, the subunits can diffuse and the polymers are actively transported, while in the subunit transport model the polymers are stationary and the subunits are actively transported. The substrate for the transport of the proteins is not yet clearly defined in either case, but candidates are discussed in the accompanying articles.

The three articles in this debate section are intended to be read as a unit. Dennis Bray's introduction sets the scene, then Baas and Brown (pages 380–384) and Hirokawa *et al.* (pages 384–388) argue in favour of two different models for the mechanism by which the microtubules, microfilaments and neurofilaments that make up the neuronal cytoskeleton are transported along axons. These discussions frequently involve very different interpretations of the same experiments, and finding the real answer is a complicated task. As Dennis Bray says, it's a fascinating riddle, and we hope that you will enjoy thinking about possible solutions.

0962-8924/97/$17.00
PII: S0962-8924(97)01134-3