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A possible mechanism for controlling processive transport by microtubule-associated proteins

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Abstract

Molecular mechanisms of axonal transport have been evaluated by several investigators. It seems that microtubules (MTs) act as a track for the transport and microtubule-associated proteins (MAPs) seem to play as a regulating factor in it. In order to transport MTs must move in the radial direction to make room for a vesicle and when the cargo passes, return to the previous position for the maintenance of neuronal structure. An inhibitor factor against the radial movement is the steric constraints resulted from presence of MAPs. In fact, inter-microtubular spaces (IMS) in the neuronal processes are resulted from the space-making role of the MAPs. Since the IMS must be locally altered to make enough room for a vesicle, it seems relevant to imagine some mechanisms that control the steric constraints for an efficient vesicular transport. Here we juxtapose the older findings and the recent ones to investigate the possible effects of MAPs on the processive transport.

Keywords: MAPs; Steric constraints; Processive transport; Inter-microtubular spaces

1. Roles of MAPs

Microtubule-associated proteins (MAPs), a group of filamentous proteins copurified with tubulin through repetitive cycle of depolymeriztion and reassembly, have various roles in the nervous system. For example, in MT promoting assembly, nucleation and flexibility (Kurz et al., 1995) as well as neuronal growth. The MAPs also play a role as regulating factor in the processive transport (Dixit et al., 2008; Marx et al., 2006), and one of the most established of their roles is in space-making (Shahani and Brandt, 2002) which determines the inter-microtubular spaces (IMS) in the neuronal processes (Belanger et al., 2002; Frappier et al., 1994). Particularly MAP2, MAP1B and tau play a critical role on the MT spacing. MAP2 is a major group of microtubule-associated proteins which has three isoforms, MAP2A, B and C. MAP2C is localized in cell bodies, dendrites, and axons of juvenile neurons, whereas MAP2A and B are localized mainly in dendrites of mature neurons (Sanchez et al., 2000) which determine the IMS in dendrites (Belanger et al., 2002). MAP1B (also known as MAP1.2, MAP1x, or MAP5) is expressed prominently during early stages of neuronal development and reported that overlap in space-making role in dendrites with MAP2 (Teng et al., 2001; Cruz et al., 2005). Tau protein is another major member of MAPs which mainly concentrated in axons and determine the IMS in the axonal cytoskeleton (Santarella et al., 2004; Frappier et al., 1994).

Regarding the inter-MT spaces in the processive cytoskeleton, MTs have to move radially in order to make room for the giant vesicle, which will not be possible without a local alteration in the IMS (Fig. 1). It was demonstrated that the adjustable IMS are resulted from the space-making role of the MAPs (Friedrich and Aszodi, 1991). We think that there are defined mechanisms that control dynamically the IMS for an efficient vesicular transport.

2. Polymer brush model

Tau and MAP2A and B were introduced originally as cross-linker proteins (Mc Intosh, 1974). However the latest reports emphasized that they neither cross-link MTs to each other nor to neurofilaments (NF), but merely determine the IMS between MTs (Marx et al., 2000). It was also stated that MAP1B play a

Abbreviations: IMS, inter-microtubular spaces; MAP, microtubule-associated protein; MT, microtubule; NF, neurofilament.

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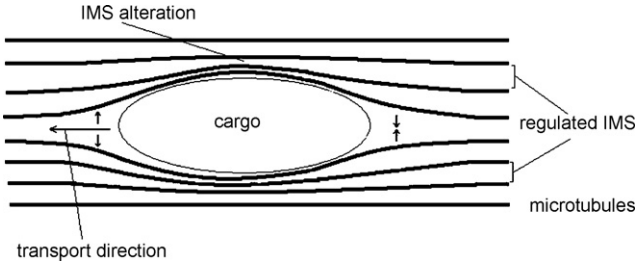

Fig. 1. Schematic representation of IMS rearrangement for movement of the vesicles.

role in keeping space between MTs in the neuronal cytoskeleton which overlaps with MAP2 (Teng et al., 2001; Cruz et al., 2005). Conventional MAPs have two distinct domains: (a) microtubule binding domain which is positively charged and electrostatically adhere onto the surface of MTs (Gustke et al., 1994). This domain is largely identical in MAP2 and tau protein (Lewis et al., 1988). (b) Projection domain which is negatively charged and protrudes out of the MT surface (Marx et al., 2000). This domain is largely flexible and the structure is poorly defined, moving in Brownian motion (Bright et al., 2001). One of the most accepted mechanisms between neighbor MT-MAPs is the polymer brush model (Mukhopadhyay et al., 2004) which suggests that there is a repulsive force between neighboring MT-MAPs and MT-MAPs and prevent the neighboring MTs from over-closing and collapsing (Fig. 2). It was also claimed that NF's side arms are functionally similar to projection domain of MAPs and determine the IMS in the same way (Zhulina and Leermakers, 2007; Brown and Hoh, 1997). The IMS are determined in terms of the projection domain's length which is ∼1400 amino acid in MAP2 and ∼242 amino acid in tau protein and the relevant IMS is ∼60–70 nm in dendrites and ∼20–30 nm in axons, respectively (Chen et al., 1992). Hence, the MTs have to move radially in order to make room for the giant vesicle, as large as mitochondria with dimension 10 μm × 0.2 μm, which will not be possible without a local alteration in the IMS. We think that there are defined mechanisms that control dynamically the IMS for an efficient vesicular transport. The determining factors of the IMS are steric constraints due to repulsive force resulted from projection domain of the MAPs (Shahani and Brandt, 2002; Belanger et al., 2002). In order to make alteration in the IMS, these steric constraints have to be adjustable and it was reported that the IMS which resulted from the MAPs are tunable (Friedrich and Aszodi, 1991). Hence the mechanisms which control the steric constraints would affect the IMS and consequently affect porcessive transport.

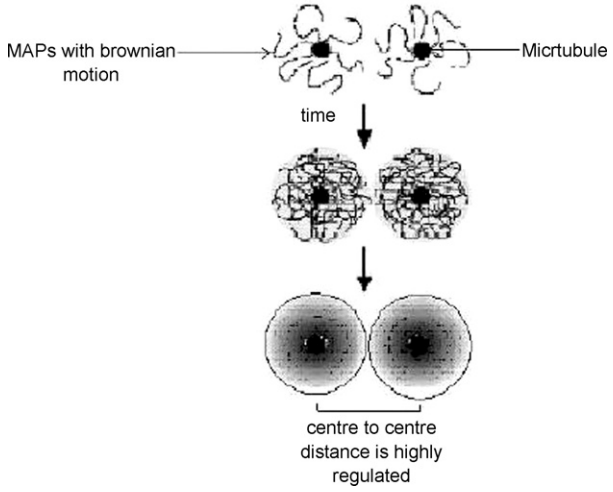

Fig. 2. The central feature of the polymer brush model is that the surface projections from microtubules are highly unstructured, in rapid Brownian motion and form a so-called polymer brush. In relatively short times, on the order of nanoseconds, these projections adopt a very large number of conformations, essentially filling some characteristic space. Proteins entering this space tend to be excluded based on entropic considerations; thus as two microtubules are brought together, the polymer brush gives rise to a repulsive interaction between the microtubules.

3. Phosphorylation of projection domain of MAPs

One of the most important effectors controlling the IMS is phosphorylation of projection domain of tau and MAP2 (Tokuda and Hatase, 1998) as well as the phosphorylation of NF's side arm (Sihag et al., 2007; Mata et al., 1992). There are several sites on the projection domain of tau and MAP2 which could be phosphorylated (Sanchez et al., 2000). With increasing the number of phosphate groups one would expect higher rigidity of the projection domain. Therefore the steric constraints would be increased and so would the IMS (Hagestedt et al., 1989) (Fig. 3) provided that the MAPs still remain on the MT surface since the highly phosphorylated tau cannot bind to MT (Avila et al., 2006). There are several kinases in the axons and dendrites which affect on MAP2A, B and tau protein (Sanchez et al., 2000) and also it was reported that the

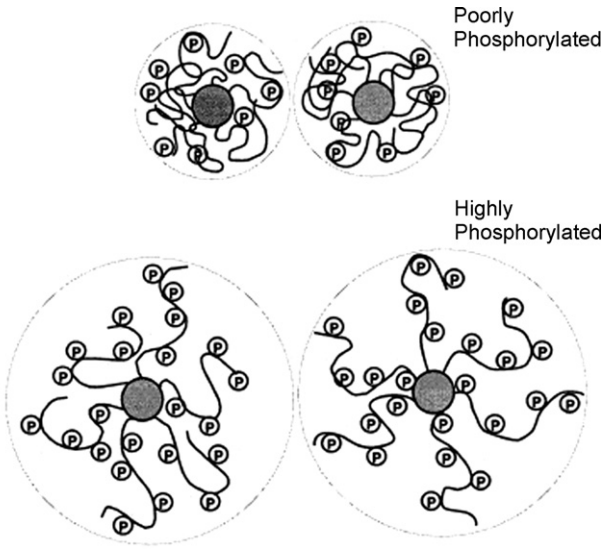

Fig. 3. Proposed regulation of MAP polymer brush by phosphorylation and dephosphorylation. Dephosphorylation reduces the intramolecular repulsion, causing the projection domains to become more compact and allows the microtubules to move closer. Phosphorylation of the projection domains causes the projection domains to expand due to an increase in intramolecular repulsion. This in turn causes the distance between adjacent microtubules to increase (from the courtesy of Mukhopadhyay, FEBS Letters, vol. 505: 374–378 with permission).