Commentary

Cruising along Microtubule Highways: How Membranes Move through the Secretory Pathway

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How microtubules (MTs)[1] influence secretion has long intrigued cell biologists. Significant insight has come from studies showing that MTs serve as highways along which transport intermediates travel between the ER and Golgi (9, 10, 21, 28, 32), making it tempting to conclude that MTs are essential for secretion. While the literature contains many additional reports supporting that view (for example 7, 31), it is also oddly replete with reports that secretion is unimpaired in cells depleted of MTs (for example 12, 18, 39, 41). Thus, although MTs are used for some steps in secretion, they may not always be required. To understand fully the role of MTs in secretion, it is therefore necessary to look beyond the question of whether secretion can occur when MTs are absent, but focus instead on how biosynthetic products are transported through the secretory pathway in the presence of MTs and how removal of MTs modifies normal transport mechanisms.

We present here a multifaceted perspective that ties together a confusing body of evidence about MTs and secretion. By recalling the classic example of fast axonal transport, we emphasize that cell morphology dramatically influences the extent to which MTs are required for secretion. By summoning more contemporary cultured cell data, we note that transport between the ER and Golgi can occur efficiently in the absence of MTs, but only under restricted conditions. Finally, the variable MT requirement for transport between the ER and Golgi is explained in terms of how distinct compartments within the secretory pathway rely upon MTs for their spatial segregation and structural integrity and how removing MTs alters endomembrane organization in a manner whose effects on secretion are time dependent.

Diffusion Cannot Account for Rapid Vesicle Transport

Can vesicle movement be accomplished by diffusion? The answer must take into account basic physical properties of cytoplasm. Transport vesicles vary in size and shape but commonly have a long axis of ∼100–200 nm. A study of secretory granule diffusion in neutrophils indicates how comparably sized vesicles in other cell types might diffuse through a cell. The diffusion coefficients of the granules were found to be ∼2.5×10^{-10} cm^2/s in control cells and in cells that had been depleted of MTs or actin filaments (13). In a modestly sized cell, therefore, a 160-nm vesicle may require only about 10 min to diffuse 10 μm from the TGN to the plasma membrane.[2] In cells that have long cytoplasmic processes, however, an intolerably long period may be required for a vesicle to diffuse to the distal end of a process.

An extreme example of this problem is presented by a 1-m-long axon in a human neuron. Numerous biosynthetic products are produced in the cell body, incorporated into secretory vesicles, and moved to the end of the axon. If a neuron relied on random diffusion for delivery of these vesicles to its axon terminal, more than 630,000 years would elapse before a 160-nm vesicle could complete the journey.[3]

Fortunately, the neuron has been endowed with a rapid transit system, based on MTs, that operates on a more acceptable time scale. Axonal MTs are uniformly polarized with their plus ends facing the axon terminal (14), and vesicle-associated MT motor proteins move their cargo along the axonal MTs at instantaneous velocities of up to 2 μm/s (38). This form of motility operates bidirectionally. Biosynthetic products move toward the axon terminal, while endocytosed material moves toward the cell body. Even if its average velocity were only 0.5 μm/s, or 25% of its maximum instantaneous rate, a vesicle would move from the cell body to the terminal of a 1-m axon in about 3 wk, more than 10^6-fold faster than could occur by diffusion.

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1. *Abbreviations used in this paper*: IC, intermediate compartment; MT, microtubule; MTOC, microtubule-organizing center; VSVG-GFP, chimaeric protein of a COOH-terminal domain of the ts045 mutant of vesicular stomatitis virus glycoprotein fused to green fluorescent protein.

2. Approximately 11 min was calculated by the equation for three-dimensional diffusion: $t = L^2/6D$, where t = time, L = length (10 μm), and D = diffusion coefficient (2.5×10^{-10} cm^2/s) for ∼200-nm-diam granules in neutrophils (13).

3. Approximately 630,000 years was calculated using the equation for one-dimensional diffusion: $t = L^2/2D$, where t = time, L = length (1 m), and D = diffusion coefficient (2.5×10^{-10} cm^2/s) for ∼200-nm-diam granules in neutrophils (13).

MTs Are Used, but Not Required for Short-Range Transport

It is easy to understand why delivery of secretory vesicles to the end of a long axon requires MTs. It is less obvious, however, why a cell that does not need to move vesicles over such long distances would use MT highways. The explanation reflects how the cytoskeleton organizes the cytoplasm, and specifically how MTs influence the distribution of other cytoskeletal structures and membranes. The cytoskeleton endows the cell with a very crowded cytoplasm, and it is likely that the integrated organization of the cytoskeleton and membrane systems provides an important barrier to the free diffusion of vesicles (22).

In considering how MTs influence the organization of membranes within the secretory pathway, we focus for illustrative purposes on cells, such as fibroblasts, whose MTs emanate from a perinuclear MT-organizing center (MTOC). The net result of this cytoarchitectural arrangement is a radial array of uniformly polarized MTs, whose minus ends converge at the cell center (35). In cells containing radially arranged MTs, the Golgi is concentrated near the MTOC (17), whereas ER is found throughout the cytoplasm (36).

The combination of a centrally located Golgi and dispersed ER is a direct consequence of the radial arrangement of MTs. Membranes move along MTs in both directions between the ER and Golgi (21, 28), and at steady state, forward (or ER-to-Golgi) transport is balanced by transport in the reverse direction. Although an obvious purpose of forward transport is delivery of nascent secretory products to the Golgi, this process also allows resident ER components, which are sorted from secretory products with less than perfect accuracy, to move toward the Golgi as well. A principal role for reverse transport is to recycle the escaped ER components (20), but recently published data support the hypothesis that imperfect membrane sorting at this stage also allows resident Golgi components to be carried to the ER by reverse transport (9, 10). ER and Golgi components thus move bidirectionally between the cell center and periphery, and forward transport may serve the further purpose of recycling escaped Golgi components. We suggest that biochemical and biophysical properties of ER and Golgi membranes promote their self sorting (1, 29), albeit imperfectly, and that the dominant MT motors that associate with the ER and Golgi dictate where these distinct compartments accumulate. If motors that move toward MT plus ends were dominant on the ER, it would be driven away from the cell center and adopt a dispersed distribution. Likewise, if minus end–directed motors were dominant for the Golgi, it would reside near the cell center, where MT minus ends converge.

Transport intermediates shuttle material bidirectionally between the ER and Golgi (33, 34). Material exits the ER in membranes that first are coated with COP II, which is rapidly exchanged for COP I (4). A principal function of COP II membranes is to concentrate secretory products as they emerge from the ER (3, 28, 32), while COP I membranes sort biosynthetic products from resident ER components (25) and deliver secretory products from the ER to the Golgi (33). Forward transport requires COP II (2), but the function of COP I is unclear. Studies in yeast suggest a COP I requirement for reverse transport (19), but

evidence from mammalian cells implies an involvement of COP I in ER-to-Golgi transport (26, 27). The forward moving COP I membranes and the recycling membranes, which may or may not contain COP I, are collectively known as intermediate compartment (IC).

Two recent papers elegantly demonstrate that transport of IC to the Golgi occurs along MTs (28, 32). In both cases, cells were transfected with VSVG–GFP, a chimaeric protein containing the COOH-terminal region of a temperature-sensitive vesicular stomatitis virus glycoprotein fused to green fluorescent protein. Synchronous transport of the fusion protein through the secretory pathway was observed in live cells by fluorescence microscopy. VSVG–GFP accumulated in the ER at 39–40°C and was released en masse into the IC within minutes after the cells were placed at 31–32°C. VSVG–GFP was also blocked in the IC at 15°C. A subsequent temperature increase to 31–32°C allowed synchronous movement of VSVG–GFP to the Golgi. In both studies, IC membranes containing VSVG–GFP moved to the Golgi along MTs. Movies of this phenomenon can be viewed via the Internet at http://dir.nichd.nih.gov/cbmb/pb1labob.html.

What happens to secretion and secretory pathway membranes when MTs are depolymerized? The answer depends on how long the MTs are absent. Soon after MTs are depolymerized, rates of Golgi-dependent protein processing drop precipitously because MT-dependent transport from the IC to the Golgi is potently inhibited (9, 11, 28, 32). This effect is dramatically illustrated in the Fig. 4 *E* movie. Shortly after the cell in the movie was exposed to nocodazole, most IC structures containing VSVG–GFP exhibited Brownian movement, but a few IC particles moved to the cell center along what probably was a single, drug-resistant MT. Removal of nocodazole from cells that had been briefly exposed to the drug allowed rapid, MT-based movement of VSVG–GFP to the Golgi (Fig. 4 *F* movie).

Curiously, a prolonged absence of MTs is not always accompanied by decreased rates of Golgi-dependent protein processing or secretion (12, 18, 39, 41). In cases in which normal rates are sustained, however, the distribution of Golgi membranes is radically altered. Instead of being segregated from the ER as an intact unit near the MTOC, the Golgi becomes fragmented into scores of ministacks that are distributed throughout the cytoplasm (30), adjacent to ER exit sites and IC membranes (9). To move from the ER to the Golgi via the IC in the prolonged absence of MTs, therefore, nascent secretory products must traverse distances far less than 1 μm. Evidently, diffusion-based membrane trafficking occurs with reasonable efficiency over such short distances. By comparison, ER and IC membranes in cells that contain MTs can be located dozens of micrometers away from the Golgi, a distance that requires directed transport along MTs to ensure efficient delivery of biosynthetic products from the ER to the Golgi.

Why MT Depolymerization Causes the Golgi to Redistribute

Although for many years MT disassembly has been known to lead to Golgi fragmentation and dispersal (30), only recently has an explanation based on direct evidence been suggested. When a cell is deprived of MTs, the Golgi con-

tinues to be a source of reversibly directed membranes that contain resident Golgi components. As mentioned earlier, it has been suggested that these membranes eventually enter the ER and subsequently emerge from ER exit sites as part of normal forward membrane flow (9, 10). Because MTs are absent, however, these ectopically located Golgi fragments, regardless of whether they actually cycle through the ER, cannot travel to the distantly located MTOC. Instead, because of their low diffusibility, the Golgi membranes accumulate at scattered sites in the cytoplasm. Resident Golgi proteins can be detected at these abnormal locations within minutes of MT disassembly, even while the centrally located Golgi appears intact (9). Once MTs reassemble, they serve as tracks along which the scattered Golgi ministacks move back toward the cell center and eventually reestablish an intact, perinuclear Golgi (9, 15).

Conclusions and Future Directions

Based on evidence cited here and summarized in Fig. 1, we conclude that the secretory pathway comprises multiple MT-dependent and -independent transport steps. In the forward direction, MTs are not involved in transport from the ER to COP II vesicles, from COP II vesicles to the IC, or for intra-Golgi transport. In contrast, MTs serve as tracks for movement of the IC to the Golgi (6, 28, 32) and of TGN-derived vesicles to the cell surface (Hirschberg, K., J. Presley, N. Cole, and J. Lippincott-Schwartz. 1997. *Mol. Biol. Cell.* 8:194a [abstract from 1997 ASCB meeting]).

Several recycling steps also involve MTs. Golgi-to-ER transport appears to be driven by the MT motor, kinesin, in cells with radially arranged MTs (21). Two recycling pathways (not shown in Fig. 1) retrieve resident Golgi proteins that escape to the plasma membrane. Retrieval may occur via endosomes, which are delivered to the cell center by MT-based transport (23). In addition, proteins such as caveolin, that move from the Golgi to caveolae, may be returned to the Golgi by MT-independent transport from caveolae to the ER and from the ER to the IC, followed by MT-dependent transport from the IC to the Golgi (11). The ER-to-IC-to-Golgi arm of the secretory pathway thus simultaneously serves both forward and recycling functions. Recent studies also imply that dynein, a motor that moves toward MT minus ends (24), transports IC membranes toward the Golgi in cells with radially arranged MTs (6, 28).

Fig. 1 also indicates how the normal MT requirements for secretion can be overridden, as long as the cell has lacked MTs sufficiently long to enable Golgi fragmentation and dispersal. Golgi-dependent protein processing is possible under these circumstances because IC-to-Golgi movement can be accomplished by diffusion over distances of mere tens of nanometers. Likewise, in cells that are not exceptionally large, secretory vesicles can efficiently diffuse within minutes from dispersed Golgi complexes to the cell surface (Hirschberg et al. 1997. *Mol.*
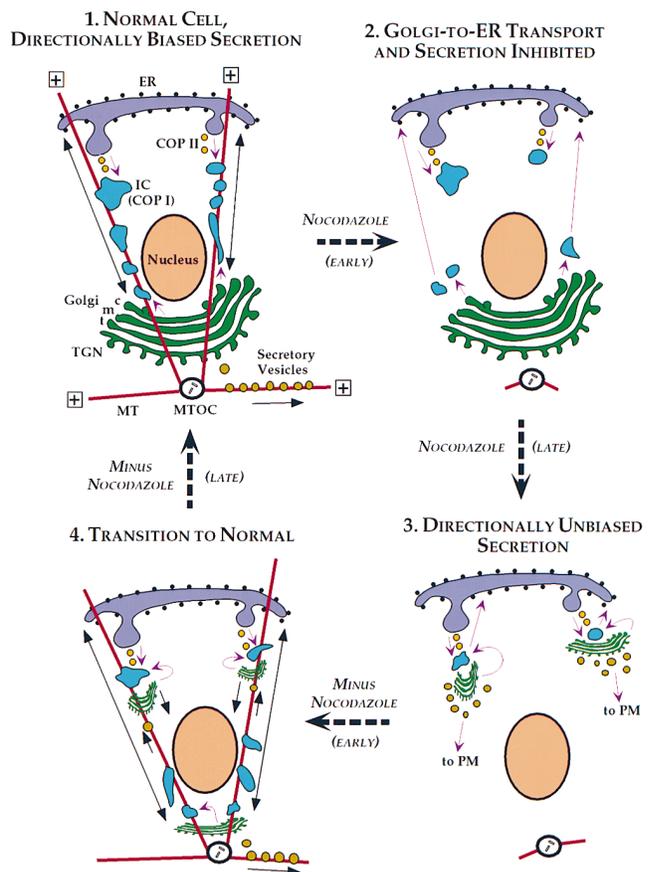
Figure 1. A model for MT functions in secretion. Black and purple arrows indicate MT-dependent and -independent transport steps, respectively. (*1*) Many cells normally contain radially arranged MTs oriented with their plus (+) ends distal to a perinu-

clear MTOC. In such cells, the IC moves along MTs bidirectionally between the peripheral ER and a centrally located Golgi, which comprises *cis* (*c*), *medial* (*m*), and *trans* (*t*) stacks and the TGN. Segregation of ER from Golgi depends on the polarized, radial arrangement of MTs and a balance between Golgi-directed membrane flow toward MT minus ends and ER-directed flow toward MT plus ends. Secretory vesicles also travel along MTs, toward their plus ends, from the TGN to the plasma membrane. Transport from ER to IC involves COP II–coated structures that move independently of MTs. IC membranes are coated with COP I for ER-to-Golgi transport, but whether they retain COP I coats for Golgi-to-ER transport has not been reported. (*2*) Membrane budding from the ER and Golgi continues after MT disassembly by nocodazole (9, 10). Until a significant amount of membrane has exited the Golgi, it remains largely intact near the cell center. During this time window, delivery of ER-derived material to the Golgi must occur by diffusion and is inefficient because of the substantial distance that separates most of the ER from the Golgi (9, 11). Consequently, Golgi-dependent protein processing and secretion are inhibited (9, 28, 32). (*3*) In the prolonged absence of MTs, Golgi components that may have cycled through the ER (9, 10) accumulate near ER exit sites and IC membranes through which they might have passed, and miniature Golgi stacks are found throughout the cytoplasm (30). The lack of MTs prevents movement of these stacks and the IC toward the MTOC. Nevertheless, the short distances that separate ER, IC, and Golgi under these circumstances permit efficient, diffusion-mediated transfer of materials among them and allow Golgi-dependent protein processing and secretion to proceed. Secretory vesicles may reach the cell surface by diffusion, but directionally biased secretion is prevented as long as MTs are absent (31). (*4*) Soon after nocodazole is removed, Golgi ministacks travel toward the MTOC and eventually reestablish a centrally located Golgi complex (15) that supports directionally biased secretion.

Biol. Cell. 8:194a [abstract from 1997 ASCB meeting]), although directionally biased secretion is not possible (31). Shortly after MTs depolymerize, however, the Golgi is still largely intact and can be separated by anywhere from a few to dozens of micrometers from most of the IC. During this transient time window, secretion of newly synthesized protein is severely impaired because the lack of MT highways prevents most IC vesicles from delivering their contents to the distantly located Golgi.

Although major strides have been made toward understanding the roles of MTs in secretion, several questions still are unanswered. For instance, membranes often can move in either direction along an MT but are not always in transit. How, then, is MT-based membrane motility initiated, what determines the direction of transport relative to MT polarity, and how is transport halted? How are MTs recruited for directionally biased secretion? Finally, how do MT motors attach to membranes? Some progress has been made toward this last question. A complex containing dynactin, spectrin, and ankyrin has been implicated as a cross-bridge between dynein and IC or Golgi membranes (5, 16, 40), and kinectin may be an ER receptor for kinesin (37). The motor receptor issue is far from resolved, however, and the questions cited here represent new defining issues for research on MT-based membrane transport.

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