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THE PATTERN AND MECHANISM OF MITOCHONDRIAL TRANSPORT IN AXONS

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1. ABSTRACT

Mitochondria in nerve axons display motility behavior that is as distinctive as their metabolic function. Unlike many other classes of organelles, mitochondria undergo net movement that is the sum of movements in both the anterograde and retrograde directions, and their net velocity is strongly influenced by their recruitment between stationary and motile states. They recently became the first specific class of organelle shown to be capable of moving along either microtubule or F-actin tracks in the axon, indicating that they probably use a diversity of molecular motors. Although we still know relatively little about how the movement of specific classes of axonal organelles is coordinated with their function in the neuron, in the case of mitochondria it is at least clear that their transport delivers them to regions of the neuron where ATP consumption is likely to be high, and disperses them when local energy needs change. In addition, although mitochondria contain both anterograde and retrograde motor activities, the modulation of their motility necessary to achieve these redistributions seems to rely largely upon regulation of the anterograde motor activity alone. A further element in the regulation of their motility and distribution is the apparent "docking" of mitochondria to microtubules or neurofilaments, a phenomenon which may serve to stabilize their distribution once regulated motility has moved them to appropriate sites. This review considers the current state of knowledge in these areas with an emphasis on the pattern of regulation of motility and how it underlies the role of mitochondria as the aerobic ATP source of the neuron.

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2. INTRODUCTION

Within the constellation of organelle types that move in the axon, mitochondria hold a special place because of both their functions and their motility properties. Their essential functions are the aerobic production of ATP and the regulation of intracellular calcium levels, and their unusual pattern of motility includes regulated, saltatory bidirectional movement and prolonged stationary phases. The theme of this review is that organelle motility and organelle function are closely related, and its purpose is to assess what is known about the relationship between mitochondrial motility and function, and to propose hypotheses informed by recent research about how these two properties are coordinated in the axon.

The past decade has seen remarkable advances in our knowledge of the biochemical and biophysical basis of general organelle transport in axons. Workers in this field have at their disposal diverse methods for studying the movement of organelles: metabolic labeling and monitoring of organelle proteins in mature nerve (1); direct

microscopic observation of organelles in a variety of neurons grown in culture (*e.g.*, 2-4); and *in vitro* systems ranging from nearly intact axoplasm devoid of its axolemma (5, 6) to simple reconstituted systems comprising no more than putative molecular motors, cytoskeletal filaments, and ATP (7). As a result, we have at present a burgeoning number of motor proteins, some of which may serve to generate force for the movement of organelles along the cytoskeletal tracks formed by microtubules (MTs) or actin microfilaments (MFs) (8-10). In addition, recent work has offered candidates for motor protein receptors on the surface of organelles and regulatory factors for transport (11-13), and some insight into posttranslational modifications of motor proteins that may serve to modulate transport (14-21).

However, we still know relatively little about how the axon responds to physiological changes by transporting specific organelle types to the regions where they are required at the appropriate time. This is because only recently has much attention been paid to the profound differences in transport of different kinds of organelles, even within the same region of the axon. Small vesicles, endosomes, autophagic vacuoles, pinosomes, and mitochondria each display different patterns of transport in the axon (22), suggesting that there exist essential organelle-specific differences in motility and its regulation.

That the appropriate regulation of the transport and distribution of mitochondria is an essential element of the life of a neuron is underscored by recent studies of diverse neurodegenerative diseases (23). Three common themes in the pathology of many such diseases -- oxidative damage to neurons (24), excitotoxicity and the failure of calcium homeostasis (25), and metabolic inadequacy in the distal axon (26) -- all come together at the mitochondrion and its functional capacities. However important it may be to gain a clear understanding of how the life cycle of mitochondria is related to that of the neuron as a whole, it will only be possible if we analyze the axonal transport of this unique organelle separately from that of other organelle types which have very different functions.

3. DISCUSSION

3.1 What is the nature of mitochondrial movement in nerve axons?

In neurons as well as most other cell types, the elongated profiles and characteristic movements of mitochondria are among the most striking features of light microscopic observation (27, 28). Three attributes distinguish mitochondrial movement from that many other organelles: first, much of their motility is saltatory, with frequent stops and starts; second, they display true bidirectional movement, often changing direction after halting; third, they spend a variable fraction of their time stationary, even as small vesicles and other organelles in the same region of the cell display movement (29-32). In nerve axons, these properties of mitochondrial motility raise several important issues that will be addressed below.

Specifically, they imply that the movement of mitochondria relies upon a system of force generation that is different -- or differently regulated -- than that of other organelles. In particular, movements in the anterograde vs. retrograde directions in axons are assumed to require two classes of molecular motors (33), implying that mitochondria contain both classes in an active form. Further, they suggest that lack of motility serves as important a role in the life of mitochondria as does their specialized motility. This review considers these peculiarities of axonal mitochondrial movement and offers the following interpretation: they reveal a coordination of organelle movement with organelle function. In particular, the pattern of mitochondrial motility underlies their unique and essential role of providing ATP via aerobic metabolism in a functionally polarized and highly elongated cell.

3.2 What are the molecular motors and cytoskeletal tracks that support mitochondrial movement?

3.2.1 Molecular motors for mitochondrial transport

The hunt for the molecular motors responsible for axonal organelle transport has given birth to an entire field of molecular genetic identification of families and superfamilies of motor proteins (9, 10, 34, 35). Although it will be the work of many years to sort out the roles of these proteins, there is general agreement about MT-based motility in axons. Anterograde axonal organelle transport is thought to be supported by members of the kinesin family of molecular motors, which drive movement toward the plus ends of MTs (8, 36, 37), while retrograde movement seems likely to be driven by members of the cytoplasmic dynein family, which support movement toward MT minus ends (38-41).

The exact identity and properties of the molecular motors that drive the axonal transport of mitochondria are not clear, but evidence from a variety of experimental approaches gives us an outline of the possibilities. Relevant here are several factors that distinguish mitochondrial motor activity from that of other axonal organelles such as small vesicles.

First, mitochondria undergo substantially slower net directional transport than other organelles, as demonstrated by metabolic labeling axonal

transport studies (42, 43) and quantitative light microscopic observation (32). Differences in organelle velocity could derive from the particular characteristics of the molecular motors that drive them or from differences in their higher order motility behavior. In fact, there is evidence that both of these factors are at play in the case of mitochondria.

Because velocity is generally assumed to be an intrinsic property of a particular molecular motor, it is reasonable to assume that mitochondria are driven by different motors than, for instance, faster-moving small vesicles. Evidence for this possibility comes from two recent studies. First, a metabolic labeling analysis of axonal transport has resolved two distinct rapidly transported isoforms of kinesin. The faster-moving isoform accompanied synaptic vesicles, while the other moved at the slower anterograde velocity of mitochondria, and was associated with mitochondrial marker enzymes (44). Second, an examination of other members of the murine kinesin superfamily has revealed a specific member, designated KIF1B, that co-localized with mitochondria in immunocytochemical studies and co-purified with mitochondria in subcellular fractionation, was able to move mitochondria along MTs in an *in vitro* assay (45). The difference in the roles played by different members of the kinesin superfamily in axonal transport of mitochondria is unclear, but the two molecular motors just described are both thought to drive specifically anterograde mitochondrial movement.

However, it is also clear from their behavior that mitochondria contain motor activities for movement in both the anterograde and retrograde directions. While small vesicles generally undergo smooth, unidirectional movement (*e.g.*, 29), mitochondria undergo saltatory, bidirectional movement (31, 32), with a duty cycle and net direction of movement that vary with the physiological state of the axon (32). This difference in motility behavior alone could explain the slower net rates of mitochondrial transport: stops and changes of direction inevitably result in slower net movement. But ultimately, differences in motility behavior must arise from the properties of the motors that drive movement. Thus it is important to note that in addition to velocity, another intrinsic property of many molecular motors is their regulation by posttranslational modification (14, 15, 17-19, 46-51). Since there is some evidence that mitochondrial motility in the axon is regulated by different factors than that of other organelles (52), it seems likely that the differential regulation of mitochondrial transport behavior has its origin in mitochondrion-specific motors with unique regulatory properties.

An additional aspect of the molecular motors associated with mitochondria that seems relevant to their axonal transport is their physical disposition on the surface of these large, highly-elongated organelles. Video-enhanced microscopic analysis of mitochondrial motility in extruded squid axoplasm strongly suggested that motor activity was distributed in discrete patches on the mitochondrial surface, and that these patches generated force essentially autonomously (53). It is obvious that independent, widely-spaced foci of force generation could underlie, at least in part, the capacity of mitochondria to stop, start, and change direction, as well as to cease motility entirely. The patchy distribution of motor proteins was confirmed by immunoelectron microscopy in a study that also revealed specific copurification of kinesin with mitochondria (54). Other copurification studies have also found kinesin on mitochondria (55).

3.2.2 Two different cytoskeletal tracks for mitochondrial movement

The axon contains all three major systems of cytoskeletal filaments in abundance -- MTs, MFs, and the neuron-specific intermediate filament type, neurofilaments (NFs). However, a large body of conventional ultrastructural and pharmacological work (reviewed in 56) indicated that microtubules alone served as the tracks for the axonal transport of mitochondria, along with other organelles. This view was strengthened by the images of axoplasm obtained by rapid-freezing electron microscopy techniques (*e.g.*, 57-60), in which apparent cross bridges between microtubules and mitochondria were particularly evident, and by observations of reactivated organelle transport in axoplasm of the squid giant axon, where video-enhanced light microscopy was correlated with electron microscopy to identify the major transport filaments as microtubules (5, 61, 62). When the latter studies rapidly spawned the exciting discovery and characterization of the MT-based molecular motor proteins kinesin (63-65) and cytoplasmic dynein (39, 40, 66, 67), the possibility that mitochondria might also move along cytoskeletal tracks other than microtubules was largely set aside.

However, there has long been good reason to consider the possibility of MF-based organelle motility in the axon. First, actomyosin-based organelle transport is found elsewhere. Perhaps the best-studied example is the giant algal cell *Nitella*, which like the neuron is a large and highly elongated cell with abundant organelle transport, and which was one of the first systems in which organelle movement was successfully reactivated and characterized *in vitro.* There, the movement is driven by myosin motors along cortical actin filaments (68). Specific mitochondrial movement on MFs in

microvilli had been suggested in a study by Bradley and Satir (69). It is also notable in this context that mitochondrial movements in yeast are now thought to be actomyosin-based (70). Second, the machinery for actomyosin-based transport is present in the axon. Neuronal tissue has long been known to be rich in actin and myosin (71, 72), and more recently specific myosin isotypes -- including some novel ones -- have also been detected there, including myosins I (73), II (74-77), V (78, 79), and VI (80). This has lead to the suggestion that these MF-based molecular motors may be involved in neuronal organelle transport (10). Finally, despite the abundance of studies showing that MT perturbation results in gross general disruption of mitochondrial transport (56), two kinds of evidence have nonetheless argued for the additional existence of MF-based motility. Not only did quantitative analysis of organelle movement in squid giant axons show partial continuation of transport after extensive MT disruption (81), but several studies also demonstrated that transport was partially inhibited by the introduction of agents that specifically disrupt MFs (82-84).

Several years ago, Kuznetsov and coworkers (85) forced a serious reevaluation of issue of which tracks support mitochondrial movement in the axon when they observed MT-independent organelle movements in extruded squid axoplasm that were strongly indicative of actomyosin-based motility. It was subsequently demonstrated that isolated axoplasmic organelles had myosin on their surfaces, and could move toward the barbed end of MFs *in vitro* (86-88). However, the role of MF-based axonal transport and its significance relative to MT-based transport in live neurons remained unclear.

Recently, two studies of intact axons have demonstrated that axonal organelle transport in general, and mitochondrial motility in particular, can occur along MF tracks. In an examination of organelle motility in the growth cone region of elongating axons of sympathetic neurons in culture, Evans and Bridgman (89) took advantage of the visibility of organelle movement afforded by the thin cytoplasm of this domain to show that individual transport filaments that were seen to support organelle motility by video-enhanced microscopy turned out to contain MFs, but not MTs, when examined by correlative immunofluorescent staining. Morris and Hollenbeck (4) performed a quantitative analysis of mitochondrial motility in axons of cultured sympathetic neurons that were pharmacologically manipulated to eliminate MTs, MFs, or both. This study revealed that mitochondria could undergo bidirectional transport on either MTs or MFs, but that their motility behavior on the two tracks was very different. Mitochondria moved at a significantly higher velocity on MT tracks than on MFs, but they also spent only half as much of their time moving on MTs as they did on MFs. In addition, while MTs alone supported net anterograde movement of mitochondria, MFs alone supported only net retrograde movement. These data indicate that the MT- and MF-based motility systems not only utilize molecular motors with different characteristics, as would be predicted, but also employ different regulation and filament organization.

The entire reexamination of which tracks support mitochondrial movement in the axon, and the demonstration that two different filament systems are competent, raises a higher-order question. Since MT-based motility alone has repeatedly been shown to be an effective system for the axonal transport of organelles both *in vitro* and *in vivo* within axons, what is the function of MF-based motility? Since it does not appear to support protracted anterograde movement (4), MF-based motility cannot play a direct role in the essential anterograde flow of material from the cell body to support the axon. Thus, mitochondrial transport along MF tracks seems most likely to provide an auxiliary system of motility, which could serve one or more of several functions. First, it could provide a "local" transport system within axons to cluster and localize mitochondria in one region of the axon. As discussed below, this is a feature of the regulation of mitochondrial transport in axons not easily explained via MT-based transport alone. Second, MF-based transport could move organelles which have become dissociated from MTs back onto MTs for continued transport over long distances in either direction. Since the capacity of organelles the size of mitochondria to diffuse within axoplasm is extremely limited (90, 91), this would improve the efficiency of axonal transport in regions of the cell where MTs are few or absent -- such as axonal branch points and growth cones (89). Also, since single MTs do not extend for the entire length of most axons (92), MF-based transport could serve to bring mitochondria that have dissociated from MTs at their ends back into contact with a MT, where they could resume long-range transport. *In toto* then, evidence suggests that the intrinsic and specialized transport properties of two cytoskeletal filament systems and their associated motor proteins are balanced so as to produce a coordinated net transport of mitochondria. How this orchestration of mitochondrial transport may serve to meet the physiological needs of the axon is discussed below.

3.3 How is mitochondrial movement regulated to support neuronal homeostasis?

3.3.1 The coordination of mitochondrial motility behavior with axonal physiology

It could be asked from first principles why neurons require any coordination of the transport of

mitochondria. After all, the primary function of these organelles is the aerobic production of ATP, a small molecule that, once released, can diffuse freely in the cytoplasm. However, diffusion of ATP within the cell seems inadequate to support energetic homeostasis, since diverse cell types of much more modest dimensions than neurons nonetheless position their mitochondria in regions of intense ATP consumption (93-95). Neurons contain several specialized regions that are likely foci for ATP consumption, including growth cones (96), synapses (97), and nodes of Ranvier (98). Indeed, it has been clear for some time that the location of neuronal mitochondria at least correlates with the likeliest sites of local energetic demand. Ultrastructural studies in a variety of systems have shown concentrations of mitochondria in the pre- and postsynaptic regions of active synapses (*e.g*., 99-101, summarized in 97). In addition, cytochrome oxidase staining, widely employed as a tool for detecting active tracts in nervous tissue, is known to reveal high densities of metabolically active mitochondria (102, 103), and to change its pattern when activity is experimentally altered (104, 105). More recently, studies using a vital dye that reports mitochondrial transmembrane potential (106, 107) have shown that significant differences in mitochondrial metabolism exist between axons and dendrites (22) which confirms and quantifies, in live cells, previous evidence from cytochrome oxidase histochemistry (108, 109).

But how is mitochondrial motility in neurons regulated to support these functionally important distributions, and what specific motility phenomena redistribute mitochondria when regional energy needs undergo change? A quantitative study of mitochondrial movement in axons of cultured sympathetic neurons has shown that motility is modulated at two different levels: regulation of motor activity and recruitment between stationary and motile states. Morris and Hollenbeck (32) manipulated the activity of growth cones at the end of highly elongated axons in order to alter the regional energy needs of the axon. Mitochondria were clustered preferentially in the immediate vicinity of an active growth cone, creating a nearly 10-fold gradient of mitochondrial density between the growth cone and a region of the axon shaft only 100mm distant. When growth cones were rendered inactive by physical barriers on the substratum or by pharmacological treatment, the distal clustering disappeared, and mitochondria became dispersed along the axon shaft. (This is strikingly similar to a reduction in presynaptic mitochondrial density following hypodynamia *in vivo* (110)). Analysis of mitochondrial motility during these redistributions showed that in axons with active growth cones, net mitochondrial movement was anterograde, with a population velocity that decreased as mitochondria approached the immediate region of the growth cone. After inactivation of the growth cone, net mitochondrial movement was retrograde, and the population velocity decreased as mitochondria moved nearer to the cell body. This coordinated reversal of transport direction was achieved almost entirely via modulation of anterograde motor activity alone: during mitochondrial redistribution, the amount of retrograde motor activity remained essentially unchanged while anterograde motor activity varied fivefold under different axonal growth conditions and determined the net direction of movement. But perhaps an even more profound modulation of mitochondrial motility was the control of the fraction of the population that was stationary vs. motile. In the immediate region of an active growth cone, fully 75% of mitochondria were persistently stationary, compared with 25% in the population approaching the growth cone from a distance. Upon inactivation of the growth cone, the majority of mitochondria resumed motility, now in the retrograde direction. The regional specificity of this balance between motile and stationary mitochondria and its dependence upon the growth state of the axon suggest that a specific “docking” phenomenon plays an important role in maintaining a mitochondrial distribution that is appropriate to the physiological state of the axon.

3.3.2 Potential signals for controlling mitochondrial motility

The question of what intracellular signals control the reversal of mitochondrial motility remains open. Some experiments have implicated proteolysis (111, 112) or acidification (2, 113) in the reversal of organelle movement from anterograde to retrograde in axons. However, these experiments involved severe insults to the cells and reversal of the direction of organelle types that are not necessarily found to reverse or even to move retrogradely under physiological conditions. Thus, they may not be relevant to the behavior of mitochondria, which change direction routinely and in a tightly controlled fashion.

Studies of axonal growth in culture systems suggest that the progress and motility of the growth cone may be controlled in part by calcium and cAMP levels (*e.g*., 114-118). This makes these agents plausible candidates for regulating mitochondrial motility, since the entire pattern of mitochondrial transport responds to the activity of the growth cone and does so most dramatically and specifically in its immediate vicinity (32). As yet though, there is no experimental evidence linking any particular second messenger to the regulation of mitochondrial transport. A promising avenue of inquiry is the apparent involvement of small GTP-binding proteins in promoting or inhibiting axonal organelle traffic

(13); however, the relevance of this regulatory phenomenon to coordinated changes of direction for any class of organelle is at present unknown.

One report suggests that high ADP concentration could be the factor that signals mitochondria to cease movements (119). This finding could provide a simple explanation for how the axon achieves clustering of mitochondria in regions of high ATP demand such as active growth cones or synapses: the ratio of ADP to ATP would be expected to be higher there, and mitochondria would thus accumulate where ATP is needed. However, such a mechanism would have to act on regulatory sites rather than the catalytic sites of molecular motors, since all known motor proteins display full activity at ATP concentrations far below those maintained in cells.

Perhaps the potential regulatory mechanism with the largest body of circumstantial evidence is local modification of the phosphorylation state of MT-based mitochondrial motor proteins or their putative receptors. As alluded to above, kinesin, its associated proteins, its putative organelle surface receptor (11), and dynein are all phosphoproteins (14-17, 21, 50, 51, 120). There is evidence that phosphorylation can affect the motor activity of both dynein and kinesin (15, 17, 50, 51, 120), and also that it can modulate the association of motor proteins with organelles (14, 18, 20). Phosphorylation could act at either or both of these levels to regulate the direction of mitochondrial motility as well as the transition between the moving and stationary states. The physiologically relevant kinases and phosphatases for kinesin and cytoplasmic dynein have yet to be determined, but it is notable that the data from growing axons described above (32) indicates that regulation of anterograde motor activity alone (presumably kinesin) is likely to account for changes in mitochondrial motility.

The eventual identification and localization of the kinases and phosphatases for motor proteins known to be associated with mitochondria will undoubtedly yield important clues concerning their possible role in regulating mitochondrial motility. However, it is important to bear in mind that the recruitment between stationary and motile states probably exerts at least as much control over mitochondrial distribution as does the regulation of motor activity.

3.4 What is the nature of mitochondrial "docking," the persistently stationary state?

As described above, the lack of transport of mitochondria is as distinctive a feature as transport itself. Under many conditions and in many regions of the axon, even mitochondria that are part of the motile pool are intermittently stationary, spending only about half of the time moving (32). While little is known about the mechanism for recruitment of mitochondria between stationary and motile states, several studies have addressed aspects of their interaction with the cytoskeleton that might underlie the phenomenon of mitochondrial docking.

Numerous ultrastructural studies have revealed associations or distinct cross-bridges between axonal mitochondria and cytoskeletal elements (*e.g.*, 57, 59, 121-123). These have been most often observed between mitochondria and MTs, and are commonly interpreted as revealing transient interactions between motor proteins and mitochondria frozen in time by rapid fixation or freezing. However, cross-bridges have also been observed between mitochondria and NFs (124), and there is evidence suggesting that some of the observed cross-bridges represent more static interactions. A static interaction with NFs would be consistent with the total lack of motility (or even Brownian motion) of mitochondria or any other organelle type in axons devoid of MTs and MFs but containing NFs (4).

Most of our information about the possible identities of static cross-bridges comes from analyses of the interactions of high molecular weight MT-associated proteins (HMW-MAPs) and MT-associated tau protein with the outer membrane surface of brain mitochondria. Studies by Leterrier and coworkers have shown that the HMW-MAPs but not tau protein bind specifically to the mitochondrial surface via their domains that project from the MT surface, probably via both a low- and a high-affinity binding site on the mitochondrion (125, 126). Other studies have also suggested a role for tau in MT-mitochondrial interactions (127). The binding of HMW-MAPs to the mitochondrial surface is not uniform, but occurs in discrete regions that also contain porin, the pore-forming protein of the outer mitochondrial membrane that admits ions and metabolites and allows release of ATP. In addition, the interaction of the HMW-MAPs with the mitochondrial surface may alter the properties of porin, suggesting a relationship between mitochondrial docking and metabolism (124, 128).

The presence of discrete foci for docking interactions between mitochondria and cytoskeletal elements recalls the patchy distribution of motor proteins on the mitochondrial surface described above (53, 54). Thus, an attractive possibility is that motor proteins and docking proteins share a single system of regulation. This could involve the physical displacement of motor proteins by docking interactions (and vice versa), or temporary inactivation of motor protein activity by the same factors that promote docking interactions. Determination of whether the binding sites for motor

proteins and for MAPs are near to each other on the mitochondrial surface would begin to address this question.

3.5 Summary

Although the mitochondria display complex motility, they provide an opportunity to understand in detail the regulatory mechanisms operating in the transport of one class of organelle. The ease of observing and purifying them, their well-understood metabolic functions, and the detailed quantification of the coordination of their transport with neuronal physiology should all make possible in the near future definitive studies of the molecular events by which neurons move mitochondria to the right place at the right time.

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