CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Mitochondrial Mobility and Neuronal Recovery

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Axonal regeneration in the adult central nervous system is extremely limited after injury. As a consequence, there is typically little functional recovery after spinal cord injury, traumatic brain injury, or stroke and related conditions that involve axonal damage and disconnection. Axonal regeneration in the central nervous system fails for two reasons. First, the environment surrounding the damaged axons is hostile, in that it contains growth inhibitors that suppress axonal growth, and second, the damaged axons themselves have a limited intrinsic ability to regenerate. Hence, much of the basic research that is relevant to nervous system injuries has focused on the question of how to push axons in the central nervous system to regenerate and achieve some level of functional recovery. Several experimental therapies for spinal cord injury and traumatic brain injury have been in development, but none has matured into a reliable, approved intervention.

Recent work by Zhou and colleagues[1] points to the possibility that a local energy deficit may prevent injured axons from growing. In neurons, most of the ATP supply is produced in the mitochondria. (ATP to the cell is like gas to the automobile.) However, unlike the static structures depicted in textbooks, the mitochondria are dynamic organelles that move around the neuron to deliver energy to locations in need. In neurons, they move primarily along microtubule tracks, and their transport is driven by molecular motor proteins, called kinesins and dyneins (Fig. 1). Neurons also have anchor proteins, such as syntaphilin, which can dock the mitochondria in areas with high-energy requirements, presumably by inactivating a kinesin in a calcium-dependent manner.[2]

Zhou and colleagues cultured neurons in microfluidic devices in which axons penetrated through microgrooves into a separate compartment. They cut these axons using laser microsurgery, vacuum aspiration, or a fine glass capillary tube and followed the fate of the proximal parts of cut axons for several days. Mitochondria that were close to the axotomy site lost their membrane potential and capacity to produce ATP, which was associated with a local energy deficit. Surprisingly, the neurons did not recruit new, healthy mitochondria from the cell body to the blunted, energy-deficient axonal ends. Zhou et al. then knocked out the gene encoding syntaphilin to enhance mitochondrial mobility and observed a recovery in mitochondrial membrane potential, an abrogation of the energy deficit, and enhanced axon regrowth.

Taken together, these discoveries suggest that local ATP supply is critical for axon regeneration. In order to recover, the neuron must summon enough healthy mitochondria with high membrane potential to the site of the injury (Fig. 1). This might be realized through genetic disruption of a mitochondrial docking protein that improves mitochondrial mobility (the strategy used by Zhou et al.) or by activation of anterograde mitochondrial movement (i.e., in the direction of the severance) or inhibition of retrograde movement. Another option would be to stimulate the cell to produce more mitochondria and thereby increase the number of mitochondria in axonal endings. Such an approach was recently used by Vaarmann and colleagues,[3] who found that increased mitochondrial ATP production in axonal endings supports axonal growth in cultured neurons.

Zhou and colleagues found that the same was true in mice that were engineered to lack syntaphilin, albeit in the context of the peripheral nervous system. The sciatic nerve of syntaphilin-knockout mice harbored greater numbers of motile mitochondria and enhanced regenerative capacity after crush injury than did such nerves in normal mice.

Does the study by Zhou et al. point to a new experimental approach to conditions that involve axonal disconnection? Possibly, but we would

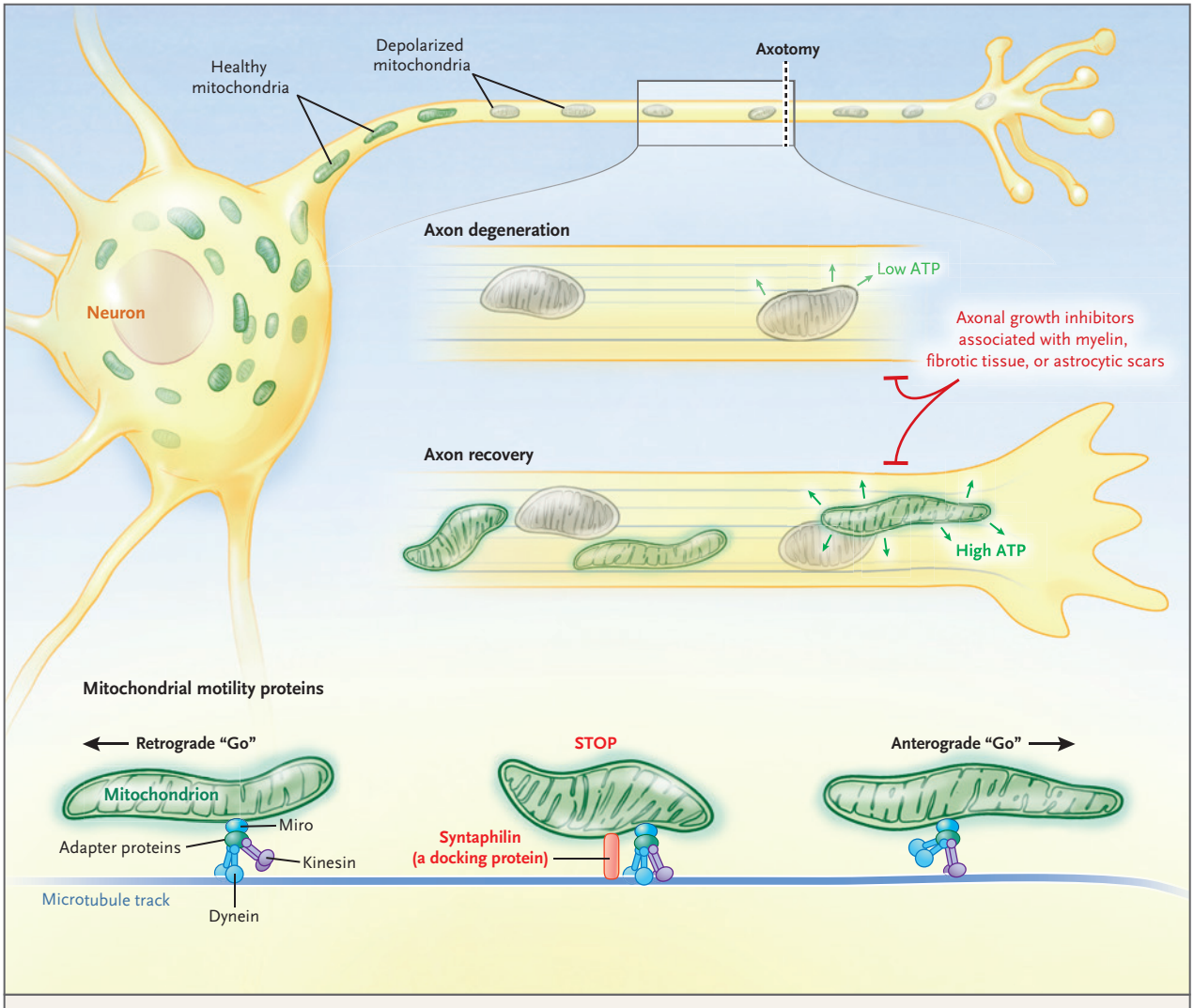

Figure 1. Mitochondrial Motility and Axon Recovery.

Mitochondria that are close to the site of axonal injury (axotomy) lose their membrane potential and do not produce ATP. In a recent study, Zhou et al.[1] found that the loss of the docking protein syntaphilin increases mitochondrial motility and is associated with the recruitment of healthy mitochondria with high membrane potential (shown in green) into the injured area, thereby enhancing the local energy supply and supporting axon recovery. Mitochondrial transport is driven by molecular motor proteins: dynein proteins, which are responsible for retrograde movement, and kinesin proteins, which are responsible for anterograde movement. Adapter proteins link these motor proteins to Miro proteins in the mitochondrial membrane. Docking proteins, such as syntaphilin, can immobilize mitochondria on microtubules.

need a safe and effective means, such as small-molecule compounds, to increase mitochondrial mobility and the energy supply local to axonal injury. And there is still a lot more that we need to know, such as whether these regenerating axons would also reconnect with their targets to the extent and in the manner required for functional recovery.

Disclosure forms provided by the author are available at NEJM.org.

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