Myo19 propelling mitochondria to filopodia by unique enzymatic adaptation

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Abstract

Eukaryotic cells are exposed to many environmental cues and stress conditions which have profound effects on mitochondria dynamics. The role of the actin cytoskeleton in relation to mitochondria function and dynamics is only now beginning to emerge, revealing new functions for actin-based motors. Here, we focus on the recently discovered actin-based motor, Myo19, which is associated with the mitochondria and on its effects on mitochondrial biology. We show that Myo19 localizes with mitochondria to filopodia tips in response to glucose starvation, ROS and EGF stimuli. However, how Myo19 localizes to mitochondria, how its enzymology allows the motility of mitochondria to filopodia, and what is the function of mitochondria at these filopodia are not known. First, we reveal that Myo19 is integrated to the outer mitochondrial membrane (OMM) through a previously unidentified binding motif in its tail domain, ensuring a highly stable interaction between Myo19 and the OMM. Point mutations within the 30 amino acids of this motif inhibit localization of Myo19 to the OMM. Secondly, using time-lapse fluorescent microscopy we show that Myo19 undergoes both anterograde and retrograde movements in filopodia, which are coupled to their extension and retraction, respectively. Thirdly, by studying the enzymology of Myo19 we provide a detailed reaction mechanism of its ATPase cycle. Both the slow ADP isomerization and ADP release prolong the time Myo19 spend in the strong actin binding state and hence contribute to its relatively high duty ratio. However, the predicted duty ratio based on our measured rate and equilibrium constants is lower than required to support motility as a monomer. Thus, we predict that an ensemble of Myo19 motors is required to efficiently propel mitochondria movement on actin filaments. Finally, we provide a model explaining how Myo19 translocation may be regulated by the local ATP/ADP ratio. Interestingly, local mitochondria concentration in neurons is correlated with increased branching of actin-based protrusions of the dendritic spines. Thus, we suggest that Myo19 acts as an ATP sensor, and translocates mitochondria to regions that demand high local levels of ATP for processes such as actin polymerization.