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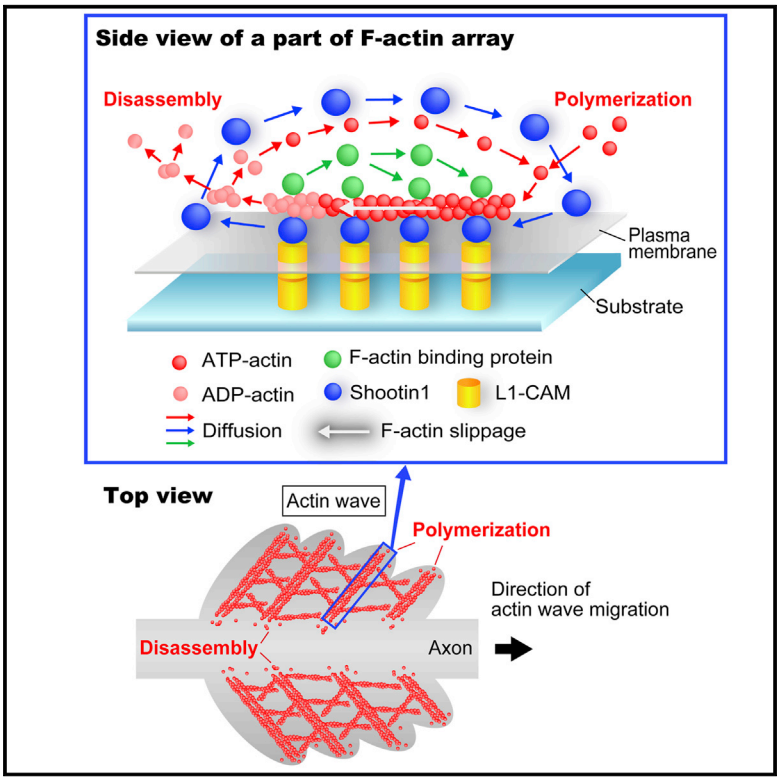
Actin Migration Driven by Directional Assembly and Disassembly of Membrane-Anchored Actin Filaments

Graphical Abstract



Highlights

- Actin waves are confirmed to translocate actin and associated proteins along axons
- F-actins in the wave are anchored to the plasma membrane and underlying substrate
- Wave migration is driven by directional assembly and disassembly of membrane-anchored F-actins
- Protein delivery by waves promotes axonal protrusion during neuronal polarization

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In Brief

Katsuno et al. use a combination of live-cell imaging, molecular manipulation, force measurement, and mathematical modeling to show that directional assembly and disassembly of membrane-anchored F-actins enables the translocation of actin and associated proteins toward the axonal leading edge. This mechanism promotes directional cell protrusion.

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Actin Migration Driven by Directional Assembly and Disassembly of Membrane-Anchored Actin Filaments

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SUMMARY

Actin and actin-associated proteins migrate within various cell types. To uncover the mechanism of their migration, we analyzed actin waves, which translocate actin and actin-associated proteins along neuronal axons toward the growth cones. We found that arrays of actin filaments constituting waves undergo directional assembly and disassembly, with their polymerizing ends oriented toward the axonal tip, and that the lateral side of the filaments is mechanically anchored to the adhesive substrate. A combination of live-cell imaging, molecular manipulation, force measurement, and mathematical modeling revealed that wave migration is driven by directional assembly and disassembly of actin filaments and their anchorage to the substrate. Actin-associated proteins co-migrate with actin filaments by interacting with them. Furthermore, blocking this migration, by creating an adhesion-free gap along the axon, disrupts axonal protrusion. Our findings identify a molecular mechanism that translocates actin and associated proteins toward the cell's leading edge, thereby promoting directional cell motility.

INTRODUCTION

Intracellular protein migration is fundamental to cellular activities, supplying essential components to functionally specialized regions. Actin and actin-associated proteins that accumulate at a cell's leading edge play key roles in various biological processes including cell polarization, motility, neurite outgrowth, and exocytosis (Madden and Snyder, 1998; Morales et al., 2000; Pollard and Borisy, 2003; Lowery and Van Vactor, 2009), and it has become increasingly clear that they migrate within the cell. Intracellular migration of actin and actin-associated proteins was first detected by radioisotope labeling of anterograde axonal transport (Black and Lasek, 1979; Willard et al., 1979; Bray et al., 1992). Based on the low velocity (~3 μm/min), their migration was categorized into the slow axonal component. The motor proteins kinesins, dyneins, and myosins, which walk along cytoskeletons, play a key role in the intracellular migration of vesicle-anchored proteins and some cytoplasmic proteins (Vallee and Bloom, 1991; Vale et al., 1996; Hirokawa, 1998; Brown, 2003; Yildiz et al., 2003; Scott et al., 2011). In contrast, the molecular basis for driving the slow transport of actin and actin-associated proteins along axons remains poorly understood (Brown, 2003).

More recently, live-cell imaging of cultured cells revealed wave-like migration of actin and associated proteins within various types of cells, including neuronal axons, *Dictyostelium*, neutrophils, fibroblasts, melanoma cells, and osteosarcoma cells (Ruthel and Banker, 1998; Vicker, 2002a; Gerisch et al., 2004; Giannone et al., 2004; Weiner et al., 2007; Carlsson, 2010a; Allard and Mogilner, 2013). Previous work has shown that inhibitors of actin polymerization block their generation and migration (Ruthel and Banker, 1998; Toriyama et al., 2006; Weiner et al., 2007; Bretschneider et al., 2009). However, how actin polymerization mediates the wave-like migration of actin and associated proteins is unknown (Carlsson, 2010a; Ryan et al., 2012; Allard and Mogilner, 2013).

To understand the mechanism by which actin and actin-associated proteins migrate within cells, we focused on the actin waves that migrate along the axonal shaft (Ruthel and Banker, 1999; Flynn et al., 2009). Because of its simple and long one-dimensional morphology, the axonal shaft provides an excellent model system to trace protein migration. In addition, the thin lamellar shape of the growth cone-like "wave" structure (Ruthel and Banker, 1998) is particularly suitable for detailed analyses of actin dynamics within it. We find, first, that networks of actin filaments (F-actins) constituting waves undergo directional assembly and disassembly, called array treadmilling (Pollard and Borisy, 2003), with their polymerizing ends oriented toward their destination, and, second, that the lateral side of F-actins in