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Journal Club

SORTING OUT MICROTUBULE-BASED TRANSPORT

To move inside cells, organelles and large macromolecular assemblies either need to be streamlined by cytoplasmic flow or transported as cargo by molecular motors along the cytoskeleton. Kinesin and dynein are two classes of motors that are specialized in cargo trafficking along microtubules. Despite decades of extensive research, our understanding of how these motors are recruited to specific cargoes and how cargoes are delivered to their correct destinations remains incomplete.

Early in vitro studies characterizing motor activity of cytoplasmic dynein were especially puzzling, as they showed dynein to be an exceptionally weak motor exhibiting little to no movement along microtubules. This was in stark contrast to the robust transport of dynein-driven cargoes in the cells. In vivo studies identified several dynein cofactors, such as dynactin or LIS1, but these factors were not sufficient to stimulate dynein movement in vitro, suggesting that other regulatory proteins are required for dynein motor activity. The turning point that started to solve this puzzle was a seminal paper by Akhmanova (Splinter et al. 2012), showing that the N-terminal coiled-coil of a protein BICD2 strengthens the interaction between dynein and dynactin and activates dynein motility in cells, thereby establishing BICD2 as a bona fide adaptor for dynein. This was followed by two elegant in vitro reconstitution studies by Vale (McKenney et al. 2014), and Carter and Bullock (Schlager et al. 2014), demonstrating that the reconstituted dynein–dynactin–adaptor complexes are able to move on microtubules long distances and with speeds comparable to dynein-driven cargoes in cells. Subsequent work characterized further adaptor proteins that link dynein to different cargoes and revealed the structural and biophysical mechanism of adaptor-mediated activation of dynein motility (see Reck-Peterson et al. 2018 for Review). At least some of these adaptors also recruit plus-end directed kinesins, highlighting the possibility that the adaptor proteins regulate the activities of opposite polarity motors to determine which direction the cargo moves.

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What remains unknown is how cargo specificity during microtubule transport is achieved — as there are fewer known adaptors than the number of cargoes. Another open question is how cargoes are sorted inside cells and delivered over long distances to multiple destinations. It has been proposed that signals that regulate motor-driven transport are deposited onto the microtubule tracks, either by post-translational modifications of tubulin or structural proteins that decorate the microtubule surface, referred to as MAPs. Owing to recent progress in reconstitution approaches, we are now in a better position to model microtubule-based transport in vitro and start tackling these questions.

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ORIGINAL ARTICLES Splinter, D. et al. BICD2, dynactin, and LIS1 cooperate in regulating dynein recruitment to cellular structures. *Mol. Biol. Cell* **23**, 4226–4241 (2012) | McKenney, R. J. et al. Activation of cytoplasmic dynein motility by dynactin-cargo adapter complexes. *Science* **345**, 337–341 (2014) | Schlager, M. A. et al. In vitro reconstitution of a highly processive recombinant human dynein complex. *EMBO J.* **33**, 1855–1868 (2014)
RELATED ARTICLE Reck-Peterson, S. L. et al. The cytoplasmic dynein transport machinery and its many cargoes. *Nat. Rev. Mol. Cell Biol.* **19**, 382–398 (2018)