Carmichael's Concise Review

Visualizing a Molecular Motor

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Dynactin works with the cytoplasmic dynein-1 motor (dynein) to transport cargo along the microtubule-based skeleton of cells. Together, these protein complexes maintain the spatial organization of the cell, return components from the periphery of the cell, and assist with cellular division. Although much is known about dynactin and dynein, a number of questions remain. For example, how does dynein bind to dynactin, and why does the interaction require the cargo adaptor Bicaudal-D2 (BICD2)? To address this and related questions, a team in the U.K. lead by Linas Urnavicius, Kai Zhang, Aristides Diamant, and Andrew Carter [1] took advantage of recent advances in cryo-electron microscopy (cryo-EM) to improve the understanding of the structure of dynactin.

For a number of technical reasons, dynactin is a challenging target for cryo-EM. Urnavicius et al. overcame the hurdles by making cryo-EM maps at resolutions between 6.5 Å and 3.5 Å and used these maps to build a model of dynactin. The dynactin filament is nine subunits long and consists of two protofilaments that wrap around each other. The presence of β-actin in the filament was controversial. The cryo-EM map that they constructed was of sufficient quality to show that one

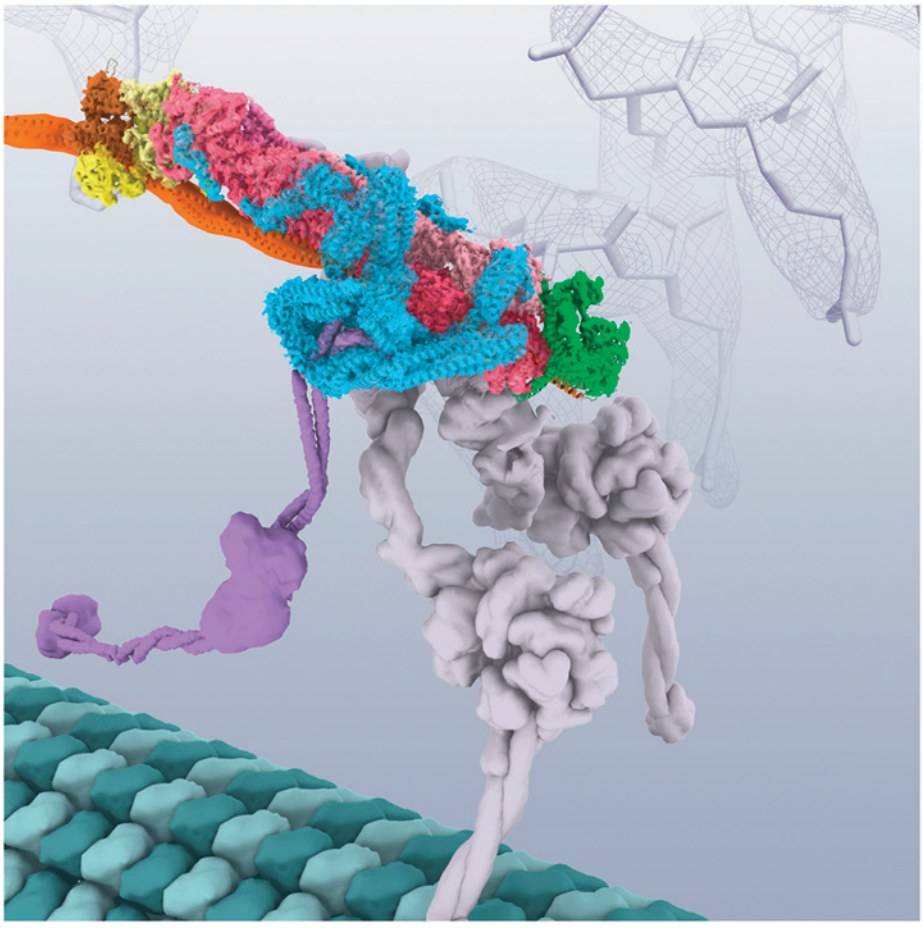

Figure 1: Model of the structure of cytoplasmic dynein (gray) bound to dynactin (multicolor) via the Golgi vesicle cargo adaptor BICD2 (orange) constructed from cryo-EM maps.

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of the subunits is β-actin; whereas the other subunits are Arp1, a protein related to actin. The presence of Arp1 and β-actin at an 8:1 ratio was confirmed by mass spectrometry-based quantitative proteomic analysis.

There are many other details of the study by Urnavicius et al. that lead to a novel hypothesis as to how the recruitment of dynactin by a cargo adaptor activates dynein. Previous studies with artificially dimerized dynein motor domains suggested that they self-associate in an auto-inhibited conformation unless they are separated. Urnavicius et al. suggested that dynactin activates the motor domains by reorienting two copies of the dynein heavy chain (DHC). Both DHC N termini are anchored parallel to each other, but the C termini are forced to twist apart because only one chain binds the second site on dynactin. This hypothesis explains why dynactin is built around an actin-like filament. The translational symmetry of the filament matches that of the DHC N termini, whereas the filament length provides additional binding sites that force dynein to adopt its active conformation. And that may be how a molecular motor works!

References

[1] L Urnavicius et al., *Science* 347 (2015) 1441–46.

[2] The author gratefully acknowledges Dr. Andrew Carter for reviewing this article.

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