Title

BicD2 and Dynactin Convert a Non-Processive Cytoplasmic Dynein to an Ultra-Processive Unidirectional Motor

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p150^{Glued}plus the projecting arm. These results suggest further dynactin regulatory complexity than previously appreciated, and provide additional insight into the mechanisms underlying the potency of CC1 as a dynein inhibitor. Supp. by NIH GM102347 and GM070676.

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Regulatory Proteins Enable the Kinesin Kip2 to Overpower Cytoplasmic Dynein

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Cytoplasmic dynein and kinesin are opposite-polarity, microtubule-based motors that create movement and spatial organization within eukaryotic cells. As a minus-end-directed motor that typically moves cargo toward the cell interior, dynein faces a directionality problem: how is dynein initially targeted to the cell periphery? Previous studies have shown that in *S. cerevisiae*, this problem is solved in part by the action of Kip2, a plus-end-directed motor that is posited to co-transport dynein and another protein called Bik1 toward the microtubule plus-end. Here, we investigate the interplay between dynein and Kip2 by coupling them to a three-dimensional DNA origami scaffold, or "chassis", and using fluorescence microscopy to visualize the emergent motile behavior of these assemblies. In the absence of regulators, dynein-chassis-Kip2 structures move predominantly in the minus-end (dynein) direction. However, the frequency of plus-end-directed movements is markedly enhanced by the addition of Bik1 (a homolog of the cytoplasmic linker protein Clip170) and Bim1 (a member of the EB [end-binding] protein family). Moreover, Bik1, Bim1 and Kip2 co-elute as a ternary complex by size-exclusion chromatography. Thus, the addition of two regulatory binding partners can enable Kip2 to overcome dynein's intrinsic minus-end-directed motility and transport dynein toward the microtubule plus-end.

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BicD2 and Dynactin Convert a Non-Processive Cytoplasmic Dynein to an Ultra-Processive Unidirectional Motor

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Cytoplasmic dynein is the predominant minus-end directed microtubule motor in metazoan cells. Dynein transports diverse cargoes over long distances in neurons, and the motor is thought to be adapted for a myriad of cellular functions through the use of several accessory protein factors that impinge on its basic biophysical characteristics. One of these accessory factors is the multisubunit dynactin complex, which has been implicated in dynein-based cargo transport and the modulation of dynein processivity and directionality. While isolated dynein from *Saccharomyces* has been shown to be a strongly processive motor, dynein from other organisms displays weakly processive, bidirectional or diffusive motility. Here we show that, on its own, cytoplasmic dynein from humans and other metazoans is not a processive motor. Previous attempts to study dynein-dynactin co-complexes have found relatively modest effects on dynein processivity and directionality by dynactin. We utilize the evolutionarily conserved coiled-coil adapter protein BicD2 to strongly induce the formation of a stable dynein-dynactin-BicD2 (DDB) supercomplex that is over 2MDa in size. Using multicolor single-molecule microscopy, we have found that, remarkably, the purified DDB supercomplex is unidirectional and ultra-processive, displaying run-lengths that greatly exceed the previously observed enhancement of single dynein run-lengths by dynactin. The DDB supercomplex accumulates at microtubule minus-ends and displays characteristics expected of a processive cargo transport motor. Our data suggest that the dynein motor is more plastic that previously thought, able to transition from a non-processive motor to an ultra-processive mode of motility upon association with external regulatory factors.