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MOLECULAR MOTORS

Hook-ing up early endosomes

> Hook proteins bridge dynein and early endosomes to support retrograde transport

Organization of intracellular structure in eukaryotes requires the bidirectional transport of organelles along microtubules, which is mediated by the opposing motor actions of plus end-directed kinesins and minus end-directed dynein. Two studies now describe a role for members of the Hook family of cytoplasmic linker proteins in recruiting such motors to early endosomes.

Both studies screened ultraviolet (UV) light-induced fungal mutants (Bielska *et al.* screened *Ustilago maydis*; Zhang *et al*. screened *Aspergillus nidulans*) for the accumulation of early endosomes at microtubule plus ends, which is indicative of a defect in dynein-mediated retrograde transport (minus end-directed). Whole-genome sequencing revealed that mutations in the genes encoding the novel Hook proteins Hok1 in *U. maydis* and HookA in *A. nidulans* were responsible for an endosomal motility defect.

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Hok1 and HookA colocalized with early endosomes in a manner dependent on the carboxy-terminal regions of the Hook proteins. Furthermore, Hok1 and HookA recruited dynein to endosomes in a manner that is dependent on the amino termini and adjacent coiled-coil regions of the Hook proteins. The N-terminal region of HookA is important for association with dynein–dynactin complexes, as indicated by biochemical pull-down assays, and both dynein heavy chain and the p25 protein of the dynactin complex are required for this association. By contrast, Hok1–dynein–dynactin interactions were not detected in pull-down assays, but Hok1 was shown to interact with *U. maydis* homologues of human fused toes (FTS) and FTS- and Hook-interacting protein (FHIP).

The movement of dynein to microtubule minus ends was not significantly different between Hok1-deficient cells and control cells; thus, Hok1 is not required for the motor function of dynein. However, dynein could not transport early endosomes to microtubule minus ends in Hok1- or HookA-deficient cells, as dynein requires Hok1 or HookA to associate with endosomes. Expression of the N-terminal region of Hok1 in these cells did not restore endosome motility, despite retrograde transport of the truncated Hok1, which indicates that the N-terminus Hok1–dynein interaction is independent of the C-terminus Hok1–endosome interaction. Consistent with this idea, HookA missing the C-terminal domain associated with dynein–dynactin, whereas HookA lacking the N-terminal domain colocalized with endosomes but failed to move them away from microtubule plus ends.

Therefore, in both fungi, Hook proteins bridge dynein and early endosomes to support retrograde transport. Unexpectedly, a peptide that was designed by Bielska *et al.* to inhibit Hok1–dynein-mediated retrograde transport also decreased the kinesin 3-mediated anterograde transport of endosomes. Deletion of a highly conserved region in the first coiled-coil domain of Hok1 markedly decreased the number of kinesin 3 molecules that were attached to early endosomes. Hence, Hok1 might also function, probably indirectly, as an adaptor for the attachment of kinesin 3 to early endosomes. It could therefore regulate the switch from anterograde to retrograde endosome transport, which is accompanied by a pause in motility that is associated with the release of kinesin 3 from endosomes before the binding of dynein.

In summary, both studies identify Hook proteins as a missing link between microtubule motor proteins and endosomal cargo. Furthermore, they propose that this might be a more widespread mechanism: Zhang *et al.* showed that HookA is also involved in the transport of peroxisomes, probably in an indirect manner; and Bielska *et al.* provide evidence that Hook-mediated regulation of motor–cargo interactions may be conserved from fungi to humans.

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ORIGINAL RESEARCH PAPERS Bielska, E. *et al.* Hook is an adapter that coordinates kinesin-3 and dynein cargo attachment on early endosomes. *J. Cell Biol.* **204**, 989–1007 (2014) | Zhang, J. *et al.* HookA is a novel dynein–early endosome linker critical for cargo momvement *in vivo*. *J. Cell Biol.* **204**, 1009–1026 (2014)