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Mechanism of Cytoplasmic Dynein Recruitment by Adenovirus

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Incoming adenovirus 5 (Ad5) is actively transported along microtubules towards the nucleus by the motor protein cytoplasmic dynein. Our lab has previously reported that dynein interacts directly with the major capsid protein hexon (Bremner et al., *Cell Host Microbe*, 2009, 6(6): 523-535). This interaction was markedly dependent on short-term exposure of adenovirus or purified hexon to decreased pH conditions, which strongly enhanced the subsequent interaction with purified dynein at neutral pH. These results imply a pH-dependent change in the hexon tertiary or quaternary structure that is crucial for dynein binding. In addition, they suggest that the passage through the acidic lumen of the endosome primes the adenovirus capsid for virus motility after endosomalysis. We have continued to explore the basis for the hexon acidification effect and find that hexon still sediments as a trimer at low pH. However, it dissociates into monomers in SDS, unlike the untreated hexon, indicative of a subtle structural change. We had also found hexon to interact with dynein through two cargo-binding dynein subunits, the intermediate chain (IC) and light intermediate chain 1 (LIC1) expressed in mammalian cells. We have tested a series of IC truncation mutants for hexon binding and identified a discrete binding region within the IC which is distinct from the established interaction site for the physiological IC-interactor, dynactin. We also find a clear defect in the redistribution of Ad5 to nuclei in A549 cells with LIC1 knock-down or overexpression, but not IC overexpression. Taken together, these data suggest that a reversible pH-dependent structural change of hexon in the endosome allows recruitment of cytoplasmic dynein to the capsid via regions of cargo-binding subunits distinct from those involved in physiological cargo transport.

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