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Discovering Control Mechanisms: The Controllers of Dynein

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Abstract

Most accounts of mechanism discovery have focused on mechanisms that perform the work required to produce a phenomenon. These mechanisms are often subject to regulation by control mechanisms. Using the example of the molecular motor dynein, this paper examines one process by which such control mechanisms are discovered—the process by which researchers, after identifying additional components required to produce the phenomenon but not directly involved in the work of producing that phenomenon, investigate both how these components act on the original mechanism and how they do so in response to measurements of conditions relevant to the operation of the controlled mechanism.

1. Introduction

Mechanisms, as described by the new mechanists in philosophy of science (Machamer, Darden, and Craver 2000; Bechtel and Abrahamsen 2005; Glennan 2017; Glennan and Illari 2018), carry out the work that organisms need to perform to maintain themselves—procure matter and energy from their environment, synthesize their physical structure, dispose of waste, etc. However, these mechanisms do not perform this work constantly, but only in the conditions in which the work is needed. Moreover, many biological mechanisms perform different work under different conditions. Both of these points are well illustrated by the molecular motor cytoplasmic dynein, which, among other things, transports cellular cargo (proteins, organelles, etc.) from the periphery of cells toward their centers by walking along microtubules. A walking motion results from the successive action of one lagging globular head of the dynein dimer releasing from the microtubule and advancing along it past the other head. Much of the time dynein is autoinhibited, not performing any transport activity. It is released from autoinhibition only when potential cargo is detected.

The work performed by such mechanisms, which I refer to as *production mechanisms*, is altered by the operation of other mechanisms, which I call *control mechanisms*. Control mechanisms differ from production mechanisms in two important respects.

First, the work they perform does not contribute directly to the work performed by production mechanisms. Rather, they perform work on production mechanisms, altering their conformation and thus initiating, stopping, or altering their activity. Second, they act on the basis of information they procure by making measurements (or relying on measurements made by other control mechanisms) of conditions in the organism or its environment. These measurements determine the conformation of the control mechanism, which in turn determines the work it performs on other mechanisms. (This account is grounded in the framework advanced by Pattee 1971; for elaboration, see Winning and Bechtel 2018.)

Many of the new mechanist accounts have focused on the discovery of mechanisms (Bechtel and Richardson 1993/2010; Craver and Darden 2013), emphasizing heuristics such as decomposition or forward or backward chaining. There has been much less work on the discovery of control mechanisms. Given the differences in what they do, the process of discovering control mechanisms is different. First, their discovery is typically derivative upon the discovery of production mechanisms. Moreover, control mechanisms are often concealed from view by the protocols used to investigate production mechanisms—these protocols are designed to generate the phenomenon and facilitate investigations into the contribution of components of the production mechanism to the phenomenon. Accordingly, these procedures often bypass the need for control mechanisms. One context in which control mechanisms are discovered is when researchers attempt to reconstitute the production mechanism from the parts that have been identified and find that the reconstituted production mechanism fails to generate the phenomenon. This failure may just point to the incompleteness of the account of the mechanism—what has been left out might just be one more part performing an activity that has not yet been recognized. But in some cases, such as the case of dynein, researchers had good reason to view the extra components as distinct from the production mechanism and as playing a control function. They did not treat these components as contributing to the work of transporting cargo but as altering the mechanisms responsible for performing that work in response to measurements the components made.

To illustrate one path to the discovery of control mechanisms, I analyze in some detail recent and ongoing research on the control mechanisms that have been identified as operating on dynein. To set the stage for that, I will briefly relate the discovery of cytoplasmic dynein in the mid-1980s and present a simplified account of how it operates to generate retrograde movement (movement towards the center of the cell) in section 2. In section 3, I will examine the research that led to the discovery of two additional components researchers identified in subsequent years as necessary to produce motor activity from purified dynein and I will analyze why these were interpreted not as parts of the mechanism but as controllers. Researchers were not satisfied with just identifying additional components that exercised control over dynein's behavior. As I discuss in section 4, researchers also sought to account for two additional features of control mechanisms I identified above: (1) how these control mechanisms operate on dynein to regulate its behavior and (2) how these mechanisms responded to measurement of conditions appropriate for dynein's activity.

Control mechanisms are far more numerous in biological organisms than the production mechanisms they control. The initial discovery of a few control mechanisms

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often results in research identifying and characterizing many additional control mechanisms operating on the same production mechanism. I illustrate this ongoing endeavor in section 5 before turning in section 6 to review the lessons about control mechanisms and their discovery stemming from this case study.

2. Discovering the production mechanism: Dynein

As emphasized by the new mechanists, mechanisms are closely tied to the phenomena they generate (Glennan 2017). This is particularly true in early research—the search for a mechanism is a search for a mechanism that could produce the phenomenon. In the case of dynein, the phenomenon was axonal transport (the transport of cellular material along axons of neurons) which was discovered, visualized, and measured between 1950 and 1980. Both anterograde (from the cell center to the axon terminal) and retrograde transport were documented (Grafstein and Forman 1980). One of the discoveries following the widespread adoption of electron microscopy in cell biology was the existence of the cytoskeleton and recognition that it consisted of three types of filaments—microtubules, intermediate filaments, and microfilaments. Video microscopy revealed that both anterograde and retrograde axonal transport occurred along microtubules, hollow cylinders that are approximately 25 nm in diameter (Vale et al. 1985).

Recognizing that such transport required a source of free energy, which was likely supplied by ATP, Vale, Reese, and Sheetz (1985) searched among the molecules that associated with microtubules for ones that would hydrolyze ATP (ATPases). They found one, which they named *kinesin* (from the Greek word *kinein*, to move), and demonstrated that it could transport cargo along microtubules. (For an analysis of the discovery of kinesin and the development of a mechanistic account of its operation, see Bechtel and Bollhagen [2021].) Vale et al. (1985) determined that inhibiting kinesin only prevented anterograde transport and concluded that another motor was responsible for retrograde movement. Shortly thereafter, Vallee et al. (1988) identified the second ATPase among microtubule-associated proteins and, employing electron microscopy, demonstrated that it was "structurally equivalent" to axonemal dynein, a motor that had been identified 20 years earlier as responsible for movement of cilia (Gibbons and Rowe 1965). The new dynein came to be known as *cytoplasmic dynein*.

Since kinesin and dynein were both molecules, researchers recognized that a mechanistic explanation of their activities would require a way to determine the molecular constitution of the two molecules. In particular, since the motors used the hydrolysis of ATP to power movement along microtubules, researchers were particularly focused on domains in the molecules responsible for the key activities of walking along the microtubule—binding and hydrolyzing ATP, binding and releasing from microtubules, and swinging the unattached head to a new binding site. Biochemical studies showed that ATP hydrolysis occurred in the globular heads of the motors. In the case of dynein, structural studies showed that the head region contained six AAA+ (ATPases associated with cellular activities) modules. Four of these are capable of hydrolyzing ATP, but only the first was found to be involved in the generation of the force used to move the unattached head along the microtubule. The region capable of binding microtubules was shown to reside at the end of a stalk projecting from the head. From these findings, researchers constructed a mechanistic

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explanation according to which the force produced by hydrolysis of ATP alters the configuration of the head, which in turn alters the stalk and the ability of dynein to bind microtubules. When the trailing head is released from the microtubule, the force generated by ATP hydrolysis and stored in a perturbed conformation of the molecule is released and propels that head past the other head so that it can bind to a new locus on the microtubule. (For a review, see Bhabha et al. 2016.)

The discovery of dynein and the development of a mechanistic explanation largely conforms to the new mechanistic account. The one departure is that research focused not just on the activities of the component parts of the molecule but also emphasized the role of energy and how its release was constrained to generate physical forces that resulted in stepping behavior. The structure of the molecule was understood to generate transport via the constrained release of energy from ATP.

3. Discovering the existence of control mechanisms

Early in the process of investigating dynein, researchers developed *in vitro* assays in which they could demonstrate movement when dynein extracted from cells was added to coverslips containing microtubules. When Schroer, Steuer, and Sheetz (1989) conducted such an assay using purified dynein, the movement they observed was much slower than that produced by non-purified extracts. The researchers concluded that some factor or factors other than dynein were required to generate normal movement. Gill et al. (1991) showed that normal dynein movement could be restored by adding a large (1.2 MDa) protein complex that they isolated from the original preparation and named *dynactin* (*dynein activator*). Moreover, Gill et al. demonstrated that when they removed dynactin completely from a preparation of moving dyneins, motility was totally suppressed. Dynactin, they concluded, was required for dynein to generate retrograde transport.

From the new mechanist perspective, the natural inference would have been that dynein and dynactin together constitute the mechanism responsible for retrograde transport. But as the derivation of the name from *dynein activator* suggests, dynactin was not considered to be a part of the mechanism, but an activator of it. Dynein itself was judged to constitute the mechanism that transformed energy from ATP into movement along microtubules, presumably because it contained both a site for ATP hydrolysis (dynactin does not) and microtubule binding domains (dynactin also contains a microtubule binding domain, but it was not assumed to be generating the walking movement along the microtubule). The idea of dynactin as an activator took on additional significance once dynein, without dynactin, was understood to autoinhibit. An early micrograph of dynein by Amos (1989) showed that it sometimes adopted a conformation (which Amos named *phi* for its shape) in which its "two heads fused together, forming a dimeric globular particle with two separate tails" (19). As the account of how dynein moved along microtubules was developed, it became clear that dynein could not do so when in the *phi* configuration, but the characterization of this as an autoinhibited state was only advanced by Torisawa et al. (2014). Once dynein was understood to autoinhibit, one function dynactin was viewed as performing was forcing a conformation change in dynein so that it is no longer autoinhibited and both heads are able to bind to a microtubule.

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When a control mechanism fails to operate, the production mechanism will no longer make its contribution to the wellbeing of the organism. The result is often disease. Diseases, therefore, provide another avenue for discovering control mechanisms. This is exemplified in the discovery of another control mechanism operating on dynein. The disease lissencephaly is characterized by the neocortex developing with a smooth rather than convoluted surface and with its six-layer structure being disrupted. Further research led to the discovery of the gene *Lis1* (*lissencephaly1*), whose mutation resulted in the disease (Dobyns et al. 1993). The deficits suggested a deficit in normal neuronal migration, which was in turn attributed to improperly locating the nucleus and centrosome with respect to each other in migrating neurons. In addition to axonal transport, dynein was known to be involved in nuclear migration. Research establishing deficits in nuclear migration as a result of mutation of the gene *NudF* (nuclear distribution F), the homologue of Lis1 in the fungus *Aspergillus nidulans*, pointed to the possibility that the protein Lis1 interacted with dynein (Morris 2000). To link this finding to mammalian brain development, Faulkner et al. (2000) demonstrated that the Lis1 protein co-immunoprecipitates with cytoplasmic dynein and dynactin while Hoffmann et al. (2001) showed that it binds to both dynein and dynactin. This research established Lis1 as important for dynein action but, as with dynactin, it was not understood to be part of the transport mechanism but as controlling it. Beyond the fact that Lis1 is not able to perform either of the key activities of generating motion—hydrolyzing ATP or binding to microtubules—a further consideration was that it was required for several specific activities to which dynein contributes. Faulkner et al. comment: "Together, these results indicate that LIS1 may have a fundamental function in the regulation of cytoplasmic dynein in cell division during the early stages of brain development."

4. Discovering how the control mechanisms work

In the previous section I described how dynactin and Lis1 were identified and treated as controlling whether dynein acted as a retrograde motor (or engaged in other activities). But researchers were not satisfied with merely establishing that it played a control function. To support their understanding of these proteins as performing a regulatory role, investigators needed to further demonstrate that the putative control component (1) operated on the production mechanism, altering its operation and (2) performed this function after procuring information relevant to the invocation of the mechanism. Researchers pursued both objectives in their subsequent investigations of dynactin and Lis1.

In the case of dynactin, two findings proved particularly helpful in deciphering its control function. The first concerned how it interacted with dynein. A cue was provided by the fact that a prominent feature of dynactin's structure is an arm that binds to both dynein's intermediate chain and the microtubule (Waterman-Storer, Karki, and Holzbaur 1995). When this structure is bound to dynein, it cannot adopt the phi formation but is forced into a conformation in which it can bind microtubules. It was thus identified as altering flexible constraints within dynein to transform it into a functional motor.

The second clue was that even though binding of dynactin to dynein was required for dynein to produce movement, the molecules do not tend to bind under

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physiological conditions and, when they do, the union is unstable. Swan, Nguyen, and Suter (1999) found that in *Drosophila*, Bicaudal D (BicD; in mammals BicD has two homologues, BicD1 and BicD2) promoted their binding. BicD also binds to Rab6, a GTPase attached to vesicles released from the Golgi apparatus. From these findings, researchers advanced an account in which BicD recruits dynactin and dynein to the vesicles needing transport (McKenney et al. 2014). Following up on this discovery, Chowdhury et al. (2015) showed that when dynein, dynactin, and BicD bind together, dynein's heads are oriented so as to facilitate processive walking. If BicD was playing a control role, it needed to procure information about when retrograde transport is required. Researchers determined that it registers the cargo in need of transport by undergoing its own conformation change. In the absence of Rab6 attached to cargo, BicD autoinhibits by bending back on itself. It only assumes a conformation in which it can promote the union of dynein and dynactin when Rab6, and hence mitochondria, are present (Liu et al. 2013).

Subsequent to the discovery of the role of BicD, several other cargo-binding proteins that bind dynein and dynactin to specific cargos and generate distinctive responses have been identified (for reviews, see Reck-Peterson et al. 2018; Olenick and Holzbaur 2019). Most of these have structures comparable to BicD; this structure enables them to bind dynein and maintain it in a form where it can walk along microtubules. Accordingly, it is now understood that BicD and other cargo-binding proteins detect cargos in need of transport and in response act to promote the binding of dynactin to dynein, enabling dynein to transport cargo.

The full story of how Lis1 performs a control function is less clear, but researchers have developed several hypotheses about how it acts on dynein. Through research on nuclear migrations in the fungus *Aspergillus nidulans*, Sasaki et al. (2000) revealed that in addition to the Lis1 homolog, NudF, another protein, NudE, was involved and that NudF/Lis1 and NudE form a heterotetramer and bind to the globular heads of dynein. By binding at a junction between the AAA3 and AAA4 domains, NudF/Lis1 interferes with the ability of the conformation change induced by ATP hydrolysis at the AAA1 binding site. This alters the stalk in a way that causes dynein to detach from the microtubule (Toropova, Katerina, et al. 2014). Drawing on findings such as these, Huang et al. (2012) proposed that Lis1 operates like a clutch that keeps dynein bound to the microtubule rather than releasing and taking steps, thereby allowing more force to be generated in response to heavy loads. Other research had, however, suggested that dynein played an incompatible regulatory role of initiating and sustaining dynein transport. Drawing upon the observation that the state of nucleotide binding at the AAA3 site can switch dynein from rapid stepping to remaining bound to the microtubule (DeWitt et al. 2015), DeSantis et al. (2017) investigated the interaction of Lis1 and the state of AAA3. They determined that Lis1 had opposite effects on stepping behavior depending on the hydrolytic state of AAA3. In addition, their investigation led to the discovery of a second site, on the stalk, at which Lis1 could bind when ATP was present at AAA3. When bound at both sites, instead of increasing the bond between dynein and the microtubule, Lis1 weakened it. They showed that binding at this second site was also critical for dynein localization in the cell and for dynein to be transported by kinesin to different locations in the cell. (For a detailed review of hypotheses as to how Lis1 plays a regulatory role, including a recent proposal that its

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role is as a check-valve preventing return to the autoinhibited phi configuration, see Markus, Marzo, and McKenney [2020].)

The research to date has provided considerable detail about how Lis1 alters the operation of dynein but has yielded less insight into what determines the action of Lis1. In light of the fact that Lis1 is required in diverse activities of dynein, Olenick and Holzbaur (2019, 3) theorize that "it is likely to be more of a global regulator of dynein motility rather than a cargo-specific adaptor." One possibility, suggested by DeSantis et al. (2017), is that it responds to the concentration of the energy source ATP. They propose that concentrations of ATP and ADP affect the hydrolytic state of AAA3, which in turn determines what effect Lis1 has. They also suggest that the physical force exerted by the load dynein is carrying can alter the hydrolytic state of AAA3 and thus the behavior of Lis1.

In the case of the two control mechanisms on which I have focused, current research has reached different stages. Research on dynactin has revealed how it acts on dynein to enable transport and how, by interacting with different cargo-binding proteins, it responds to cargo in need of transport. In the case of Lis1, research has indicated ways in which it acts as a control mechanism. There are hypotheses, but not a generally accepted understanding, of the conditions in the cell that Lis1 measures and to which it responds.

5. Finding additional control mechanisms: An ongoing saga

While discovery of the responsible production mechanism and how it works figures centrally in the initial development of explanations of biological activities, once the basic mechanism is worked out, much of the focus turns to the question of how the mechanism is controlled. Often many control processes are found to operate on the same production mechanism, altering its activity appropriately for multiple conditions. This motivates ongoing inquiry to identify additional control mechanisms acting on dynein. I briefly describe current research that is revealing a new dimension of dynein control—how it is coupled with the control of the anterograde motor kinesin.

A striking observation is that cargos such as mitochondria often move bidirectionally, proceeding for a period in one direction before reversing. Investigations revealed that mitochondria are often bound to both kinesins and dyneins. An early hypothesis was that the two motors engaged in a tug-of-war to determine the direction of movement (Muller, Klumpp, and Lipowsky 2008), but more recent work has suggested that a control mechanism determines which motor moves the mitochondrion. Fenton, Jongens, and Holzbaur (2021) found that each motor generates more movement when the other motor is also present and hypothesized that the two motors form a complex. These researchers focused on TRAK2, a protein that binds mitochondria to the dynein-dynactin complex, and offered evidence that it binds both kinesin and dynein at overlapping regions, creating a two-motor complex. Citing evidence that TRAK2 undergoes conformation changes, they proposed it acts as a switch. One question this raises is: what sets the switch? Fenton et al. identify two candidate molecules that can bind to TRAK2, alter its conformation, and set the switch so the complex moves in a particular direction: Disrupted-In-Schizophrenia 1 (DISC1), which they proposed promotes anterograde transport by kinesin, and NudE, which favors retrograde transport by dynein. They hypothesize that "The association of these transport effectors,

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combined with the specific TRAK and Miro isoforms in complex with microtubule motors on mitochondria, could then allow for local regulation of motor activity in response to cellular signals" (11).

Fenton et al.'s research is one example of ongoing research that is advancing proposals as to how different cargoes that need to be transported regulate the behavior of dynein (and kinesin). It is too soon to know whether their hypothesis or some alternative will be vindicated, but it is clear that investigating how dynein is regulated has become a major focus of research.

6. Conclusion

Although new mechanists in philosophy of science have provided important insights into the discovery of production mechanisms, they have not examined the discovery of control mechanisms. By focusing on one production mechanism, dynein, I have advanced an account of the discovery of control mechanisms operating on it. The discovery followed from the determination that only when additional components were present could dynein perform its activity and that these entities lacked the ability to contribute directly to the generation of the phenomenon of retrograde transport. This led to research into how these additional components act on dynein to release it from autoinhibition and link it to different cargos and how the behavior of these control elements in turn is responsive to conditions in the cell, such as the conditions that determine what cargo needs to be transported. As the ongoing research on control mechanisms operating on dynein suggests, often multiple mechanisms operate to control a single production mechanism. Discovering production mechanisms and how they work is just one topic for philosophical research on mechanisms. As suggested by the examples considered here, another rich topic is how researchers discover and investigate control mechanisms.

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