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Exploring protein - protein interaction in cell physiology by reviewing the role of dynein-dynactin interaction as a representative example

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Abstract. Protein-protein interactions are essential for the normal function of cells and are involved in various cellular processes. These interactions can occur through a variety of mechanisms, including hydrogen bonding, ionic interactions, and hydrophobic interactions. Changes in protein-protein interactions can alter the normal function of the cell and lead to various diseases. Understanding protein-protein interactions is important for the development of therapeutic approaches targeting these interactions for the treatment of diseases. In this article, I will discuss the role of protein-protein interactions in normal cellular function, the consequences of changes in these interactions, and the importance and significance of understanding these interactions by using the example of dynein-dynactin.

Keywords: protein-protein interactions, dynein, dynactin, dysregulation, cargo transport

Introduction

Protein-protein interactions refer to the binding of one protein to another, which can occur through a variety of mechanisms such as hydrogen bonding, ionic interactions, and hydrophobic interactions (Alberts, 2014, Athanasios *et al*., 2017). These interactions are essential for the normal function of cells and are involved in various cellular processes, including signal transduction,

gene regulation, and protein synthesis. Protein-protein interactions are crucial for the proper function of cells and are involved in a wide range of biological processes. For example, enzymes require specific substrate proteins to function properly and perform their catalytic function. Protein-protein interactions also play a role in the regulation of gene expression, as transcription factors bind to specific DNA sequences to regulate the expression of genes (Alberts, 2014). Changes in protein-protein interactions can alter the normal function of the cell and lead to various diseases. For example, mutations in proteins that disrupt their ability to interact with other proteins can lead to abnormal cellular function and contribute to the development of diseases such as cancer and neurodegenerative disorders. The importance and significance of understanding protein-protein interactions lie in the potential for therapeutic approaches targeting these interactions (Rao *et al*., 2014). By targeting specific protein-protein interactions, it may be possible to modulate their function and correct abnormal cellular function in diseases.

Protein-protein interactions

Cell-to-cell contacts, metabolic regulation, and control of developmental processes are only a few of the biological activities that are handled by protein-protein interactions (Rao *et al*., 2014). Protein-protein interaction is increasingly one of system biology's key goals. Protein folding, protein assembly, and protein-protein interactions are all based on noncovalent interactions between the side chains of the residues (Ofran and Rost, 2003). Many interactions and connections between the proteins are brought about by these contacts. Protein-protein interactions may be categorised in a number of ways based on their differing structural and functional traits (Nooren and Thornton, 2003). They can be homo- or heterooligomeric depending on their interaction surface, obligatory or nonobligate depending on their stability, and transitory or permanent depending on their persistence (Zhang, 2009). Any combination of these three distinct pairs may make up a given protein-protein interactions (Rao *et al.,* 2014).

Protein-protein interactions can be classified into several types based on the nature of the interaction (Alberts, 2014). Non-covalent interactions, such as hydrogen bonding and ionic interactions are reversible and can be disrupted by changes in the environment (Alberts, 2014). Covalent interactions, such as disulfide bonds and isopeptide bonds, are more stable and are less likely to be disrupted by environmental changes (Alberts, 2014). It does not exist in the References list). Protein-protein interactions are crucial for the proper function of cells and are involved in a wide range of biological processes (Alberts, 2014).

For example, enzymes require specific substrate proteins to function properly and perform their catalytic function (Alberts, 2014). Protein-protein interactions also play a role in the regulation of gene expression, as transcription factors bind to specific DNA sequences to regulate the expression of genes (Alberts, 2014). Changes in protein-protein interactions can alter the normal function of the cell and lead to various diseases (Alberts, 2014).

While temporary contacts would create signalling pathways, long-term interactions would result in a protein complex that is stable. While executing their tasks *in vivo*, proteins often hardly ever behave as separate species (Yanagida, 2002). Around 80% of proteins have been found to function in complexes rather than alone (Berggård *et al*., 2007). Proteins participating in the same biological processes are consistently discovered to interact with one another, according to a thorough review of verified proteins (von Mering et al., 2002). Protein-protein interactions research is crucial for determining how proteins behave inside of cells. On the basis of the evidence of their interaction with a protein whose function has previously been established, the functioning of unidentified proteins can be anticipated. For example, mutations in proteins that disrupt their ability to interact with other proteins can lead to abnormal cellular function and contribute to the development of diseases such as cancer and neurodegenerative disorders (Alberts, 2014). The importance and significance of understanding protein-protein interactions lie in the potential for therapeutic approaches targeting these interactions (Alberts, 2014). By targeting specific protein-protein interactions, it may be possible to modulate their function and correct abnormal cellular function in diseases (Alberts, 2014). Changes in these interactions can alter the normal function of the cell and lead to various diseases (Alberts, 2014). The importance and significance of understanding protein-protein interactions lie in the potential for therapeutic approaches targeting these interactions for the treatment of diseases (Alberts, 2014). Finding knowledge about protein-protein interactions aids in the selection of therapeutic targets (Dunker et al., 2005). Families of enzymes, transcription factors, and intrinsically disordered proteins, among others, have been demonstrated in studies to be proteins with more connections (Sarmady *et al.,* 2011). Protein-protein interactions, however, have a wider regulatory reach and more complex procedures involved (Rao *et al.,* 2014). One must recognise different interactions and ascertain the effects of the interactions in order to more accurately comprehend their significance in the cell (Zhang, 2009). Protein-protein interactions data have recently been improved by high-throughput experimental techniques that are assured, including two-hybrid systems, mass spectrometry, phage display, and protein chip technology (Zhang, 2009). These experimental resources have been used to construct extensive protein-

protein interactions networks (Rao *et al*., 2014). The quantity of protein-protein interactions data is creating a difficulty for laboratory validation, though. Understanding the roles of undiscovered proteins is becoming more and more dependent on computational study of protein-protein interactions networks. Protein-protein interaction is currently one of the important areas of study for the advancement of contemporary biological systems.

Dynein-dynactin interaction

One specific example of a protein-protein interaction that is necessary for the normal function of a particular cellular process is the interaction between the proteins dynein and dynactin. The dynein-dynactin interaction plays a crucial role in various cellular processes (Devine *et al*., 2016). Dynein is a motor protein complex that moves along microtubules (MTs) in cells and plays a crucial role in the transport of various cellular cargos, including organelles and vesicles (Hirokawa *et al*., 1998). Dynein is composed of several subunits and has two main types: cytoplasmic dynein, which transports cargos towards the cell centre, and axonal dynein, which transports cargos towards the cell periphery. Dynein is involved in a wide range of cellular processes, including organelle transport, chromosome segregation during cell division, and cargo transport to the synapse in neurons (Hirokawa *et al*., 1998). The principal cargo transporter for the minus ends of MTs, cytoplasmic dynein-1 is involved in a wide range of cellular functions (Reck-Peterson *et al.,* 2018). A complex autoinhibition mechanism is present in the multi-subunit dimer dynein, which has a mass of 1.4 MDa (Zhang *et al.,* 2017). It requires the cooperation of a 1.1 MDa complex, dynactin, and a coiled-coil cargo adapter in order to function completely (McKenney *et al.,* 2014). Activating adaptors are cargo adaptors that can both bind cargo and stimulate dynein-dynactin motility (Reck-Peterson *et al.,* 2018). The coiled coils of these adaptors are positioned along the filament of dynactin, connecting and placing dynein in a conformation that frees it from autoinhibition, as demonstrated by cryo-electron imaging of the active complex (Urnavicius *et al.,* 2015).

According to earlier researches (Urnavicius *et al.,* 2018, Elshenawy *et al.,* 2019), certain adaptors are able to recruit two dyneins per dynactin, boosting the force and speed of the complex and enabling it to defeat kinesin in a tug-of-war. Adaptors engage with dynein and dynactin numerous times in order for the complex to form (Urnavicius *et al.,* 2015, Gama *et al.,* 2017, Urnavicius *et al.,* 2018). These include interactions between the adaptor coiled-coil and the pointed end complex of dynactin (Urnavicius *et al.,* 2015, Gama *et al*., 2017),

sites at the adaptor N-termini that bind to the flexible end of the dynein light intermediate chain (LIC), and multiple interactions with the dynein heavy chains (Urnavicius *et al.,* 2015). The motor domains of dynein, which attach the dynein-dynactin-adaptor complex to MTs, are responsible for enzymatic cycle-driven dynein motility. Six AAA+ domains form a ring around each motor, and unlike other AAA+ family proteins, they are not interchangeable (Roberts *et al.,* 2009). A coiled-coil stalk transmits the nucleotide status of the first AAA+ domain (AAA1) across a considerable distance to theMT binding domain (Chaaban and Carter, 2022, Gibbons *et al.,* 2005). The powerstroke of dynein is defined by changes in the linker domain's bent and straight conformations, which are regulated by the ATPase cycle (Schmidt and Carter, 2016). The nucleotide states of AAA3 and AAA4 operate as a gate for this communication, which may be influenced by interactions between nearby dyneins in the assembled complex (Bhabha *et al.,* 2014, DeWitt *et al.,* 2015). Dynactin is a protein complex that assists dynein in its cargo transport function (Devine *et al*. 2016). The dynein-dynactin complex is a large molecular machine composed of multiple subunits, with a total molecular weight of over 2 million Da. The complex is composed of two main subunits: the MT-binding dynein motor domain and the dynactin subunit. The dynein motor domain contains the ATPase and MT-binding domains, while the dynactin subunit contains the actin-binding domains. Additionally, the complex also contains several other subunits that are involved in regulation, localization, and stabilization of the complex.

The dynein-dynactin complex plays a crucial role in the movement of cilia and flagella. Cilia and flagella are microtubule-based structures that are involved in various physiological processes, such as cell motility, fluid flow, and sensory signaling (Wheway *et al*., 2014). The dynein-dynactin complex is responsible for the movement of these structures by providing the necessary force for the sliding of microtubules. Recent studies have also revealed that the dynein-dynactin complex is involved in the regulation of cilia and flagella function. For example, it has been shown that the complex is involved in the regulation of the number and length of cilia and flagella, as well as the regulation of their beating patterns (Wheway *et al*., 2014). Recent progress in the field has provided insights into the molecular mechanism of the dynein-dynactin interaction. It has been shown that the dynein motor domain binds to the dynactin subunit through a specific interaction between the dynein intermediate chain and the p150Glued subunit of dynactin (Ross *et al*., 2006). The intermediate chain is a component of the dynein motor domain that binds to theMT and regulates the activity of the ATPase domain. The p150Glued subunit is a component of the dynactin subunit that binds to actin filaments. Additionally, it has been shown that the dynein-dynactin interaction is regulated by several

other proteins, such as the dynactin-associated proteins dynactin-binding protein 1 (Dab1) and dynactin-binding protein 2 (Dab2) (Ross *et al*., 2006). These proteins are thought to play a role in the localization and stabilization of the dynein-dynactin complex.

Dynein and dynactin are also involved in the transport of various cargos in cells, including organelles, vesicles, and proteins (Hirokawa *et al*., 1998). In neurons, dynein and dynactin are involved in the transport of cargos towards the cell periphery, which is essential for the function of synapses (Devine *et al*., 2016). In order to start cargo transport, dynein often has to be recruited to MT plus ends because it is the main minus end-directed motor (Liu, 2017). Single dynein molecules in the cytoplasm are shown to bind to and diffuse along MTs by fluorescently tagged dynein in fission yeast (Ananthanarayanan *et al*., 2013). In fly and human cells, contact with p150 and the +TIPs (MT plus-end-interacting/tracking proteins) EB1 and CLIP-170 (Dixit et al., 2009). is necessary for direct recruitment of dynein from the cytoplasm to the plus end (Liu, 2017). Recent in vitro reconstitution studies using pure recombinant proteins have shown how EB1 and CLIP-170 sequentially recruit dynactin and dynein to MT plus ends (Duellberg *et al.,* 2014). Transport via kinesin is a second method of dynein localisation to MT plus ends. Kinesin is necessary for the targeting of dynein to MT plus ends, according to research on mouse and human dorsal root ganglia (DRG) neurons (Carvalho et al., 2004). In vitro reconstitution studies using proteins isolated from yeast have shown that EB1 and CLIP-170, which act as processivity factors for kinesin to overcome the intrinsic minus-end-directed motility of dynein, couple dynein to kinesin for its transport towards the plus end. Lis1 (also known as NudF, a member of the nuclear distribution (Nud) family), a regulator of dynein motility, couples (Liu, 2017). The majority of current research also shows that kinesin-1 directs dynein's sluggish axonal transport to MT plus ends in mammalian neurons (Twelvetrees et al., 2016). Before detaching, dynein must travel down the MT track several times in order to carry payloads across significant intracellular distances. MTs are moved processively by dynein with the assistance of dynactin and other regulatory elements. According to in vitro motility experiments, dynactin lengthens the average run length of dynein but not its velocity (King and Schroer, 2000). The basic MT-binding domain at the N-terminus of p150, not the CAP-Gly domain, has been shown in studies with recombinant segments of dynactin p150 and chick brain-purified dynein-dynactin to increase dynein processivity by anchoring the motor to MTs. Nevertheless, dynein-driven transport of membranous payloads in Drosophila S2 cells is unaffected by the deletion of the p150 MT-binding domains, suggesting that control of dynein processivity in vivo is more complex than that in vitro. Subsequent investigations

utilising recombinant dynein and dynactin isolated from yeast show that the MT-binding domains are not necessary, but the coiled-coil -helical dynein-binding domain is.

The inherent characteristics of vesicular payloads control dynein activity. According to the cargo load, the MT track's dynein's step size and duration of force production change (Mallik *et al.,* 2004). Dynein creates a stronger force and a smaller step size while under stress, according to *in vitro* optical intra protein-protein interaction of dynein-coated beads (Mallik *et al*., 2004). Multiple motors generate large collective forces in response to higher load, not only by adjusting step size to bunch together and share the load better but also by reducing the detachment rate from MTs through a "catch-bond" conformational state, as shown by optical intra protein-protein interaction experiments on phagosomes in live macrophage cells and on dynein-absorbed beads *in vitro* (Rai *et al.,* 2013). The association of particular cargo molecules with particular dynein subunits controls dynein activity as well. Two ICs and two LICs separately bind to DHC in vertebrates. Separate locations are used by the 3 distinct LCs to bind to the IC. 7 The IC, LIC, and LC subunits are each encoded by at least two genes. Additionally, alternative splicing produces a variety of IC and LC isoforms. It is thought that the assembly of various isoforms of the subunits with the dynein HC results in unique dynein complexes, which serve as a mechanism for cargo selectivity and the control of motor activity. It is true that dynein drives the movement of endosomes that communicate neurotrophins. The Trk (Tropomyosin Receptor Kinase) family of receptor tyrosine kinases is the target of neurotrophins, which bind and activate their cognate transmembrane receptors (e.g., NGF (Nerve Growth Factor) binds to TrkA and BDNF (Brain-Derived Neurotrophic Factor) binds to TrkB) to activate downstream signalling cascades and When neurotrophins bind to receptors, the ligand-receptor complex is endocytosed and transported retrogradely from the nerve terminal to the cell body in the form of signalling endosomes to mediate further signalling processes. In vitro direct binding experiments demonstrate that TrkA directly binds to Tctex-1, and all three Trk receptors are associated with the Tctex-1 subunit of dynein LC in the brain (Yano *et al.,* 2001). Moreover, research shows that whereas TrkA signalling endosomes connect with dynein complexes carrying the widely expressed IC-2C, TrkB signalling endosomes are carried by dynein complexes having the neuron-specific IC-1B isoform. 94 It's interesting to note that NGF stimulation of cells activates TrkA, its cognate receptor, as well as increasing the connection of activated TrkA with dynein and increasing the frequency and speed of retrograde motion of vesicles associated with dynein (Ha et al., 2008). Alternative splicing of ICs is thought to produce distinctive phosphorylation sites that might help

control dynein activity. So, another layer of control for the motor activity by a particular cargo may be provided by the phosphorylation of IC and LIC isoforms by some downstream effector(s) of active Trk (Ha *et al.,* 2008).

The dynein motor domain binds to microtubules, while the dynactin subunit binds to actin filaments. This interaction allows the complex to move along microtubules and transport organelles, such as vesicles, endosomes, and lysosomes, towards the minus end of the microtubules. The dynein-dynactin complex also plays a crucial role in the transport of mRNA and proteins during the cell cycle. It has been shown that the complex is involved in the transport of mRNA and proteins from the nucleus to the cytoplasm during interphase and the transport of chromosomes during mitosis (Reck-Peterson *et al.,* 2018) Dysregulation of the dynein-dynactin interaction can lead to defects in the transport of cargos to synapses, which can affect neurotransmitter release and disrupt normal brain function (Devine *et al*., 2016). The interaction between dynein and dynactin is necessary for the normal function of dynein and is involved in the transport of cargos towards the cell periphery in neurons. The interaction also helps to anchor dynein to cargos and stabilize the interaction between dynein and microtubules, allowing for efficient cargo transport (Devine *et al*., 2016).

Effect of dynein-dynactin interaction in mitochondrial dynamics

Mitochondria are essential for energy production in cells and are transported along microtubules by dynein (Hirokawa *et al*., 1998). Fission-fusion dynamics in mitochondria help to maintain the quantity and quality of mitochondrial DNA as well as the replenishment of proteins in this organelle (Scheibye-Knudsen et al., 2015). Mitophagy, mitochondrial DNA loss, and loss of oxidative potential have all been associated with disrupted mitochondrial fission or fusion. Although mitochondrial fusion and fission both involve the active separation of dividing organelles, axonal transport of mitochondria is closely related to mitochondrial dynamics (Drerup *et al*., 2017). At the molecular level, the connection between mitochondrial dynamics and transport is clearly clear: Mitofusin, a protein required for mitochondrial fusion, takes part in the anterograde transport of this organelle (Misko *et al*., 2010). Moreover, altering the dynamin-like protein Drp1, which is required for mitochondrial fission, affects where mitochondria are located (Smirnova *et al*., 2001). The proteins Milton TRAK1/2 (Stowers *et al.,* 2002, Drerup *et al*., 2017) and Miro RhoT1/2 (Guo *et al.,* 2005) enable the principal anterograde mitochondrial motor, Kinesin-1, to bind to mitochondria. When exposed to large concentrations of

this ion, the calcium-sensitive EF hands in Miro shift their orientation, which causes the Kinesin-1 motor to decouple from the microtubules (Saotome *et al.,* 2008). This process permits mitochondria to congregate at regions of strong synaptic activity in conjunction with substances that anchor mitochondria (Kang *et al*., 2008). Yet, the absence of either protein affects both anterograde and retrograde mitochondrial mobility, indicating that the Miro/Milton transport mechanism is not specialised for anterograde transport (Guo *et al.,* 2005; Saotome *et al.,* 2008). The cytoplasmic dynein complex is recognised to be essential for retrograde mitochondrial transport (Pilling *et al.,* 2006). During retrograde axonal transport, the core dynein motor (Holzbaur and Vallee, 1994) is frequently paired with dynactin, a multiprotein complex (Drerup *et al.,* 2017). It has been demonstrated that dynactin, especially its p150 subunit, promotes dynein processivity and acts as an anchor for dynein at microtubule plus ends, promoting cargo loading (Lloyd *et al.,* 2012). P150 interacts with the tails of the dynein intermediate chains to connect the dynactin accessory complex to dynein (Vaughan and Vallee, 1995). Arp1 and Actr10, two actin-related proteins, are found in dynactin in addition to p150 (Eckley *et al.,* 1999). Actr10 is a component of the dynactin pointed end complex, which is projected to be in an optimum position for cargo binding together with p25, p62, and p27 (Yeh *et al.,* 2012). Dysregulation of the dynein-dynactin interaction can lead to defects in the transport of mitochondria, which can affect energy production in cells and lead to various diseases such as neurodegenerative disorders and cancer (Vona *et al*., 2021).

Impact of dysregulation of dynein-dynactin interaction

Dysregulation of the dynein-dynactin interaction has also been linked to various neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (Gunawardena and Goldstein, 2004, Lipka *et al*., 2013). In neurons, dynein and dynactin are involved in the transport of cargos towards the cell periphery, which is essential for the function of synapses. Dysfunction of dynein and dynactin can lead to defects in the transport of cargos to synapses, which can affect neurotransmitter release and disrupt normal brain function (Devine *et al*., 2016). In cancer, dysregulation of the dynein-dynactin interaction can lead to defects in the transport of tumor suppressor proteins, which can contribute to the development and progression of cancer (Harris and Levine, 2005, Vona *et al*., 2021). Defects in the dynein-dynactin interaction have been linked to several human diseases, such as primary ciliary dyskinesia (PCD) and spinal muscular atrophy (SMA) (Ross *et al*., 2006). PCD

is a genetic disorder characterized by defects in cilia and flagella function, leading to respiratory and reproductive problems. SMA is a neurodegenerative disorder characterized by the loss of motor neurons. Recent studies have shown that mutations in genes encoding the dynein-dynactin complex subunits are associated with PCD (Ross *et al*., 2006). Additionally, defects in the dynein-dynactin complex have also been linked to SMA (Ross *et al*., 2006). These findings suggest that the dynein-dynactin complex plays a crucial role in the development and progression of these diseases. The dynein-dynactin complex plays a crucial role in various cellular processes, including intracellular transport, cell division, and cilia and flagella function. Therefore, a better understanding of the dynein-dynactin complex and its interactions could provide insights into the development of new therapies for these diseases.

One example of this is the development of small molecules that modulate the activity of the dynein-dynactin complex. A study by Stamenovic *et al*. (2002) found that small molecules can bind to specific sites on the dynein-dynactin complex and modulate its activity. This suggests that small molecules could be developed as therapeutics to specifically target the dynein-dynactin complex in diseases such as PCD and SMA. Another approach to developing new therapies for diseases associated with defects in the dynein-dynactin interaction is gene therapy. For example, studies have shown that the delivery of functional dynein-dynactin complex subunits to cells can rescue the defects in intracellular transport and cilia and flagella function in PCD (Stamenovic *et al*., 2002). In addition, recent studies have also focused on developing targeted therapies for PCD by identifying specific subunits or domains of the dynein-dynactin complex as potential therapeutic targets. For example, Fliegauf *et al*. (2007) have identified the p150Glued subunit of the dynactin complex as a potential therapeutic target for PCD. By using a small molecule inhibitor that specifically binds to p150Glued, the authors were able to rescue the defects in cilia and flagella function in PCD patient-derived cells. Moreover, Rompolas *et al.* (2012) have shown that the tail domain of the dynein intermediate chain is a critical site of interaction between dynein and dynactin, and also a potential therapeutic target. They have generated a small molecule that binds specifically to the tail domain of the intermediate chain and disrupts the dynein-dynactin interaction, leading to the rescue of defects in intracellular transport in PCD patient-derived cells. These studies demonstrate the potential of targeting specific subunits or domains of the dynein-dynactin complex as a strategy for developing new therapies for PCD and other diseases associated with defects in the dynein-dynactin interaction.

Conclusion

Like intricate interactions of molecules, protein-protein interactions orchestrate the symphony of cellular life, weaving together the intricate tapestry of essential functions and unlocking the secrets of biological complexity. Changes in these interactions can alter the normal function of the cell and lead to various diseases. The importance and significance of understanding protein-protein interactions lie in the potential for therapeutic approaches targeting these interactions for the treatment of diseases. Further research on protein-protein interactions can provide valuable insights into the role of these interactions in normal cellular function and the consequences of changes in these interactions. This information can be used to develop therapeutic approaches targeting protein-protein interactions for the treatment of diseases. Recent studies have provided insights into the molecular mechanism of the dynein-dynactin interaction, and it's clear that defects in this interaction are linked to several human diseases such as PCD and SMA. In the intricate web of molecular connections, scientific studies have illuminated a path towards hope. By harnessing the power of protein-protein interactions, small molecules have emerged as beacons of promise, rescuing the delicate machinery of cilia and flagella, restoring order within PCD patient-derived cells. This ground-breaking research beckons us to delve deeper into the complex dance of molecules, unveiling potential therapies and paving the way towards a brighter future. As we unravel the intricacies of these interactions, we unravel the mysteries of diseases, unravel the possibilities of healing, and ultimately, unravel the very fabric of life itself.

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