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Role of Dynein and Dynactin (DCTN-1) in Neurodegenerative Diseases

Rajib Dutta[1*] and Swatilekha Roy Sarkar[2]

Affiliation

[1]Consultant Neurology, China

[2]Consultant Orthodontist, India

***Corresponding author:** Rajib dutta, MD, Consultant Neurology, China, Email: rajibdutta808@gmail.com

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Abstract

The pathophysiology and concept of degeneration in central nervous system is very complex and overwhelming at times. There is a complex mechanism which exists among different molecules in the cytoplasm of cell bodies of neurons, antegrade and retrograde axonal transport of cargoes and accumulation of certain substances and proteins which can influence the excitatory neurotransmitter like glutamate initiating the process of neurodegeneration. Neurons have extensive processes and communication between those processes and the cell body is crucial to neuronal function, viability and survival over time with progression of age. Researchers believe neurons are uniquely dependent on microtubule-based cargo transport. There is enough evidence to support that deficits in retrograde axonal transport contribute to pathogenesis in multiple neurodegenerative diseases. Cytoplasmic dynein and its regulation by Dynactin (DCTN1) is the major molecular motor cargo involved in autophagy, mitosis and neuronal cell survival. Mutation in dynactin gene located in 2p13.1,is indeed studied very extensively and is considered to be involved directly or indirectly to various conditions like Perry syndrome, familial and sporadic Amyotrophic lateral sclerosis, Hereditary spastic paraplegia, Spinocerebellar Ataxia (SCA-5), Huntingtons disease, Alzheimer's disease, Charcot marie tooth disease, Hereditary motor neuropathy 7B, prion disease, parkinson's disease, malformation of cortical development, polymicrogyria to name a few with exception of Multiple Sclerosis (MS).

Keywords: Dynein, Dynactin, DCTN1, Neurodegeneration.

Abbreviations: DCTN1-Dynactin, MS-Multiple Sclerosis, MND-Motor Neuron Disease, NDDs-Neurodegenerative Diseases, AD-Alzheimer's Disease, PD-Parkinson's Disease, HD-Huntingtons Disease, HSP-Hereditary Spastic Paraplegia, SCA-Spinocerebellar Ataxia, FTD-Frontotemporal Dementia, CD-Cytoplasmic Dynein, MAP1C-Methionine Aminopeptidase 1C, ATP-Adenosine Triphosphate, IFT-Intraflagellar Transport, BICD-Bicaudal D, RILP-Rab7-Interacting lysosome protein, PCT-1-Choline-Phosphate Cytidylyltransferase, TGN-Trans-Golgi Network, JNK-c-Jun N-terminal kinase, LIC-Light Intermediate Chain, HDAC-Histone Deacetylases, BDNF-Brain Derived Neurotropic Factor, PGC1α-Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha.

Introduction

Neurodegenerative Diseases (NDDs) come under certain group of pathological entity characterized by the degeneration of a subset of neurons. Once the degeneration process starts it either remains localized or spread to different parts of brain resulting in less or no communication among neurons. This degenerative phenotype covers several distinct events that include disappearance in dendritic compartments, cell bodies or axonal shrinking and over time decreasing communication across the nerve cells.

Role of excitatory neurotransmitters like glutamate should also be considered in the whole process. NDDs include pathologies such as AD, PD, HD, MND, HSP and SCA etc. It can either inherit or appear sporadically in non-previously affected families and generations. The socio-economic burden is strongly increasing worldwide with time, mostly because of its association with aging, the current increase in lifespan thus mechanically leading to increased frequencies of NDDs in the geriatric population.

The end point to all NDDs is the occurrence of neuronal degeneration accumulating over time. Symptoms of a number of NDDs are caused by loss of synaptic connections rather than loss of neuronal cell bodies themselves [1]. Different symptoms in different NDDs affecting different age group and ethnicity are caused by either nature or localization of the affected neurons i.e., degeneration might be widespread and very severe like in prion diseases or affect only a small neuronal population in a given location like basal ganglia dopaminergic neurons in PD or front temporal lobe in Front Temporal Dementia (FTD).

This initial nerve cell selectivity however remains relative during the starting of disease process and nothing can be said why one location of the brain more affected as compared to other parts. However it is seen in previous literatures that degeneration involves a number of other cell types and not a single cell type [2]. Common semiology exists between different NDDs. Commonest histopathological feature of NDDs is the presence of protein aggregates [3]. These aggregates might be intracellular or extracellular. The core biochemical composition of

protein aggregates guides the pathogenic mechanism involved in NDD [4,5]. Secondly neuronal degeneration is due to events both intrinsic and extrinsic to neurons and thirdly impairment of retrograde axonal transport. Exchange of cargoes between the axonal tip and neuronal cell body is called axonal transport. Role of cytoskeletal structures is very important when we consider transport across neurons either towards the plus or minus end.

Long distance transport is carried out on microtubules, while short distance is mediated by actin. Microtubules constitute the cytoskeletal tracks on which molecular motors are able to carry cargoes from the cell body to the synapse (anterograde axonal transport) or from the synapse to the cell body (retrograde axonal transport). Anterograde axonal transport is carried out by kinesin like motors, while retrograde axonal transport is performed mostly by a single motor, cytoplasmic dynein. There seems to be a race between kinesin and dynein as cargoes move opposite to each other.

Most of the studies have demonstrated that axonal transport machinery is impaired during the process of neurodegeneration. Stress induced (CDK5) Cyclin Dependent Kinase-5 activation disrupts axonal transport via Lis1/Ndel1/Dynein [6-8]. In this article, we will focus on one major cytoskeletal motor protein dynein, its structure, regulation and dysregulation which can lead to different types of NDDs. We will also discuss its role in retrograde axonal transport and as the molecular motor responsible for transport of misfolded proteins for their degradation and its clearance from cytoplasm.

Cytoplasmic Dynein

Structure

Cytoplasmic dynein is the most complex mammalian cytoskeletal motor protein. Dynein motors are very different in their structures, localizations and functions [9,10]. There are two molecular complexes called “cytoplasmic dynein” (CD1 and CD2). CD2 is mostly present in ciliated cells and is involved in intraflagellar transport in lower eukaryotes [11,12]. However, King a et al recently reported mutations in (CD2) complex which causes Short-Rib Thoracic Dystrophy Syndromes (SRTDs), characterized by impaired bone growth and life-threatening perinatal respiratory complications [13]. CD1 (dynein in this article) is expressed in most tissues, including brain, testis, lung, liver and kidney [14].

Dynein as a molecular motor is capable of moving cargo towards the minus-end of the microtubules i.e. from the periphery to the cell center, thus, they are called "minus-end directed motors". Dynein, at first named as MAP1C, was discovered in 1987 [15] and was initially identified as a component of microtubule preparations. Dynein was shown to possess ATP-hydrolyzing activity and microtubule translocation properties and to be able to produce force in a direction opposite to that observed for kinesin-1, suggesting that it constituted a retrograde motor [16,17]. However, literature has also reported ability of dynein to move cargoes using variable step sizes, but also lateral steps and processive runs toward both the minus- and plus-end of the microtubule surface [18,19].

Recently Ping Xie reported about the force dependence of the number of ATP molecules consumed per mechanical step, indicating that under no or low force the motors exhibit a tight chemo mechanical coupling and as the force increases the number of ATPs consumed per step increases greatly [20]. Cytoplasmic dynein is a large and complex molecule. Core of the enzyme consists of a dimer of two heavy chains (DYNC1H1) [21] each of which folds to form a motor domain composed of six AAA motifs, followed by a less well-characterized 7th domain, yielding a donut-shaped head with 7 distinct subdomains [22].These heads are the sites of ATP binding and force production, the microtubule binding site localizes to a stalk that projects from the head domain [23].

Mg^{2+}-free ATP regulates the processivity of native cytoplasmic dynein [24]. The N-terminal domain of the dynein heavy chain forms an extended stem, which dimerizes to form a two-headed molecule. These polypeptides are thought to function primarily in cargo association and regulation. Apart from the two heavy chains of 530 kD [25,26] that constitute the motors themselves, dynein is a multi- complex protein composed of a number of noncatalytic subunits, notably two intermediate chains of 74 kD and four light intermediate chains of 55 kD and a number of less characterized light chains such as LC8, Tctex1 or Rp3[27,28].

The tail domain of dynein heavy chain interacts with intermediate light and light chains to form the cargo-binding complex. A key assembly factor specifically required for the stability of axonal dynein heavy chains in cytoplasm is WDR92 and suggests that cytoplasmic/IFT dynein heavy chains use a distinct folding pathway [29]. The accessory proteins of the dynein complex are probably crucial in the cargo association, regulation selectivity of the motor [30]. Dynein light chain binding determines complex formation and posttranslational stability of the Bcl-2 family members BMF and BIM apoptotic activity [31].

Regulated associations of dynein with cargo may be mediated by rab proteins. Rabs are an extensive family of small GTPases that associate with specific membrane compartments in the cell [32]. Activated rab 6 recruits dynein to TGN derived vesicles via the proteins BICD or BICD2 [33], while rab7 and RILPLIP recruit dynein to lysosomes [34]. Thus, rab induced recruitment could provide specific and regulatable interactions between motor and cargo for a broad range of cellular transport functions. Activating adaptors such as BICD2 and Hook1 enhance the stability of the complex that dynein forms with its required activator dynactin, leading to highly processive motility toward the microtubule minus end. Furthermore, activating adaptors mediate specific interactions of the motor complex with cargos such as Rab6-positive vesicles or rib nucleoprotein particles for BICD2 and signaling endosomes for Hook1 [35].

Puja Goyal and colleagues reported the role of coiled-coil rRegistry shifts in the activation of human bicaudal D2 for dynein recruitment upon cargo binding. Recent report suggested three structural elements protruding from the motor domain-the linker, buttress, and stalk-together regulates directional tension-sensing. Dynein’s anisotropic response to directional tension is mediated by sliding of the coiled-coils of the stalk, and that coordinated conformational changes of dynein’s linker and buttress control this process [36]. The authors also demonstrated that the stalk coiled-coils assume a previously undescribed registry during dynein’s stepping cycle [37] .The role of the stalk in regulating motor activity and coupling conformational changes across the two halves of the AAA ring is also reported by Stefan Niekamp and colleagues [38].

Regulation

Dynein is associated with dynactin [39,40] another multi-protein complex with ten subunits including p150Glued, p135Glued, p62, p50 (dynamitin) and Arp1 [41]. Interaction of dynein and dynactin is through dynein intermediate chain and p150Glued [42]. Particularly the Arp1 subunit of dynactin binds to β-III spectrin a filamentous protein that is found on the cytosolic side of a number of intracellular vesicles [43]. DCTN1 is known to increase dynein processivity [44]. Dynein activity is modulated by a number of ubiquitous cofactors such as UNC-83 [45], LIS1-Ndel1-Nde1 and Bicaudal-D [46,47].

Dynein has been shown to interact with huntingtin and huntingtin-associated protein 1 [48] and Act mediated phosphorylation of huntingtin is able to promote anterograde transport through kinesin-1 recruitment, while dephosphorylating of huntingtin stimulates dynein dependent retrograde transport [49]. Two cyclin dependent kinases, CDK-5 and PCT-1 and the cyclin CCY-1 [50] have been shown to negatively regulate dynein in nematode model and the JNK kinase pathway might also be involved in the regulation of dynein [51].

Simon Bullock, et al., reported egalitarian as a selective RNA-binding protein, linking mRNA localization signals to the dynein motor and molecular strategies that are likely to be of general relevance for cargo transport by dynein [52]. Recent report suggested KIF1C and dynein/dynactin can exist in a complex scaffold by Hook3. Full-length Hook3 binds to and activates dynein/dynactin motility and may regulate bidirectional motility, promote motor recycling, or sequester the pool of available dynein/dynactin activating adaptors [53]. Sanchez et al demonstrated mechanistic insight into the polarization of cytoskeletal regulators and close coordination between microtubule and F-actin architecture at the Immunological Synapse (IS) [54].

Function

Dynein has a large variety of functions and is involved in a number of different cell processes. The most well documented function is the minus end-directed transport of membranous organelles [55]. In neurons, dynein is responsible for retrograde axonal transport [56]. Dynein is able to transport a large variety of cargoes such as mitochondria, proteins (neurofilaments, trophic factors like brain-derived neurotropic factor, RNA particles) [57]. Dynein also participates in endoplasmic reticulum membrane tubules organization [58], is required in vitro for the formation of endoplasmic reticulum networks [59], and for the centrosomal localization of the Golgi complex [60].

Dynein maintains the microtubule networks [61] and is involved in the lysomal trafficking [62], and in the vesicular transport from early to late endosomes [63]. Dynein is also involved in the clearance of protein aggregates since mutation in dynein impairs their autophagic clearance [64]. Dynein is required for mitosis since it was found on kinetochores [65], and drives them to the spindle poles [66,67]. Dynein is also able to drive lipid droplets [68] participates indirectly in their formation [69] and breakdown [70]. Richard B. Vallee and colleagues reported LIC1, through BicD2, is required for apical nuclear migration in neural progenitors.

In newborn neurons, specific roles exist for LIC1 in the multipolar to bipolar transition and glial-guided neuronal migration. In contrast, LIC2 contributes to a novel dynein role in the little-studied mode of migration which is known as terminal somal translocation. Together, they provided a novel insight into the LICs' unique functions during brain development and dynein regulation overall [71]. Regulation of in vivo dynein force production by CDK5 and 14-3-3ε and KIAA0528 dynein force adaptation can control the severity of lysosomal tug-of-wars among other intracellular transport functions involving high force [72].

Dysfunction

Numbers of dynein functions have been, directly or indirectly, linked with NDDs.

- Dysfunction in dynein transport was long associated with decreased retrograde axonal transport [73].
- Synaptogenesis and synaptic maintenance are largely driven by retrograde messengers [74].
- Neurotrophin retrograde signaling is completely dependent upon the formation of signaling endosomes carried to the cell body by dynein [75].
- Axonal injury activates a number of signaling events that lead to transport signal to the nucleus through dynein dependent processes [76,77].
- Dynein is critically involved in intracellular membranes trafficking it is required for endosomal and lysosomal transport [18,78]. Both dynein and endosomal transport are required for dendritic morphogenesis [79-81]. Dendritic morphogenesis is thought to be linked to dynein role in retrograde movement of neurofilaments [82].
- Disruption of endosomal trafficking might lead to abnormal autophagic vesicle trafficking [64,83]. For example, cholesterol sensing in cells requires endosomal trafficking and is dynein dependent [84,85].
- Dynein interacts with HDAC6 and this is required for the formation of aggresome a subcellular structure located at the microtubule organizing center and required for misfolded protein clearance [86,87].

Dynein dysfunction is generally considered as a pathogenic event in post-mitotic neurons. However, dynein is also crucial for mitosis and through its function in mitotic spindle orientation; dynein appears critically involved in neurogenesis [88,89]. Impairment of dynein function at adult age might thus also decrease neurogenesis and have an impact on cognition.

On contrary, motor neurons in zebra fish embryos and larvae depleted for dynactin 1a point toward a local role for this protein in stabilizing the neuromuscular synapses, impairing its function, without leading to motor neuron death, novel role for dynactin1 in ALS pathogenesis, where it acts cell-autonomously to promote motor neuron synapse stability independently of dynein-mediated axonal transport [90]. Immunolocalization of dynein, dynactin, and kinesin was seen in the cerebral tissue in traumatic brain injury in postmortem examination [91].

Discussion

Dynactin and bicaudal D regulate not only the function of dynein but also of kinesins [92,93]. In a similar way huntingtin modulates the activity of dynein and kinesin and also have transcriptional effects on BDNF expression and PGC1α co-activator function [94,95]. Besides regulation of intracellular transport, p150 Glued protein has been shown to act as a docking protein and has been recently suggested to affect gene transcription through direct modulation of transcription factors [96,97].

In this respect, it is striking to note that dynein heterozygous mice appeared grossly normal while a point mutation on a single dynein heavy chain allele is sufficient to lead to a number of neurologic and peripheral phenotypes suggesting that the mutant allele possess a toxic gain of function over at least one crucial function for dynein in neuronal physiology [98]. Here again, genetic deletion of dynein in neurons of interest might show the dose dependency of neuronal survival to dynein motor activity.

Matthew G Marzo and colleagues recently established yeast as a medium-throughput model system that can be used to assess the molecular basis for dysfunction of disease-correlated dynein mutants [99]. Since the discovery of dynein, almost 25 years ago, studies has mostly demonstrated that this molecular motor might play a key role in neurodegenerative diseases. Indeed, a number of cellular processes in our body are almost entirely dynein-dependent.

Moreover a number of dynein interactors or regulators are mutant in various neurodegenerative diseases, clearly showing that the motor activity of dynein is certainly critical for neuronal survival. Direct proofs of involvement of dynein motor itself in NDDs are largely lacking. This lack of evidence might well be due to the obligate need of dynein for embryonic development. It remains unknown whether the motor activity of dynein is rate-limiting in neuronal survival or whether it is rather the quality of the material transported that bears any importance.

Conclusion

Dynein as a cytoskeletal molecular motor plays a key role in neurodegenerative diseases. Indeed, a number of cellular processes are dependent on dynein-dynactin motor complex like retrograde axonal transport of neurotrophic factors, injury signaling, misfolded protein

degradation, endosomal and lysosomal trafficking. Lot of published studies has evidence about role of dynein, however , currently we have only indirect evidence, mostly based on dynamitin overexpression or on overexpression of mutant P150 Glued or other mutant interactors of dynein.MS which is a degenerative process was not associated with dynactin gene mutation. So, more studies are required at molecular level to understand the complexity of molecular motor pathomechanisms and interactions involved in degeneration of neurons.

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Search strategy

We identified relevant full articles in English by searching PubMed with no language restrictions for articles published till October, 2019 and reference lists from relevant articles. We used the search terms: “dynein”, “dynactin”, “DCTN1”, “neurodegeneration”, for this article. We included only references published related to the topic plus few hand searched articles from other databases as accepted manuscripts. The final reference list was made on the basis of relevance to the theme of this review.

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