Dynein: One Motor, Multiple Neurodegenerative Diseases

Cytoplasmic dynein 1 (hereafter referred to as dynein) is a 1.6 MDa multi-protein complex that serves as the primary ATP-hydrolyzing motor responsible for retrograde axonal transport along microtubules (MTs) in eukaryotic cells (Fig. 1A). Additionally, dynein is essential for many other cellular processes, including mitochondrial movement, endosomal and lysosomal trafficking, transporting mis-folded proteins bound for degradation, nuclear positioning, and mitosis 1-3 (Fig. 2).

The dynein multi-protein complex consists of two ~530 kDa heavy chains that homodimerize along with multiple intermediate, light-intermediate, and light chains (Fig. 1A). The homodimer heavy chain heads are ATPases which provide the energy for movement along the MTs. Binding of the dynein complex to cargo and dynein’s processivity is dependent upon dynein’s own-present binding protein dynactin1-3 (Fig. 1B) and specific adaptor proteins such as presenilin, LIS1, NUDEL, MuMA, Miro, Milton, BimL, and BimEL1-3.

Mutations in dynein (or dynactin) underlie some neurodegenerative diseases in humans, manifested by axonal transport defects, neuron degeneration, locomotor abnormalities, and/or other neural deficits4-8 (Figs. 1A, 1B). Likewise, animals modeling dynein dysfunction or mutations display motor and neural impairments similar to these human patients3,9-11 (Fig. 1A). The observed neuron loss, protein aggregation, and/or axonal transport deficits are all pathophysiological hallmarks of neurodegeneration, thus motivating further examination of dynein’s role(s) in various neurodegenerative diseases (Fig. 2).

Neurodegenerative Diseases

Researchers have examined the role dynein has in neurodegenerative diseases of the basal ganglia, dementias such as Alzheimer’s disease (AD), and diseases of motor neurons that include amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and spinocerebellar atrophy (SCA)2. Research has identified at least three dynein mutants (Legs at odd angles [Loa], Cramping1, and Sprawling) that affect dynein’s function, leading to motor and/or sensory neuron loss and impaired motor behavior in mice expressing these dynein mutants3,10,12-14 (Fig. 1A). Of these mutants, the Loa mutation (F580Y point mutation in dynein heavy chain) alters dynein’s affinity for dynactin as well as the expression, assembly, and interaction of the protein subunits that compose the dynein complex15. The Loa mutation has been implicated in ALS with reports that mice modeling this disease via overexpression of the Cu/Zn superoxide dismutase enzyme (SOD1) have delayed motor neuron death and an extended lifespan when crossed with Loa+.

Figure 1: Domains of cytoplasmic dynein heavy chain (A) and dynactin p150Glued (B). (A) Dynein domains include the positions of mouse and human mutations as well as the buttress (light blue), stalk + MT binding domains (MTBD) (green), 6 AAA ATPase domains (blue), and intra-dynein complex binding domains (turquoise). Human mutations are grouped by color to indicate possible phenotypic similarities (yellow has only motor deficits, while all others have motor deficits and brain malformations [green, blue, red], and intellectual deficits [green, orange, blue, red], and epilepsy [green]). (B) Dynactin p150Glued domains include the coiled-coil (CC) and dynein and MT binding domains and the positions of human mutations (all in MT binding domain). Adapted from reference 3 (A) or 20 (B). Scales indicate amino acid number.
In vitro, this dynein mutation induces striatal atrophy and alters the SOD1 mutant mice3. The mechanism(s) mediating and storage, has been linked to Huntington's disease using an mouse model13.

In vivo, (Y1055C) which results in abnormalities in motor behavior as well as fat metabolism reduced retrograde transport of cell stress-associated proteins, altered expression senile plaques19. Thus, dynein-mediated changes in endocytosis appear to play a key role in early AD pathology.

Conclusions

Although the various studies cited above strongly implicate dynein dysfunction in the pathophysiology of several neurodegenerative diseases, its exact role remains unresolved given the indirect (i.e., correlational) nature of most of the studies. Thus, additional research into the role of dynein and its associated protein complexes are necessary to unravel the role this retrograde motor has in normal and disease functions in the central nervous system. At Cytoskeleton, we offer custom-purified cytoplasmic dynein and are developing dynein ATPase assays that can be used to identify inhibitors and enhancers of dynein function. Contact us at tservice@cytoskeleton.com for more information about any of our dynein products.

References