Mutant Dynamin 2 and Neuromuscular Disorders

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The DNM2 gene located on human chromosome 19 encodes for dynamin 2, a ubiquitously expressed protein. As observed for other classical dynamins, the dynamin 2 protein features an amino terminal GTPase domain responsible for GTP hydrolysis, a middle domain (MD) involved in its self-assembly; a pleckstrin homology domain (PH), which binds with specific phospholipids; a GTPase effector domain (GED) that participates in self-assembly and GTPase activity regulation; and a C-terminal proline-rich domain (PRD) that binds to SH3 domain-containing binding partners (Praefcke & McMahon, 2004). Functionally, dynamin 2 has been shown to associate with nascent clathrin-coated pits in a helical fashion, and induce "pinching off" or release of vesicles in a GTP-depending dependant manner. Accordingly, it appears to be involved in clathrin-independent endocytosis during the formation of phagosomes and caeolae as well as in micro- and macropinocytosis. Dynamin 2 also localizes to the Golgi apparatus, where it may participate in the vesicular sorting machinery by regulating the trafficking of vesicles from the trans-Golgi network (TGN). The binding of DNM2 to actin-binding proteins including Abp1, and cortactin, which is an important element of the clathrin-mediated endocytosis machinery, highlights the relevant role that DNM2 plays in regulating actin-based endocytosis, vesicle formation, and trafficking.

Based on the known cellular functions of dynamin 2 is involved on, it is not surprising that mutations in this protein could result in disease (Durieux et al., 2010). Indeed, it has lead to centronuclear myopathy (CNM), a congenital myopathy, as well as two forms of Charcot-Marie-Tooth (CMT), an autosomal dominant peripheral neuropathy. To date, many DNM2 mutations have been reported that result in CNM (Susman et al., 2010). Histopathologically, CNM is

characterized by centrally located nuclei in muscle fibers. CNM manifests as a progressively deteriorating disorder featuring delayed motor milestones; facial and generalized muscle weakness, which can results in inability to run in childhood; ptosis (or "drooping eyelid"); and ophthalmoplegia. Some patients also develop pes cavus (or raised arch) even before symptomatic muscle weakness presents (Susman et al., 2010). CNM patients with DNM2 mutations showed a mild axonal neuropathy without reduction in motor conduction velocities (NCV). Clinical severity ranges from typical mild forms to very severe forms showing onset at infancy. The molecular basis for such variability in severity of symptoms is unknown.

Charcot-Marie-Tooth (CMT) disease is a set of relatively common progressive genetic peripheral neurological disorders with five classes linked to more than 40 genes (Patzko et al., 2011). CMT is characterized by muscular weakness and atrophy, pes cavus foot deformity, depressed tendon reflexes, sensory loss and prominent axonopathy (Niemann et al., 2006). In some reported cases, axonal neuropathy is also associated with asymptomatic neutropenia (abnormally low number of neutrophils) and early-onset cataracts. Several point mutations in DNM2 that result in CMT have been reported (Durieux et al., 2010). Intriguingly, some mutations result in Charcot-Marie-Tooth type 2 (CMT2), whereas others lead to a variation of CMT known as dominant intermediate Charcot-Marie-Tooth (DI-CMT). Electrophysiologic studies on some dynamin-2-associated CMT patients show intermediate or axonal motor median NCV at or near normal values (≥45m/s), while other mutations that cause DI-CMT show NCVs ranging from normal to almost 50% reduced. The majority of mutations in DNM2 leading to CMT are located in the PH domain, with while two other mutations are mapped on the MD and the PRD.

The ubiquitous tissue expression of dynamin 2 and the multiple cellular functions proposed for this protein raised many important questions on the pathogenic mechanisms underlying CMT and CNN. Why are specific cell types affected? How do different mutations (sometimes located immediately adjacent to each other) in the same gene result in different diseases? A molecular basis underlying the increased vulnerability of selected cell types to DMN2 mutations is currently unknown, but likely results from alterations in the functional specializations of these neuronal cell types. In this regard, it has been proposed that DNM2 mutations may affect protein trafficking and axonal transport of vital material for the axons (Patzko et al., 2011) (see Ch. 8). It is unclear why deficits in axonal transport induced by different mutant versions of dynamin 2 would differentially affect muscle cells and sensory/motor neurons, but differences in the composition, amounts, and regulation of axonal transport in these cell types have all been documented.

References

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