A link between spastin and lipid metabolism

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SPAST, encoding spastin, is the most commonly mutated gene in patients affected by autosomal dominant hereditary spastic paraplegia (HSP). Spastin is a conserved microtubule (MT)-severing protein, involved in several processes that require rearrangement of the cytoskeleton and membrane remodeling. Spastin function has been implicated in neurite branching, axonal growth, midbody abscission, and endosome tubulation. Two isoforms of spastin (spastin-M1 and spastin-M87) are synthesized from alternative initiation codons located in the first exon of the gene. We now show that in mammalian cells spastin-M1 can sort from the endoplasmic reticulum to pre- and mature lipid droplets (LDs). We have identified the N-terminal hydrophobic domain to be necessary and sufficient for recruitment to LDs. Mutation of arginine 65 to glycine in this region abolished LD targeting. Increased levels of spastin-M1 expression lead to reduced number of bigger LDs, while expression of a spastin mutant unable to bind and sever MTs causes clustering of LDs. The role of spastin in LD formation and lipid metabolism is evolutionary conserved. Downregulation of Dspastin and expression of a dominant-negative variant decrease LD number in *Drosophila* nerves and skeletal muscle, while Dspastin overexpression leads to an opposite phenotype. Ubiquitous downregulation or upregulation of Dspastin levels affects triacylglycerol levels in a consistent fashion. Moreover, we found reduced amount of fat stores in intestinal cells of worms when the *spas-1* homologue was either depleted or deleted. Taken together, our data uncovers a role of spastin in LD metabolism and suggest that dysfunction of LDs in axons may contribute to the pathogenesis of HSP.