Dynamin 2 mutations associated with human diseases impair clathrin-mediated receptor endocytosis

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Dynamin 2 (DNM2) is a large GTPase involved in the release of nascent vesicles during endocytosis and intracellular membrane trafficking. Distinct DNM2 mutations, affecting the middle domain (MD) and the Pleckstrin homology domain (PH), have been identified in autosomal dominant centronuclear myopathy (CNM) and in the intermediate and axonal forms of the Charcot-Marie-Tooth peripheral neuropathy (CMT). We report here the first CNM mutation (c.1948G>A, p.E650K) in the DNM2 GTPase effector domain (GED), leading to a slowly progressive moderate myopathy. COS7 cells transfected with DNM2 constructs harboring a disease-associated mutation in MD, PH, or GED show a reduced uptake of transferrin and low-density lipoprotein (LDL) complex, two markers of clathrin-mediated receptor endocytosis. A decrease in clathrin-mediated endocytosis was also identified in skin fibroblasts from one CNM patient. We studied the impact of DNM2 mutant overexpression on epidermal growth factor (EGF)-induced extrac