ABSTRACT

Membrane remodeling is required for dynamic cellular processes such as cell division, polarization and motility. BAR domain proteins and dynamins are key molecules in membrane remodeling that work together for membrane deformation and fission. In striated muscles, sarcolemmal invaginations termed T-tubules are required for excitation-contraction coupling. *BIN1* and *DNM2*, which encode a BAR domain protein BIN1 and dynamin 2, respectively, have been reported to be causative genes of centronuclear myopathy (CNM), a hereditary degenerative disease of skeletal muscle, and deformation of T-tubules is often observed in the CNM patients. However, it remains unclear how BIN1 and dynamin 2 are implicated in T-tubule biogenesis, and how mutations in these molecules cause CNM to develop.

Here, using an *in cellulo* reconstitution assay, we demonstrate that dynamin 2 is required for stabilization of membranous structures equivalent to T-tubules. GTPase activity of wild type dynamin 2 is suppressed through interaction with BIN1, whereas that of the disease-associated mutant dynamin 2 remains active due to lack of the BIN1-mediated regulation thus causing aberrant membrane remodeling. Finally, we show that *in cellulo* aberrant membrane remodeling by mutant dynamin 2 variants is correlated with their enhanced membrane fission activities, and the results can explain severity of the symptoms in patients. Thus, this study provides molecular insights into dysregulated membrane remodeling triggering the pathogenesis of *DNM2*-related centronuclear myopathy.