Impaired malin expression and interaction with partner proteins in Lafora disease

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AIM & METHODS

Lafora disease (LD) is characterized by the presence of Lafora Bodies (LB), which are formed from the aggregation of abnormally shaped glycogen molecules. LD arises from mutations in EPM2A (laforin) or EPM2B (malin). Laforin and malin are proteins that regulate the shape of glycogen. Laforin binds to glycogen and acts as a scaffold for other proteins and can remove phosphate from glycogen. Malin is an E3-ubiquitin ligase: it marks proteins to be broken down or transported, preventing glycogen accumulation. However, the lack of tools to detect malin in mice make it difficult to determine which proteins it interacts with and its role in preventing Lafora disease. To overcome this challenge, researchers created malin-myc mice, giving malin a detectable marker. Researchers can now measure malin in mouse tissue samples to identify the proteins that interact with malin.

RESULTS

Malin binds to laforin and is stabilized by forming a malin-laforin complex capable of interacting with glycogen and other proteins involved in glycogen breakdown. These proteins include Glycogen debranching enzyme (AGL), which cuts glycogen branches, and Glycogen phosphorylase (PYGM), which breaks down glycogen even further to produce glucose. Additionally, the data suggest malin and laforin could work together to interact with Glycogen synthase (GYS1), which is responsible for storing glucose into glycogen, and Glycogenin (GYG1), which is responsible for starting the process of glycogen synthesis. However the mechanism for these interactions needs more study.

CONCLUSION

Through the malin-myc mice mouse model, researchers can understand how malin influences LD development through its interactions with laforin and other glycogen metabolism proteins, revealing potential therapeutic targets.