Research Paper

Lack of p62 Impairs Glycogen Aggregation and Exacerbates Pathology in a Mouse Model of Myoclonic Epilepsy of Lafora

AUTHORS

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THE ACCUMULATION OF GLYCOGEN AGGREGATES IS THE CAUSE OF LAFORA DISEASE

Glycogen is a glucose polymer that is used to store energy in animal cells. Several groups, including us, have demonstrated that the cause of Lafora disease is the accumulation in the brain of glycogen aggregates known as Lafora bodies. Glycogen in Lafora bodies has an abnormal structure, which causes it to be insoluble, accumulate, and have a neurotoxic effect. Blocking or reducing brain glycogen synthesis in Lafora disease mouse models prevents the progression of the disease. This has identified glycogen synthesis as a promising target for the treatment of the disease.

The mechanisms that drive the formation and clearance of Lafora bodies have not been identified yet. Furthermore, it remains to be determined whether the sequestration of abnormal glycogen into Lafora bodies is protective (to minimize the toxic consequences of glycogen accumulation) or deleterious (Lafora bodies themselves being the toxic agent). Clarifying these points is essential for fully understanding the disease and finding new possible treatments.

P62 AND AUTOPHAGY

In addition to glycogen, Lafora bodies also contain a number of proteins, among them one called p62. This protein participates in a cellular process called autophagy by which the cells remove unnecessary or dysfunctional components. Defects in autophagy have been linked to several human diseases, including neurodegeneration. Thus, interest in modulating autophagy as a potential treatment for these diseases is growing rapidly.

In order to understand the role of p62 in the formation of Lafora bodies and its participation in the pathology of Lafora disease, we generated a mouse model of the disease lacking p62.

WHAT WE HAVE DISCOVERED ABOUT P62 AND LAFORA DISEASE

Our results show that p62 participates in the aggregation of abnormal glycogen into Lafora bodies. In the absence of p62, Lafora bodies are not properly formed and the toxic consequences of the accumulation of abnormal glycogen are worsened.

Our results shed light on the mechanisms that drive the formation of Lafora bodies and suggest that the generation of these bodies is a protective mechanism from the cells to minimize the toxic consequences of the accumulation of abnormal glycogen in the brain.

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