Lafora Epilepsy - Basic mechanisms to therapy

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6a

Of all the severe and intractable epilepsies, Lafora disease (LD) is among the most severe. LD is a fatal, recessive neurodegenerative epilepsy that presents as in the 2nd decade of life. A biochemical hallmark of LD is the accumulation of cytoplasmic, hyperphosphorylated, water- insoluble glycogen-like particles called Lafora bodies (LBs). These inclusions occur throughout the body, but the disease itself results from acute neurotoxicity due to the sensitivity of neurons to energy perturbations. LD results from mutations in either of the genes encoding laforin, a glycogen phosphatase, or malin, an E3 ubiquitin ligase. Identification of the genetic basis for LD has ushered in a new era in our understanding of the cause of LD, leading to rapid progress in the field and opening up the possibility of a cure.

Mutations in either the malin or laforin gene cause glycogen to transform into malformed (starch- like), aggregated accumulations called Lafora bodies (LBs). LBs overtake the cytoplasm of dendrites, and drive the progressive refractory seizure disorder. It is now understood that glycogen synthesis must be tightly controlled in neurons because overexpression leads to neuronal apoptosis. LD offers a unique window into how neurons respond to perturbations of glycogen stores. Also, it is becoming clear that multiple cellular insults arise that contribute to the cascade of clinical sequela of disease progression that ultimately result in death. LD neurons show defects in protein homeostasis including increase in misfolded proteins, defects in protein degradation, ER- stress, oxidative stress, and eventually undergo apoptosis. These defective pathways provide additional therapeutic options.

Collectively, data from the PIs associated with this poster definitively demonstrate that reversal of abberant glycogen accumulation eliminates LB formation and cures LD in mouse models. Thus, we are uniquely positioned to realize the dream of personalized diagnoses coupled with treatments to cure LD patients. To that end, we are establishing the Lafora Epilepsy Cure Initiative (LECI) Center. The leading LD clinical and research groups from around the world have united to form the LECI Center, which will: 1) Coordinate synergistic LECI Center activities, 2) Develop diagnostics and therapies, and 3) Test therapies and cures.

Reflecting the complexity of the brain, intractable epilepsy, which occurs in over 30% of patients, comprises multiple different pathologies. Because of this understanding and treating intractability more broadly will benefit from, and ultimately requires, detailed understanding of its component diseases. LD offers a unique window into both normal neuronal glycogen metabolism and epileptic disease implications when the process is perturbed. Our multi-disciplinary approaches to target the disease at multiple levels will be an exemplar for the treatment of other severe epileptic and neurodegenerative diseases.