Targeting miRNAs as a novel therapy for STXBP1 epileptic encephalopathy

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Abstract

STXBP1 epileptic encephalopathy is caused by mutations in the STXBP1 gene. In neurons, STXBP1 regulates the release of neurotransmitters from synaptic vesicles. Reducing the amount of functional STXBP1 protein impairs neurotransmitter release, which in turn leads to uncontrolled neuronal activation, epilepsy, intellectual disability and motor impairments. In cases of STXBP1 epileptic encephalopathy, we have developed a novel gene therapy approach using cell-aggregate mediated delivery of miRNA precursors.

Results: Antagonism

Inhibition of miR-218 or miR-424 with antagonoRs increase STXBP1 mRNA and protein

Results: SBOS

RNA-based therapeutic technology: Steric Blocking Oligonucleotides (SBOS)

SBOS targeting the 3'UTR of STXBP1 increase STXBP1 protein expression in SHSY-5Y cells (preliminary)

Background

What is STXBP1?

- Synaptic Binding Protein 1 (also known as Munc18-1)
- Located on chromosome 5, coding region 1.74 kb
- Protein size: ~945 amino acids, ~106 kDa
- Forms a complex with the SNARE proteins

STXBP1 Encephalopathy

- Complex neurodevelopmental disorder first described in 2008
- 1:60,000 to 1:100,000 (also known as Munc18-1 haploinsufficiency)
- Clinical Features:
  - Severe microcephaly or mental retardation (almost all are non-verbal)
  - Epilepsy (seizures control in ~50% of patients)
  - Varying levels of autism features and motor retardation (45% learn to walk assisted, hypotonia, abcs, tremor commonly seen)
  - Brain MRI normal in ~50% while cerebral atrophy, hypomyelination, frequent age-related findings

Conclusions and Future Directions

- We have identified that delivering STXBP1 is a subject of mRNA-mediated expression by miR-218 or miR-424 in a human neuronal cell line.
- We developed a synthetic gene therapy for high throughput screening of compounds designed to prevent miR-mediated expression of STXBP1.

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