

2004 Workshop - Type I

Gene therapy in von Gierke's disease (GSD-Ia)

By Dwight Koeberl, Div Medical Genetics/Dept Pediatrics, Duke University Medical Center

GSD-Ia, von Gierke's disease

Recessive inheritance of glucose-6-phosphatase (G6Pase) deficiency

Life-threatening hypoglycemia, seizures

Dietary therapy with uncooked cornstarch ameliorates hypoglycemia, and improves growth and renal failure

However, long-term complications are not prevented by dietary therapy

Genetics of GSD-Ia

A few point mutations underlying GSD-Ia, R83C is most common

1 in 100,000 live births world-wide

As common as 1 in 5,000 live births in New York City*

Early diagnosis and referral to GSD centers is the norm

*Dr. David Weinstein, Harvard Medical School

Impact of GSD-Ia

Long-term complications are not prevented by current therapy

Health costs are considerable

Long-term complications with current therapy

Recurrent hypoglycemia* (55%)

Progressive renal failure* (30%)

Osteoporosis* (frequent)

Gout* (60%)

Hyperlipidemia* (frequent)

Anemia of chronic disease (50%)

Hepatic adenomas* (16-50%)

Short stature* (35%)

Delayed puberty* (56%)

Bleeding tendency (25%)

Diarrhea* (35%) – cornstarch therapy?

How would gene therapy be efficacious in GSD-Ia?

The presence of 10% of normal G6Pase levels most likely would prevent hypoglycemia

Liver transplantation has corrected the biochemical abnormalities in GSD-Ia, indicating that correction of G6Pase deficiency in the liver would be therapeutic

Achieving at least 10% of normal G6Pase activity in the liver is feasible

Animal models for GSD-Ia

Naturally occurring canine model

Engineered G6Pase-knockout (G6Pase-KO) mouse

Canine GSD-Ia

Maltese dogs are commonly carriers for GSD-Ia

A colony of GSD-Ia carriers was established at NCSU College of Veterinary Medicine

Maltese x Beagles = Malteagles

Autosomal recessively inherited, 25% of offspring are affected

Correction of GSD-Ia with gene therapy

AAV vectors for delivery of G6Pase *in vivo*

Gene therapy with AAV vectors in GSD-Ia?

AAV vectors deliver introduced genes to liver, followed by long-term gene expression

AAV infection not associated with any disease in human
Minimal immune response to transduced cells, and no associated hepatotoxicity
8 serotypes of AAV; AAV8 features improved tropism for liver
G6Pase-KO mice as a model for GSD-Ia

Phenotype of G6Pase-KO mice closely resembles human and canine GSD-Ia

Hepatomegaly and growth failure
Hypoglycemia and hypercholesterolemia; however, no lactic acidemia in G6Pase-KO mice
Nonetheless, >85% mortality by 3 weeks of age if untreated by glucose infusions; don't survive past weaning

Will alternative AAV serotypes provide efficacy in GSD-Ia?

Package the AAV vector as AAV8 (AAV2/8 vector)
Inject the AAV2/8 vector in GSD-Ia mice
Monitor mice for correction of hypoglycemia

Mortality in G6Pase-KO (-/-) mice

Very poor survival related to hypoglycemia from birth
3 times/day glucose injections sustained the affected mice until weaning*
Schedule is hard to maintain
We chose to administer AAV vector early, forego glucose injections and administered:
IH, vs.
IH + IV, vs.
Hi-dose IH
*Sun MS et al. Hum Mol Genet 2003; 11:2155-2164.

Intravenous AAV2/8 vector during mid-infancy

Most patients with GSD-Ia present at 6 months of age with hypoglycemia, seizures, and hepatomegaly
To develop pre-clinical data
2x/day glucose injections to support affected mice until 2 weeks of age
Administer AAV2/8 vector intravenously
Monitor glucose during fasting to demonstrate correction of hypoglycemia
Blood glucose during fasting following AAV2/8 administration
Blood glucose during fasting following AAV2/8 administration

Conclusions: AAV vector in G6Pase-KO mice

Developed an AAV2/8 vector for GSD-Ia
G6Pase promoter to drive regulated G6Pase expression
Administered the AAV2/8 vector:
Prolonged survival
Improved growth
Corrected glycogen storage in liver

Conclusions

Enhanced efficacy by intravenous AAV2/8 administration in 2 week-old GSD-Ia mice
Normal blood glucose during fasting, an important clinical outcome measure in GSD-Ia
Predict normal life expectancy with this protocol
Complete biochemical correction
Lack of early demise
Normal G6Pase level in liver