Successful dietary treatment in CDG and outlook for future therapies

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Glycosylation is a step-wise metabolic process

Sugar by sugar: building the “glycan” chain
Glycosylation
Abnormal glycosylation
How can we develop new dietary therapies in CDG?

1. Diagnosis
   - Diagnosis of a disease with a glycosylation defect
   - Understand the biochemical mechanisms

2. Therapy
   - Is dietary therapy possible?
   - Is it safe?
Biochemical testing in blood to diagnose congenital disorders of glycosylation.

Barcode for disease

Control  MGAT2  B4GALT1  SLC35A1  COG7  ATP6V0A2  HUS
Glycosylation staining in cells

Healthy (control) skin cells in culture
Sugar activation is essential for sugar chain synthesis.
Sugar activation is essential for sugar chain synthesis.
Abnormal glycosylation in CDG cells

Immune histochemistry
Skin biopsy cells grown in culture media and stained for glycosylation
Mannose feeding restores glycosylation in MPI-CDG

+ 0.75mM Mannose

Before mannose

After mannose
MPI-CDG (CDG Ib)

Liver disease
Bleeding
Diarrhea

Mannose 1 g/kg/day (iv or oral)
Clinical mannose therapy in MPI-CDG

Mannose 1 g/kg/day (iv or oral)

Significant improvement of laboratory results but slow progression of liver fibrosis led to the first two cases of successful liver transplantation
Discovery of a new, treatable type of CDG

Muscle pain
Low blood sugar
Bleeding risk
Hormonal disturbance
Heart disease
Normal intelligence!

Diagnosis in blood:
1. Glycosylation screening
2. Enzyme measurement
3. Protein assay (Western blot)
Screening for abnormal glycosylation in blood

ABNORMAL “barcode”
Sugar activation is essential for sugar chain synthesis.

- Activated glucose
- Activated mannose

**PGM1-CDG**
PGM1-CDG

Hypoglycemia
Heart disease
Bleeding
Hormone problems

Galactose 1 g/kg/day (iv or oral)
Galactose feeding improves glycosylation in PGM1-CDG

+ 0.75mM Galactose

Before galactose

After galactose
Coagulation and anticoagulation factors improve in patients rapidly.
Discovery of a new, treatable type of CDG

Muscle pain: decreases
Low blood sugar: improves
Bleeding risk: decreases
Hormonal disturbance normalizes
Heart disease: no effect
Measuring the PGM1 protein in patients

Western blot

Galactose increases PGM1 level

Control protein
Increase in gene expression by sugar therapy

- Several CDG genes show increase in gene expression and protein expression on galactose therapy

- Which metabolite has this effect, needs to be further studied

- Chaperon therapy can increase protein expression and improve glycosylation in different types of CDG I
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