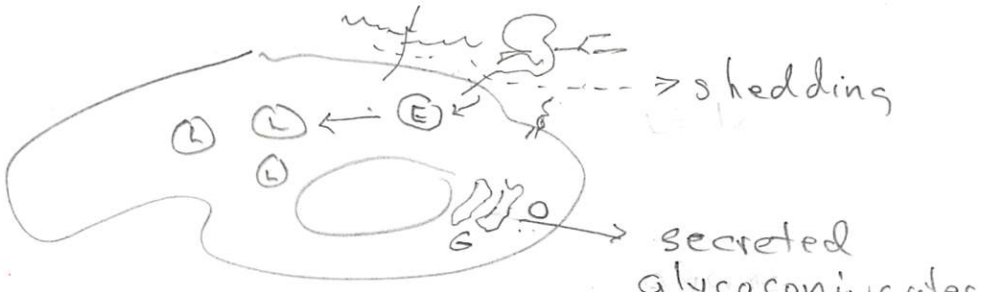
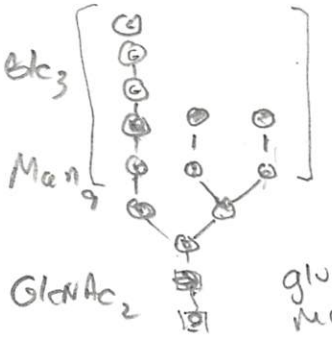
Where do glycans go to die? Lecture 13

Glycoconjugates and glycans turnover



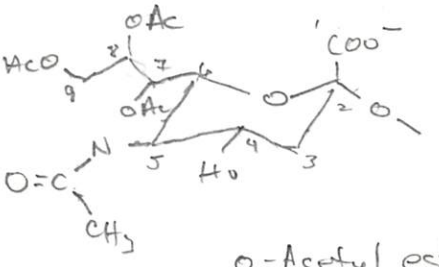
L = lysosomes
E = Endosomes
G = Golgi

① Processing during biosynthesis
- ✓ Glc/Man in N-linked glycans
- ✓ endosulfatases act on heparan sulfate at plasma membrane
- ✓ esterase(s) act on sialic acid acetyl esters



glucosidases
mannosidases

Sulfs

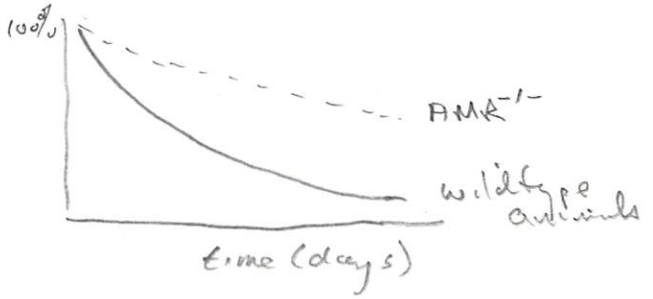


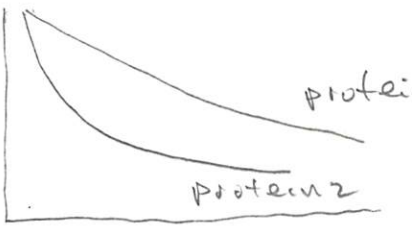
O-Acetyl esterases

- ✓ O-GlcNAc
- ✓ peptidoglycan / chitin – autolysins required for cell division / expansion
- ✓ pectinases in plants

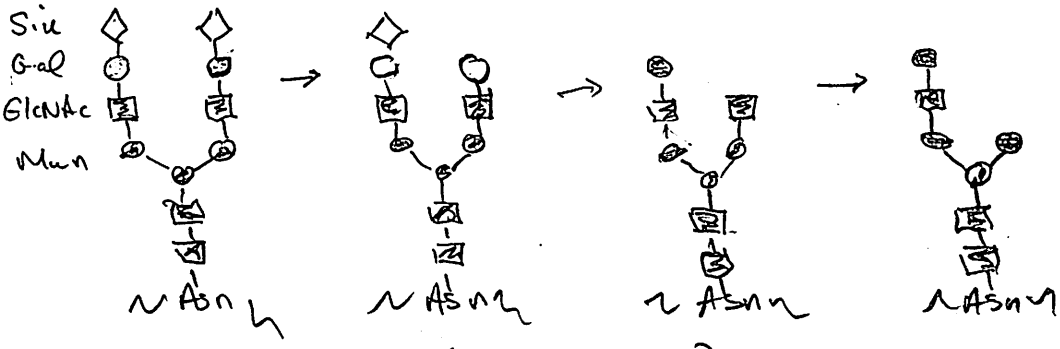
② Protein aging and turnover – terminal sugars turnover faster than sugars toward the reducing end

- Inject biotin-NHS ; Slide 1





- Endogenous glycosidases
  Sialidases (Neu1, Neu3), β-galactosidase, β-hexosaminidase



- basal rate varies – Why?
- Endocytic lectins mediate clearance
  - ASGR (hepatocytes) - Gal terminated
  - MMR (macrophages) - Man "
  - Integrin αM (Leukocytes) - GlcNAc "

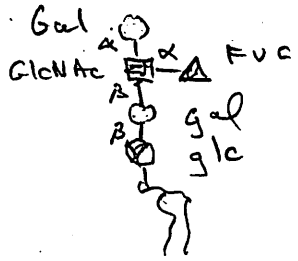
  } add turnover in ASGR-/- mice to figure

- EPO and other cytokines cleared in kidney based on size
  - 3 Sia terminated N-glycans
    1 Sia " O-glycan
    } Half life in blood affected by degree of sialylation
  - Addition of N-glycan can greatly increase t½

(3) Lysosomal Turnover

~60 soluble hydrolases, generally low pH optima (4.5–5.5)
- endolytic
- exolytic (common)
- sulfatases

- Commonly work from NRE



α-fucosidase
α-galactosidase
β-hexosaminidase
β-galactosidase
} might be cleaved in other degradative pathways

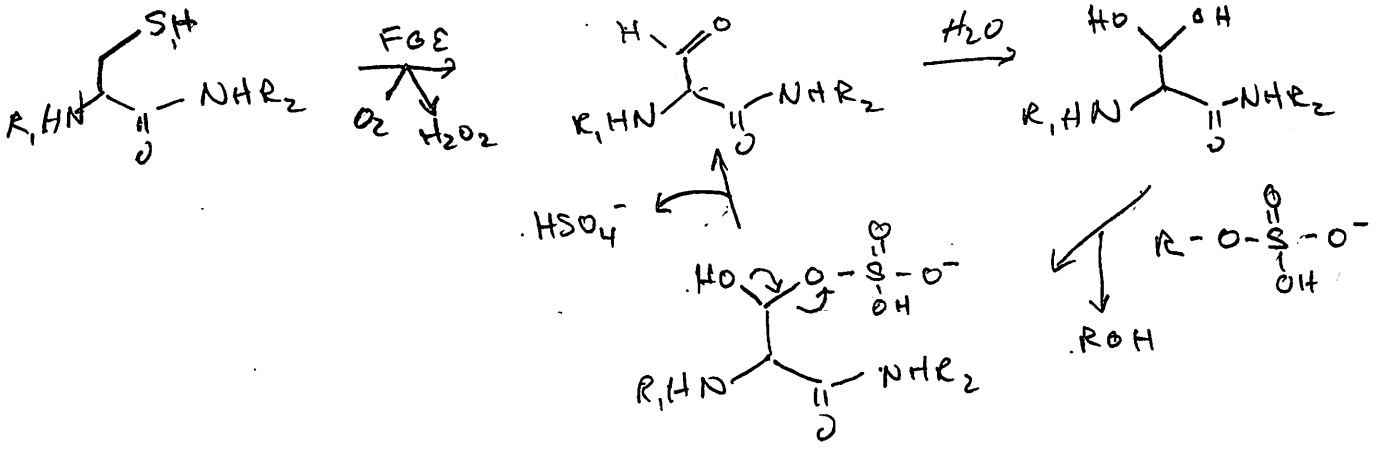
glucocerebrosidase → unique (Gaucher)

- other unique enzymes needed to remove aglycone:

(Krabbe) ↓ galacto-cerebrosidase → Gal + ceramide
↓ glycosylasparaginase → glycosylamine + Asp
↓ chitobiase GlcNAcβ1,4 GlcNAc-Asn
(Schindler) ↓ α N-acetylgalactosaminidase - GalNAcα-O-Ser

- Saposins - "liftases"
  - glycolipids form complexes with saposins to partially expose glycan for degradation

- Sulfatases
  Generally, there are no conserved glycosidase catalytic domains
  Sulfatases have a signature
  Cysteine in active site $\xrightarrow[FGE]{}$ Formylglycine



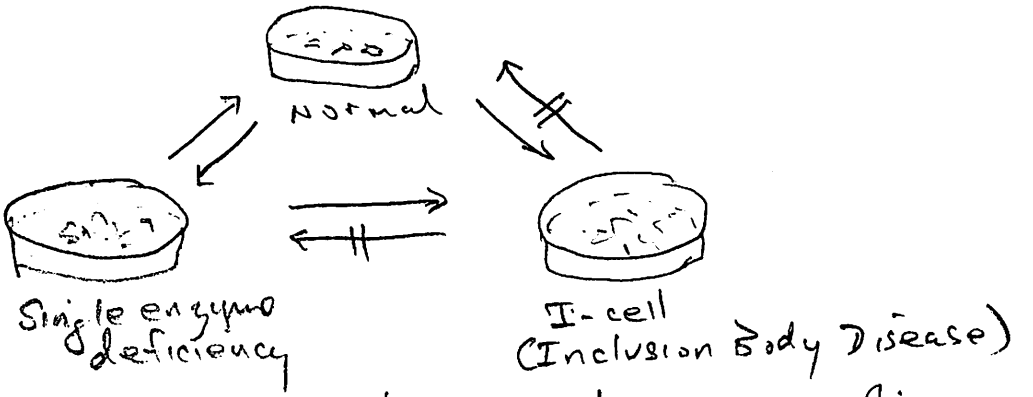
- Overall:
  Monosaccharides, Sulfate, phosphate, sphingosine } recycles or oxidative metabolism
  ↓ requires lysosomal transporters

(4) Lysosomal Storage Disorders (LSD)

~ 1 : 5,000 - 10,000 births
~ 50 different inherited diseases
- Overlapping symptoms
- Some unique features. — may reflect unique glycans that accumulate or predominance of glycan in particular tissues
  eg. Dermatan sulfate in skin, bone, joints (Morquio; MPS IV)
  Gangliosides in brain

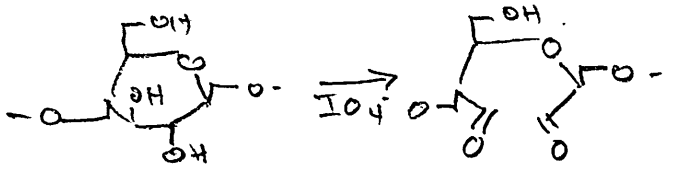
(5) Enzyme Replacement Therapy (ERT)

Elizabeth Neufeld Cross correction experiment

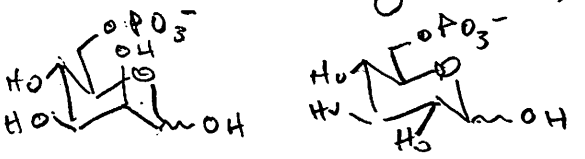


∴ I-cells lack the ability to make a specific recognition marker

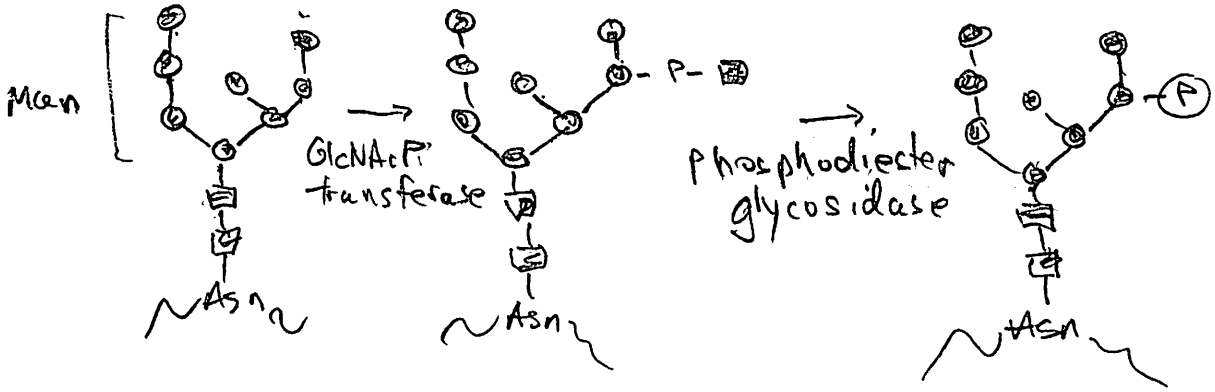
- marker was periodate sensitive



- uptake blocked by M6P, but not G6P



- uptake mediated by M6P containing glycans



- recognition by M6P receptors (P-type)

Slide 2