Lysosomal Storage Diseases

Common considerations

• What substance is stored?
  – How is it made?

• Where does the storage occur?
  – Tissues
  – Time frame

• How does storage lead to symptoms of disease?

• Can we predict disease course?

• How do various therapies work?
  – Prevent storage.
  – Alter disease symptoms.
Lysosomal Storage Diseases

Common observations

• Disease heterogeneity.

• All are progressive multi-system diseases.

• All are genetically inherited.

• No complete understanding of how individual disease complications arise.
Lysosomes
Lysosomes

- nucleus
- nucleolus
- glycogen
- lysosome

Lysosome
Lysosomal Storage in MPS

Normal liver  
MPS liver

All tissues and all cell types have some degree of lysosomal storage.
Lysosomes

Main function is to contain enzymes which recycle various complex molecules that cells make.
Biochemical Basis of MPSs

- A series of lysosomal storage disorders related to an inability to degrade glycosaminoglycans (GAGs).

- GAGs represent an important constituent of connective tissue as well as cell surface receptors and cellular proteins.

- The exact mechanisms by which the accumulated GAGs result in disease is unknown.
Glycosaminoglycans

- Long chains of complex sugars:
  - Constantly made and recycled.
  - They are recycled in the lysosome of all cells.
Glycosaminoglycans

Important components of many extra cellular proteins.

- **Heparan sulfate.**
  - Connective tissue, CNS structural proteins, and cell receptors.

- **Dermatan sulfate.**
  - Connective tissue and extra cellular matrix proteins.

- **Chondrotin sulfate.**
  - Connective tissue.

- **Keratan sulfate**
  - Connective tissue.
# Biochemical Basis of MPSs

<table>
<thead>
<tr>
<th>MPS disease</th>
<th>GAGs</th>
<th>Enzyme</th>
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<tr>
<td>MPS I Hurler, Scheie</td>
<td>hep, derm.</td>
<td>iduronidase</td>
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<tr>
<td>MPS II Hunter</td>
<td>hep, derm</td>
<td>iduronate sulfatase</td>
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<td>MPS III Sanfilippo A-D</td>
<td>hep</td>
<td>4 different</td>
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<td>MPS IV Morquio</td>
<td>kerat, chon</td>
<td>B-gal, gal-6-sulf</td>
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<td>MPS VI Maroteau Lamy</td>
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<td>arylsulfatase B</td>
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<td>MPS VII Sly</td>
<td>hep, derm, chon</td>
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<tr>
<td>ML II-III I-Cell/ Pseudo</td>
<td>hep, derm, chon</td>
<td>Processing enzymes</td>
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<td></td>
<td>Hurler</td>
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Iduronidase deficiency causes a block in the sequential breakdown of glycosaminoglycans containing uronic acids.

MPS Disorders: Biochemistry

MPS II

MPS I

MPS VI

e.g. Dermatan Sulfate Degradation
MPS Disorders
Complex Pathway to Disease
MPS Disorders
Complex Pathway to Disease
Glycosaminoglycans and proteoglycans in tissues
Lysosomal Storage Correction
Clinical Features of MPSs

- dependent on the specific enzyme deficiency
- variability is seen in all of the disorders
- all show progressive disease
  - Variable rate of progression.
- all are multi-system
  - each disorder has a series of systems that are affected
  - often does not appear to be a correlation between the degree of involvement of various systems
Disease Heterogeneity

Hurler syndrome  Hurler/Scheie  Scheie syndrome

MPS I
Multi-System Involvement

- Skeletal
- Connective tissue
- Gastrointestinal
- Ocular
- Respiratory
- Cardiovascular
- Gastrointestinal
- Neurological
Pathogenic Cascades

- Primary block in GAG degradation in the MPSs

- Secondary effects on other complex biochemical pathways.
  - These may be the actual mediators of disease
Pathogenic Cascades

12 year old leaves the water running in the up stairs bath.
Pathogenic Cascades

Bath fills up with water (storage phase)
Pathogenic Cascades

water spills out the bath onto the floor and begins to warp the Brazilian hardwood floor that was recently installed
the hot air floor vent begins to drain water into the space between the floors causing the ceiling on the main floor to collapse into the kitchen
Pathogenic Cascades

The collapsed kitchen ceiling catches fire because dinner was slow cooking on the stove.
Pathogenic Cascades

The flames set the kitchen on fire which then proceed to leap from your house to the neighbors garage.
Pathogenic Cascades

The neighbors vintage 68 mustang explodes sending flaming shrapnel high in the air which knocks out the main power line to 50,000 homes in the area.
Pathogenic Cascades

- Sequential but complex sequences were set up that are very distant from the primary event.

- Reducing the amount of water in the bath at this point
  - Very little effect on the distant “complications”
Implications of Cascades

- Primary storage may be too simplistic
  - Uni-dimentional
  - Implies that reduction of storage leads to alleviation of symptoms

- Activation of cascades
  - Symptoms may not be caused directly by storage
  - The cascades once initiated may not be affected by reducing storage
  - Likely relates to the progressive nature of the LSDs
  - Brings in the concept of timing for intervention to have the best outcome.
Joint and Skeletal Disease

Progressive storage in synovium, periarticular tissues, and bone

Clinical features:

- Joint stiffness
- Joint contractures
- MPS IV: joint laxity
- Joint pain
- Severe skeletal deformity
- Loss of mobility
Joint and Skeletal Disease
Joint and Skeletal Disease

Dysostosis Multiplex
Articular cartilage
- Gag deposition
- enhanced chondrocyte apoptosis
- increased nitric oxide production
- increased cytokine and chemokine production
- macrophage recruitment
- activation of TLR4 pathway
- increased MMPs, TNF α

Growth plate
- Gag deposition
- altered growth plate morphology
- altered trabecular architecture
- osteoclast dysfunction
- inhibition of collagenase activity of Cathepsin K
- alteration of STAT pathway
- decreased IL6 chemokines
Cardiac Disease in MPSs

Storage in heart valves, coronary arteries and aorta

Clinical Features

- Valvular disease
- Pulmonary hypertension with right heart failure
- Cardiomyopathy: early endocardiocfibroelastosis
- Coronary artery/vascular disease
- Congestive heart failure
Elastogenesis Defect

Braunlin et al., 2006 Ped Res 59, 27-32
Brain Disease

- Gangliosides GM3
- Cholesterol
- Ubiquitin
- SCMAS
- Lysozyme
- Paired Helical Filaments
- P-Tau
- Neuro-inflammation: Microglia activation
GAG storage
Ganglioside storage
GM₂, GM₃
Cholesterol storage
P-tau

Macrophage activation

Altered cell surface proteoglycans
glypican
Syndecan
FGFr

Activation of SERPINs
PDEGF
HC II
MPS Disorders: Complex Diseases

Complex interplay of the following

• Direct storage of GAGs leading to some disease symptoms.
  • These may be reversible by replacing the enzyme.

• The storage of GAGs alters other proteins that themselves lead to disease symptoms.
  • May not be so easy to reverse.

• Progressive disease involvement leads to a disease continuum.
MPS Disorders: Complex Diseases

Disease continuum
Dynamic diseases in which at any one time one has:

- Disease symptoms that may be reversible.
- Disease symptoms that may be preventable.
- Disease symptoms that are irreversible.
Major Unanswered Issues

- Ultimate reversibility of disease.

- Identification of disease biomarkers.

- Identification of alternative / additional therapeutics.

- Determination of recombinant dose regimes.

- Clear understanding of the exact mechanisms that are responsible for the disease symptoms?