The Cellular Basis of Disease
Cell Injury 4B

Intracellular Accumulations

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we will briefly talk about intracellular accumulations and clinico-pathological implications.
Objectives

Identify sub lethal cell injury caused by lysosomal accumulation of endogenous and exogenous material.

Explain the etiology, pathologic and clinical manifestations of lysosomal storage diseases.

Describe and understand the pathophysiology and clinical implications of intracellular accumulations including Lipids, Proteins, Glycogen, Pigments

Describe and understand Pathologic Calcification and differentiate between dystrophic and metastatic calcification.
Intracellular accumulations

4 different intracellular accumulations

Lipids
  - Steatosis
  - Cholesterol and Cholesterol Esters

Proteins

Glycogen

Pigments
Abnormal metabolism – Steatosis (Fatty change)
- Usually affect the liver, sometimes the heart
- Accumulation of lipid particles

Abnormal protein folding – Alpha 1 antitrypsin deficiency
- Misfolded proteins accumulate in the ER

Lack of enzyme – Lysosomal storage disease
- Blockage in the digestion pathway, causing accumulation of product upstream of the blockage

Indigestible material – Carbon or heme
- Coal miners get a lot of this
Causes of Steatosis (Fatty Liver)

- Alcohol is a hepatotoxin that leads to increased synthesis and reduced breakdown of lipids.
- Nonalcoholic fatty liver disease is associated with diabetes and obesity.
- \( \text{CCl}_4 \) and protein malnutrition cause reduced synthesis of apoproteins. Apoproteins are required for lipid metabolism.
- Hypoxia inhibits fatty acid oxidation. Important in fatty deposition in myocardium too.
- Starvation increases mobilization of fatty acids from peripheral stores. Usually seen in patients with other underlying illness, such as cancer.
an example of fatty liver
- smooth surface: important distinction from other liver diseases where livers develop irregular surfaces
- cut surface is shiny: greasy and yellow
hepatocytes distended by the lipid vacuoles

architecture of the liver is normal, with normal hepatic triad
Intracellular Lipid Accumulation
Cholesterol and cholesterol esters

Atherosclerosis
Xanthomas
Cholesterolosis
Niemann-Pick Disease Type C

common causes of many diseases
less common

lipid storage disease
Atherosclerotic Plaque

- **Smooth muscle**
- **Lumen compromised by the plaque**
- **Artery in trichrome stained cross section**
- **Fibrosis and scarring on top of the cholesterol**
- **Cholesterol**
Xanthoma

- Knobby appearance: clue that the patient may have a defect in lipid metabolism
- Lipid accumulation in the dermis
Cholesterolosis

ciliated epithelium

accumulation of lipid in gall bladder submucosa
-- may be an indicator of other underlying diseases
Intracellular Protein Accumulations

Excessive amounts of normal proteins (Multiple myeloma - Russell Bodies)

Defective intracellular transport and secretion (Cystic fibrosis)

Aggregation of abnormal proteins (Alpha-1 Antitrypsin deficiency; Systemic Amyloidosis)

proliferation of plasma cells, causing accumulation of immunoglobulin

accumulation of mucin
Excessive normal proteins (Russell bodies)

PathGuy
Defective intracellular transport and secretion (Cystic fibrosis)
Aggregation of abnormal proteins (Amyloid in Liver)

accumulation of amyloid proteins outside of the cell, compressing the nearby hepatocyte and impairing their function
Indigestible material Pigments

Exogenous Pigment – Carbon in lung = **anthracosis**

Endogenous Pigments

- Hemosiderin- multiple transfusions
- Lipofuscin- aging pigment
- Melanin- skin and neurotransmission
- Bilirubin- hepatocytes
Exogenous pigment

Anthracotic pigment in Lung

Coal dust particles and/or silica fragments injures the lung tissue and causes it to scar. Carbon materials which may associated with coal dust (or car exhaust) are too heavy to be exhaled and are deposited within those scars.
Endogenous pigment
Hemosiderin in Liver

same tissue section, different stain

H & E stain

with time, these hemosiderin deposits will impair hepatic function and lead to cirrhosis
Pathologic Calcification

**Dystrophic** Calcification – occurs in areas of necrosis and atherosclerosis.

implies there is damage of underlying organ

**Metastatic** Calcification – occurs in normal tissues when there is hypercalcemia.

implies increased levels of circulating calcium
an example of dystrophic calcification -- commonly seen in atherosclerosis and as a complication of rheumatic heart disease (autoimmune damage to the myocardium and necrosis)
Metastatic Calcification

Excess Parathyroid hormone
Destruction of bone
Vitamin D disorders
Renal failure

most common

inadequate control of parathyroid function

increases circulating Ca2+ level and can lead to bone lysis. -- can be caused by vitamin D disorder and renal failure
A 22 year-old woman has congenital anemia that has required multiple transfusions of RBCs for many years. Which of the following findings would most likely appear in a liver biopsy specimen?

A. Steatosis in hepatocytes  
B. Bilirubin in canaliculi  
C. Glycogen in hepatocytes  
D. Amyloid in the liver  
E. Hemosiderin in hepatocytes

possible: bilirubin is a metabolite of hemoglobin, but we often see this in hepatic failure
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Summary

Intracellular accumulations

Lipids  
- often seen in atherosclerosis

Proteins  
- associated with neoplastic or genetic disorder

Glycogen  
- also often associated with genetic disorder

Pigments

Pathologic Calcification  
- dystrophic or metastatic
Conclusions

- Cell injury may occur by a variety of mechanisms and sources - endogenous (ischemia/inflammation) or exogenous (drugs/toxins).

- Cell injury can be reversible or irreversible.

  - Reversible cell injury can result in changes which may recover when the cause is removed, or which may persist.

  - Irreversible (lethal) cell injury may cause only transient functional impairment if the dead cells can be replaced.

  - Alternatively, lethal cell injury may lead to permanent functional impairment if the dead cells cannot be replaced.

- Cell death (apoptosis) is a normal mechanism to remove damaged cells which can be activated in pathologic conditions.

- Substances may be deposited within cells in response to cell injury.
All clinical disease arises from abnormal cell structure and function.