Sublethal Cell Injury: Lysosomes

John Shelburne MD, PhD
Departments of Pathology
Duke University Medical Center
Veterans Administration Medical Center
Heterophagy

something from the outside enters the lysosomal system

Phagocytosis (endocytosis)

Phagolysosome (secondary lysosome)

Primary lysosome

Autophagy

Primary lysosome

Autophagic vacuole

Residual body

Lipofuscin pigment granule

Exocytosis

Residual body

both heterophagy and autophagy can produce lipofuscin granule and lead to intracellular accumulation

debris from residual body is removed by exocytosis

similar to phagocytosis, but instead of engulfing a substrate from the outside, substrate within the cell enters the lysosomal system, and is degraded the same way an engulfed bacterior would be degraded

this accumulation can occur over the course of your lifetime

the brain, liver, and heart do not have the ability exocytose debris from lysosomal digestion, and these remains became lipofuscin pigments
phagocytosis

phagosome fused with primary lysosome to make SECONDARY LYSOSOME

autophagy is important for cell modeling, such as embryogenesis, cancer biology (apoptosis), lysosomal storage disease, etc

lysosomal diseases are normally genetic, but can be induced such as the use of antimalaria drug, which interfere with the lysosomal digestion (interferes with digestion of phospholipid)

degradation of inner wall by fusion with primary lysosome

mitochondrion then DIES but the cell is fine

smooth ER engulfing a mitochondria, forming a double wall vacuole
Lysosomes: Sublethal Changes

now we will examine each of the following

• Heterophagy - exogenous material or endogenous material
• Autophagy - endogenous material - role in storage diseases
• Aging pigment - lipofuscin
Heterophagy: Exogenous Material

Ruptured Breast Implant
macrophages form giant syncitial cells
- so large that it can be seen with the naked eye
- trying to eat the plastic polymer
- macrophages release inflammatory mediators causing pain

polymer material from the implant are recognized as foreign by the body
- polymer in the interstitial space
we did not evolve to have the enzyme to digest those artificial polymers and as macrophages continue in their attempt to phagocytose the material, it releases inflammatory signals that attract other WBC such as neutrophils. This can be very painful for the patients.

hundred of macrophages form a syncytial cells in an attempt to engulf and phagocytose the polymers
Heterophagy: Exogenous Material

Cigarette Smoke
Smoker's Lung

When smoked, carbon particles are absorbed into the alveolar space and phagocytosed by macrophages.
EM of the lung tissue from a cigarette smoker, note how variables the lysosomal vacuoles are.

Whole big thing is alveolar macrophage

Lysosomes = variable content - smoke is variable

Nucleus
we can't digest those carbons, and some of us have good clearance and can cough those carbons out, but others can't. In the latter case, these carbon would then just continue to accumulate in our body. usually,
Anthracotic Pigment

Accumulation of pigment with age (all of us have this); it is not very clinically important.
Some heavy cigarette smokers might not even have that much anthracotic pigment.

Many of us have anthracotic pigments even if we don't smoke. And to reiterate a point made earlier, some of us have good cilia beating to clear out those pigments, others don't (Cartagener's syndrome).

Those macrophages eventually die and the those black remaining materials are the anthracotic pigment.
Heterophagy: Endogenous Material

Heart Failure Cells
Hemosiderin
BP in capillaries are increased, RBC leaks out and macrophages phagocytosed those RBC. The macrophages then metabolize the hemoglobin into hemosiderin, filled with iron.
mixing of autophagic and heterophagic content in common secondary lysosomes
Autophagic Vacuoles

- Autophagic vacuoles with dead mitochondria
- Normal mitochondria
- This is a hepatocyte

We all have some degree of autophagy going on in our body.
Lysosomal Storage Diseases

- Pompe’s Disease
- Lack of lysosomal glucosidase results in glycogen accumulation
neonatal heart of patient with Pompe's disease

normal
Pompe’s Disease--Heart

accumulation of glycogen in cardiomyocytes during the 9 months of gestation
Pompe’s Disease -- Liver

accumulation of glycogen also occurs in the liver
Lysosomal Storage Diseases

- Gaucher’s Disease
- Lack of lysosomal glucocerebrosidase
- Cerebroside accumulation
- Slide 404 – 5,050 gm spleen

(normal is only a couple hundred grams)
Gaucher’s Disease

- 35 yo male presented for inguinal hernia repair
- Hx of fatigue, bone pain
- W/U - anemia, leukopenia
- Imaging - enlarged spleen, liver
Gaucher’s Disease--Spleen

adult onset in this case

large accumulation of leukocyte
Normal Spleen

white and red pulp present, not that many macrophages
spleen filled with macrophages with cerebroside that has been accumulating in those cells throughout the patient's life
how to you treat storage disease? we can give the missing enzyme systematically, it can then be phagocytosed, and will eventually meet the vacuoles in the 2ndary lysosome and degrade the metabolite.

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however, this is not always successful, we may not always have the enzyme and the body may develop antibodies against those enzymes

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so the best solution is still to fix the genetic abnormality in the DNA.
Lipofuscin

- Insoluble, brownish-yellow intracellular pigment
- Accumulates with age
- Complexes of lipid and protein derived from peroxidation of polyunsaturated lipids of subcellular membranes
those lipofuscin bodies look yellow in H & E. They are usually not harmful.
trend: more lipofuscin accumulation with age
most tissue have intracellular accumulation, but the important tissues are heart, brain and liver, where defects can be medically seriously vs defects in other areas of the body can be treated or fixed.