Pathology

Lecture #3

Apoptosis is another type of cell injury that involves cell death. It’s different than necrosis, as we mentioned before, necrosis is a cell or a group of cells death follow an exposure to injurious agent. While apoptosis is cell death initiated by a stimuli that effect the cell by either binding to its receptor on its surface or comes from the cell itself in a process we will discuss later on.

Apoptosis may be caused by either physiologic “for example: cells that are unwanted or completed their function during development and other conditions” or pathologic causes, while necrosis occur only upon pathologic events.

Another key for differentiating between apoptosis and necrosis is that apoptosis doesn’t initiate inflammatory response which in the other hand is a main sign for necrosis.

Apoptosis may start in individual cells but it can proceed into necrosis if it has been complicated with other factors:

Apoptotic cells undergo DNA damage which stimulates some reactions include the ones in enzymes called poly-ADP polymerase which decreases the concentration of some important molecules in the cell like NAD which will decrease the production of ATP. And once the depletion of ATP occurs the cell will proceed into necrosis.

Apoptotic cells are abnormal dead cells, recognized under the microscope due to some significant changes than normal cells:

1. First thing noticed is that the cytoplasm looks very eosinophilic, that’s why apoptotic cells stand out within a tissue, the color appear deeper and more intense than the rest of the tissue.
2. The chromatin in the nucleus get more condensed and clumping. In normal cells there is a dark area in the nucleus separated by lighter areas due to the distribution of the chromatin. However in apoptotic cells the chromatin clump and the light areas disappear in result the nucleus looks much darker and fragmentation of the chromatin follow.
3. Cell size decrease.
4. Cytoplasmic components and proteins clamps accumulate within the cytoplasm resulting what is called apoptotic bodies.

However, again, no inflammatory response initiated and usually happens in individual cells rather than groups like in necrosis.

So in the slide no.101 it displays hepatic cells of the liver which shows apoptotic cells in many occasions and diseases such as in exposure to toxins. You can easily differentiate between normal and apoptotic cells by : 1. Nucleus color 2.Color of the cytoplasm 3. Shrinkage size

Extra notes in reference to the comparison table in slide no.102:

1. Necrosis is usually due to an injury like in most cases ischemia which causes swelling of the cell while apoptotic cells undergoes shrinkage in size and looks much smaller than necrotic cells.
2. The cell membrane is preserved in apoptosis while is necrosis cell membrane get lysed and the cell actually disappears into a thick liquid as we mentioned before in necrosis.
3. In necrosis enzymes are released and digest its components while in apoptosis no enzyme release so the cell doesn’t disappear and apoptotic bodies form within the cell.

**Physiologic causes of apoptosis:**

1. During embryogenesis: different cells exist during development in the intrauterine life, however after organ recognition and completion these cells become no longer wanted and go through apoptosis.
2. Hormone-dependent physiologic involution Like menstrual cycle loss of cells and after lactation the cells responsible for milk production complete their function and must be eliminated.
3. In intestinal epithelium some cells are responsible for proliferation. However if the need for division stops these germinal cells are lost by apoptosis. So it depend on its need.
4. Production of abnormal lymphocytes in the body: These lymphocytes might be sensitive to self-antigen. They are harmful to the body because they can be recognized as foreign bodies and initiate an immune reaction which can end up with the destruction of the whole tissue and that’s why apoptosis is needed to eliminate theses destructive lymphocytes to prevent the development of diseases.

Actually we have a lot of diseases , which are basically immune reaction towards self-antigens, related to the presence of such lymphocytes. And these diseases are a sign for the body’s failure of conducting apoptosis and elimination of theses lymphocytes.

1. Lymphocytes or immune cells particularly can mature to different types of cells and response to infections, however after infection is eliminated this used mature stimulated cells must be eliminated.
2. Inflammatory cells are also eliminated by apoptosis at the end of it to get rid of any excess cells in the tissue.

So as we see all physiologic causes work in the benefit of the body.

**Pathologic causes:**

1. Cells with DNA damage or gross abnormality of the DNA are not compatible with life and that’s why cells once sustain a large cdamage or loss of the DNA undergo apoptosis.
2. Cells might have abnormal proteins that get misfolded then they can’t be excreted. These abnormal misfolded proteins accumulate within the cell and go through apoptosis.
3. Cells which are infected with viruses.
4. Sometimes organs with secretory ducts can be obstructed. Once obstruction occurs the cells in the parenchyma of that organ can get injured and die and this process is well known upon the obstruction of a major duct like in pancreas and parotid gland.

**What’s the mechanism of apoptosis ?**

In order for the cell to go through apoptosis it undergoes some kind of changes or signaling.

The fundamental step of apoptosis is the activation of enzymes. These enzymes are mainly proteases that act on different cell components particularly proteins. This group of enzymes are called caspases.

Caspases are present in the cell however their activation requires cleavage of the enzyme once it’s cleaved it gets into its active form that can act in any component of the cell whether in the cytoplasm or membrane. In addition to other enzymes that act on proteins.

Once these enzymes act on the vital sites of the cell that means the cells is destroyed and dead.

The cascade of this process goes through one of two pathways:

* Intrinsic
* Extrinsic

In the extrinsic pathway: the signal comes from outside the celland these signals bind to its receptor and then initiate the rest of the pathway.

In the intrinsic pathway which is known as mitochondrial pathway, the initial signal starts from within the cell.

**Mitochondrial pathway:** “intrinsic pathway”

Initial signal that starts the apoptosis process is the presence of any cell damage like for ex. Loss of growth factors or the presence of misfolded proteins within the cell. All these can be a stimuli associated with activation of group of genes called Bcl-2 family “apoptotic genes” because they control apoptosis.

Group of this family enhance apoptosis other group of the same family prevent apoptosis from happening and upon the equilibrium between the two groups and their opposite effect the cell survive within a tissue:

Stimulation of Bax and Bak proteins “genes” initiate apoptosis process “proapoptotic”. While activation of Bcl-2 and Bcl-xl prevent apoptosis from happening. Though all the previous genes (Bax,Bak,Bcl-2,Bcl-xl) are from the same Bcl-2 family.

So the first thing to occur in this pathway is increasing mitochondrial permeability.

So when damage to the cell occur 🡪 mitochondrial permeability increases.

Which will lead to leakage of some enzyme systems used to be present in the mitochondria to the cytoplasm and activation of these enzymes. The most important kind of such enzyme systems is cytochrome c enzymes which contain many types of enzymes which can act on various cell components.

Once it’s released to the cytoplasm stimulation of the enzyme occur.

First enzyme to be stimulated is caspase 9, once caspase9 is activated cascade of other enzymes activation occurs until caspase3 is activated.

Caspase3 is called the execution caspase that once it’s activated cause the degradation of the protein components of the cytoplasm.

At the same time of the activation of caspases, activation of enzymes which are called nucleases responsible for the breakage and degradation of DNA occurs.

So the end result: 1. Protein degradation

2. fragmentation and degradation of the nucleus

In order to reach complete cell death.

**Death receptor pathway:** “extrinsic pathway”

The signal comes from the outside of the cell and the most important pathway is through the TNF receptor family “ tissue necrosis factor receptor” and also known as Fas(CD-95) and as death receptor.

Exist almost in all cells of the body.

Because as it’s ligand bind to this receptor like TNF or other protein it means that this receptor gets activated🡪 this binding is transmitted to the inner surface of the plasma membrane 🡪 activation of the caspases starts with caspase 8 🡪 this caspase cause the activation of serial other enzymes which end up with caspase 3 🡪 once caspase 3 is activated degradation starts.

Accompanied with the previous activation, increased mitochondrial permeability occurs followed by the steps of the intrinsic pathway.

**What really increase the mitochondrial permeability?**

The signaling whether from inside ( damage of the cell) which stimulates the genes or from outside ( ligand bind to TNF receptor) which will also stimulates the genes (bax, Bak from Bcl-2 family genes) and increase the mitochondrial permeability.

Dead cells ( apoptotic cells ) stimulates phagocytosis. Once cells are fully damaged and its components are degraded “upon apoptosis” phospholipid components of the membrane get exposed and secretion of soluble factors occurs which will stimulate macrophages.

Macrophages are cells with the capacity to engulf dead cells in the tissue cause final degradation of the cell cytoplasm and complete elimination of the dead cells .

**Intracellular accumulations**

Another type which is considered as cell injury. Normal viable cells even though they can store some substances within their cytoplasm any increase of that substance cause damage to the cells.

So in conclusion it doesn’t have to be foreign substance accumulated within the cell to be considered as an injury or to cause harm, even substances needed for the survival of the body if they exceeded their concentration they cause significant damage.

Some of the examples of such incident is fatty change such in liver due to accumulation of fat in these cells which cause damage which main cause is alcoholism, obesity, diabetes, toxicity from carbon tetra chloride and other causes. Though these cells do not normally die as a result but their function can be effected and they might have abnormalities.

Some genetic abnormality which can be acquired may be associated with the increase in substances in the cell like storage diseases. Storage disease are well known diseases have many types characterized by the absence of some enzymes, each disease has its own specific enzyme absent which will cause deposition of carbohydrates, lipids or proteins within the cytoplasm which can occur in the liver, muscles especially cardiac muscles.

Excess of these substances, again, associated with diseases.

Sometimes even proteins which are synthesized by the cell if their structure was abnormal as we said before it can not be excreted and accumulate in the cytoplasm of the cell like alpha-antitrypsin deficiency in this patient we have genetic abnormality it’s an inherited disease and the patient have in (in min 25:50 till 25:53 I couldn’t hear the word but I think she said that’s autosomal recessive manner which is true) that’s why it occurs in homozygous patients they have abnormality in the synthesis of this enzyme. And alpha-1-antitrypsin is an enzyme however because they inherited some abnormalities the structure of the protein of this enzyme is abnormal and that’s why it get misfolded and that’s why this enzyme can’t be excreted outside the cell – resulting in the deficiency. It’s synthesized in the liver. That’s why alpha-1-antitrypsin primarily cause liver disease and there are other diseases related to it as a result of the accumulated protein in the cytoplasm of the hepatocyte.

Also the accumulation of the substance occur outside the cell and very famous examples of exogenous deposition of substances are anthracosis and silicosis.

Anthracosis is due to the position of carbon. Carbon exist in all air we inhale. And this carbon particles engulfed by the macrophages in the lung that’s why everybody has a degree of anthracosis. This degree can be higher in individuals who are smokers or live in a polluted city. Anthracosis describe a situation with no clinical consequence however it can be increased and associated with disease in the lung called occupational lung disease or coal worker disease because they inhale large amount of carbon particles.

Silicosis another form of molecules that can be inhaled from the air. Small particles which is silica comes from sand “soil” so people who are more likely to suffer from this are mine workers. Silica particles are very small can go down the airways to the lung parenchyma accumulate in the macrophages of the lung.

Other form of deposition is xanthomas. What is xanthomas? It’s group of cells that has increased fatty substances like cholesterol which is usually small molecules & cholesterol esters within the macrophages and form small bulges under the skin that is seen in different situations in elderlies (local collection of cholesterol in the skin). Under the epidermis in the dermis we have lots of macrophages where deposition may occur that’s why they enlarge in size and small pumps form. Usually these xanthomas associated with diseases related to of the liver particularly biliary tract  
Also atherosclerosis which consist of the deposition of fat within the media which is the cells that line the heart. And it’s a very serious condition regarding the vessels it can lead to a very serious consequences like ischemia

We also have conditions that involves excess protein deposition within the cytoplasm of the cells like in plasma cells once they are stimulated they produce antibodies. Once they undergo extensive stimulation they may produce large number of these immunoglobulins or antibodies and they appear in the cytoplasm so the cell become enlarged and we call them Russell bodies.

Mallory bodies occur in the hepatocyte consist of proteins. During the process of injury to the cell cytoskeleton of the cytoplasm collapse and accumulations occur within the cytoplasm following the collapsing which we all Mallory bodies. Mallory bodies are intermediate filaments that are part of the collapsed cytoskeleton. So Mallory bodies are indication of cell injury due to exposure to drug or chemical or anything else.

Neurofibrillary tangles are another example of protein accumulation. Well known findings in patients with Alzheimer. These patients have dementia found in their neuro building abnormal deposition of proteins and this is probably related to the loss of the function of this neuron that’s why they get dementia.

In slide no.120 demonstrate tubules of the kidney you can see the protein excreted reabsorbed. The red granules inside the cytoplasm of the duct epithelial cells are proteins and the more proteins which is excreted earlier in the tract reabsorbed will cause us the same problem that’s why patients with kidney disease and they lose the protein albumin mostly and the amount of the reabsorbed of protein increase so we find cytoplasm of the epithelial cells are stuffed with protein. Though this protein is harmless still quantity wise is associated with damage.

In slide 122 neurofibrillary tangles in neurons in brain notice the cytoplasm of the neuron contain depositions in long rods that’s why we call it tangled.

Silde 123 alpha-1-antitrypsin how did we know they exist? Because we can see it without microscope we see depositions of this material in the cytoplasm. Globules depositions inside the cytoplasm looks in the slide like RBCs with red pink color abnormal alpha-1-antitrypsin proteins can not be excreted.

Don’t forget to study the slides there are some parts where the doctor skipped but required from us.

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