CELL INJURY AND CELL DEATH

This pdf was developed by
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for ReviewPathology.com

Note on References

See box to the right for reference notations.

PubMed references usually link to abstracts, which provide useful information. But most abstracts link to a free, full-text article for in-depth reading.

Image references usually link to a whole page of images. The images themselves may be useful, but care must be taken to ensure that they relate to the topic of the text. Images are most valuable as a gateway to publications related to the topic. Clicking on the image will take you to the publication. However, to get the full publication it sometimes may be necessary to copy the url and transfer it to your browser.

- **Reference notations: when references are listed, the following suffixes indicate:**
- **pm = PubMed**
- **w = Wikipedia**
- **i = Images (usually Google images)**
- **rg = ResearchGate**
- **yt = YouTube**
- **sd = Science direct**
- **ow = Other website**
- **Selected text = PubMed, Wikipedia, or images**

What is meant by pathogenesis?

- Mechanisms (processes) of disease
- Related topic: mechanobiology of disease (1ow)

What is meant by etiology?

- Etiology: the cause, set of causes, or manner of causation of a disease or condition.
- Types of causation
  - Inherited genetic susceptibility
  - Environmental triggers of disease

Cell Injury

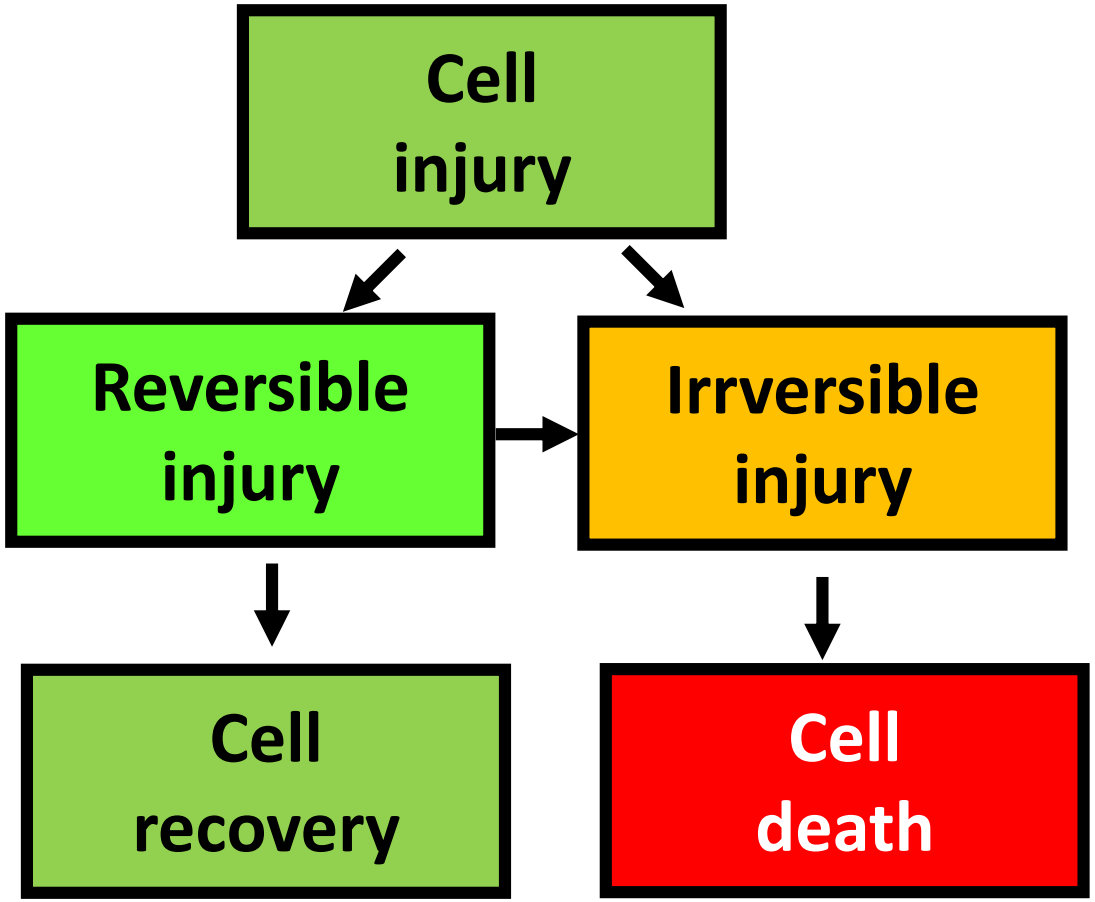
What are the major causes of cell/tissue injury? (to be considered in more detail below)

- Hypoxia (oxygen deficiency)
- ischemia (reduced blood supply)
- Toxins
- Infectious agents
- Immunologic reactions
- Genetic abnormalities
- Nutritional imbalances
- Physical agents
- Aging

What are two major kinds of cell injury?

Major kinds of cell injury are:

- **Reversible injury → potential recovery**
- **Irreversible injury → cell death**



Reversible Cell injury → Cell Recovery

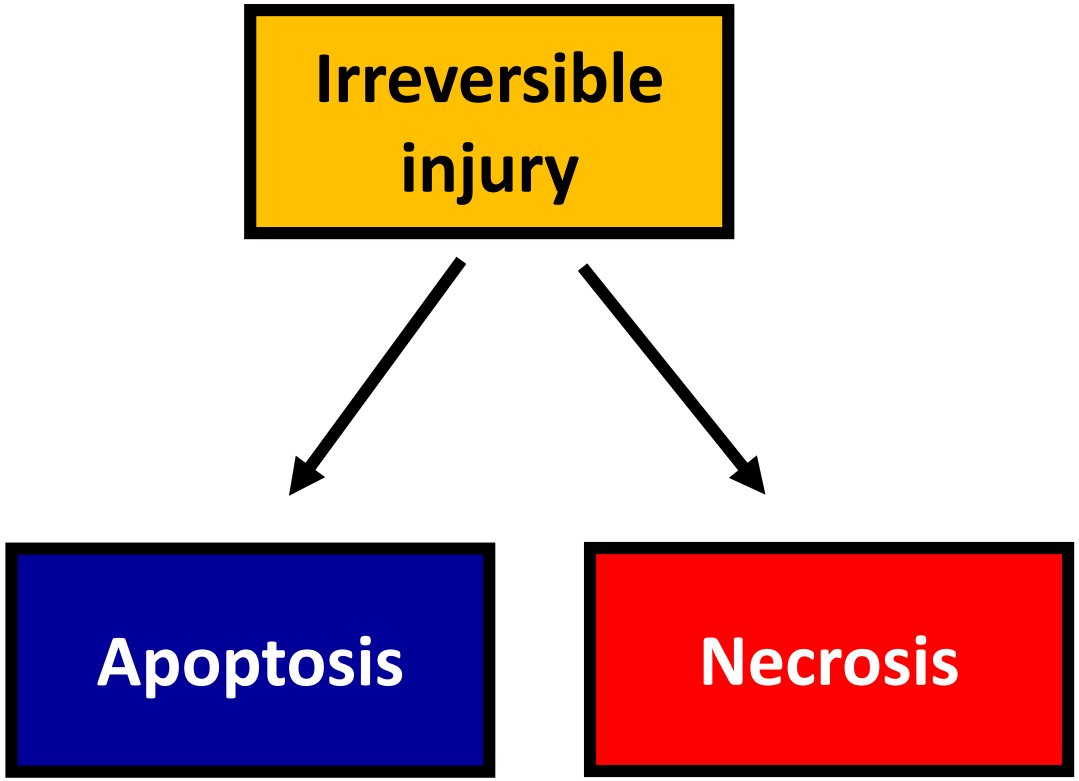
What morphological changes occur with reversible cell injury?

1. Cellular swelling
   - Due to failure of energy dependent ion pumps in plasma membrane
   - Accumulation of clear vacuoles in cytoplasm
2. Fatty change (1i-1, 1i-2)
   - Accumulation of small and large lipid vacuoles in cytoplasm
3. Various alterations in cellular membranes

Irreversible Cell Injury → Cell Death

What are two pathways in cell death (1ow)?

- Necrosis (1i): Cell death secondary to severe injury
- Apoptosis (1i): Programmed cell death



Cellular Necrosis

What are the cellular features of necrosis?

Cellular Features (1pm, 2pm, 3ow)

- Cell size: swelling or fatty change
- Cytoplasm: increased eosinophilia; glassy and moth-eaten appearance
- Nucleus: pyknosis (chromatin condensation)→ karyorrhexis(chromatin disruption) → karyolysis (nuclear distruction)
- Plasma membrane: disrupted (cellular contents leaked out)
- Inflammation: none

What are the different patterns of necrosis? (1pm, 2ow, 3ow)

- Coagulative necrosis.
- Liquefactive necrosis.
- Caseous necrosis.
- Fat necrosis.
- Fibroid necrosis.
- Gangrenous necrosis.

What coagulative necrosis?

- In coagulative necrosis (1i, 2i, 3i, 4i), tissue is preserved for several days after injury (typical of ischemic necrosis)

What is liquefactive necrosis?

- With liquefactive necrosis (1i, 2i, 3i, 4i), there is rapid tissue destruction and accumulation of inflammation. Tissue becomes liquefied.

What caseous necrosis?

- Caseous necrosis has a cheese-like appearance. Microscopically, the cellular architecture is characterized by acellular pink areas of necrosis surrounded by a granulomatous inflammatory process. It is typical of tuberculous necrosis (granulomas).

What is fat necrosis?

- Fat necrosis (1i, 2i) results from the action the enzyme lipase on adipose tissue. Fatty acids released by lipolysis complex with calcium to form soaps. Fat necrosis is most often seen in areas adjacent to the pancreas in cases of pancreatitis, or in breast tissue after surgery.

What is fibrinoid necrosis?

- Fibrinoid necrosis consists of proteinaceous material. It occurs in the walls of arterioles in malignant hypertension. It also occurs when complexes of antigens and antibodies deposit in arteries.

What are the different forms of gangrenous necrosis (gangrene)?

- Dry gangrene: Chronic ischemia without infection
- Wet gangrene: Chronic ischemia with infection
- Gas gangrene: A bacterial infection (e.g., Clostridium perfringens) that produces gas in necrotic tissues in gangrene
- Internal gangrene: Necrosis of an internal organ (e.g., small intestine or colon)
- Necrotizing fasciitis: Rapid spread of necrosis in soft tissue

What is a granuloma?

A granuloma consists of:

- A form of caseous necrosis
- A nodular lesion
- A collection of macrophages and other inflammatory cells
- An example: tubercular granuloma

Apoptosis: Programmed Cell Death

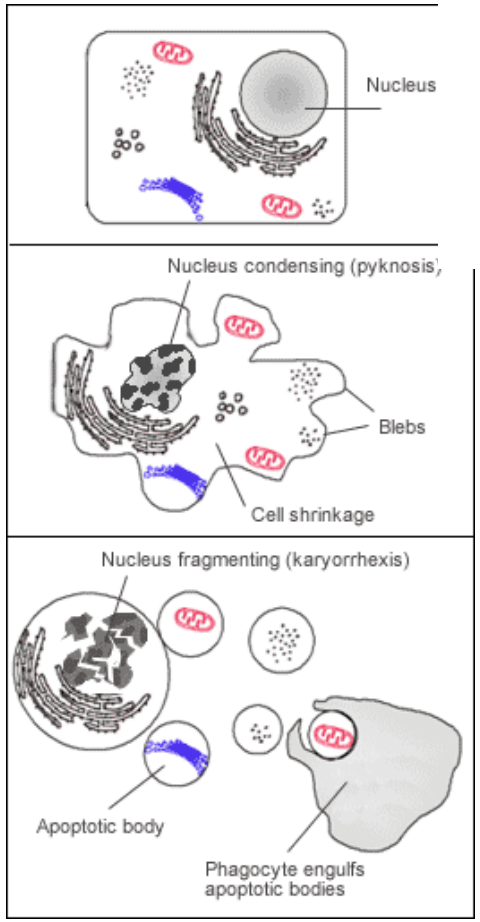
What is apoptosis?

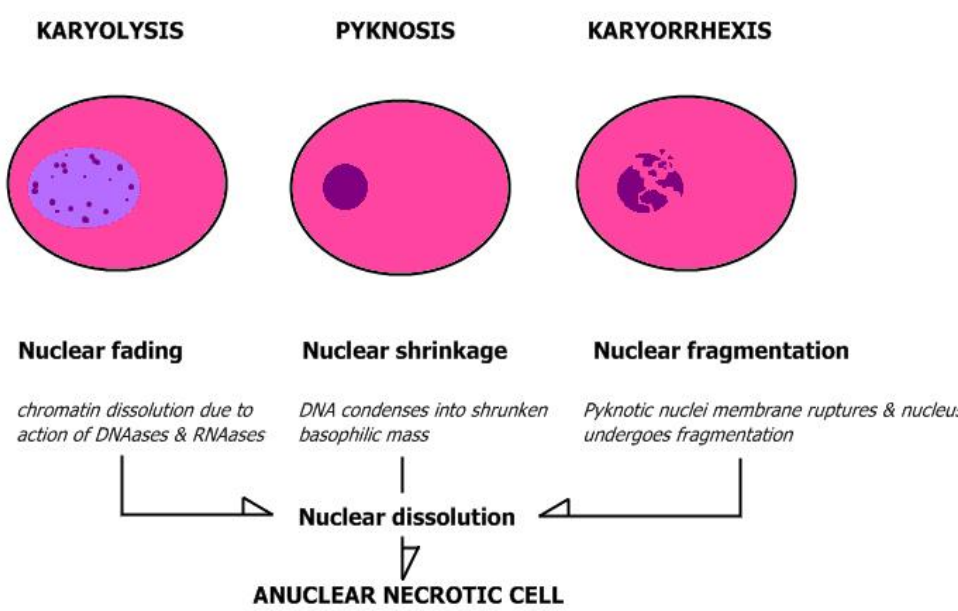
Apoptosis (1pm, 2w, 3i) is:

- **Programmed cell death, or apoptosis, is a distinct energy-dependent biochemical mechanisms for normal cell turnover.**
- **Apoptosis is necessary for development and functioning of the immune system, hormone-dependent atrophy, embryonic development and chemical-induced cell death.**

What are cellular and nuclear changes associated with apoptosis?

- Blebbing (1w,)
- Cell shrinkage
- **Nuclear changes**
  - Chromatin and DNA condensation (pyknosis)
  - DNA fragmentation (karyorrhexis)
- mRNA decay.

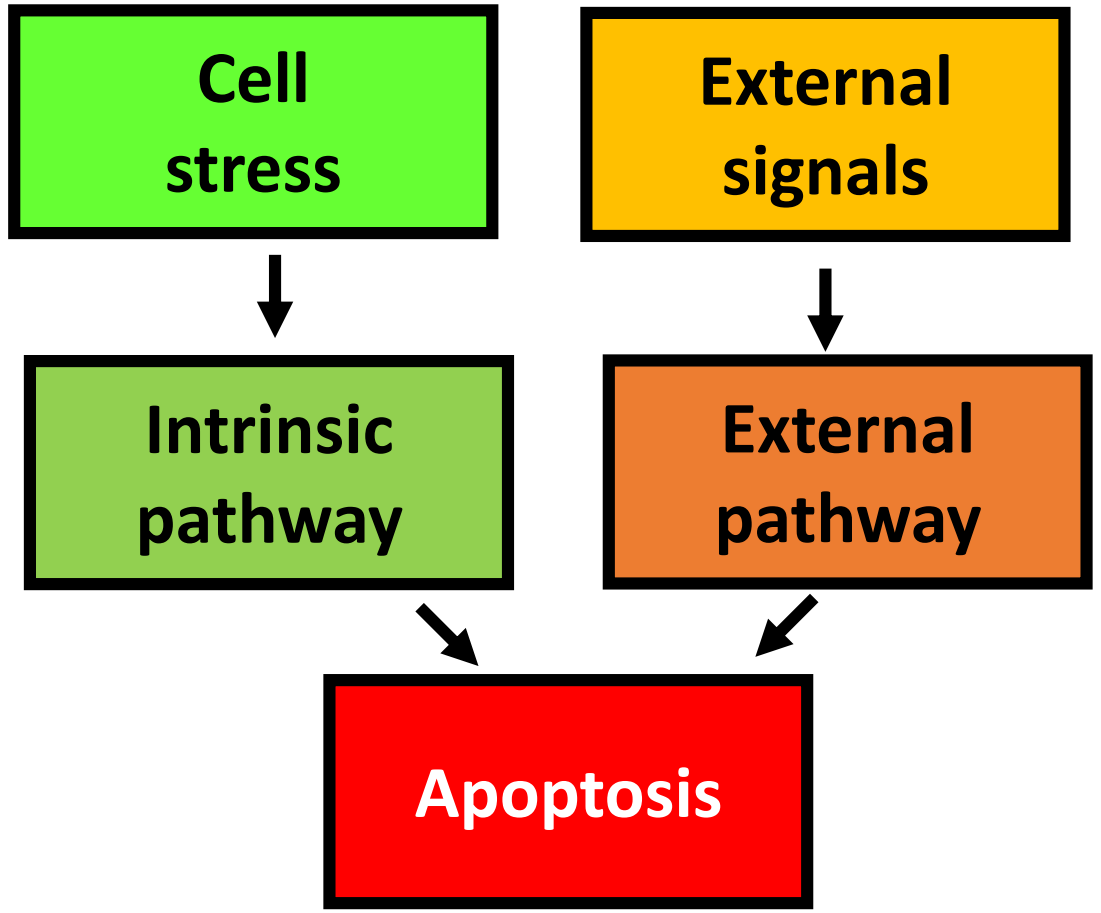




From Wikicommons

What are the pathways of apoptosis?

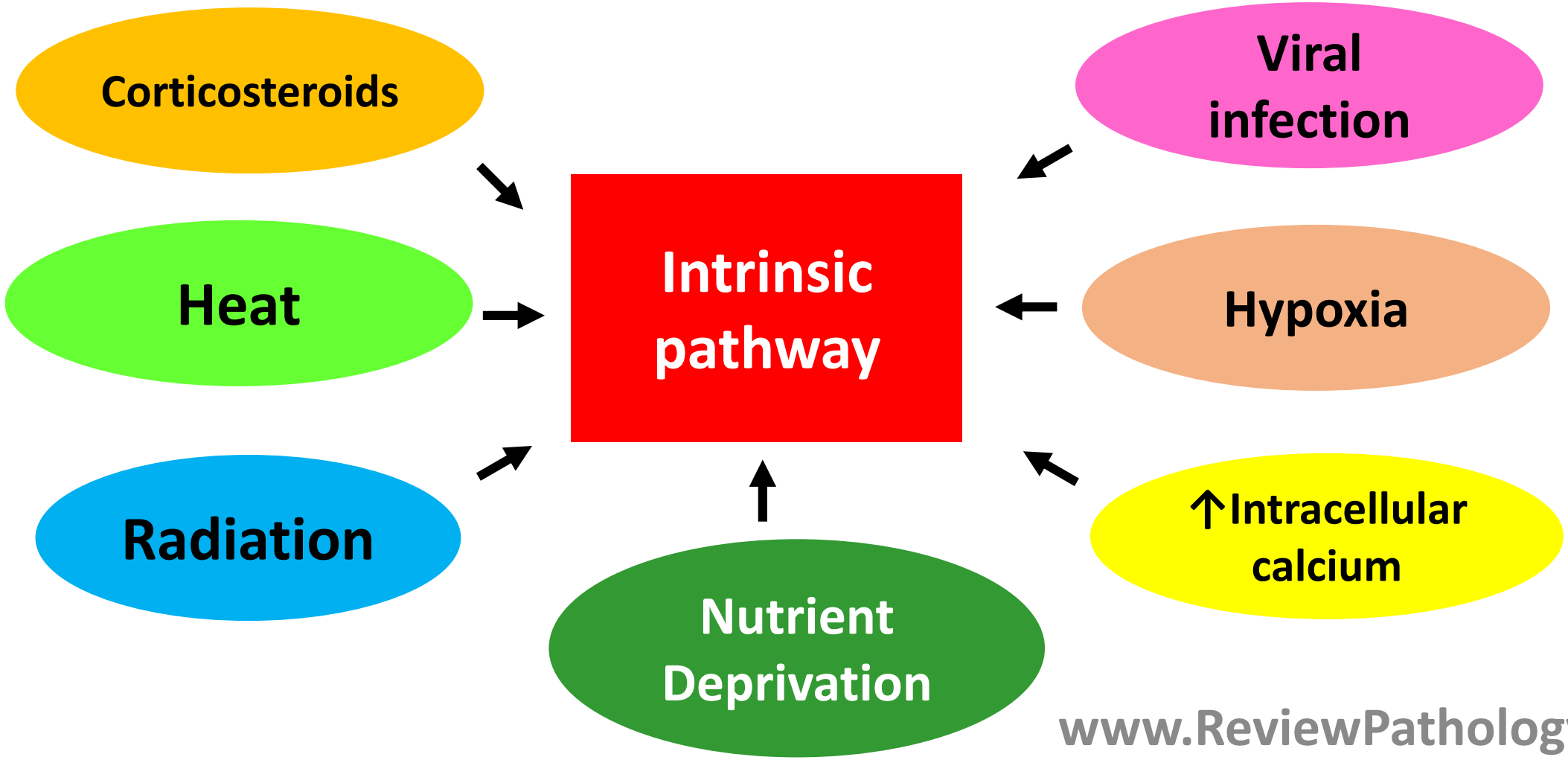
- Intrinsic (mitochondrial) pathway: stimulated sensing cell stress (1i, 2i)
- Extrinsic pathway: stimulated by signals from other cells (1ow, 2i, 3i, 4i)



What are triggers that initiate the intrinsic pathway of apoptosis?

- Glucocorticoids
- Heat
- Radiation
- Nutrient deprivation
- Viral infection
- Hypoxia
- Increased intracellular calcium concentration

What are triggers that initiate the intrinsic pathway of apoptosis?



What role does nitric oxide play and apoptosis?

- Nitric oxide can prevent or induce apoptosis.
- It action depends on its concentration, cell type, and the oxidative milieu.
- It inhibits apoptosis by S-nitrosylation of caspase.
- It enhances permeability of mitochondrial membranes, causing release of cytochrome C, which can trigger the intrinsic pathway.

What are the key mediators of apoptosis?

- Caspases (cysteine-aspartic proteases, cysteine aspartases or cysteine-dependent aspartate-directed proteases) are a family of protease enzymes that carry out apoptosis (1w, 2ip, 3rgp).
- Types of Caspases
  - Initiator caspases (caspase 2, 8, 9 and 10): activates executioner caspases
  - Executioner caspases (caspase 3, 6 and 7): kill the cell by degrading proteins

What is necroptosis?

- Necroptosis (1i, 2i, 3ip): cell death with features of both necrosis and apoptosis.
- Extrinsic signals that trigger apoptosis normally activate the death-inducing signaling complex (DISC) (1a-w, 1b-i, 2i, 3i). But when DISC components are mutated or inhibited, extrinsic death signals activate the necrosome (a complex consisting of RIP1, RIP3, and Fas-associated protein with death domain)(1pm, 1i, 2i, 3ip), facilitating necroptotic cell death.

What is pyroptosis?

- Pyroptosis: apoptosis initiated by proinflammatory cytokines (1a-w)

Apoptosis: Role of Protein Degradation Systems

How does protein degradation regulate apoptosis?

- Proteasomes are protein complexes which degrade unneeded or damaged proteins
- Proteins are targeted for degradation by tagging with a small protein called ubiquitin--followed by attachment of additional ubiquitin molecules (polyubiquitination).
- Degradation of signaling proteins for apoptosis by proteasomes is one regulator of apoptosis.
- Degradation of intracellular proteins through other mechanisms also affects apoptotic pathways.

What are the protein degradation systems?

- Ubiquitin-proteasome system (1w, 2i)
- Caspase (1w, 2i)
- Autophagy-Lysosome system (1w, 2i, 3i,)
- Calpain system (1w, 2i, 3i)

What is the ubiquitin-proteasome system?

- One pathway for the degradation of proteins is via the ubiquitin-proteasome system (UPS).
- Degradation begins by conjugation of protein to chains of ubiquitin.
- The conjugate is then directed to the 26S proteasome (1w, 2i, 3i) a macromolecular protease.
- The outcome is digestion of proteins, causing cell atrophy

Kleiger and Mayor.Trends Cell Biol. 2014 Jun;24(6):352-9

What is the calpain system?

- Calpains (1a-w, 1b-i, 2i) are enzymes belonging to the family of calcium-dependent, non-lysosomal cysteine proteases. Their functions are not well understood. They appear to be involved in cell mobility and cell cycle progression. They may also regulate blood clotting and the diameter of blood vessels, and play a role in memory. Calpains are thought to contribute to apoptotic cell death, as well as cellular necrosis.

What is the caspase system?

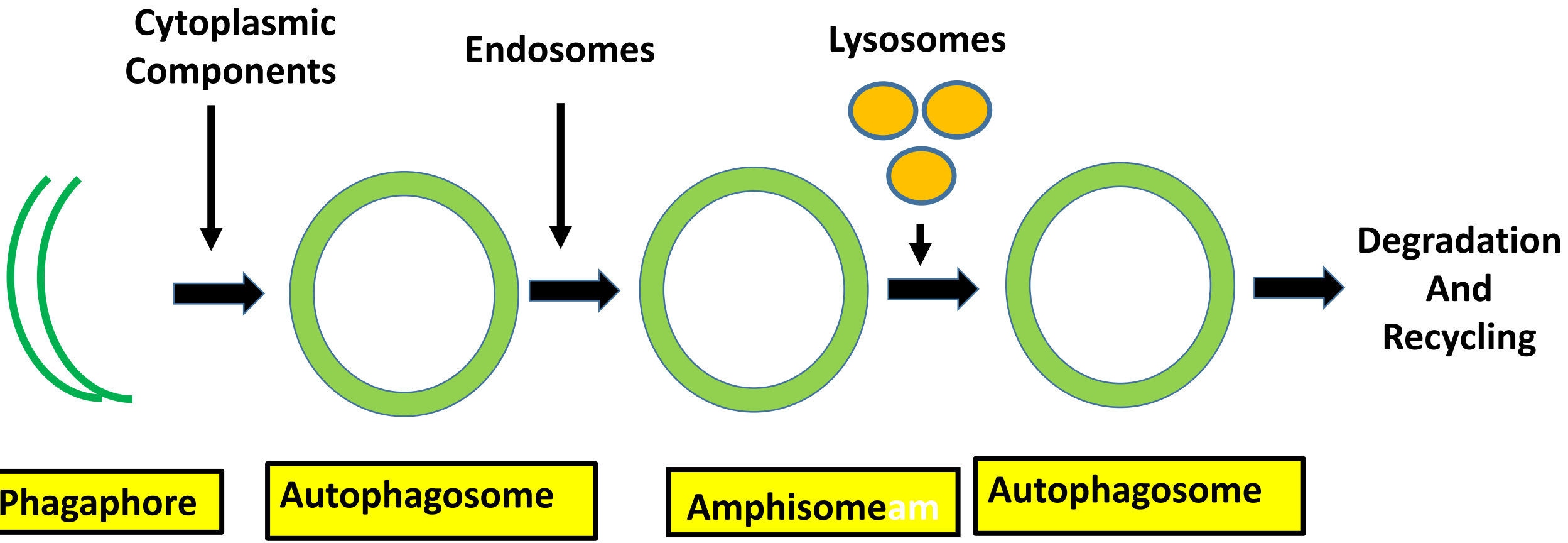
- Caspases (1w, 2i, 3rg)are a family of protease enzymes playing essential roles in programmed cell death (including apoptosis, pyroptosis and necroptosis) (see below); there are 11 or 12 known caspases in humans (1i).
- Activation of caspases leads to degradation of cellular components in a controlled manner, carrying out cell death protecting surrounding tissues from damage.

Autophagy

What is autophagy?

- Autophagy (1w, 2i, 3rg) is a mechanism for destruction of cellular components. It is a normal homeostatic mechanism for turnover of destroyed cell organelles.
- Autophagy occurs in the lysosomal system.

What are the steps in autophagy?



What is a phagaphore?

- A phagaphore (1i, 2rg) is a double membrane that encloses and isolates cytoplasmic components during macroautophagy.

What is an autophagosome?

- Bilayered phospholipid membranes are key components of the living cell.
- During autophagy, cytoplasmic components become enclosed by a double bilayered membrane, called the autophagosome (1w, 2i, 3i).
- This double-membraned vesicle fuses with lysosomes--the contents of which are degraded and recycled.

What are endosomes?

- Endosomes (1w, 2i, 3rg) are membrane-bound compartments that contain molecules internalized from the plasma membrane (e.g. low density lipoproteins).
- Endosomes mature into late endosomes (multivesicular bodies), which feed into the lysosomal system.
- Contents of the endosome also can be recycled to the plasma membrane to maintain its functionality.

What is an amphisome?

- Amphisomes (1pm, 2i, 3rg) are intermediate organelles resulting from fusion between autophagosomes and endosomes.

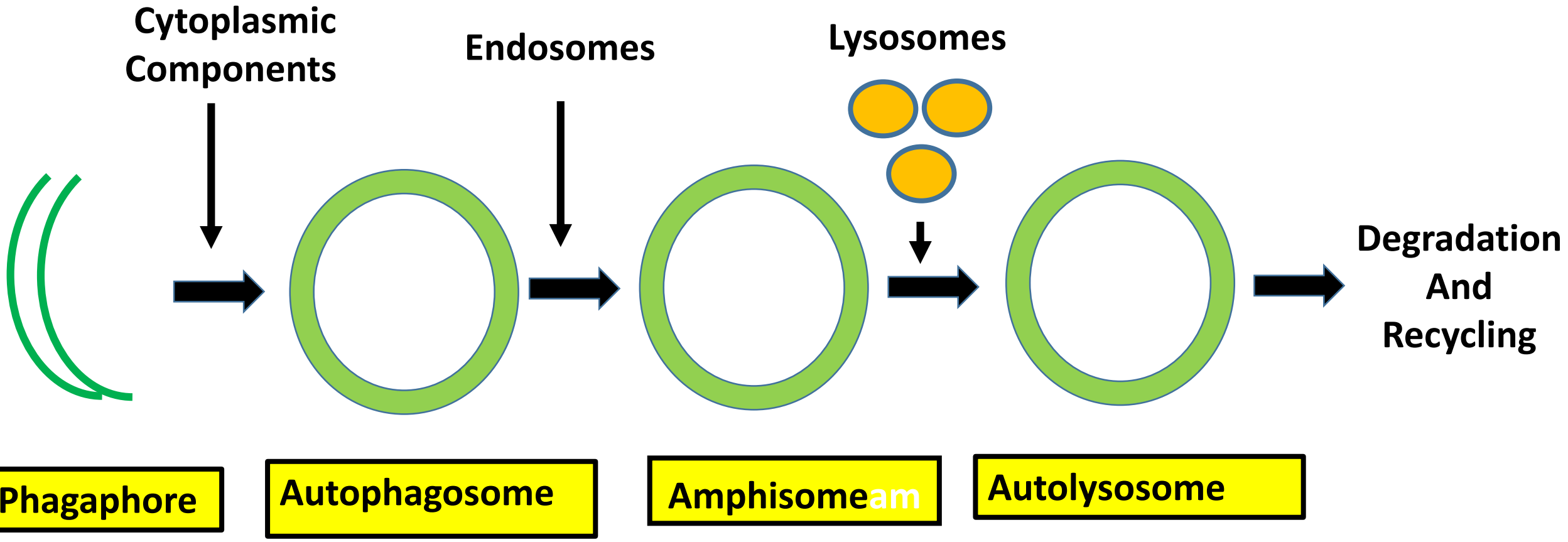
What is an autolysosome?

- An autolysosome (1pm, 2i, 3i, 4i) is the product of the fusion of a autophagosome and a lysosome.

What is an lysosome?

- A lysosome (1pm, 2pm, 3pm, 4w, 5i, 6i, 7rg) is a membrane-bound spherical vesicle containing hydrolytic enzymes that degrade a variety of biomolecules
- The lysosome is involved in various cell processes, including secretion, plasma membrane repair, cell signaling, and energy metabolism.
- Defects in lysosomal degradative function causes lysosomal storage diseases (1i, 2rg)

What are the steps in autophagy?



What are 3 forms of autophagy?

- Macroautophagy (1pm): removes damaged cell organelles or unused proteins
- Microautophagy (1rg, 2rg): direct engulfment of cytoplasmic material into the lysosome.
- Chaperone-mediated autophagy (1pm, 1a-pm, 2w, 3i): chaperone-dependent selection of soluble cytosolic proteins that are targeted to lysosomes for degradation.

What are 3 functions of autophagy?

- Disposal of cell organelles
- Disposal of macromolecules
- Disposal of cytoplasmic material

Who named autophagy?

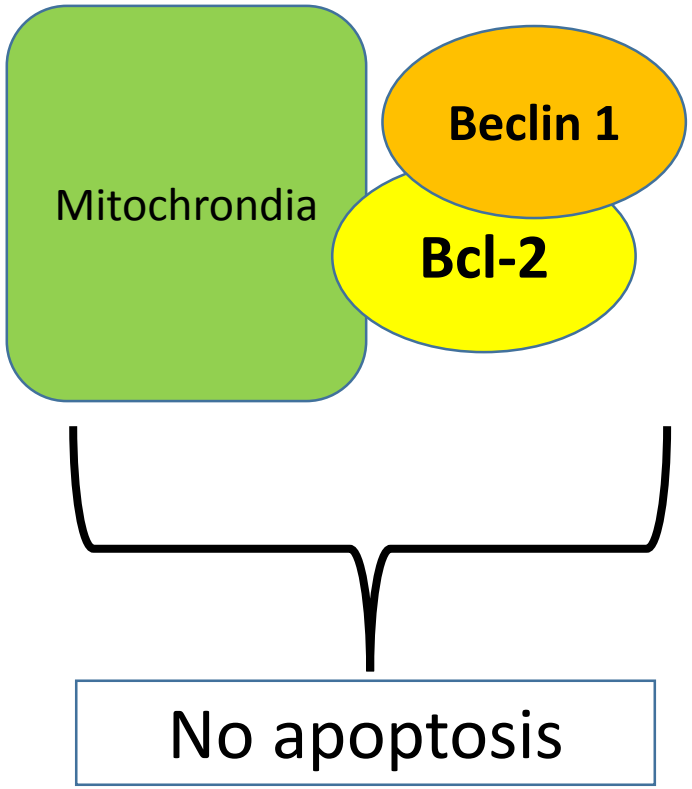
- Belgian biochemist Christian de Duve won the Nobel Prize in 1974 for discovery of autophagy.
- De Duve and student Russell Deter (1pm) first showed that lysosomes are responsible for protein (glucagon)-induced autophagy.

What is mitophagy?

- Mitophagy (1pm, 2pm, 3w) is selective degradation of mitochondria by autophagy
- Promotes mitochondrial turnover.
- Regulated by PINK1 and parkin proteins.

How does Atg6/Beclin 1 protect against apoptosis?

- Atg6/Beclin 1 is an autophagy-related protein.
- It is part of a lipid kinase complex and plays a central role in the cytoprotective function of autophagy and opposing apoptosis.



What are some key functions of autophagy?

Important functions of autophagy (1pm, 2pm, 3i, 4rg) include:

- **Nutrient starvation: removal of un-needed nutrients**
- **Xenophagy: degradation of infectious particles**
- **Repair: degrades damaged organelles**
- **Programmed cell death**
- **Basal metabolic homeostatis**
- **Preventing and causing cancer (tumor suppression)**

What are differences in cell size between necrosis and autophagy?

- Necrosis → swollen cells
- Autophagy → shrunken cells

What is the difference in plasma membranes between necrotic and apoptotic cells?

Necrotic cell membranes: disrupted

Apoptotic cell membranes: intact but altered

Mechanisms of Cell Injury

What are major mechanisms of cell injury?

- Hypoxia
- Ischemia-perfusion injury
- Oxidative stress
- Protein misfolding (ER stress)
- DNA damage
- Inflammation

What are the main targets of cell injury?

- Cell membranes
- Mitochondria
- Cytoskeleton
- Cellular DNA

Hypoxia, Ischemia, and Cell Injury

How does hypoxia cause cellular damage?

- Hypoxia causes a deficiency of ATP.
- Oxygen is required for generation of ATP.
- This occurs via the electron transport chain in which the mitochondrial membrane houses a series of complexes that transfer electrons from electron donors to electron acceptors, which couples with the transfer of protons across the membrane. These protons drive the generation of ATP via ATPase (1pm, 2w).
- Hypoxia disturbs cellular metabolism in other ways too.

What is ATP used for?

- Membrane pumps and transport
- Protein synthesis
- Lipogenesis
- Phospholipid turnover
- Inclusive (1i, 2i, 3i)

What are hypoxia-inducible factors (HIF)?

- Hypoxia-inducible factors (HIF) (1pm, 2w, 3i) are a family of proteins that protect against low oxygen levels .

What proteins are stimulated by HIF-1?

1. Vascular endothelial growth factor (VEGF)

   (Signal protein that stimulates the formation of blood vessels)

2. Proteins enhancing glucose uptake

   (these proteins promote GLUT4-mediated glucose uptake in the skeletal muscle cells)

How do liver and striated muscle protect against hypoxia?

- **Through production of ATP by anaerobic glycolysis.**

What causes swelling of cells during hypoxia?

- Loss of ATP causes failure of the ATP dependent pumps (Na^+/K^+ pump and Ca^{2+} pump)
- This causes a net influx of Na^+ and Ca^{2+} ions leading to osmotic swelling (1i, 2i, 3i, 4i)

How does lactic acid accumulate during hypoxia?

- Hypoxia favors anaerobic glycolysis.
- Anaerobic glycolysis ends in lactate (1i)
- Lactic acid accumulation results in lactic acidosis (1i)
- Lactic acidosis is a form of metabolic acidosis.
- Symptoms may include nausea, vomiting, rapid breathing, and cardiovascular collapse (1i, 2i, 3i, 4i).

What is the principle form of cell death caused by hypoxia?

- Cellular necrosis (but may include apoptosis).
- Apoptosis may be prevented by anti-apoptotic proteins, Bcl-2 and Bcl-X,

How does cyanide simulate hypoxia?

- Cyanide inhibits cytochrome oxidase (1i, 2i, *3i*, 4i)
- This impairs ATP production
- Cyanide can be released by burning of several types of plastic
- Cyanide was used as a poison in Nazi gas chambers

Reactive Oxygen Species and Cell Injury

What are reactive oxygen species?

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen that may damage cell structures (oxidative stress). Examples include:

- Superoxide
- Peroxides
- Hydroxyl radicals
- Singlet oxygen
- Nitric oxide

What is a superoxide?

- A superoxide is a compound that contains the superoxide anion and with the chemical formula O_2^-
- It is produced by acquisition of a free electron on oxygen (O_2).
- Superoxide is a precursor to other reactive oxygen species produced by the immune system to kill invading microorganisms.

What are the biological properties of superoxide?

- Superoxide is produced incomplete reduction of oxygen during mitochondrial oxidative phosphorylation and by phagocyte oxidase in leukocytes
- Superoxide is converted to another reactive oxygen species, hydrogen peroxide, by superoxide dismutase.
- Superoxide damages lipids, proteins, and DNA.

What is the main biological function of reaction oxygen species (ROS)?

- ROS are produced by neutrophils and macrophages for the purpose of destroying invading microorganisms

What are peroxides?

- Peroxides are compounds with the structure

R-O-O-R.

- The O–O group is called peroxide or peroxo.
- The most common peroxide is hydrogen peroxide (HOOH).

What are the biological properties of hydrogen peroxide?

- Hydrogen peroxide is derived from superoxide by action of superoxide dismutase.
- It is converted to water and oxygen by catalase and by glutathione peroxidase.
- It can be converted to hydroxide ion and perchlorate ions, which can destroy microbes and cells.

What are hydroxyl radicals?

- The hydroxyl radical is •OH -- not a hydroxide ion (OH^-).
- Hydroxyl radicals can be produced by action of UV light on hydrogen peroxide.
- They are also formed by decomposition of hydroperoxides (ROOH).

What is singlet oxygen?

- Singlet oxygen (O=O or $^1O_2$) is a high-energy form of oxygen (▪0).
- Ingestion of certain pigments can produce singlet oxygen when activated by light.
- This reaction in the skin can cause severe photosensitivity of skin resulting in phototoxicity and photodermatitis.

How does nitric oxide act as a reactive oxygen species?

- Nitric oxide (NO) is a free radical. (▪NO)
- In inflammation, nitric acid act as a reactive oxygen species.
- NO also is a signaling molecule having multiple actions: vasodilatation, neurotransmission, and immune activation.
- The Nobel Prize in Physiology or Medicine 1998 was awarded jointly to Robert F. Furchgott, Louis J. Ignarro and Ferid Murad "for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system.

What enzymes or reactions generate free radicals?

- NAPDH Oxidase: converts oxygen to superoxide (O_2^-)
- Myeloperoxidase (MPO): converts peroxide (H_2O_2) into hypochlorous acid (HOCl)
- Fenton Reaction (using iron) generates hydroxide (OH^-) from peroxide (H_2O_2)

What is the Fenton reaction?

- The Fenton reaction (1i) results in the creation of hydroxyl radicals (OH·) from hydrogen peroxide and an Iron (II) catalyst.

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\cdot + OH^-$

- Hydroxyl radicals attack DNA at deoxyribose and bases, producing mutagenic changes.

What enzymes destroy free radicals?

- Superoxide dismutase: converts superoxide to peroxide (H_2O_2)
- Catalase: converts peroxide (H_2O_2) to water
- Glutathione peroxidases: converts hydroxide to water

What is superoxide dismutase (SOD)?

- Superoxide dismutase alternately catalyzes the dismutation (or partitioning) of the superoxide (O_2^-) radical into either ordinary molecular oxygen (O_2) or hydrogen peroxide (H_2O_2)
- SOD is an important antioxidant defense in nearly all living cells exposed to oxygen.

What are the 3 forms of superoxide dismutase (SOD) and where are they located?

- SOD 1: Cytoplasm
- SOD 2: Mitochondria
- SOD 3: Extracellular

What is catalase and what its functions?

- Catalase is an enzyme that catalyzes breakdown of hydrogen peroxide into water.
- It is a highly active enzyme and destroys hydrogen peroxide that a great rate.
- Catalase polymorphisms have been linked to various common diseases.

Where is catalase located?

- Perioxisomes (1i, 1b-i, 1c-i, 2rg) are small vesicles with a single membrane containing oxidative digestive enzyme for breaking down toxic materials.
- The major oxidative enzyme in proxisomes is catalase.

What are glutathione peroxidases and what are their functions?

- Glutathione peroxidases are a family of enzymes that protect against free radical damage.
- Glutathione peroxidases catalyze breakdown of hydrogen peroxide into water.

What are sources of ROS?

- Radiant energy (sunlight/X-rays)
- Exogenous chemicals (xenobiotics/cigarette smoke)
- Inflammation (cytokines and growth factors)
- Metals

How does radiant energy produce ROS?

- The absorption of radiant energy (e.g., ultraviolet (UV) light (1rg) and x-rays produce reactive oxygen species.
- Ionizing radiation can hydrolyze water into hydroxyl (•OH) and hydrogen (H•) free radicals.

How do exogenous chemicals produce ROS?

- Various mechanisms have been implicated, depending on the chemical.

Where do ROS come from?

- The endogenous sources of ROS include different cellular organs such as mitochondria, peroxisomes and endoplasmic reticulum, where the oxygen consumption is high.
- During inflammation, ROS are producing large amounts by white blood cells (leukocytes).

What are endogenous sources of ROS?

Organelles and cells

- Mitochondria
- Peroxisomes
- Endoplasmic reticulum
- Phagocytes

Intracellular constituents

- Cytochrome P450
- NADPH oxidases
- Nitrogen oxide synthase
- Xanthine oxidase
- Heme proteins
- Metal Ions

What is a respiratory burst?

- Respiratory burst is the release of ROS from immune cells, e.g., neutrophils and monocytes, as they come into contact with different bacteria or fungi.
- Its actions are to degrade internalized particles and bacteria.
- Driving factors include:

  NADPH oxidase

  Myeloperoxidase

What are major dietary antioxidants?

- Vitamin E
- Vitamin A
- Vitamin C (1w, 2i)
- Beta-carotene

What is oxidative stress?

- Oxidative stress (1w) is tissue damage produced by reactive oxygen species (among other definitions and concepts [1i, 2rg])

What are some of the conditions in which oxidative stress has been implicated?

- Cellular aging
- **Chemical and radiation injury**
- **Tissue injury caused by inflammatory cells**
- Ischemia-reperfusion injury.
- Cell death (necrosis, apoptosis)
- Atherosclerosis
- Diabetes
- Cataract (1i)
- Retinal degeneration (1i, 2rg)
- Rheumatoid arthritis (1rg)
- Parkinson's disease (1pm, 2pm)
- Alzheimer disease (1pm, 2pm)
- Psoriasis

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What are some of the products of signaling cascades that generate ROS?

- Tumor necrosis factor-alpha
- Monocyte chemoattractant protein-1
- Colony-stimulating factor-1;
- Nuclear factor-kB
- Interleukin
- Heat shock protein Cyclooxygenase-2
- Interferon-gamma
- Platelet derived growth factor
- Mitogen-activated protein kinase
- Nitric oxide synthase (1w)
- Epidermal growth factor (1W)
- c-Jun NH2-terminal kinase (1W)
- Phospholipase A2
- Heparin-bound EGF
- Fibroblast growth factor-2
- Insulin growth factor I
- Hepatocyte growth factor
- Transforming growth factor

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Thannickal and Fanburg Am J Physiol Lung Cell Mol Physiol. 2000; 279: L1005-28

What post-translational modifications are affected by ROS, which influence intracellular signaling?

- Phosphorylation
- Ubiquitination
- Acetylation
- Oxidative modification
- Nitrosative modification

Hu N and Ren J. Reactive Oxygen Species 2(4):264–271, 2016

Endoplasmic Reticulum (ER) Stress and Cellular Injury

What is endoplasmic reticulum (ER) Stress?

- ER stress is endoplasmic reticulum overloaded with unfolded proteins .
- Unfolded/misfolded proteins elicit the unfolded protein response (1w, 2i).
- This response promotes unfolded protein removal by chaperone proteins.

What is kinase IRE-1?

- Kinase IRE-1 (1w, 2i) is a molecular sensor of ER stress.
- It triggers the adaptive unfolded protein response (1pm)

Mitochondria in Cell Injury and Cell Death

What is the role of mitochondria in cell injury and cell death?

- Defective oxidative phosphorylation → cell necrosis
- Excess oxidative phosphorylation → ↑ROS → apoptosis
- Mitochondrial damage → release of cytochrome C into cytoplasm → apoptosis

Cellular Toxicity

What are xenobiotics?

- Xenobiotics (1i) are chemicals present in cells that are not naturally present.
- Examples include carcinogens, drugs, environmental pollutants, food additives, hydrocarbons, and pesticides
- Xenobiotic metabolism (1i) involves multiple pathways.

How does the body rid itself of xenobiotics?

- Primary modification consists of Interactions with hepatic microsomal cytochrome P450 enzymes (1i). Reactions include
  - Oxidation
  - Reduction
  - Hydrolysis
  - Hydration
- Secondary modification consists of conjugation (1a-pm, 1b-i, 1c-I, 2pm) with
  - Glucuronic acid
  - Sulphuric acid
  - Glutathione

What are potential dangers of xenobiotics?

- Oxidative stress
- Inflammation
- Cell necrosis
- Apoptosis (1pm)
- Carcinogenesis
- Other potential dangers (1pm, 2pm, 3pm)

What is a toxin?

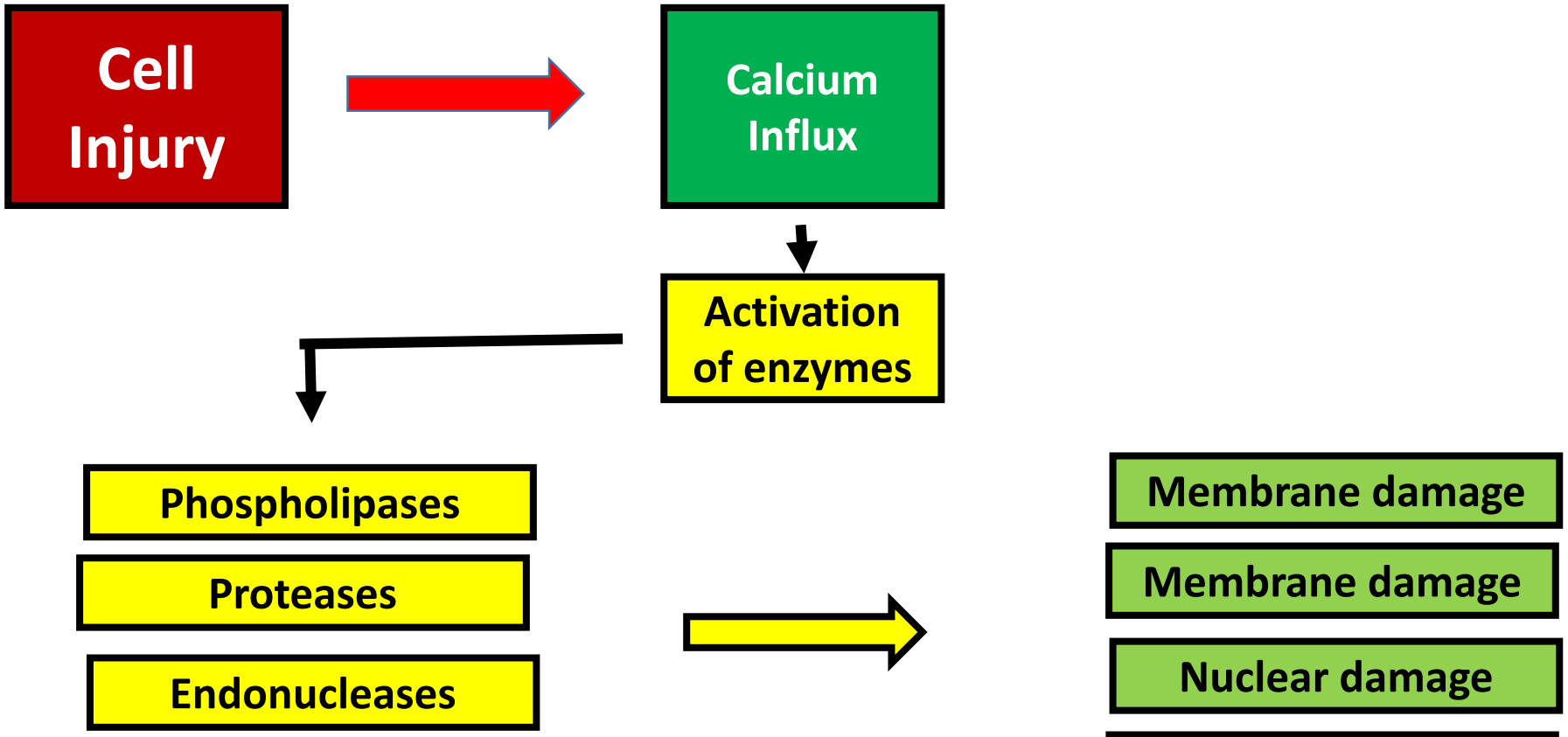
- **"... the term "toxin" means the toxic material or product of plants, animals, microorganisms (including, but not limited to, bacteria, viruses, fungi, rickettsiae or protozoa), or infectious substances, or a recombinant or synthesized molecule, whatever their origin and method of production..."**

Title 18 of the United States Code

What are the major categories of toxins?

- **Direct-acting toxins: Combine with cell component or molecule**
- **Latent toxins: Not inherently toxic, but must be converted to direct-acting toxin**

What role does intracellular calcium play in reversible cell injury?



Cellular Adaptations to Stress

What are major cellular adaptations to cellular stress/injury?

- Hypertrophy (1i, 2yt): increased cell size
- Hyperplasia (1i, 2yt) Increased cell number
- Atrophy (1i): Degeneration of cells
- Metaplasia (1i, 2yt): transformation of one differentiated cell type to another differentiated cell type
- Dysplasia (1i, 2yt): Acquired abnormality of cellular development or differentiation
- Cellular or tissue accumulations of abnormal substances.

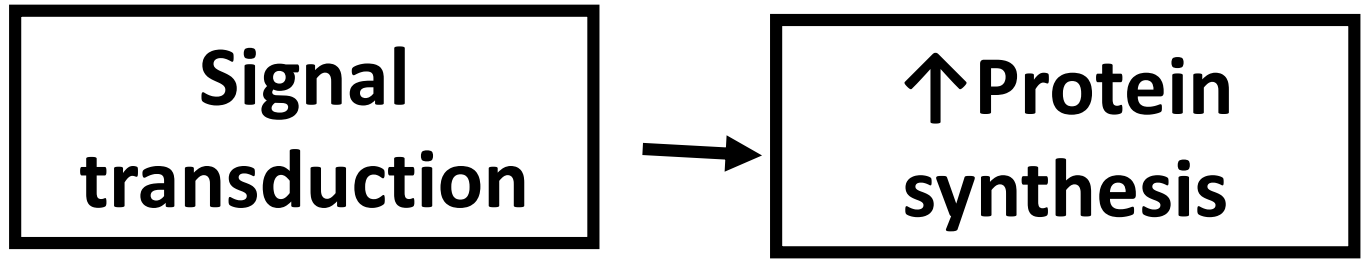
What are examples of organ hypertrophy?*

- Heart: Left ventricular hypertrophy (hypertension, valvular disease, heart failure); Right ventricular hypertrophy (congenital heart disease, obstructive lung disease); hypertrophic cardiomyopathy
- Kidney: compensatory hypertrophy after loss of one kidney
- Gravid uterus: pregnancy
- Bladder: lower urinary tract obstruction
- Skeletal muscle: exercise

* May increase some increase n cell number as well as increased cell size

What is the stimulus to cellular hypertrophy?

- Mechanical
- Biochemical



(Excessive stimulation → degenerative changes)

What are the categories of hyperplasia?

- Hormonal hyperplasia: proliferation of the glandular epithelium
  - Physiological: normal hormonal stimulation
  - Pathological: driven by growth factors
- Compensatory hyperplasia: regrowth from loss of tissue
- There are several examples of hyperplasia under the above categories.

What are examples of hormonal hyperplasia?

- Breast epithelium: pregnancy
- Prostate: benign prostatic hyperplasia (histopathology)
- Endometrium: estrogen stimulation (histology)

What is cellular/tissue atrophy?

- **Atrophy is the partial or complete wasting of cells, tissues, organs , or parts of the body.**

What are the causes of atrophy?

Causes of atrophy include:

- Genetic mutations
- Poor nourishment
- Impaired, circulation
- Loss of hormonal support
- Loss of nerve supply to and organ
- Excessive apoptosis
- Lack of exercise
- Tissue disease
- Loss of hormonal input

What is metaplasia?

- Metaplasia (1i, 2yt) is the change of one differentiated cell type to another differentiated cell type.
- If the stimulus causing metaplasia is removed, the tissue returns to normal pattern.
- Sometimes, metaplasia may be the first change in the development of a cancer.

What is dysplasia?

- Dysplasia (1i, 2yt) is a pathological change in a tissue, usually epithelial tissue, that may precede the development of cancer.

Storage Diseases

What are examples of cellular or tissue accumulations of abnormal substances?

- Atherosclerosis: cholesterol
- Amyloidosis: amyloid protein
- Metastatic calcification: calcium
- Hemochromatosis: iron
- Porphyria: various porphyrins
- Lysosomal storage diseases: cholesterol, various lipids, glycogen

DNA Damage

What are types of DNA damage?

- 1. Oxidation of bases
- 2. Alkylation of bases (usually methylation)
- 3. Hydrolysis of bases
- 4. Bulky adduct formation
- 5. Mismatch of bases (due to errors in DNA replication)
- 6. Monoadduct damage cause by change in single nitrogenous base of DNA
- 7. Diadduct damage

What are the features of DNA damage caused by various forms of cellular toxicity?

- DNA damage can occur "naturally" or pathologically changes the structure of DNA that prevents normal replication .
- Errors in replication can lead to mutations or epigenetic alterations that can be passed on to subsequent cell generations.
- Damaged DNA can modify gene expression (and may contribute the development of cancer)

What are some of the products of DNA damage?

- Breaks in a strand of DNA
- DNA base deletion (1rg)
- DNA base changes (mutations)

  -Example: formation of 8-oxo-2'-deoxyguanosine (8-oxo-dG)

What is the significance of 8-oxo-2'-deoxyguanosine (8-oxo-dG)?

- Cellular concentrations of 8-oxo-dG a measure of oxidative stress.
- 8-oxo-dG appears to promote methylation of DNA, which can produce epigenetic changes in DNA expression.

What are the mechanisms of DNA repair?

- Base excision repair (1i, 2i, 3i, 4i)
- Nucleotide excision repair (1i, 2i, 3i)
- Homologous recombinational repair (1sd, 2i, 3i)
- Transcriptional pausing to scout ahead for DNA damage