
Cell Death Lecture Notes DRAFT

Fall 2020

Keywords: Cell death, cancer, apoptosis, necrosis, caspases, autophagy,

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Summary

Here I will summarize the topic of cell death and how it is related to other parts of our course. Cell death includes apoptosis, necrosis, and autophagy. Each of these have specific and unique properties. And understanding each one of them can help assess treatments for diseases such as cancer.

Normal Cell Division

Cells can divide and reproduce in two different ways through either mitosis (somatic) and meiosis (gametes) (Figure 1). Cell differentiation happens when stem cells become specialized and distinct from one another, giving rise to blood cells, fats cells, neurons, and muscle cells to name a few (Figure 2). All multicellular organisms regulate the total number of cells in their organism by cell division and cell death. Cellular death is essential for organisms to grow and survive. Cells can undergo death by either injury, being exposed to harmful environments, or a regulated/programmed process of disintegration. When cells are no longer needed they will undergo a pathway called programmed cell death, otherwise known as apoptosis.

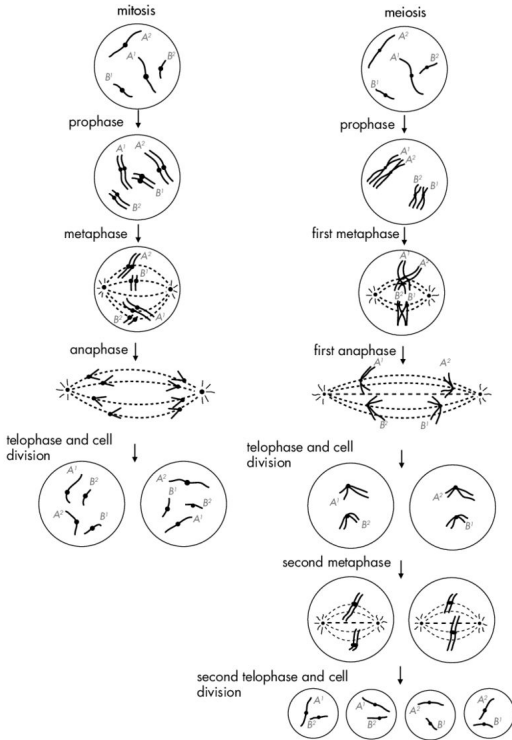
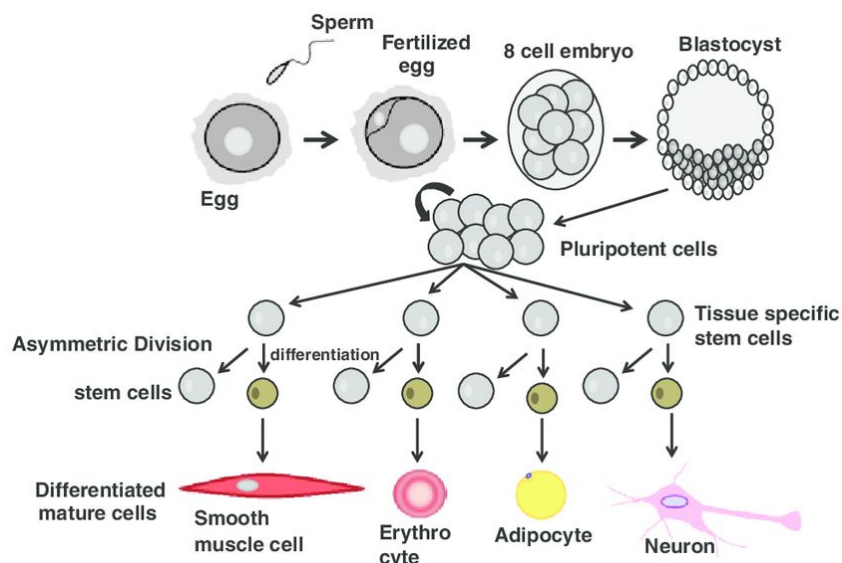


Figure 1. Cell Division: Meiosis and Mitosis¹Figure 2. Cell Differentiation²

Apoptosis

Apoptosis (“apo” = away, “ptosis” = fall, aka “cell suicide”) is also known as programmed cell death and is brought about by a protease enzyme called caspase. It is one of the main modalities of cell death; the other biological mechanisms include necrosis and autophagy. Apoptosis is a natural process in which the body has actively programmed a way for cell death. It is carried out in response to intracellular or extracellular signals. Intracellular signals can originate from DNA lesions, mitosis defects, oxidative stress or other stresses. Extracellular signals respond to death messages emitted by other cells. Apoptosis leads to the activation of proteases, called caspases, able to hydrolyse the cell constituents independently from the proteasome. Cell death can be pathological, a sign of disease and damage, or physiological, a process that is essential for normal health. Thus, apoptosis plays many fundamental roles during embryology and tissue homeostasis.³ In the pathological process, conditions such as tumors, viral infections (HIV/AIDS), and graft versus host disease can occur.

¹ Genetic Guidelines for Fisheries Management - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Mitosis-and-meiosis-Mitosis-produces-normal-diploid-2n-somatic-cell-s-Meiosis-produces_fig1_267222977 [accessed 6 Nov, 2020]

² https://doi.org/10.1007/978-94-017-7273-0_14

³ Robert, J. (2015). CH 18 Apoptosis Induction and Regulation. In 1033813467 792230942 J. Robert (Author), *Textbook of cell signalling in cancer: An educational approach* (pp. 221-240). Cham, France: Springer.

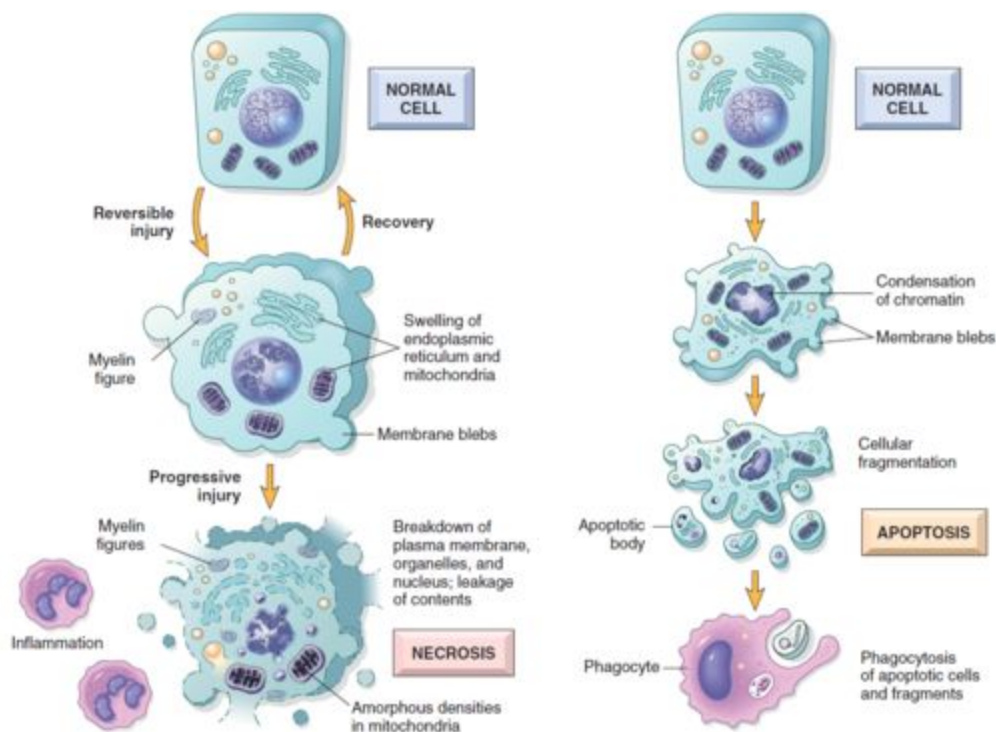


Figure 1-6 Cellular features of necrosis (left) and apoptosis (right).

Figure 3. Necrosis vs. Apoptosis

Caspases: A Family of Enzymes

Caspases are a family of 12 different enzymes. Caspases stands for Cysteine dependent ASPartate directed proteASE. Many enzymes are activated by specific proteolytic cleavage, including caspases. The zymogen (proenzyme, precursor form), procaspases is the inactive form of caspase.⁴

Signaling Pathways

Apoptosis is an event that is initiated by two pathways: Fas pathway and Bax pathway. These pathways lead up to the eventual activation of a protease called caspase. As a result, the cell will break down into fragments (called apoptotic bodies), caused by the cleavage at the cysteine-aspartate site.⁵ How this works, shown in Figure 4:

1. Fas Pathway (starting at the top)

⁴ Berg, J. M., Tymoczko, J. L., Stryer, L., & Stryer, L. (2015). Biochemistry. New York: W.H. Freeman.

^{5,6} Kierszenbaum, A. L., & Tres, L. L. (2012). Histology and Cell biology: An Introduction to Pathology. Philadelphia, PA: Elsevier Saunders.

- a. A Fas ligand from adjacent cells (paracrine effect) or programmed cell death (autocrine effect), will bind to the Fas receptor.
 - i. **Note:** Fas (aka APO-1 or CD95) = cell membrane protein, belongs to tumor necrosis factor (TNF) receptor family.
 - ii. **Note:** The Fas ligand binds to Fas receptor and will cause cell-signaling cascade. This will activate procaspases into active caspases.
 - iii. The caspases will cleave two DNA repair enzymes → poly-ADP-ribose polymerase (PARP) and DNA protein kinase. Results in chromatin fragmentation
 - b. Ligand binding will initiate the coupling of adaptor proteins that will activate caspase-8. In turn, caspase-8 will activate other caspases for cell breakdown
2. **Bax Pathway (maroon)**
- a. A Bax protein (channel protein) will insert into the mitochondrial membrane.
 - b. This will cause leakage of cytochrome c from the mitochondria.
 - i. Cytochrome c is an activator of caspases
 - c. Cell death will happen when chromatin is fragmented and the cell's structural components are released outside the cell as apoptotic bodies.
 - i. **Note:** cell damaging effect of Bax is blocked by binding of protein bcl-2 to Bax
 - d. Outside the cell, macrophages will phagocytize (“cell eating”) the apoptotic bodies.

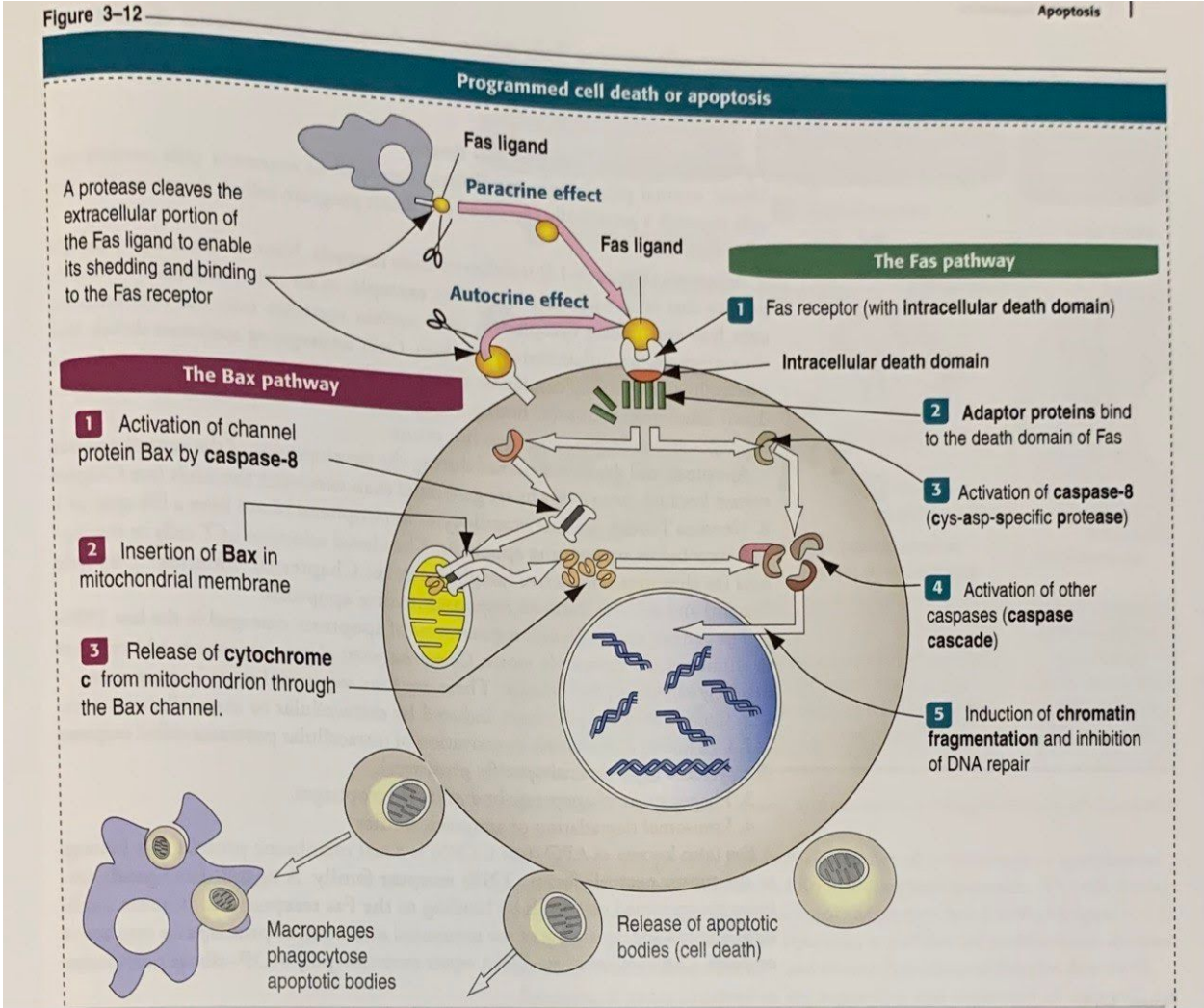


Figure 4. Apoptosis Pathways⁶

Here is a diagram depicting the different stages of an apoptotic cell. (Read diagram, Figure 4)

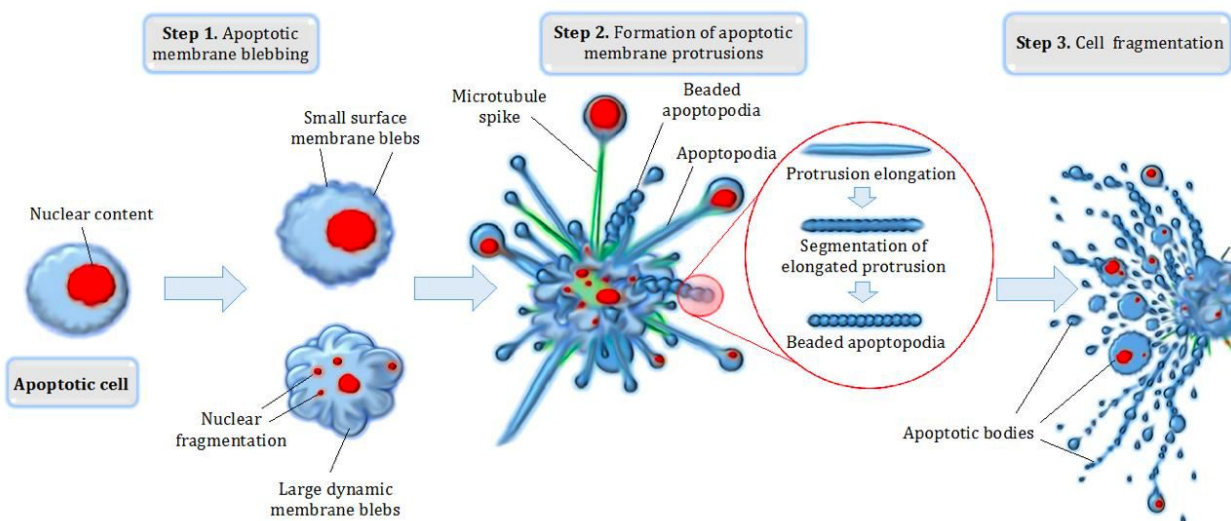


Figure 5. Nuclear fragmentation and bleb⁶

NOTE: Apoptosis occurs in four steps: (1) extracellular and intracellular factors induce cell death, (2) cell killing is activated by caspases (intracellular proteases), (3) phagocytosis of apoptotic bodies by macrophages, (4) lysosomes degrade apoptotic bodies.

⁶ [https://en.m.wikipedia.org/wiki/Bleb_\(cell_biology\)](https://en.m.wikipedia.org/wiki/Bleb_(cell_biology))

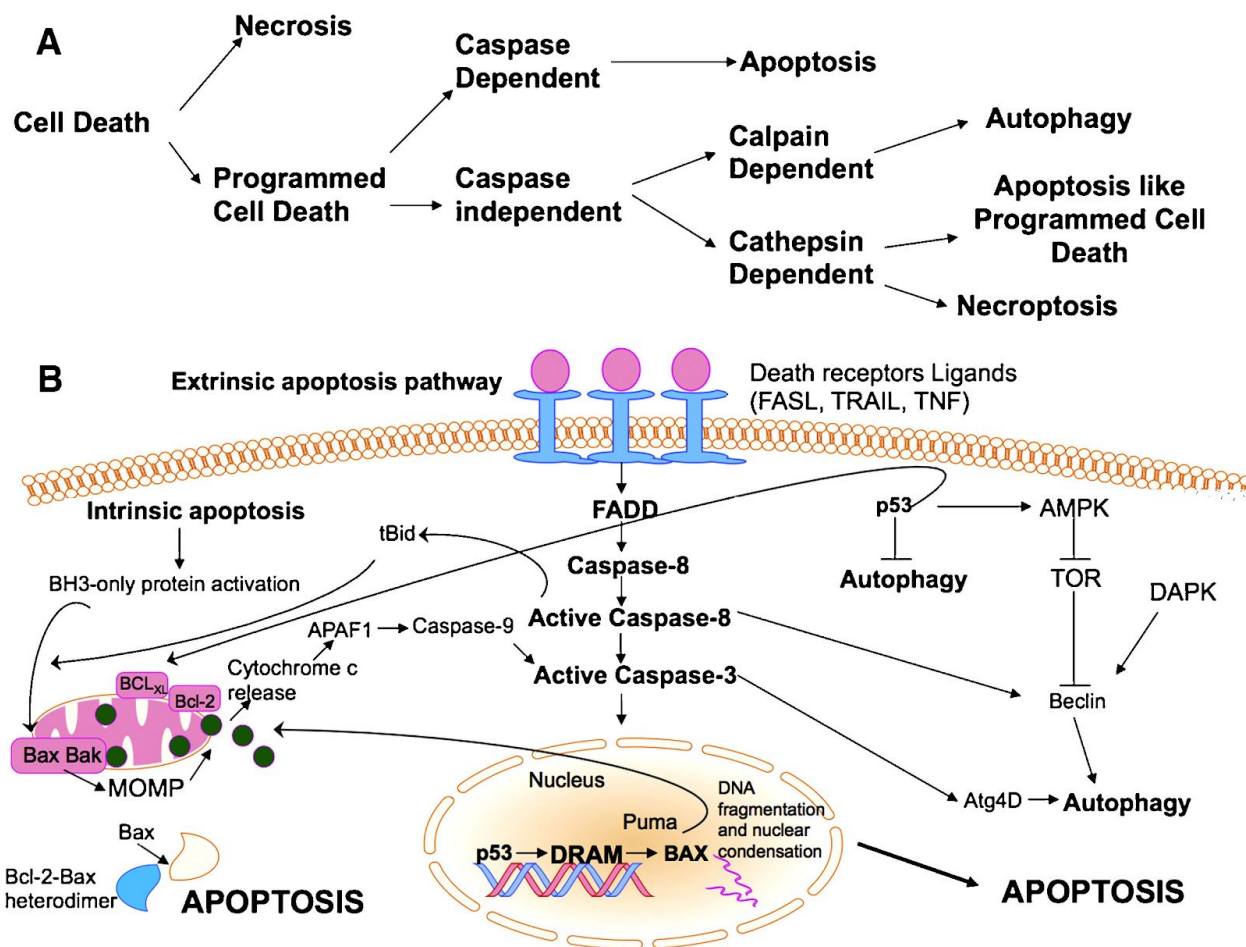


Figure Intrinsic and Extrinsic Pathways of Caspase.⁷

Note: The intrinsic and extrinsic pathways meet at caspase-3.

Intrinsic Pathway

The mitochondria plays a key role in apoptosis. “In the intrinsic pathway, the event of mitochondrial outer membrane permeabilization (MOMP) is what causes the cytochrome c to be released into the cytosol. This pathway can be activated by DNA damage, ER stress, metabolic stress, UV radiation or growth-factor deprivation (non-receptors). Mitochondria play key roles in activating apoptosis in mammalian cells. Bcl-2 family members regulate the release of proteins from the space between the mitochondrial inner and outer membrane that, once in the cytosol, activate caspase proteases that dismantle cells and signal efficient phagocytosis of cell corpses”⁸

⁷ <https://doi.org/10.1016/j.semcancer.2015.03.001>

⁸ <https://doi.org/10.1146/annurev-genet-102108-134850>

Extrinsic Pathway

“The extrinsic pathway involves stimulation of members of the tumor necrosis factor (TNF) receptor subfamily, such as TNFRI, CD95/Fas or TRAILR (death receptors), located at the cell surface, by their specific ligands, such as TNF-alpha, FasL or TRAIL, respectively”.⁹

Necrosis

Necrosis (“unprogrammed”) is a cellular condition in which healthy cells are destroyed by external processes, like inflammation. In this case, cell death will cause a loss of functional tissue and premature cell death in living tissues by autolysis. One condition that is related to necrosis is hypoxia, which is a broad term that describes how the body's oxygen demand is greater than the oxygen supply. When this happens ATP levels drop and cellular functions can not be maintained and when this lasts long enough cells die.

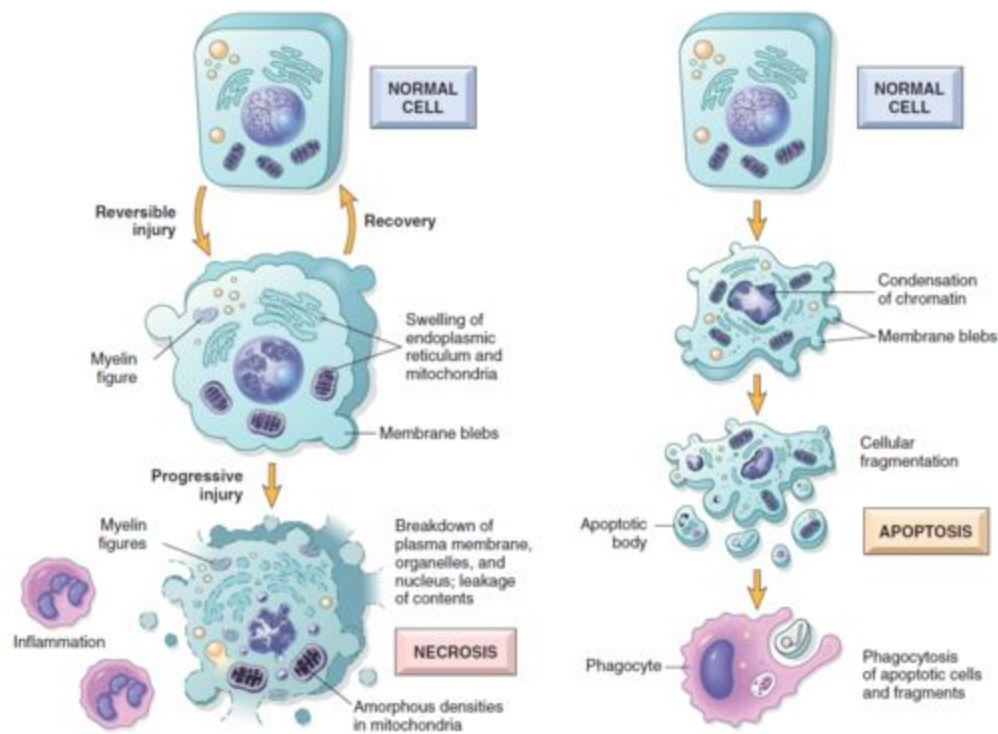


Figure 1-6 Cellular features of necrosis (left) and apoptosis (right).

Types of Necrosis

- a. Coagulative necrosis

⁹ https://www.genome.jp/dbget-bin/www_bget?ko04210

Accidental cell death in the tissues (multiple cells) caused by a lack of blood flow. Can be observed in the kidney, heart, and adrenal glands.

- i. Myocardial infarction = tissue death in the heart (“myo” = muscle, “cardio” = heart)
 - ii. Gangrene (coagulation necrosis)¹⁰ = insufficient blood supply or infection in deeper tissues
- b. Liquefactive necrosis (colliquative necrosis)
Bacterial (pus-forming) or fungal infection, results in tissues becoming a liquid viscous mass.¹¹
- i. Brain abscess = pus-filled swelling in the brain¹²
- c. Caseous necrosis
Type of cell death in tissues where the cellular outline is lost and tissues appear cheese-like and crumbly.¹³
- i. Tuberculosis
- d. Fat Necrosis
- i. Acute pancreatitis
 - ii. Breast injury
- e. Fibrinoid necrosis blood vessels
- i. Malignant hypertension
 - ii. Vasculitis

Autophagy

Define and picture

Cancer

Define

Cellular Senescence

Cellular senescence in cancer.....

¹⁰ <https://www.news-medical.net/health/Types-of-gangrene.aspx>

¹¹ <https://www.sciencedirect.com/topics/medicine-and-dentistry/liquefactive-necrosis>

¹² <https://www.nhs.uk/conditions/brain-abscess/>

¹³ <https://www.dictionary.com/browse/caseous-necrosis>