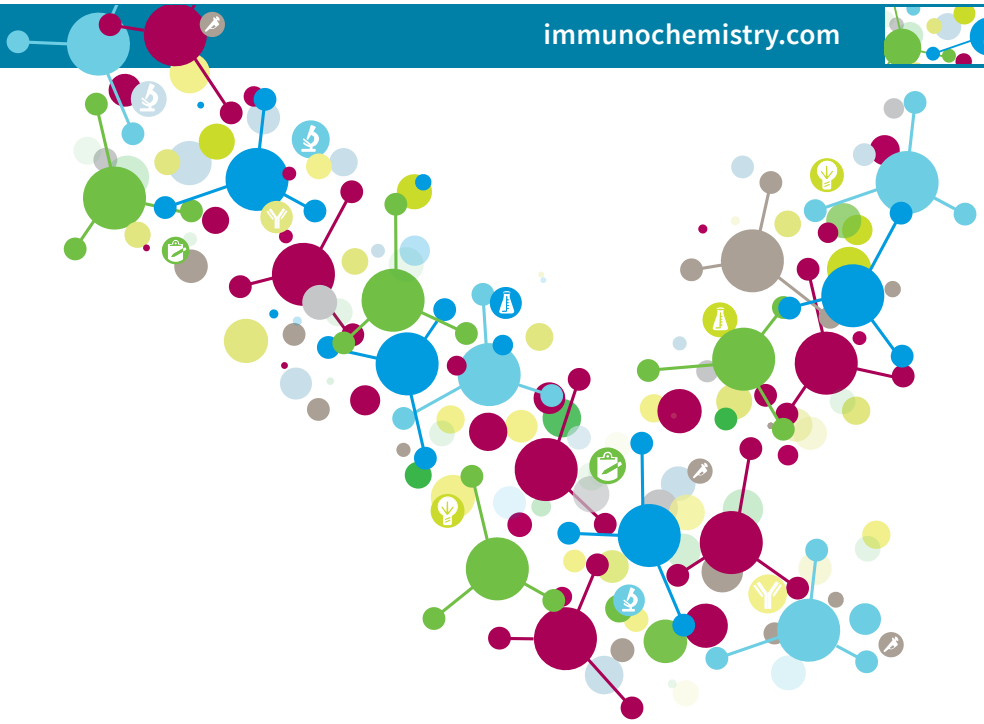

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Necrosis vs Necroptosis vs Apoptosis

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Introduction

Necrosis is a form of cell death which results in the unregulated digestion of cell components. Typically occurring as the result of cellular-trauma induced by physical/environmental factors, it leads to the premature death of cells in living tissue by a process of autolysis. A few common environmental factors known to induce necrosis include: infection, toxins, mechanical trauma, ischemia, and thermal damage from extreme high or low temperature exposure. Cellular death due to necrosis does not follow the apoptotic signal transduction pathway, but rather is characterized by loss of cell membrane integrity and an uncontrolled release of cellular components into the extracellular space. This release initiates an inflammatory response attracting leukocytes and nearby phagocytes to eliminate the dead cells and its products by phagocytosis. Initially, neutrophils rapidly infiltrate into the tissue site quickly followed by accumulations of monocytes. This response to injury is so methodical that pathologists use these sequential events as a means for establishing the date and time of tissue injury, e.g. in a myocardial infarction. Although the necrotic form of cell death is universally observed, its underlying mechanisms are poorly understood.

In direct contrast to the unregulated necrosis type cell-death event, necroptosis represents an example of a regulated version of the necrotic cell death pathway. As was the case with the necrotic cell death, necroptosis is also caspase independent. However, in a manner analogous to apoptosis, necroptosis is triggered by the binding of TNF-α and Fas ligand to their respective cell surface receptors which also is observed within classic extrinsic apoptosis induction. Ligand binding to TNF family surface receptors triggers a signal transduction event leading to sequential phosphorylation (kinase activity based) of receptor interacting protein kinase 1 (RIPK1) and receptor interacting protein kinase 3 (RIPK3) to form a RIPK1-RIPK3 heterodimer scaffold complex. This heterodimer complex formation allows for the further recruitment of free RIPK3 leading to RIPK3 auto-phosphorylation and subsequent recruitment of mixed lineage kinase domain-like protein (MLKL) forming the necrosome. MLKL is correspondingly phosphorylated by RIPK3 leading to the formation of MLKL homo-trimers which migrate to the plasma membrane, where it inserts, leading to the release of intracellular contents into the extracellular space.

Morphologically, necrosis is quite different from apoptosis. During unregulated necrosis, cells exhibit a number of morphological features that may vary by cell type. Some of the common structural signs of necrosis include: plasma membrane swelling, cytoplasmic vacuole formation, ruptured mitochondria and lysosomal organelles, and eventual breakdown of the plasma membrane leading to release of cytosolic content into extracellular regions and induction of an inflammatory response. In contrast, apoptotic cells will shrink and exhibit condensed nuclear structure. Apoptotic cells eventually break down into membrane-enclosed apoptotic bodies which are promptly phagocytized and removed from circulation. Their removal is critical to the avoidance of physiologically detrimental inflammatory response. Biochemical hallmarks of apoptosis such as activation of specific proteases (caspases) and oligonucleosomal DNA fragmentation are absent in necrotic cells. Necrosis is an uncontrolled and passive process that usually affects large fields of cells whereas apoptosis is a controlled and energy (ATP)-dependent event usually limited to individual or small clusters of cells. Necrotic cell injury is mediated by two main mechanisms; interference with the energy supply of the cell and direct damage to cell membranes.

Causation Factors of Necrosis

Ischemia

Ischemia is a restriction in blood supply to tissues, causing a shortage of oxygen and glucose that is necessary for cell survival. Ischemia is generally associated with problematic blood vessel function (e.g. atherosclerosis, thrombosis), causing damage to or dysfunction of affected tissue regions. Avascular necrosis (AVN), also called osteonecrosis or bone infarction, is defined as death of bone tissue due to interruption of the blood supply, often in the femoral head. Other well-known forms of ischemia causing necrosis are myocardial infarction, stroke, and gangrene.

The most common form of severe ischemia is coagulative necrosis, a condition characterized by the formation of a gelatinous substance in dead tissues in which the architecture of the tissue is maintained, and by protein denaturation, causing albumin to transform into a firm and opaque state.

Infection

Pathogen invasion can create a competition for energy resources and nutrients with the host. When the pathogen (such as a virus or bacterium) propagates intracellularly, necrosis may be the net result, leading to the release of the multiplied pathogen to infect neighboring cells. Syphilis is a sexually transmitted infection caused by the bacterium *Treponema pallidum*. Left untreated, syphilis infections may progress to a tertiary stage (usually 3-15 years after infection) of the disease. A small fraction of tertiary stage infections will evolve into gummatous syphilis. Gummatous syphilis is characterized by the formation of chronic gummas, which are soft, tumor-like balls of inflammation (granuloma) around a necrotic center. These central regions begin to die through coagulative necrosis, as they retain some of the structural characteristics of previously normal tissues. In contrast, in the granulomas of tuberculosis (caused by the bacterium *Mycobacterium tuberculosis*) preexisting structures are obliterated by a form of cell death known as caseous necrosis. Dead cells from caseous necrosis disintegrate but are not completely digested, leaving granular particles. Gummas are most commonly found in the liver (gumma hepatis), but can also be found in brain, heart, skin, bone, testis, and other tissues, leading to a variety of potential problems including neurological disorders or heart valve disease. Liquefactive necrosis (or colliquative necrosis), in contrast to coagulative necrosis (see ischemia), is characterized by the digestion of dead cells to form a viscous liquid mass.

This is typical of bacterial, or sometimes fungal, infections because of their ability to stimulate an inflammatory response. The necrotic liquid mass is frequently creamy yellow due to the presence of dead leukocytes and is commonly known as pus.

Toxins and venoms

In the United States, only spider bites from the Brown Recluse spider (genus Loxosceles) routinely progress to necrosis. In other countries, spiders of the same genus, such as the Chilean Recluse in South America, have the potential to cause necrosis around the area of the spider bite. Toxins such as snake venoms may inhibit enzymes leading to necrotic cell death. Necrotic wounds have also resulted from the stings of Vespa mandarinia. High doses of acetaminophen have been reported to cause hepatocellular necrosis. Bacterial toxins like SLT2 and Toxin A can also induce necrosis.

Physical trauma

Tissue damage incurred by physical force can lead to cellular breakdown and loss of blood supply, leading to necrosis. This is in addition to necrosis by ischemia and infection that may develop later because of the trauma.

Thermal damage

Elongated exposure to freezing conditions may cause ice crystals to form in the tissues (starting with the skin at nose, finger tips and toes), which causes damage at the cellular level, leading to necrosis.

A burn is a type of injury caused by heat, cold, electricity, chemicals, friction, or radiation. Burns that affect only the superficial skin layers are known as superficial or first-degree burns. In a full-thickness or third-degree burn, the injury extends to all layers of the skin. A fourth-degree burn additionally involves injury to deeper tissues, such as muscle, tendons, or bone. Up to second degree burns form blisters that will ultimately heal on their own.

Fat necrosis

Fat necrosis is a benign non-suppurative inflammatory process of adipose tissue which was initially described in the breast, presenting itself as a subcutaneous hard lump resembling cancer. In fat necrosis, the enzyme lipase releases fatty acids from triglycerides. The fatty acids then complex with calcium to form soaps that will disintegrate membranes. Fat necrosis is associated with trauma of the pancreas or with acute pancreatitis, but it can also occur in the salivary gland and in neonates after a traumatic delivery.

Immune-mediated vascular damage

Fibrinoid necrosis is observed when there are immune complex deposition events occurring within the blood vessel walls. This action leads to activation of the complement cascade and the subsequent chemotactic influx of neutrophil and monocytic cells associated with a classic Type III hypersensitivity reaction. Deposits of these immune complexes, together with fibrin that has leaked out of vessels, result in a bright pink and amorphous appearance in H&E stains, called “fibrinoid” (fibrin-like) by pathologists. If necrotic cells and cellular debris are not promptly destroyed and reabsorbed, they tend to attract calcium salts and other minerals and may become calcified. In small vessel vasculitis, fibrin plugs frequently occur in the vessel lumen, but the term fibrinoid usually refers to material outside the lumen of a vessel. Fibrinoid necrosis also occurs in the walls of arterioles in malignant hypertension (blood pressure greater than 200/130 mmHg), immune vasculitis (e.g. polyarteritis nodosa), and hyper-acute transplant rejection.

Secondary necrosis

Necrosis also occurs when apoptosis happens at such scale that phagocytosis of the apoptotic bodies can no longer keep up, or when phagocytosis for other reasons is not available, thus resulting in lysis of apoptotic cells. Then the necrosis is considered secondary to apoptosis, although the argument is made that secondary necrosis is a natural finish of the apoptotic process. It is important to note that in many pathologies, necrosis and apoptosis happen side-by-side while it is not always clear which was first. There is still a lot to be discovered with respect to the roles that apoptosis, necrosis, and necroptosis play in the genesis of neurodegenerative and cardiovascular diseases, and cancer.