Self-annihilation
A Cell’s Story of Suicide

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This article presents an analysis of cell death. An in-depth review of the pathophysiology of apoptosis is presented. This article is not typical of those usually seen in DCCN but is of importance because it describes the process of cell death, which occurs in all patients. Keyword: Apoptosis, Cell death, Cell suicide, Self-annihilation

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INTRODUCTION
Cell death occurs through 1 of 2 mechanisms: necrosis or apoptosis. Although most clinicians are familiar with the concept of necrosis, many are not as comfortable discussing apoptosis. Apoptosis is a normal, physiologic form of cell death that is silent, predictable, and highly organized. It is a powerful tool that is unleashed only when signals indicate that a cell is no longer needed or is damaged. Apoptosis prevents an accumulation of unwanted or unhealthy cells within an organism. Dysregulation—either too much or too little regulation—of apoptosis has been implicated in tumor formation, keloid formation during wound healing, the progression of congestive heart failure, and secondary injury with neurotrauma. In contrast, necrosis is a form of cell death that is characterized by cellular swelling and the loss of membrane integrity in response to an unexpected insult such as hypoxia or trauma leading to a cellular energy crisis. Although apoptosis and necrosis are 2 morphologically distinct phenomena, it is important to note that these processes may overlap.

APOPTOSIS
Apoptosis or cellular suicide is orchestrated by a precise and tightly controlled chain of events that ultimately allows the cell’s carcass to be removed without disruption of adjacent healthy cells. A form of self-annihilation, apoptosis is morphologically different from necrosis with respect to the nuclear and cytoplasmic changes that occur. The morphologic trademarks of apoptosis include chromatin condensation, membrane blebbing, cell shrinkage, and the subsequent breakage of the cellular components into apoptotic bodies.

REVIEW OF PHYSIOLOGY
Chromatin is Greek for “colored body.” It is the part of the cell’s nucleus that contains all of the DNA material found within that nucleus. DNA is always associated with other proteins, and the combination of these proteins and the nuclear DNA is called chromatin.

Mitochondria are frequently called the powerhouse of the cell. The mitochondria extract energy from many nutrients, including oxygen. Mitochondria are present in the cytoplasm of the cell and the quantity found can be as few as several hundred to several thousands. This is dependent on the energy needs of the cell.

There are 3 core elements of apoptosis. These elements include the activation of the process, the inhibition using inhibitors of apoptosis proteins (IAPs), and the execution. IAPs are a part of a check and balance system within the cytoplasm. They prevent inappropriate activation of the apoptosis process. When these proteins are blocked by substances called second mitochondrial activator of cell death (SMAC) caspase-dependent apoptosis ensues, allowing the cell to be disassembled.
Apoptosis differs from necrosis in that apoptosis generally does not involve the recruitment of inflammatory cells or mediators to complete its task. What this process does depend on is the activation of an enzyme cascade that systematically cleaves proteins including the cell’s nuclear DNA. A variety of stimuli can activate the cell’s death program, using 2 pathways: the Receptor pathway and the Mitochondrial pathway. Regardless of which pathway is initially triggered, the end result is cell death.3

The Receptor pathway is dependent on the stimulation of death receptors on the cell membrane. Signals received through these cell membrane or surface receptors lead to the activation of a family of enzymes called caspases. In some cell types, activation of the Receptor pathway may be sufficient to kill the cell. In other cell types, it is necessary to involve the Mitochondrial pathway to achieve execution.3

The exact mechanism involved in the Mitochondrial pathway continues to be debated and its mechanisms revealed.3 One theory is the Mitochondrial pathway is initiated when the outer membrane of the mitochondria becomes more permeable after exposure to a stressor. When a cell is stressed by ischemia, oxidative injury, or exposure to toxins, the outer membrane of the mitochondria swells. Membrane swelling leads to an increase in permeability and the subsequent leakage of a substance called cytochrome C. Cytochrome C leaks out of the mitochondria into the cytoplasm and becomes a key protein in the apoptosis sequence. Cytochrome C binds to apoptosis activation factor 1 (Apaf-1). This complex leads to the activation of caspase-9, which in turn leads to the downstream activation of caspase-3, known as the executioner caspase (Figure 1). SMAC is also released from the mitochondria and suppresses the IAPs, which would normally keep caspase-9 in check.4

Caspases are categorized into 3 different groups, one of which is involved in the inflammatory response while the other 2 groups are considered to be apoptotic caspases. Species ranging from insects to humans (although humans have a more sophisticated program) rely upon caspases to eliminate cells that are no longer healthy. Each of the 12 caspases found in humans are stored within different compartments of the cell. Stored caspases are inactive and are called procaspases. Successful completion of a cell’s eradication rests on the activation of these enzymes until ultimately an executioner caspase is unleashed on the cells vital protein structures. The executioner caspase is the cell’s assassin. Caspase-3 has been identified as the executioner or the key moderator of death in human cells using the Mitochondrial pathway.4 Caspase-3 cleaves or “chops up” dozens of different proteins within the cell, leading to its demise. It is important to note that this cascade requires energy in the form of adenosine triphosphate (ATP) for the process to be completed.

In addition, the damage to the outer membrane of the mitochondria leads to the release of apoptosis-inducing factor (AIF), a substance that snips the cell’s nuclear DNA into fragments, independent of caspases (Figure 1). It is the combined activation of executioner caspase-3 and AIF that creates the killing machinery that can finalize the cell’s “death dance.”2 The fragments that are created are then encased in membrane vesicles and are called apoptotic bodies (Figure 2). Interestingly, the term apoptosis is Greek for “falling off” (similar to leaves dropping from trees) and offers a wonderful, visual description of how the apoptotic bodies are formed. Once formed, the bodies are recognized by macrophages and are phagocytosed without stimulating the inflammatory response.3

Oxidative stress and ischemia are known triggers of mitochondrial pathway activation and the subsequent caspase cascade. Activation of the mitochondrial pathway is described as a “point of no return.” In other words, once the cell reaches this phase, it is committed to dying. It is curious that the tools the cell normally uses to repair itself, that is, DNA replication and repair, are “turned off” during this phase.

Each phase of apoptosis is contained and precise, thus preventing collateral damage to adjacent cells. As stated earlier, apoptosis requires energy and if the mitochondria were not able to provide energy during this process, then the dying cell’s attempt at apoptosis would be abandoned and the more muddled process of necrosis would predominate. Although cellular death is the ultimate result of necrosis or apoptosis, the process by which that death occurs is significant.
COMPARING NECROSIS AND APOPTOSIS

Necrosis is a very different process than the one described above. The precipitating event for necrosis is usually unexpected and, therefore, not carefully regulated. Necrosis is a messy and disordered process resulting from a severe energy shortage leading to the loss of membrane sodium/potassium/ATP-ase pumps. The loss of these pumps causes cells to swell and ultimately rupture. Apoptotic cells have cell membranes that remain intact and ultimately envelop fragmented nuclear DNA.

The cellular explosion evident in necrosis leads to spillage of intracellular contents into the surrounding region, creating collateral tissue damage. Necrosis also leads to the recruitment of inflammatory mediators, many of which lead to secondary damage or injury. Unlike apoptosis, where the death process can literally focus on one cell at a time, necrosis can involve significant amounts of the involved tissue and/or organ bed.

Apoptosis requires an energy source. The mitochondria are the purveyors of this energy. A lack of ATP will result in the apoptosis program being aborted in favor of necrosis. The chaotic process of necrosis and its subsequent collateral tissue damage can leave in its wake organ dysfunction, while apoptosis leaves adjacent cells intact.

CONCLUSION

Although apoptosis is part of the natural cycle of cellular life, accelerated apoptosis has been implicated in post-myocardial infarction and ischemic cardiomyopathy. Diffuse myocyte apoptosis may also play a significant role in the progression of heart failure where areas of the myocardium have been subjected to milder forms of ischemia, which did not result in necrosis. Inhibited apoptosis may result in an overproduction of cells as is found with keloid formation in a healing wound bed or the development of a cancerous tumor. Understanding and potentially controlling specific events during apoptosis is an exciting and growing area of medical research worthy of the clinician’s attention.

REFERENCES


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