Apoptosis

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Abstract

Apoptosis, also known as programmed cell death, is a normal cell process required for the development of cells and maintenance of homeostasis in the tissues of organisms. In contrast to what its name may suggest, apoptosis in general does not harm the organism. In fact, it is a vital process in all living organisms that permits selective elimination and removes excess cells from a mushrooming population. For instance, without apoptosis, humans are more susceptible to cancers and other diseases such as AIDS (Autoimmune Deficiency Syndrome) and EBV (Epstein-Barr Virus). This paper aims to explain the purposes, causes, triggers, and signs of apoptosis. It will also provide some examples of apoptosis and discuss the consequences of a lack of apoptosis.

Apoptosis

The term “apoptosis” was coined in 1972 by Kerr et al (Alnemri, 2002). It is derived from a Greek word meaning the dropping of leaves from trees. Apoptosis commences when a cell has an adequate amount of time to organize several events in it that will lead to its destruction (Ibelgaufts, 2009). Apoptosis serves a wide variety of purposes. First and foremost, it is vital to the development and maintenance of cells in the organism. For example, organisms undergoing embryonic development, metamorphosis, or tissue atrophy require apoptosis to “sculpt” the shape of the organs (Jakubowski, 2002). Second, apoptosis keeps the total number of cells in an organism under control. Third, it eliminates cells that pose threats, such as cells with damaged DNA and cancer cells, as well as cells of the immune system that have already completed their tasks. Lastly, apoptosis weakens the spread of a virus by killing cells infected by the virus (Ibelgaufts, 2009).

Importance

Clearly, apoptosis is an imperative process in a living body. Human diseases can be traced directly or indirectly to failures in the process of apoptosis (Fadeel and Orrenius, 2005). This is because of the fact that when apoptosis is not successfully carried out, extraneous cells survive, which leads to abnormalities in the organism and a heightened chance of cancer. Additionally, apoptosis aids in the adaptation of an organism to its environment, releases pro-inflammatory mediators, and precludes the release of harmful contents from diseased cells (Ibelgaufts, 2009).

Examples

Apoptosis arises during many natural and biological processes. It takes place during embryonal development, morphogenesis (when an organism develops its shape), metamorphosis (when an organism develops after it is born), endocrine tissue atrophy (when the endocrine tissue

wastes away), tissue turnover (when new cells replace old cells), and tumor regression (Ibelgaufts, 2009). Frogs undergo apoptosis to remove the tails they had as tadpoles. Without this process, humans, chickens, and ducks would have all their digits conjoined. Furthermore, humans depend on apoptosis to remove extra cells in the brain so that proper connections between neurons in the brain can be formed (Kimball, 2009).

Steps and Signs of Apoptosis

Apoptosis consists of four steps. First of all, the cell must make the decision to activate the apoptosis pathway. Following it, the cell will undergo the actual process of programmed death (i.e., suicide). Later, phagocytes (immune cells) engulf the remains of the cell. Eventually, any remnants of the apoptotic cell will be removed by the process of degradation (Jakubowski, 2002).

Several signs indicate the occurrence of apoptosis. Initially, chromatin in the nucleolus will disappear, and blebs will occur on the surface of the cell (Robey, 2006). Afterwards, the chromatin will form a border inside the nuclear membrane. Finally, DNA in the cell will become fragmented.

In order for apoptosis to occur, the cell nucleus must condense and separate into pieces. Then, the cytoplasm must also condense and separate, forming apoptotic bodies with membranes. In the end, chromosomes in the cell disintegrate into fragments with many nucleosomes (Jakubowski, 2002).

Causes

A variety of factors can cause apoptosis, including oxidative stress, DNA damage, and abnormal protein folding (caspases.org, 2004). Oxidative stress occurs when there is a disturbance in the equilibrium of pro-oxidant/anti-oxidant systems in cells, which produce and

detoxify oxidants during aerobic metabolism. DNA damage refers to mutations in the DNA, which leads to incorrect or illogical coding during protein synthesis. Apoptosis can also be caused by enzymes incorrectly copying the sequence before mitosis or meiosis. Improper protein folding happens when proteins do not return to their original conformation, which may hinder them from performing their biological function.

Triggers

Apoptosis can be triggered by multitudinous stimuli, although not all cells die in response to a specific stimulus. Stimuli can be classified as either internal or external (Jakubowski, 2002). Internal signals include virus infection, oxidative damage, and ionizing radiation (caspases.org, 2004). These lead Bcl-2, a protein that assists in the process of apoptosis, to activate Bax, a protein that in turn makes holes in the membrane of the mitochondria. Cytochrome c, another protein, then infiltrates the cytoplasm and binds onto Apaf-1, a gene, producing complexes that amass into apoptosomes. The apoptosomes then activate caspase-9, which adheres to both caspase-7 and caspase-3. Caspase-3 and caspase-7 initiate a series of proteolytic activity, prompting structural protein digestion, DNA degradation, and finally, phagocytosis.

In comparison, external signals that can trigger apoptosis include hormones, a lack of a "survival" signal and cell to cell contact (Jakubowski, 2002). These external signals mainly involve FasL and TNF-alpha/beta. These two proteins bind to the Fas and TNF receptors on the cell membrane, thus activating caspase-8. Subsequently, caspase-8 acts similarly to caspase-9 and releases a proteolytic cascade, which begins phagocytosis. Furthermore, the Apoptosis-Inducing factor (AIF) is another pathway by which cells may undergo apoptosis. AIF is prevalent in neurons and does not involve any caspases. When AIF is discharged from the mitochondria, where it is usually located, it voyages to the nucleus of the cell, secures itself to

the DNA, and starts DNA degradation. The degradation of the DNA will eventually end in the death of the cell. Sometimes, though, cells already have a death pathway. In those cases, in order to prevent their deaths, the cells have to block those pathways using survival factors (Henkart, 1999).

Caspase Activation

Scientists are currently investigating the mechanisms by which caspases are activated. The activation of caspases appears to be irreversible, and the process undoubtedly ends with the death of the cell (Henkart, 1999). It is hypothesized that procaspases, caspases that have large pro-domains, assemble to autoactivate the caspases. Some experiments have shown that mitochondria play a role in one crucial pathway that involves the activation of pro-caspase-9. At the same time, other experiments suggest that ligands crosslinking death receptors prompt the synthesis of a cytoplasmic complex where pro-caspase-8 is compiled and activated. In both

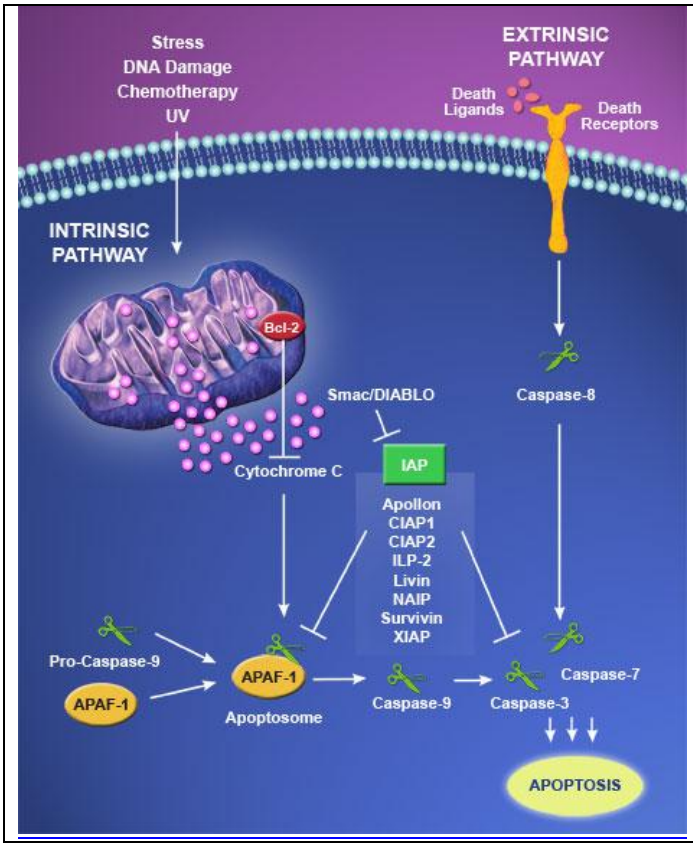

Figure 1. A schematic diagram illustrating two distinctive signal transduction pathways (intrinsic and extrinsic) that can lead to the activation of various caspases and eventually apoptosis. (Imgenex, 2006)

cases, initiator caspases activate other pro-caspases, which ultimately ends with the death of the cell.

DNA Fragmentation

Wyllie described DNA fragmentation in 1980 (Henkart, 1999). In the experiment, DNA from cells dying from apoptosis was analyzed by agarose gel electrophoresis. The results were ladders with about 200 bp (base pairs) repeats. There were also signs of histone protection in the nucleosomes of the chromatin. Later results yielded DNA separated into even larger portions. Because of the fact that it only requires a few double stranded DNA breaks to prevent a cell from successfully completing mitosis, the DNA fragmentation clearly manifested the death of the cells. Nevertheless, scientists have conducted experiments where enucleated cells (i.e., ones deprived of their nuclei) still underwent apoptosis and died. Hence, this process does not require the presence of a nucleus in the cell.

Necrosis vs. Apoptosis

Necrosis is a process that may appear similar to apoptosis at first glance, but these two processes are extremely dissimilar. During the first step of necrosis, the chromatin clump together and the organelles become swollen. Later, disintegration happens, contents within the cell are released, and there is a high probability of inflammation. Necrosis is a pathological process that occurs when the cell sustains an injury. In contrast to apoptosis, necrosis is both unordered and accidental, involves sheets of cells, and does not require additional energy consumption. Cells that undergo necrosis typically swell, and their membranes are lost. The necrotic cells are not evolutionarily conserved (Hall, 2002).

In comparison, during the first step of apoptosis, there is mild convolution in the cell and condensation of the cytoplasm, but the chromatin remains compact and isolated. Afterwards, nuclear fragmentation and blebbing take place to produce apoptotic bodies. The end result is an apoptotic body which is consumed by a phagocytic cell. Unlike necrosis, apoptosis can be physiological or pathological. It is a regulated cell process that involves single cells and requires energy. During apoptosis, cells shrink in size, but the membrane is kept intact. The apoptotic cells are evolutionarily conserved (Hall, 2002).

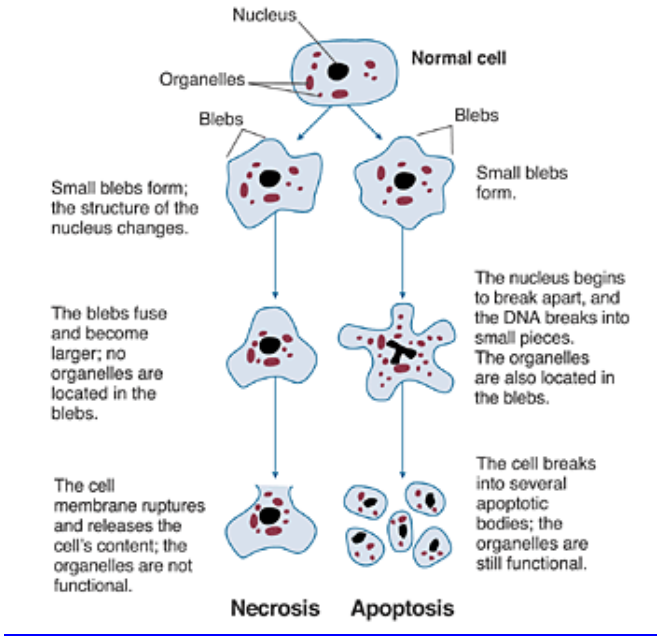

Figure 2. Comparison of the dissimilar processes involved in cell death produced by necrosis and apoptosis (NIAA, 2005)

Consequences of a Lack of Apoptosis

Unfortunately, serious consequences may be induced by a lack of regulation of apoptosis. A lack of regulation may cause or intensify AIDS, neurodegenerative or viral diseases, stroke, and cancer (Jakubowski, 2002). In the case of AIDS, the number of T Helper cells plunge because they are fooled into killing themselves. Strokes may be exacerbated when the amount of blood flow to the brain is restricted by apoptosis, which in turn leads to neural death. Cancer poses a greater threat when tumor cells can no longer undergo apoptosis, leading to their exponential

growth and duplication. Lastly, a person with an autoimmune disease may suffer when self-reactive immune cells delude normal body cells into committing suicide through the process of apoptosis.

Conclusion

Undoubtedly, there is still much to be discovered about the process of apoptosis. However, it is known for sure that apoptosis plays an integral part in normal and abnormal biological processes. All organisms need apoptosis to keep the number of cells in their bodies under control. Apoptosis is extremely important when an organism is undergoing embryonic development, metamorphosis, or tissue atrophy. Apoptosis is also important for cells infected by a virus or cells that suffer DNA damage. A lack of regulation of apoptosis may cause or intensify AIDS, cancer, stroke and neurodegenerative or viral diseases. In the future, scientists may work to better understand and to manipulate apoptosis. They will be able to use it in therapy to treat various types of diseases, including cancer, heart disease, stroke, AIDS, and neurodegenerative or viral diseases (Henkart, 1999). All in all, apoptosis is a natural biological process waiting to be further explored and utilized in the prevention and treatment of human diseases.

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