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Short Communication

Mechanisms Involved in Apoptosis

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DESCRIPTION

Apoptosis is a form of programmed cell death. Biochemical occasion prompts cell morphological changes. These modifications incorporate blebbing, cell shrinkage, atomic fracture, chromatin buildup, DNA discontinuity, and mRNA decay [1]. German scientist Carl Vogt was first to define the principle of apoptosis in 1842. An average adult human loses cells of about 50 to 70 billion cells per day due to apoptosis. An average human child between eight and fourteen years old, loses around twenty to thirty billion cells per day. Apoptosis is an organized process in which the cell's substances break down and are wrapped into small packets of membrane for "garbage collection" by immune cells. Apoptosis plays a significant role in physiology and pathology, and can be caused by numerous stimuli, including ischemia, hypoxia, exposure to certain drugs and chemicals, immune reactions, infectious agents, high temperature, radiation, and various disease states. Increased expression of Anti-apoptotic proteins like BCL-2 (B-Cell Lymphoma 2) and down instruction of pro-apoptotic proteins like BAX (BCL2-Associated X Protein) are two methods for cells to resist apoptosis. The defects in the apoptosis permit tumor cells to resist traditional therapies such as chemotherapy and radiotherapy.

Mechanism of apoptosis

The initiation of apoptosis is regulated by activation mechanisms, because once apoptosis has initiated, it predictably leads to the death of cell. Apoptosis have various types of pathways such as intrinsic pathway, extrinsic pathway, TFN pathway, Fas pathway.

Intrinsic pathway

The intrinsic pathway is also known as the mitochondrial pathway. Mitochondria are essential for multicellular life. The pathway has been divided into four stages: Induction, Early, Mid and Late phase.

Stage 1: Induction phase: Induction of the intrinsic pathway arises in response to internal pro-apoptotic stimuli such as DNA damage. DNA damage can be brought by a number of external factors characterized as a bolt of lightning. These external factors include UV light, osmotic stress and growth factor extraction among others.

Stage 2: Early phase: Subsequent to DNA damage, the B-cell Lymphoma 2 (BCL-2) family signaling cascades are stimulated as exposed in the early intrinsic phase. DNA damage initiates pro-apoptotic members of the BCL family which leads to inhibition of the anti-apoptotic members such as BCL-XL and BCL-2. When free of inhibiting action of BCL-xL and BCL-2; BCL-2 homologous Antagonist Killer (BAK) and BCL-2-Associated X protein (BAX) are free to introduce into the mitochondrial membrane [2]. In the mid stage, this will lead to loss of mitochondrial membrane integrity. In children, immunological responses to rotavirus and T-cell immunity is important. Children had circulating rotavirus specific T-cells, according to lymphoproliferative tests. The absence of multiplication in infant, restricted expansion in babies under one year old and expanding multiplication with age are steady with rotavirus openness in youth.

Stage-3: Mid phase: The intrinsic pathway is categorized by permeabilization and depolarization of the mitochondrial membrane and by release of Ca2+ and other factors into the cytoplasm. The damage of mitochondrial membrane integrity results in the requirement of cell irreversibility to apoptosis. Cytochrome C is also released from the conceded mitochondria along with other proteins such as Apoptotic Protease Activating Factor-1 (APAF-1). In the cytoplasm, cytochrome C, APAF-1 and pro-caspase-9 form the apoptosome which leads to stimulation of caspase-9. Caspase-9 activation initiates activation of the effector caspases (caspase-3/7) and later exposure of Phosphatidyl-Serine (PS) to the extracellular side of the cell membrane.

Extrinsic pathway

The extrinsic pathway includes,

Stage 1: Induction phase: The extrinsic pathway is stimulated by binding of ligands to adherents of the tumor necrosis factor receptor super family including CD120a, CD120b, CD95/FAS, Death Receptor (DR) 3, CD261/DR4, CD262/DR5, CD266 and CD358/DR6. The primary apoptosis persuading ligands are TNF-alpha, lymphotoxin-alpha, FasL/CD178 and TNF Related Apoptosis Inducing Ligand (TRAIL) [3].

Stage 2: Early phase: After binding of ligand to receptor, signaling pathways are stimulated which leads to formation of signaling complexes such as the Death Inducing Signaling Complex (DISC). Some of the DISC individual components are exposed to forming downstream CD120a/b whereas DISC is represented as a single unit

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beneath CD95/DR3/4/5. The final outcome of the early phase of the extrinsic pathway is the stimulation of the initiator caspase, i.e., caspase-8. Within this phase, there is a potential crosstalk with the intrinsic pathway via caspase-8 mediated initiation of BH3-Interacting Domain (BID) death agonist. Full length BID is cleaved by caspase-8 and yields an active 15 kDa fragment which is referred to as Truncated BID (TBID).

Stage 3: Mid phase: Caspase-8 initiates the effector caspases, caspase-3 and caspase-7. Caspase-3/7 starts key apoptotic measures such as the exposure of PS to the extracellular side of the cell membrane. It is the point of junction for the extrinsic and intrinsic apoptotic pathways.

Stage 4: Late phase: At this phase of apoptosis, the extrinsic and intrinsic pathways have combined. The late phase initiates with activation of caspase-3/7 and results in DNA fragmentation and cell membrane disruption/blebbing. Caspase-3/7 releases DFF40 from its inhibitor DFF45 (Dual Form Factor) allowing DFF40 to contribute in DNA fragmentation. Endonuclease G released from the mitochondria is also capable of fragmenting DNA [4]. PARP-1 (Poly Adenosine diphosphate-Ribose Polymerase) is cleaved by caspase-3 inhibiting the ability of PARP-1 to repair damaged DNA. Caspase-3/7 also activates the serine/threonine kinase ROCK1 by cleavage of the C-terminal inhibitory area. Active ROCK1 (Rho-associated Coiled-coil Containing Kinases) leads to actomyosin dependent membrane blebbing as an interruption of the membrane. Late stage apoptosis is considered morphologically by cell shrinkage and phagocytosis of the apoptotic cell by macrophages.

TNF pathway

TNF stands for Tumor Necrosis Factor. TNF-alpha is a cytokine twisted mainly by stimulated macrophages. It is the major extrinsic mediator of apoptosis. Most of the cells in human body have two receptors for TNF-alpha: TNFR1 and TNFR2. The binding of TNF-alpha to TNFR1 has shown to activate the pathway that leads to caspase stimulation via the intermediate membrane proteins TNF Receptor-Associated Death Domain (TRADD) and Fas-Associated Death Domain protein (FADD). Cellular Inhibitor of Apoptosis Protein ½ (CIAP 1/2) can inhibit TNF-α signaling by binding to TRAF2 (Tumor necrosis factor Receptor–Associated Factor 2). FLIP inhibits the initiation of caspase-8. Binding of this receptor can also indirectly leads to the stimulation of transcription factors involved in cell survival and inflammatory responses [5]. However, signaling through TNFR1 may also induce apoptosis in a caspase-independent manner. The TNF-alpha receptor super family also contains Death Receptors (DRs), such as DR4 and DR5. These receptors bind to the protein TRAIL and mediate apoptosis. Apoptosis is recognized to be one of the primary mechanisms of targeted cancer therapy. Luminescent Iridium complex-Peptide Hybrids (IPHs) have recently designed, which mimic TRAIL and bind to death receptors on cancer cells, thus inducing their apoptosis.

Fas pathway

The Fas receptor (First apoptosis signal) is a trans membrane protein of the TNF family which binds the Fas Ligand (FasL). The interface between Fas and FasL results in the development of the Death-Inducing Signaling Complex (DISC), which contains the FADD, caspase-8 and caspase-10. In specific types of cells (type I), processed caspase-8 directly initiates other members of the caspase family, and activates the execution of apoptosis of the cell. In other types of cells (type II), the Fas-DISC starts a feedback loop that spirals into enhancing the release of pro-apoptotic factors from mitochondria and the amplified stimulation of caspase-8 [6].

CONCLUSION

Apoptosis is a multi-functional defense system which protects the host's body from infectious, genetical and immunological diseases and disorders. Instantaneously, apoptosis mediates an enzymatic cascade system which plays an important role in the process of apoptosis. The presence or absence, the rate and concentration of each enzyme expose the situation of the body and control the type of diseases. Hence, the investigation of the type and concentration of the caspase enzymes is valued basis for diagnosing and treatment. In conclusion, the apoptosis and related systems are 3-layered process which is utilized for body security, sickness conclusion and therapy Thus, although many years of investigation, there still remain countless unanswered questions in the regulation of cell survival by apoptosis.

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