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Short Communication

A Short Communication on Apoptosis

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INTRODUCTION

Apoptosis (or cell-death) is a form of programmed cell death (PCD) or cellular suicide that occurs in multicellular organisms. The apoptosis is different from necrosis, in which cells die due to injury.

The biochemical events lead to characteristic cell changes and death. These changes include blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, chromosomal DNA fragmentation, and global mRNA decay. The apoptosis produces cell fragments called apoptotic bodies that phagocytic cells are able to engulf and remove before the contents of the cell can spill out onto surrounding cells and cause damage to them. The Apoptosis is an orderly process in which the cell's contents are packaged into small packets of membrane for garbage collection by immune cells.

Apoptosis schematics

There are two best-understood activation mechanisms that are intrinsic pathway (also called the mitochondrial pathway) and the extrinsic pathway.

Intrinsic pathway

Induction phase: It occurs in response to internal pro-apoptotic stimuli such as DNA damage. DNA damage can be induced by a number of external factors represented as a bolt of lightning. These external factors include UV light, osmotic stress and growth factor withdrawal amongst others.

Early phase: Following DNA damage, the B-cell Lymphoma 2 (Bcl-2) family signaling cascades are activated. DNA damage activates pro-apoptotic members of the Bcl- family (PUMA, Bcl-2-associated agonist of cell death (Bad) and NOXA) leading to inhibition of the anti-apoptotic members Bcl-xL and Bcl-2. Once free of the inhibiting action of Bcl-xL and Bcl-2, Bcl-2 homologous antagonist killer (BAK) and Bcl-2-associated x protein (BAX) are free to insert into the mitochondrial membrane. In the mid stage this will lead to loss of mitochondrial membrane integrity.

Mid phase: The intrinsic pathway is characterized by permeabilization and depolarization of the mitochondrial membrane. The loss of mitochondrial membrane integrity is an event which commits the cell irreversibly to apoptosis. Cytochrome c is also released from the compromised mitochondria along with other proteins such as APAF-1. In the cytoplasm, cytochrome c, APAF-1 and pro-caspase-9 form the apoptosome which then leads to activation of caspase-9. Caspase-9 activation instigates activation of the effector caspases (caspase-3/7) and subsequent exposure of phosphatidylserine (PS) to the extracellular side of the cell membrane.

Extrinsic pathway: It is activated by the binding of ligands to members 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 inducing ligands are TNF-alpha, lymphotoxin-alpha, FasL/CD178 and TNF-related apoptosis-inducing ligand (TRAIL).

Early phase: Following ligand binding to the receptor, signaling pathways are activated leading to formation of signaling complexes such as the Death Inducing Signaling Complex (DISC). Several of the DISC individual components are shown forming downstream CD120a/b while DISC is represented as a single unit beneath CD95/DR3/4/5. The ultimate outcome of the early phase of the extrinsic pathway is the activation of the initiator caspase, caspase-8. Within this phase, there is a potential crosstalk with the intrinsic pathway via caspase-8 mediated activation of BH3-interacting domain death agonist (BID). Full length BID is cleaved by caspase-8 and produces an active 15 kDa fragment which is referred to as truncated BID (tBID).

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

Late phase of apoptosis

At this phase of apoptosis, the extrinsic and intrinsic pathways have converged. The late phase begins 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 allowing DFF40 to participate in DNA fragmentation. Endonuclease G released from the mitochondria is also capable of fragmenting DNA. PARP-1 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 domain. Active ROCK1 leads to actomyosin-dependent membrane blebbing as a disruption of the membrane. Late stage apoptosis is characterized morphologically by cell shrinkage and phagocytosis of the apoptotic cell by macrophages.

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