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Caspases: An apoptosis mediator

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ABSTRACT

The process of programmed cell death, or apoptosis, is generally characterized by distinct morphological characteristics and energy - dependent biochemical mechanisms. Apoptosis is a widely conserved phenomenon helping many processes, including normal cell turnover, proper development and functioning of the immune system, hormone dependent atrophy etc. Inappropriate apoptosis (either low level or high level) leads to many developmental abnormalities like, neurodegenerative diseases, ischemic damage, autoimmune disorders and many types of cancer. To use cells for therapeutic purposes through generating cell lines, it is critical to study the cell cycle machinery and signalling pathways that controls cell death and apoptosis. Apoptotic pathways provide a fundamental protective mechanism that decreases cellular sensitivity to damaging events and allow proper developmental process in multi-cellular organisms. Major mediator of apoptosis is a family of proteins known as caspases. There are mainly fourteen types of caspases but out of them only ten caspasese have got essential role in controlling the process of apoptosis. These ten caspases have been categorized into either initiator caspases (caspase 2, 8, 9, 10) or executioner caspases (caspase 3, 6, 7). Although various types of caspases have been identified so far, the exact mechanisms of action of these groups of proteins is still to be fully understood. The aim of this review is to provide a detail overview of role of different caspases in regulating the process of apoptosis.

Keywords

Apoptosis, Caspases, Cell, Extrinsic pathway, Intrinsic pathway, Perforin pathway

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INTRODUCTION

Apoptosis and necrosis are two distinct process of cell death that occurs inside tissues. Necrosis is a passive form of cell death occurs accidentally mainly under environmental perturbations and pathological conditions (i.e. hypothermia, hypoxia, infection, toxins, and trauma) with uncontrolled release of inflammatory cellular contents. Apoptosis is a controlled programmed cell death which is energy dependent and occurs naturally under normal physiological conditions where cell is an active participant in its own demise (also known as cellular suicide) (Steller, 1995). This phenomenon is characterized by distinct biochemical and morphological changes in cell that includes membrane blebbing, shrinkage, cytoskeletal disassembly, nuclear fragmentation, chromatin condensation and chromosomal DNA fragmentation (Kroemer et al., 2008). Apoptosis is responsible for the removal of undesired or damaged cells during the developmental process. Caspases are a family of cysteinyl dependent aspartate directed proteases, play essential roles in regulating apoptosis at cellular level, which finally causes cellular demise through a cascade of molecular events (Thornberry and Lazebnik, 1998; Luthi and Martin, 2007).

DIFFERENT FORMS OF CASPASE AND THEIR ACTIVATION

Caspases, major mediators of apoptosis, are synthesized as pro enzymes and get activated by various internal and external stimuli (Li and Yuan, 2008). Ten major types of caspases have been identified

viz initiator caspases with a long pro-domain (caspase 2, 8, 9, 10), effectors or executioner caspases with a short pro-domain (caspase 3, 6, 7) and inflammatory caspases (caspase 1, 4, 5) (Cohen, 1997; Rai et al., 2005). Upon activation, effector caspases proteolytically cleave a range of substrates in a cascade, leading to cellular death (Fischer et al., 2003).

ROLE OF CASPASES IN REGULATION OF APOPTOSIS

The mechanism of apoptosis is highly complex and involves energy - dependent cascade of molecular events. It is mediated mainly through three pathways, (1) extrinsic or death receptor pathway, (2) intrinsic or mitochondrial pathway and (3) perforin /granzyme pathway (Danial and Korsmeyer, 2004; Kurokawa and Kornbluth, 2009).

The Extrinsic pathway begins outside a cell, when conditions in the extracellular environment determine that a cell must die. The extrinsic pathway (**Figure 1**) is activated by external signals, such as Fas ligand (FasL) and tumour necrosis factor α (TNFα) (Locksley et al., 2001; Suliman et al., 2001; Rubio Moscardo et al., 2005). FasL binds to Fas receptor, a death receptor and Fas - associated death domain (FADD) (Hsu et al., 1995; Wajant, 2002). Binding of FasL to Fas & FADD, activates the formation of death inducing signalling complex protein (DISC), which converts pro caspase - 8 to active caspase - 8 (Kischkel et al., 1995). Active caspase - 8 has got two roles , either it activates executioner caspases (caspase - 3) or cleave the BH3 - only protein (Bid), to cleved Bid (tBid) and BH3. The tBid then activates the intrinsic apoptotic pathway by triggering oligomerization of the proapoptotic proteins, Bax and Bak (Kurokawa and Kornbluth, 2009).

Injury inside the cell triggers the intrinsic pathway. Intrinsic stresses such as oncogenes, direct DNA damage, hypoxia, and survival factor deprivation activate this pathway. The active tBid generated from the extrinsic pathway is the connecting link between the extrinsic and the intrinsic pathway. In a different cascade, activated caspase - 2 also cleaves Bid to tBid which initiates intrinsic pathway (Kurokawa and Kornbluth, 2009). The tBid translocates into the mitochondria, which triggers the activation of Bcl - 2 proteins (Bax/Bak). Bax/Bak induces mitochondrial outer membrane permeabilization (MOMP) and release the cytochrome C from intermembrane space of mitochondria into the cytolplasm (Saelens et al., 2004). Inside the cytoplasm, Cytochrome C induces ATP - dependant oligomerization of the adaptor protein Apaf -1(apoptotic protease activation factor - 1), which forms active caspase - 9 (through formation of the apoptosome complex) and finally activates caspase - 3 (**Figure 1**) (Chinnaiyan, 1999; Hill et al., 2004; Kurokawa and Kornbluth, 2009). Other apoptogenic molecules released from the mitochondria along with cytochrome C, are AIF (apoptosis inducing factor) and Smac (second mitochondria derived activator of caspase, also called DIABLO) (Du et al., 2000; Garrido et al., 2006). AIF directly translocates to the nucleus and triggers caspase - independent nuclear changes (Susin et al., 2000; Joza et al., 2001). Smac, activates apoptosis by neutralizing the inhibitory activity of IAPs (inhibitory apoptotic proteins) those inhibit caspases (Du et al., 2000).

There is an additional pathway that involves T - cell mediated cytotoxicity and perforin - granzyme - dependent killing of the cell. The perforin/granzyme pathway (**Figure 1**) can induce apoptosis via either granzyme B or granzyme A, family of serine proteases (Elmore, 2007). Granzyme A pathway causes cell death via single stranded DNA damage which is caspase independent (Martinvalet et al., 2005) where as granzyme B mediated cascade is caspase dependant leading to activation of caspase - 3 either directly or through caspase - 10 (Elmore, 2007). Granzyme B also utilizes the mitochondrial pathway for amplification of the death signal by specific cleavage of Bid and induction of cytochrome C release (Barry and Bleackley, 2002; Russell and Ley, 2002).

FINAL COMMON PATHWAY OF APOPTOSIS BY ACTIVE CASPASE - 3

The extrinsic, intrinsic and perforin pathways all end at a common point leading to the commencement of the final pathway of apoptosis. Caspase - 3, caspase - 6, and caspase - 7 function as effector or "executioner" caspases, that ultimately cause the morphological and biochemical changes seen in apoptotic cells (Slee et al., 2001; Elmore, 2007).

Caspase - 3 is considered to be the most important of the executioner caspases and is activated by any of the initiator caspases (caspase - 8, caspase - 9, or caspase - 10). Caspase - 3 specifically activates the endonuclease CAD (caspase activated DNAse I). In proliferating cells CAD is complexed with its inhibitor, ICAD (inhibitor of caspase activated DNAse I) but in apoptotic cells, activated caspase - 3 cleaves ICAD to release CAD

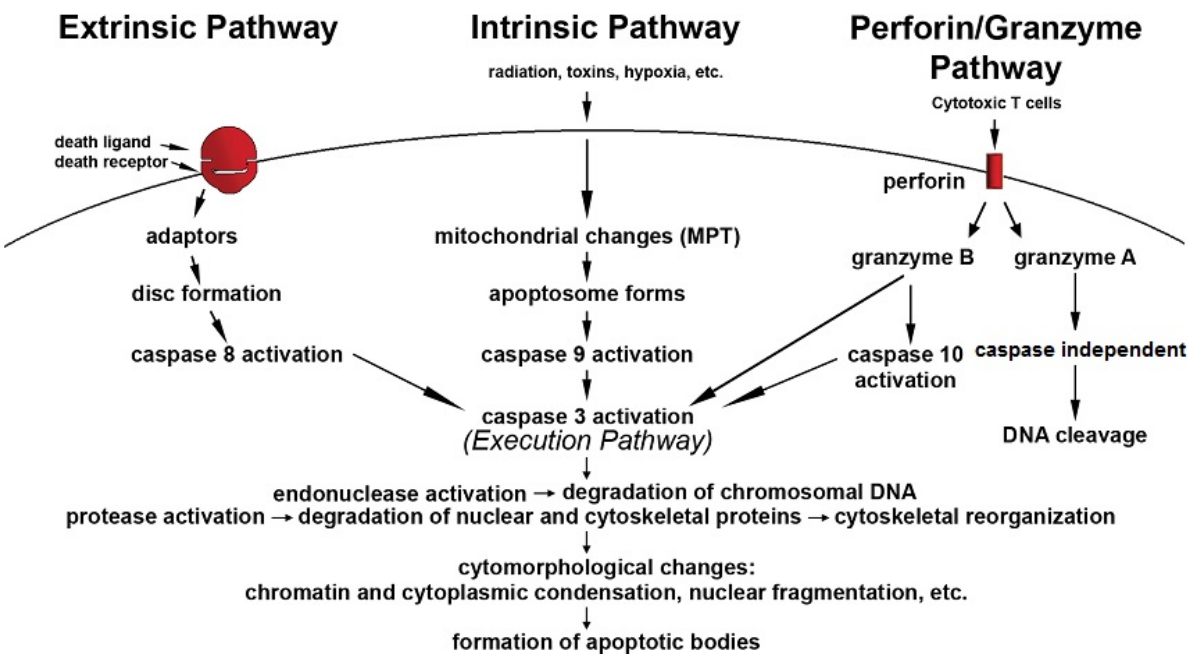

Figure 1: Extrinsic, intrinsic and perforin/granzyme pathway leading common pathway to cell death. Susan (2007) (with slight modifications)

(Sakahira et al., 1998; Elmore, 2007). CAD then degrades chromosomal DNA within the nucleus and causes chromatin condensation, results in DNA fragmentation finally cell death and uptake by phagocytic cells.

CASPASES IN DISEASES AND AS THERAPEUTICS

Caspases are a family of proteins important for maintaining homeostasis through regulating cell death and inflammation. Defective caspase activity along with inadequate apoptosis results in cancer where as excess caspase activation leads to neurodegenerative diseases. Moreover hypo activation of caspases involved in inflammatory conditions that resulted in increased succeptibility to infection, whereas hyperactivation of caspases are pro inflammatory in nature. Caspase - 8 is mostly used as a therapeutic target in cancer (Stupack, 2013). Caspase - 8 suppresses the ability of normal cells to transform into oncogene (Krelin et al., 2008). High level of caspase - 8 expression is seen in malignant neuroendocrine tumors, such as neuroblastoma (Donaldson et al., 2000), as well as in brain tumors such as medulloblastoma (Ebinger et al., 2004). Caspases (3, 6 and 8) have been implicated in a number of neurodegenerative diseases including Alzheimer's, Parkinson's and Huntington's disease (Mogi et al., 2000; Graham et al., 2006). Deregulation of the inflammatory response leads to the development of autoimmune and autoinflammatory disorders. Caspase - 1 activates a number of cytokines (IL-1β, IL-18 and IL-33) required for the inflammatory response (Davis et al., 2011). Several caspases function as critical mediators of innate immune responses rather than proapoptotic factors. Caspase 1, 4, 5, and 12 are the inflammatory factor in humans, whereas caspase 1, 11, and 12 have got similar function in mice (Mcllwain et al., 2013). Therefore, caspases are the target to prevent auto immune and inflammatory diseases.

CONCLUSION

Caspase groups of protein are one of the chief mediators of apoptosis causing natural cell death. Regulation of apoptosis in a proper way is paramount for using cells in various therapeutic strategies into diseases like cancer, neurodegenerative and auto immune disorders. Understanding the exact molecular mechanisms of apoptosis will be helpful in immortalizing cells. Along with caspases other mediators like HSPs (heat shock proteins) and various cytokines like FGF (fibroblast growth factor), TGF-β (transforming growth factor β), IGF-1(insulin like growth factor - 1) etc should be explored which is beyond this review.

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