E-ISSN: 2320-1215
P-ISSN: 2322-0112

Research and Reviews: Pharmacy and Pharmaceutical Sciences

Caspases Significance in Apoptosis

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Opinion Article

Received: 12/09/2016
Revised: 22/09/2016
Accepted: 26/09/2016

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Apoptosis, also referred to as programmed cell death is evidenced as a prime pathway for regulating growth of an organism. Apoptosis aids in establishing a natural balance between cell death and cell renewal by destroying excess damaged or abnormal cells. It offers the most potent defense against cancer as it aids elimination of potentially deleterious damaged cells. A few factors triggering apoptosis include DNA damage, disruption of cell cycle, hypoxia, and detachment of cells from their surrounding tissue and loss of tropic signaling. Apoptosis induces cell shrinkage, chromatin condensation and fragmentation of the cells into compact membrane-enclosed structures. These are the apoptotic bodies. They are engulfed by macrophages and removed from the tissue in a controlled manner. Such morphological changes are brought about by biochemical and molecular events. Most notably amongst them include activation of proteolytic enzymes resulting in cleavage of a procaspases, precursors of an important group of enzymes resulting in activation of caspase cascade and resulting in clearance of unwanted cells in an orderly fashion.

Caspases, cysteinyl aspartate-specific proteases, were identified during genetic analysis of the nematode *Caenorhabditis elegans*, as essential for the developmental cell death. About 14 caspases have been cloned and partially characterized in mammals. Caspases are highly specific in their substrate preferences. The mammalian cell death proteases are divided into upstream (initiator) caspases-8, -9, -10 and downstream (effector) executioner caspases -3, -6, -7, based on their sites of action in the proteolytic caspase cascade. Two types of interaction modules detected are death effector domain (DED) or caspase activating and recruitment domain (CARD). CED-3 in nematode and caspases -1, -2, -4, -5, -8, -9, -10, -11, -12 and -13 in mammals have prodomains with DEDs or CARDs. The DEDs and CARDs connect with the initiator caspases via homophilic interactions and critical regulatory molecules.

Three major pathways to apoptosis-associated caspase activation have been identified in mammals: the extrinsic or death receptor pathway, the intrinsic or apoptosome pathway and the cytotoxic lymphocyte-initiated granzyme B pathway. The order of events of each of these pathways to caspase activation is currently well understood and originally defined in cell-free systems. Caspase-cascade is initiated with the release of mitochondrial cytochrome-c due to the opening of Bax/Bak channel. It results in the assembly of the Apaf-1/ caspase 9 apoptosome formation and initiates activation of caspase-9 within this complex. Caspase-9 propagates a cascade of further caspase processing events by directly cleaving and activating caspase-3 and caspase-7. Caspase-7 in-turn processes caspase-6 and -2. Caspase-6 processes caspase-8 and -10 downstream. On the other hand, caspase-8 synthesized as an inactive single polypeptide chain is activated by proteolytic cleavage, though, either auto activation after recruitment into a multimeric complex or trans-cleavage by other caspases. The next step involves ligand binding-induced trimerization of death receptors resulting in recruitment of receptor specific adapter protein Fas-associated death domain (FADD) that in-turn recruit's caspase-8. Activated caspase-8 propagates the apoptotic signal either by directly cleaving and activating downstream caspases or by cleaving the BH3-Bcl2-interacting protein. This results in release of cytochrome c from mitochondria triggering the activation of caspase-9 in a complex with dATP and Apaf-1. Further activated caspase-9 activates downstream caspases. A critical element to these pathways is the involvement of caspase-3/7, which results in cleavage and inactivation

of key cellular proteins including DNA repair enzyme poly(ADP-ribose) polymerase (PARP). In addition, mitogenic and stress responsive pathways are involved in the regulation of apoptotic signal.

Apoptosis as preferred mechanism of executing cytotoxicity, is at the forefront of drug development. Evaluation of potential cytotoxic anti-cancer agents leading to apoptosis of tumor cells, theoretically arresting their growth and spread of neoplasms has been adapted in many manuscripts describes anticancer properties for medicinal plants. Several bio actives from medicinal plants and/or dietary agents are reported to generally induce oxidative stress and down-regulate anti-apoptotic molecules such as Bcl2 or Bcl-x, upregulating proapoptotic molecules such as Bax or Bak. It is evidenced that these agents appear to exhibit some degree of specificity for neoplastic cells while sparing normal cells. Lupeol, β-carotene, sulforaphane, curcumin, di-indolylmethane, epigalactocatechin, genistein, apigenin, leuteolin, diallyl disulfide induce cell death via intrinsic or mitochondrial pathway of apoptosis.

Studies from our laboratory reported *p*-coumaric acid (*p*-CA), an ubiquitous plant phenolic acid, induced cytotoxic effect to neuroblastome N2a cells. *p*-CA at a concentration of 150 µmol/L upon exposure for 72 h, stimulated cells to apoptosis as evidenced by flow cytometer studies mediated through elevated levels of ROS. This excess ROS production activated structural injury to mitochondrial membrane, observed as dissipation of its membrane potential and followed by the release of cytochrome-*c*. Sensitizing neuroblastome cells for induction of apoptosis by *p*-CA identified p53-mediated upregulated accumulation of caspase-8 messenger RNA.