Role Of Protein Kinase Enzymes In Apoptosis

Introduction

Protein Kinase

A kinase is an enzyme serves as catalyst which facilitates the transfer of phosphate groups from high-energy, phosphate-donating molecules to specific substrates. This process is known as phosphorylation, where the substrate gains a phosphate group (and become phosphorylated substrate) and the high-energy ATP molecule donates a phosphate group (and become as ADP). On the other hand, the de-phosphorylation process is when the phosphorylated substrate donates a phosphate group back to the ADP which become as ATP accordingly. The phosphorylation state of a molecule (whether it is a protein, carbohydrate or lipid) can affect its activity, reactivity, and its binding ability to other molecules. Therefore, kinases are critical in metabolism, cell signaling, protein regulation, cellular transport, secretory processes, and many other cellular pathways, which make them very important to human physiology. Protein kinases are also found in plants and bacteria, and include the pseudo-kinase sub-family, which exhibit unusual features including atypical nucleotide binding and weak, or no, catalytic activity.

The programmed cell death that occurs in multicellular organisms is called Apoptosis. The biochemical events results to characteristic cell changes (morphology) and death. These changes include blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, chromosomal DNA fragmentation, and mRNA decay.

Apoptosis is a highly regulated process Because of the fact that it cannot be stopped once it has begun. Apoptosis is initiated through two possible pathways. First, in the intrinsic pathway the cell kills itself due to cell stress sensation, while in the extrinsic pathway the cell kills itself because of signals from other cells. Both pathways induce cell death by activating caspases, which are proteases, or enzymes that degrade proteins. Both pathways activate initiator caspases, which intern activates executioner caspases, which then kill the cell by degrading proteins indiscriminately.

Death Associated Protein Kinases (DAPk) And Related Proteins

DAPk belongs to a family of related death kinases, all of which share significant sequence and functional homology. The family includes two closely related homologues of DAPk: ZIPk (ZIP kinase, also known as Dlk or DAPk3) and DRP-1 (DAPk-related protein 1, also known as DAPk2). The human genes share 83% and 80% identity at the amino acid level, respectively, with DAPk's catalytic domain. More distantly related are human DRAK-1 and DRAK-2 (DAPk-related apoptosis-inducing protein kinase-1 and -2), whose kinase domains are only 50% identical to DAPk. Phylogenetically, the DAPk family is most closely related to the family of CaM-regulated kinases, in particular to myosin light chain kinase (MLCK), which shares 44% identity within the corresponding catalytic domain. DAPk orthologues exist in rodent and in Caenorhabditis elegans but not in Drosophila or lower organisms. In contrast, ZIPk and DRP-1 are only present in mammals.

Role of Protein kinase enzymes in apoptosis:

Cellular Functions of DAPK Family Proteins

DAPk's primary function is, as its name suggests, to regulate cell death. There is, in fact, a strong body of evidence that shows that DAPk is an essential component of different cell death signaling pathways. Endogenous DAPk undergoes activation in response to various death stimuli, and death stimuli have been associated with an increase in DAPk catalytic activity (6, 52).

ZIPk and DRP-1 are mostly guilty by association with their more famous relative DAPk. The evidence to support ZIPk's and DRP-1's roles as cell killers is rather circumstantial and is based mainly on their ability to promote cell death–related morphologies when overexpressed (5,11, 13, 14, 23, 40, 41, 43, 56).

Increased activity of DAPK family proteins results in pronounced death-associated cellular changes, which include cell rounding, membrane blebbing, detachment from extracellular matrix, and formation of autophagic vesicles [1,2,4–6,9,13–19].

Among DAPK family proteins, DAPK1 controls cell cycle, apoptosis, autophagy, tumor metastasis, and oxidative stress. Several reports demonstrate that complex regulation of DAPK1 activity by various signaling pathways modulates the balance between pro-apoptotic and pro-survival pathways [20].

DAPK2 is known to be involved in pro-inflammatory responses mediated by granulocytes, which might be linked to the mechanism of myosin light chain (MLC) phosphorylation by DAPK2 [22]. Besides, DAPK2 has also been associated with differentiation processes in the erythropoietic lineage. DAPK2 knock-in mice showed a decreased response to erythropoietin treatment, suggesting that DAPK2 might exert fundamental regulatory effects on pro-erythroblast development [23].

The biological role of DAPK3 has been gradually investigated [24]. DAPK3 is pro-apoptotic [3] and executes this function either by inducing apoptosis or activating autophagy with or without the involvement of caspase proteins [25,26]. DAPK3 was also shown to mediate inflammatory signals including L13a (ribosome protein), ERK, and interferon (IFN)--activated inhibition of translation [27].

The DAPk family has been linked to several cell death–related signaling pathways.

Overview of The DAPk Signaling Network

Schematic map for DAPk family signaling network shown in appendix # includes both upstream regulators and functional arms that emanate from the active kinases (Figure 2). DAPk can be activated by several mechanisms (Figure 2a), including binding of Ca2+ activated CaM, phosphorylation of Ser735 by ERK, and dephosphorylation of Ser308 by an unknown phosphatase, which can be activated by several death signals. Other triggers lead to increases in DAPk expression through p53- and/or Smad-mediated transcriptional upregulation of the DAPk gene. Once activated, DAPk can trigger a range of death responses leading to multiple

phenotypes (Figure 2b, I–V).

DAPk predominantly triggers the formation of autophagic vesicles, which results in a slow Type II death (I). The substrates responsible for this phenotype are unknown, although syntaxin or other related proteins that are involved in vesicle fusion are possible candidates. Autophagy can be accompanied by cytoskeletal rearrangements and global contractility (II), most likely caused by direct phosphorylation of cytoskeletal substrates, including, but not necessarily restricted to, MLC. Through these contractile changes, and/or phosphorylation of unknown substrates, DAPk inactivates integrins and blocks their signaling, leading to decreased adhesion to cell matrix and, consequently, cell rounding (III). In the proper signaling context, alternate pathways can also be initiated. For example, in cells where ECM provides an essential survival signal and p53 is present, inhibition of integrins can additionally lead to anoikis, a caspase-dependent apoptotic pathway initiated by loss of matrix adherence (IV). p53 also serves to link DAPk to the caspase-dependent, mitochondrial-based death pathway through the p19ARF regulatory loop, although the identity of the exact in vivo substrate in this pathway is not yet known. Once activated, p53 triggers a caspase-dependent Type I death process involving the hallmarks of apoptosis, such as DNA degradation, and cellular fragmentation, as well as membrane blebbing and cell rounding (V).

This pathway can also be activated by DAPk independently of p53. In addition, DAPk can potentially promote death by shutting off survival pathways that function in parallel, such as those activated by ERK and CaMKK, the former through cytoplasmic retention of ERK, and the latter through direct phosphorylation of CaMKK.

The choice of which of these pathways will be followed will ultimately depend on the cell context, the initial substrates that DAPk encounters, and the presence or abundance of factors that interact with or modulate these substrates and the signaling pathways that they regulate.

In addition to the multiple signaling pathways emanating from DAPk, an additional level of complexity arises from the presence of multiple family members. There seems to be cross talk among the family members because DAPk, DRP-1, and ZIPk are all capable of interacting through their respective kinase domains and because DAPk can trans-phosphorylate ZIPk. Furthermore, the levels of killing achieved by co-expression of low, nonfatal quantities of DAPk and WT ZIPk, but not the nonphosphorylatible ZIPk mutant, were much greater than the additive effect of expressing either one alone, indicating that the two synergize to induce cell killing. This suggests a hierarchical relationship among the kinases, with perhaps the most downstream kinase, ZIPk, acting as the effector kinase. Alternatively, the family members may collaborate in parallel to activate a common pathway, mediated by phosphorylation of shared substrates. In this case, the cross talk between DAPk and ZIPk may reflect an internal amplification loop within the overall network to ensure maximal phosphorylation of the common.

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