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APOPTOSIS REGULATOR BCL-2

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ABSTRACT

Apoptosis (programmed cell death) is required for the removal of infected, damaged or unwanted cells. Inadequate cell death is a major contributing factor to tumorigenesis, while excess cell death contributes to neurodegeneration and autoimmune diseases.

Current investigations suggest the mechanisms by which Bcl-2 might prevent cell death. Bcl-2 family members mediate anti-apoptotic signals in a wide variety of human cell systems. Bcl-2 protein family, through its role in the regulation of apoptotic pathways, is possibly related to cancer pathophysiology. This review article discribes some pathways how apoptotic cell death is controlled by this protein family.

Keywords: *apoptosis, B- cell lymphoma-2, Bcl-2 family*

MAIN TEXT

The cells of a multicellular organism are members of a highly organized community. The number of cells in this community is tightly regulated – not simply by controlling the rate of cell division, but also by controlling the rate of cell death. If cells are no longer needed, they commit suicide by activating an intracellular death program. This process is therefore called the programmed cell death, although it is more commonly called apoptosis (from a Greek word meaning "falling off," as leaves from a tree) [1].

Apoptosis, also called the programmed cell death (PCD), plays a key role in developmental biology and in the maintenance of the steady state in continuosly renewing tissues. The PCD is a selective process of physiological cell deletion [21, 24].

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Apoptosis is characterized by two major markers. The first is composed of morphological features such as reduction in the cell volume, the chromatin condensation, and the nuclear fragmentation, resulting in apoptotic bodies. The other marker is DNA cleavage by a Ca^2 /Mg^2 – dependent endonuclease into oligonucleosomal-length fragments detected as a ladder pattern on gel electrophoresis [25].

One of the oncogenes regulating apoptosis is Bcl-2 (B-cell lymphoma 2). Bcl-2, encoded by the BCL2 gene, is the founding member of the Bcl-2 family of the regulator proteins that regulate apoptosis [3, 16].

Bcl-2 family member proteins are the anti-apoptotic molecules that are known to be overexpressed in most cancers. The pro-apoptotic Bcl-2 family members are Bax, tBid, Bak, Bax, Bik, Bok, Bim, Krk, Mtd and others. The anti-apoptotic subfamily comprises Bcl-2, Bcl-xL, Bcl-w, Mcl-1, A1(Bfl-1), and Bcl-B.

The major function of Bcl-2 family members is to control directly mitochondrial membrane permeability and thereby regulate the release of apoptogenic factors from the intermembrane space into the cytoplasm [6, 10, 17, 18, 27]. Apoptogenic factors known to be released include cytochrome c, Smac Diablo [4], AIF [14], heat shock protein 60 [13], and endonuclease G. Smac Diablo and cytochrome c are involved in the activation of caspases. AIF and endonuclease G are thought to play roles in the induction of caspase-independent apoptotic changes in nuclei. Anti-apoptotic members of the Bcl-2 family inhibit the release of these apoptogenic factors, whereas pro-apoptotic members promote it [19].

The "point of no return" in this pathway is defined by mitochondrial outer membrane permeabilization (MOMP), which leads to the release of cytochrome c [2]. Bcl-2 family proteins regulate MOMP and thereby determine the cellular commitment to apoptosis. From the above discussion, it is clear that MOMP is a greatly organized process, principally controlled through interactions between pro- and anti-apoptotic members of the B cell lymphoma 2 (Bcl-2) family [15].

The intrinsic (mitochondrial) apoptotic pathway is controlled by the balance between anti-apoptotic proteins belonging to the Bcl-2 family and pro-apoptotic proteins bearing a single BH3 domain. In healthy cells, pro-apoptotic proteins, Bax, Bid and Bad reside in the cytosol. On the initiation of apoptosis, these pro-apoptotic proteins translocate to the outer mitochondrial membrane, causing the mitochondria to lose membrane potential.

It is well documented that Bcl-2 functions through heterodimerization with the proapoptotic members of the Bcl-2 family to prevent mitochondrial pore formation and prevent cytochrome *c* release and the initiation of apoptosis [22]. The mitochondrial (intrinsic) pathway is regulated by the Bcl-2 family and activated by mitochondrial disruption with subsequent cytochrome c release. The initiators of this pathway include UV irradiation and cytotoxic drugs. An 'apoptosome' is formed by the interaction of cytochrome c, Apaf-1, d-ATP/ ATP and procaspase-9 with the subsequent initiation of the caspase cascade.

Among the investigations which are now suggesting the mechanisms by which Bcl-2 might prevent cell death are also the local inhibition of free radical production and the formation of an ionic conductance channel in membranes [8]. The extensive oxidative injury in ischemic neuronal death suggests that an antioxidant mechanism for Bcl-2 would be beneficial and might exhibit a greater contribution in those cases where oxidative damage is a significant component of the cell death triggering event.

The Bcl-xL protein contains two central hydrophobic helices surrounded by five amphipathic helices [11], a structure similar to the pore-forming domain of certain bacterial toxins. Minn et al. [9] demonstrated that Bcl-xL can insert into membranes and form an ionic conductance channel that is cation selective at physiological pH. The implications for ischemia include the possibility that Bcl-xL could regulate the sequestration of intracellular calcium that is an important component of the excitotoxic cell death mechanism.

Bcl-2 related proteins form a part of the core apoptotic machinery conserved in the species as diverse as *Caenorhabditis elegans* and mammals. Functionally, the Bcl-2-related proteins either inhibit or promote apoptosis, and interaction(s) between the proteins belonging to opposing factions determines whether a cell lives or dies. Perhaps the best understood pathway is that in the worm C. elegans, where detailed genetic studies have shown that two Bcl-2 related proteins (pro-apoptotic EGL-1 and pro-survival CED-9) are essential for controlling developmentally programmed somatic cell deaths [7]. The expression of EGL-1, the death trigger, is inducedby damage signals. Binding of EGL-1 to CED-9, the worm Bcl-2 ortholog, releases the adapter protein CED-4 from CED-9. Once released, CED-4 binds to and activates the caspase CED-3 to cause cellular demise [23].

The damage to the Bcl-2 gene has been identified as a cause of a number of cancers, including chronic lymphocytic leukemia [12], neurodegenerative diseases and autoimmunity [5]. It is also a cause of resistance to cancer treatments. As the knowledge about the mechanisms of Bcl-2 proteins influences on apoptosis, it may help develop new therapies for treating cancer, autoimmune conditions, and neurological diseases. Further resarch is essential in this area.

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