

REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Logical complexity of Bcl-2 family proteins function in the intrinsic apoptosis

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**SUMMARY**

Apoptosis (type of programmed cell death) is an active process of cellular self-destruction in multicellular organisms. It is characterized by distinctive histomorphological, biochemical, and molecular features. Multiple cellular pathways trigger apoptosis, two of them are the best known: intrinsic and extrinsic. Multiple cellular signals and interactions can influence the course of apoptotic pathways. Bcl-2 family proteins play a key role in regulatory mechanisms of intrinsic apoptosis. Mitochondrial outer membrane permeabilization (MOMP) is an essential step for intrinsic apoptosis that is controlled by pro-apoptotic and anti-apoptotic members of Bcl-2 protein family. Pro-apoptotic effector proteins Bax and Bak represent the only Bcl-2 proteins inducing formation of MOMP, whose pores facilitate the subsequent releasing of several pro-apoptotic proteins from mitochondrial intermembrane space into cytosol. These proteins initiate a caspase cascade, resulting in rapid elimination of the doomed cells.

Keywords: intrinsic apoptosis; Bcl-2; Bax; Bak

INTRODUCTION

Apoptosis (form of programmed cell death, type I cell death) is an evolutionary conserved death machinery activated by a wide range of diverse stimuli, both physiological and pathological. This is a genetically controlled death pathway, which occurs in normal development and aging, and maintains proper cell homeostasis. Apoptosis is considered a potent defense program serving to remove supernumerary, undesirable, useless, and cells damaged by disease. It also plays an essential role in the immune reactions [1, 2]. Apoptosis is an active and physiological, energy-dependent form of cell death. In order to maintain normal function and cooperation of all tissues, organs, and systems, millions of cells die and proliferate every day. Imbalance between cell death and proliferation is implicated in many diseases. Thus, dysfunction or dysregulation of the apoptotic program may cause a wide spectrum of pathological conditions, such as neurodegenerative disorders, autoimmune diseases, ischemic diseases, and a variety of cancers [3–7].

Morphologically, at light microscope level, apoptosis affects individually dispersed cells, but the broad tissue architecture remains undisturbed. Apoptotic cells are easily identifiable in low magnification because they are located within an unstained “halo” around them. Large apoptotic cells fragment into small apoptotic bodies with an intact membrane. Smaller cells, such as apoptotic granular layer cells of the cerebellar cortex, do not usually fragment. Apoptotic bodies are rapidly and discretely taken up by macrophages or neighboring cells

with phagocytic activity. In contrast to necrosis, there is no inflammatory response of the surrounding tissue [8, 9].

At electron microscope level, apoptotic cells are characterized by shrinkage and condensation of the cytoplasm as a result of water content reduction. Cytoplasmic organelles are packed together, although initially they are morphologically preserved and functionally active. Nuclear chromatin presents organized condensation, margination, and fragmentation. Cell junctions and other surface specializations are lost, but the plasma membrane remains, displaying blebbing [1].

The multiple cellular pathways trigger the apoptotic process. Two of them are characterized the best: an intrinsic or a mitochondrial pathway, and an extrinsic or a death receptor pathway [10]. These two main pathways are related via specific molecules in one pathway that can influence a course of the other [11]. In addition, a perforin/granzyme pathway (granzyme B and granzyme A) can induce apoptosis. It is known that extrinsic, intrinsic, and granzyme B pathway may terminally converge on the execution phase of the apoptotic cascade. The granzyme A death course is caspase-independent [1].

Nevertheless, the Nomenclature Committee on Cell Death (NCCD) proposed an updated classification of cell death subroutines focused mainly on molecular principles of demise machinery. In the most recent paper, NCCD recognizes intrinsic apoptosis, extrinsic apoptosis, mitochondrial permeability transition (MPT)-driven necrosis, necroptosis, ferroptosis, pyroptosis, parthanatos, entotic cell death, NETotic cell death, lysosome-dependent cell death, au-

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tophagy-dependent cell death, immunogenic cell death, cellular senescence, and mitotic catastrophe [8].

INTRINSIC APOPTOSIS

Bcl-2 family proteins

Mitochondria are the intracellular organelles which represent a nodal point for many death signals (Figure 1). They may converge to trigger both mitochondrial membranes permeabilization and mitochondrial proteins release.

One of the most famous groups of signals controlling complicated death machinery is the Bcl-2 family protein.

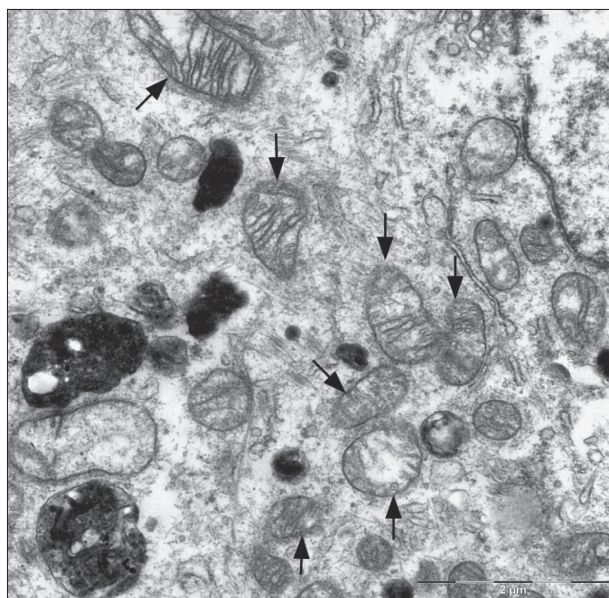


Figure 1. Transmission electron microscope image of a thin section through cell of MCF7 cell line showing numerous mitochondria (arrows); origin of cell line: human breast adenocarcinoma

For the first time, Bcl-2 gene was discovered in B-cell follicular malignant lymphoma [12, 13]. There is t(14; 18) translocation, where Bcl-2 gene is translocated from its normal location on the long arm of chromosome 18 to a region adjacent to promoter in the immunoglobulin heavy-chain locus on the long arm of chromosome 14. Gene activation and over-production of the encoded proteins lead to inhibition of cell death and the promotion of lymphomagenesis [14, 15].

Bcl-2 proteins have either pro-apoptotic or anti-apoptotic function and they are key regulators of intrinsic apoptotic pathway.

The group of Bcl-2 proteins consists of at least 25 members to date [3]. They are classified into three subgroups, based on their function in apoptotic process and the number of Bcl-2 homology domains (BH1, BH2, BH3, and BH4) [16]. Interestingly, they share several common features. All of them are composed of alpha helices. These alpha helical structures possess one to two central hydrophobic helix (helices) which are surrounded by six to eight amphipathic helices. The structural similarity of Bcl-2 alpha helices to the membrane-translocation domain of the diphtheria toxin and the bacterial colicins suggests that Bcl-2 family proteins are capable of pore forming activity in lipid membranes [17]. A flexible loop is present in all three main subgroups; it is known to be a regulatory structure. The Bcl-2 homology domains (BH1, BH2, BH3, and BH4) are localized either in one alpha helix or through two helices. They function in interactions between proteins. There are also alpha helices, which are involved in membrane connections (membrane-binding region). However, structural variations of Bcl-2 family proteins are known both in the number and the arrangements of helices, in the number of BH domains and in the structure of a loop [18, 19].

The first subgroup, the anti-apoptotic or pro-survival Bcl-2 proteins possess four BH domains (BH1–BH4)

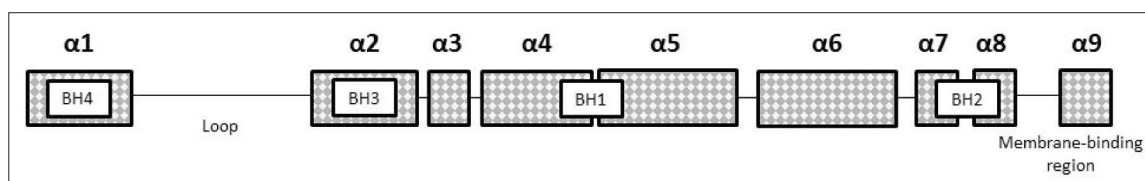


Figure 2. Basic schematic structure of anti-apoptotic Bcl-2 proteins subgroup

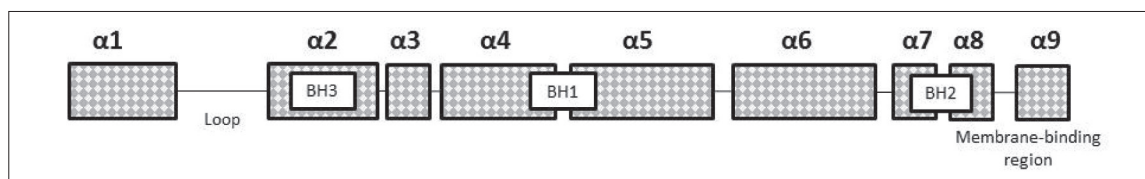


Figure 4. Basic schematic structure of pro-apoptotic effector Bcl-2 proteins subgroup

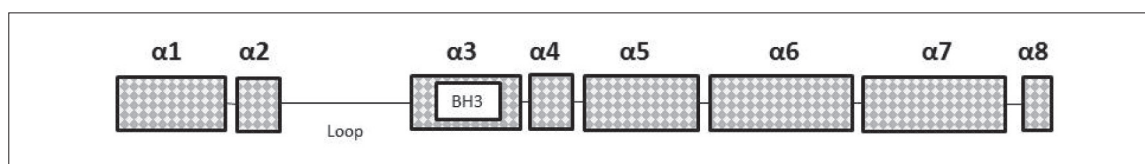


Figure 6. Basic schematic structure of BH3-only pro-apoptotic Bcl-2 proteins subgroup

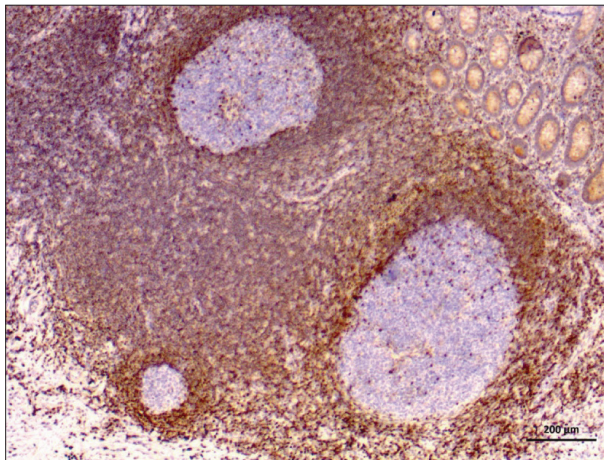


Figure 3. Immunohistochemical reaction with anti-Bcl-2 antibody in human appendix lymphoid tissue

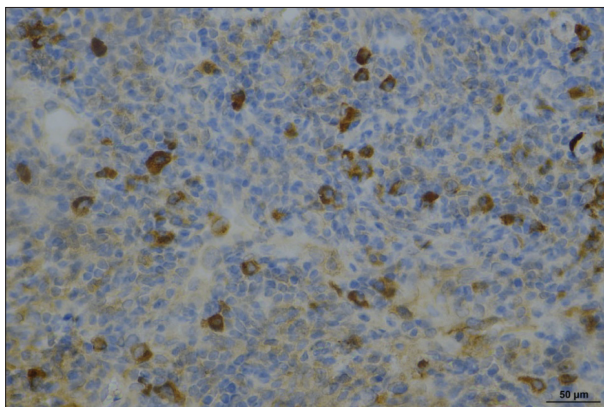


Figure 5. Immunohistochemical reaction with anti-Bax antibody in breast adenocarcinoma

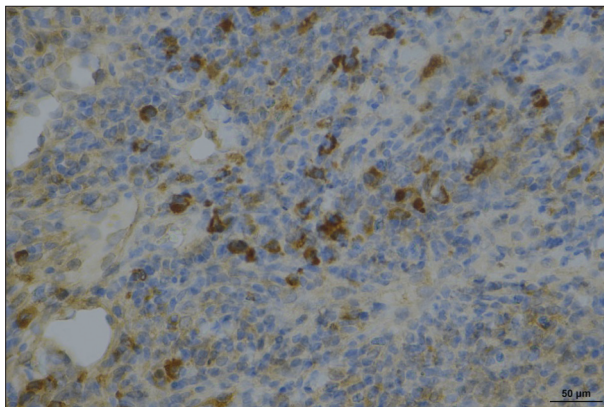


Figure 7. Immunohistochemical reaction with anti-Bid antibody in breast adenocarcinoma; both anti-Bax and anti-Bid antibodies were applied on the tissue sections from an identical paraffin block

(Figure 2). They act as suppressors of cell death by direct binding and inactivating the pro-apoptotic Bcl-2 proteins. Bcl-2 itself (Figure 3), Bcl-XL, Mcl1, Bcl-W, and A1 proteins are members of the anti-apoptotic subgroup [18, 20, 21].

The second multidomain subgroup, the pro-apoptotic effector proteins Bax (Figure 5), Bak, and Bok, contains three BH domains (BH1–BH3) (Figure 4) and directly permeabilizes the outer mitochondrial membrane to release apoptogenic factors [18, 22, 23].

The third subgroup, pro-apoptotic members of Bcl-2 protein family, contains a single BH3 domain (Figure 6)

and is very heterogeneous [18]. The BH3-only pro-apoptotic proteins can be further divided as “activators” if they directly interact with mitochondrial Bax and/or Bak to cause conformational changes with subsequent activation, which is necessary for mitochondrial outer membrane permeabilization (MOMP) (Bid – Figure 7, Bim, Puma, Noxa) [17, 24, 25]. In contrast, “sensitizers” or “inactivators” bind and inhibit anti-apoptotic Bcl-2 proteins (Bad, Bmf, Hrk, Bik) [22, 26, 27].

In order to regulate apoptotic machinery, Bcl-2 proteins interact with each other and generate a complicated interaction network. This plays an executive role in the decision whether a cell will live or die [3, 28].

The essential step for intrinsic apoptotic pathway is MOMP. This directly causes an irreversible release of different mitochondrial intermembrane space proteins into cytosol with subsequent activation of caspase cascade [22, 29]. MOMP is controlled by outstanding features of pro-apoptotic and anti-apoptotic members of the Bcl-2 family. These proteins are localized in the mitochondria either constitutively or by induction. Mutual interactions between Bcl-2 proteins act as central regulators of MOMP [30].

Physiologically, the outer mitochondrial membrane (OMM) is permeable to proteins up to 5 kDa. In contrast, MOMP pores facilitate the passage of proteins larger than 100 kDa to cytosol [31, 32]. Pro-apoptotic effector proteins Bax and Bak represent the only Bcl-2 proteins able to form pores across the OMM [20, 21]. The third effector protein Bok can act as a trigger for the induction of MOMP in response to endoplasmic reticulum stress insults. Bok activation does not depend on interaction with other Bcl-2 proteins [33, 34].

In healthy conditions, Bak is constitutively membrane bound, it resides on the OMM and shows only a small cytosolic fraction caused by retrotranslocation. Bax continuously cycles between the cytosol and the OMM [3, 32, 35].

ACTIVATION OF BAX AND BAK BCL-2 PROTEINS

The BH3-only pro-apoptotic proteins can be activated by various cytotoxic stresses with subsequent direct interaction with Bax/Bak. The BH3 domain of the BH3 activator – only Bid and Bim proteins bind to the BH3 domain – binding groove in Bax and Bak [36, 37]. Worthy of note, Bid and Bax interact in this way only when both of them are on mitochondrial membranes. In Bax and Bak effectors are activated, the “latch” region of proteins represented by $\alpha 6$ – $\alpha 8$ moves away from the core region formed by $\alpha 1$ – $\alpha 5$. This transiently exposes the BH3 domain localized in $\alpha 2$ and is an essential step for Bax dimerization [37, 38, 39]. As a consequence, the bent core region becomes straightened and then interacts with the MOM by exposure of C-terminal hydrophobic domain in $\alpha 2$ – $\alpha 5$. Generally, the hydrophobic segment of Bcl-2 is required for anchoring the protein in question to various intracellular organelles, including mitochondria, endoplasmic reticulum, and nuclear outer membranes. In the meantime, the exposed $\alpha 2$ /BH3 domain of the effector protein binds to

the groove of an adjoining effector protein and this mutual BH3–groove interaction forms dimer. Formation of the dimer displaces the BH3 domain of direct activator BH3-only proteins, accounting for the “kiss-and-run” model [22, 23, 40, 41]. According to the “kiss-and-run” model, the BH3-only direct activators bind transiently to Bax, they do not remain coupled with the pro-apoptotic effectors. Thus, activated Bax and Bak form homodimers and further dimer-by-dimer oligomerization [42, 43, 44]. Bax/Bak oligomers permeabilize the OMM and induce the formation of membrane pores (MOMP).

For Bax, another binding site has been reported. When the Bax is soluble in the cytosol, its BH groove is associated with the carboxy-terminal $\alpha 9$ helix of the protein. The Bim BH3 domain does not bind to the canonical hydrophobic groove but it binds to the “rear” activation site on the opposite side of the hydrophobic groove (helices $\alpha 1$ – $\alpha 6$) [27]. It is followed by the Bax conformational changes and subsequent exposure of the carboxy-terminal $\alpha 9$ helix. This $\alpha 9$ helix is exposed for other interactions and additionally merges with MOM. At that point, BH groove becomes accessible to the BH3 domain of direct activator proteins, Bax oligomerizes and induces MOMP [22, 27, 39]. MOMP takes only a few seconds per mitochondrion. However, the onset of this process for each mitochondrion in a cell can vary; around five minutes are needed for all mitochondria in one cell to be permeabilized [23]. Of note, a partial MOMP can occur, which does not cause cell death following sublethal stresses. In the incomplete MOMP, most but not all mitochondria within a cell show MOMP. In minority MOMP, only a few mitochondria experience MOMP [23].

The BH3 domain of sensitizer BH3-only proteins interacts with BH3 domain-binding groove of anti-apoptotic Bcl-2 proteins, inhibiting their function.

In fact, this BH3-in-groove interaction represents an essential mechanistic facet of Bcl-2-controlled intrinsic apoptosis.

MOMP is inhibited by anti-apoptotic Bcl-2 family members. This group of pro-survival proteins possesses all BH domains and they are embedded into OMM or endoplasmic reticulum (ER) membrane. Pro-survival Bcl-2 proteins prevent oligomerization of Bax and Bak and pore-forming function by two mechanisms: directly, by their physical sequestration at the OMM, or indirectly, by the sequestration of BH3-only activator pro-apoptotic proteins [20, 25, 45].

It is believed that MOMP is also influenced by shape and size of mitochondria [46, 47]. Mitochondrial lipid composition can participate in the activation of Bcl-2 proteins. Cardiolipin, localized on the mitochondrial inner membrane, may facilitate tBid-mediated activation of Bax and

later large pore formation in liposomes [48]. Ceramides are also involved in the apoptotic process. They are synthesized at the ER through the sphingomyelin pathway and accumulated in the MOM during apoptosis. Ceramides in the MOM play a role in Bax activation and, in turn, Bax can activate synthesis of ceramides [49, 50]. Furthermore, two metabolites within the sphingolipid pathway, sphingosine-1-phosphate and aldehyde 2-trans-hexadecanal, directly promote Bak and Bax activation, respectively [51].

BOK BCL-2 PROTEIN

Unlike Bak and Bax, Bok is localized at the ER membrane and contributes to its homeostasis [52]. Bok appears to be constitutively active and may be antagonized by the endoplasmic reticulum-associated degradation (ERAD) pathway. It is not inhibited by anti-apoptotic Bcl-2 proteins [33]. If ERAD system becomes affected, Bok might accumulate and move to mitochondria, where it induces MOMP. Bok functions independently of Bak and Bax or other Bcl-2 proteins [39, 53].

CONCLUSION

Intrinsic apoptosis is controlled by Bcl-2 intra-family interactions involving pro-apoptotic and anti-apoptotic molecules. Pro-apoptotic effector proteins Bax and Bak oligomerize in the MOM to form MOMP with subsequent releasing of several pro-apoptotic proteins from mitochondrial intermembrane space into cytosol [27]. Once released to cytosol, they can initiate or promote apoptotic pathways. These proteins can be divided into two groups. The first group is composed of cytochrome c, Smac/DIABLO, and HtrA2/OMI. They induce the activity of the caspase system, leading to cell self-destruction. The second group proteins, AIF and endonuclease G, can translocate into nucleus and cause DNA disintegration by the caspase-independent mode [26].

NOTE

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Логичка комплексност функције породице протеина *Bcl-2* у унутрашњој апоптози

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САЖЕТАК

Апоптоза (врста програмиране ћелијске смрти) активан је процес ћелијског самоуништења вишећелијских организама. Карактерише се различитим хистоморфолошким, биохемијским и молекуларним одликама. Различити ћелијски механизми доводе до настанка апоптозе, од којих су најпознатији унутрашњи и спољашњи. Вишеструки ћелијски сигнали и интеракције могу утицати на ток апоптозе. Породица протеина *Bcl-2* игра кључну улогу у регулаторним механизмима унутрашњих чинилаца апоптозе. Пермеабилација спољашње мембране митохондрија (ПСММ) кључни је

корак за почетак унутрашње апоптозе, који је контролисан проапоптотичким и антиапоптотичким протеинима породице протеина *Bcl-2*. Проапоптотички ефекторни протеини *Bax* и *Bak* једини су *Bcl-2* протеини који индукују настанак ПСММ, чије поре олакшавају следствено ослобађање неколико проапоптотичких протеина из митохондријалног међумембранског простора у цитосол. Ови протеини иницирају каскаду каспазе, доводећи до брзе елиминације апоптозом захваћене ћелије.

Кључне речи: унутрашња апоптоза; *Bcl-2*; *Bax*; *Bak*