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Review article
Pregledni članak

APOPTOSIS REGULATION BY INHIBITORS OF PROGRAMMED CELL DEATH

REGULACIJA APOPTOZE PREKO INHIBITORA PROGRAMIRANE ĆELIJSKE SMRTI

Danica Marković, Vidosava Đorđević

Center for Medical Biochemistry, Clinical Center, Niš, Serbia

Summary: Apoptosis is a form of cell death which is important in many physiological processes. Four apoptotic mechanisms have been identified but two have been well examined: the intrinsic and the extrinsic mechanism. Due to many pro/antiapoptotic factors, these processes take place on a physiologically useful level. In cases of apoptosis dysregulation, illnesses occur such as neurodegenerative diseases combined with an increased level of cell death or cancerogenesis associated with uncontrolled cell proliferation. Apoptosis can be triggered by the activation of the first caspase in a series and stopped by its deactivation, which represents a new challenge: determining the »point of no return«. Besides the antiapoptotic proteins (Bcl 2, Bcl XL), a family of proteins called the Inhibitors of Apoptosis Proteins (IAPs) play a key role in the regulation of apoptosis. Members of the IAP family are: cIAP1, cIAP2, XIAP, Survivin, Livin and TsIAP. Domain BIR is the most important in the IAP structure since it determines their specificity for caspases. The interaction of IAPs with caspases is complex and not completely understood, however, IAPs are considered to be important target proteins in the therapy of tumor and autoimmune diseases.

Keywords: IAP protein (apoptosis), caspases, programmed cell death type I

Kratak sadržaj: Apoptoza predstavlja oblik ćelijske smrti i važna je u mnogim fiziološkim procesima. Postoje četiri oblika ćelijske smrti a dva su dobro proučena: unutrašnji i spoljašnji. Zahvaljujući mnogim pro/antiapoptotičkim faktorima, ovaj proces se odvija na fiziološki korisnom nivou. U slučaju disregulacije apoptoze nastaju bolesti kao što su neurodegenerativna oboljenja udružena sa povišenim nivoom ćelijske smrti ili karcinogeneza udružena sa nekontrolisanom ćelijskom proliferacijom. Apoptozu može pokrenuti aktivacija prve kaspaze u nizu i prekinuti njena deaktivacija, što predstavlja novi izazov: odrediti »tačku bez povratka«. Pored antiapoptotičnih proteina (Bcl 2, Bcl XL), familija proteina nazvanih inhibitori apoptoze (eng. Inhibitors of Apoptosis Proteins, IAPs) igra ključnu ulogu u procesu regulacije. Pripadnici familije IAP su: cIAP1, cIAP2, XIAP, survivin, livin i TsIAP. Domen BIR je najznačajniji u strukturi IAP budući da određuje specifičnost ka kaspazama. Interakcija IAP sa kaspazama je kompleksna i nedovoljno istražena, međutim, smatra se da IAPs predstavljaju važne ciljne proteine u terapiji tumora i autoimunih oboljenja.

Ključne reči: IAP protein (apoptoza), kaspaze, programirana ćelijska smrt I tipa

Address for correspondence:

Danica Marković
Vizantijski bulevar 124/11
18000 Niš, Serbia
Mob.: 069/1983411
e-mail: bobi@ptt.rs

List of abbreviations: IAP, Inhibitors of Apoptosis Proteins; NAIP, Neuronal Apoptosis Inhibitory Protein; RZF, RING zinc-finger domain; cIAP, cellular IAP1; XIAP, X chromosome linked IAP; TsIAP, Testis specific IAP; TNFR2, Tumor Necrosis Factor Receptor 2; NFkB, Nuclear Factor kB; CARD, Caspase Recruitment Domain; NOD, Nucleotide-binding and Oligomerisation domain; XAF1, XIAP-associated factor 1.

Introduction

Apoptosis is a special form of cell death which normally occurs during the growth and aging and as a homeostatic mechanism maintains cell population in tissues. It is considered to be a vital component of various processes (1). Some authors refer to apoptosis simply as a form of cell death used by an organism to eliminate unwanted or harmful cells (2). It can be a consequence of weakening/absence of positive signals necessary for cell survival or receiving negative signals. Apoptosis can be activated by external and internal stimuli (3). Recent approaches are presented with the aim to analyse mechanistic relationships between human diseases, and dysregulated apoptosis seems to be connected with the occurrence of certain diseases. Thus, suppression of cellular apoptosis may lead to the occurrence of tumor or autoimmune disease, while its increased activation contributes to neurological diseases pathogenesis (3–6).

The central dogma of the cell apoptosis is the so-called »point of no return« determination, and for a long period of time it was believed that it was impossible to stop the apoptotic process after the first caspase activation. Also, there were claims that the caspase activation and apoptosis are the same process and that caspases are the only proteins involved in apoptosis. Later, however, it became clear that caspases also participate in processes such as: T and B lymphocyte proliferation and erythrocyte, monocyte and epidermal cell differentiation and maturation. The research has, in fact, proved that caspases could be regulated, and that the Inhibitor of Apoptosis Proteins (IAP) family members are the main controllers of this process. The mechanism of IAP action is well known, however, there are certain variations in the pathways of caspase inhibition and in the parts of specific proteins' structure that still need to be explored. The fact is that IAPs have a seemingly simple structure and a very complex function, and this makes them central molecules in the future therapy research (7–9).

Function and Inhibition of Caspases

Caspases represent the central components of the apoptosis initiation machinery, and other proteins (caspases, IAP, Smac/DIABLO, etc.) are responsible for the regulation of their activity. Caspases involved in apoptosis are divided in two groups: the initiator caspases (caspases 2, 8, 9 and 10) and the effector caspases (caspases 3, 6 and 7). After their activation, the initiation caspases cause cascade activation of downstream caspases by proteolysis and this step is difficult to block. Thereby, a complex of specific molecules is needed for the activation of initial caspases and those molecules join only if there are extracellu-

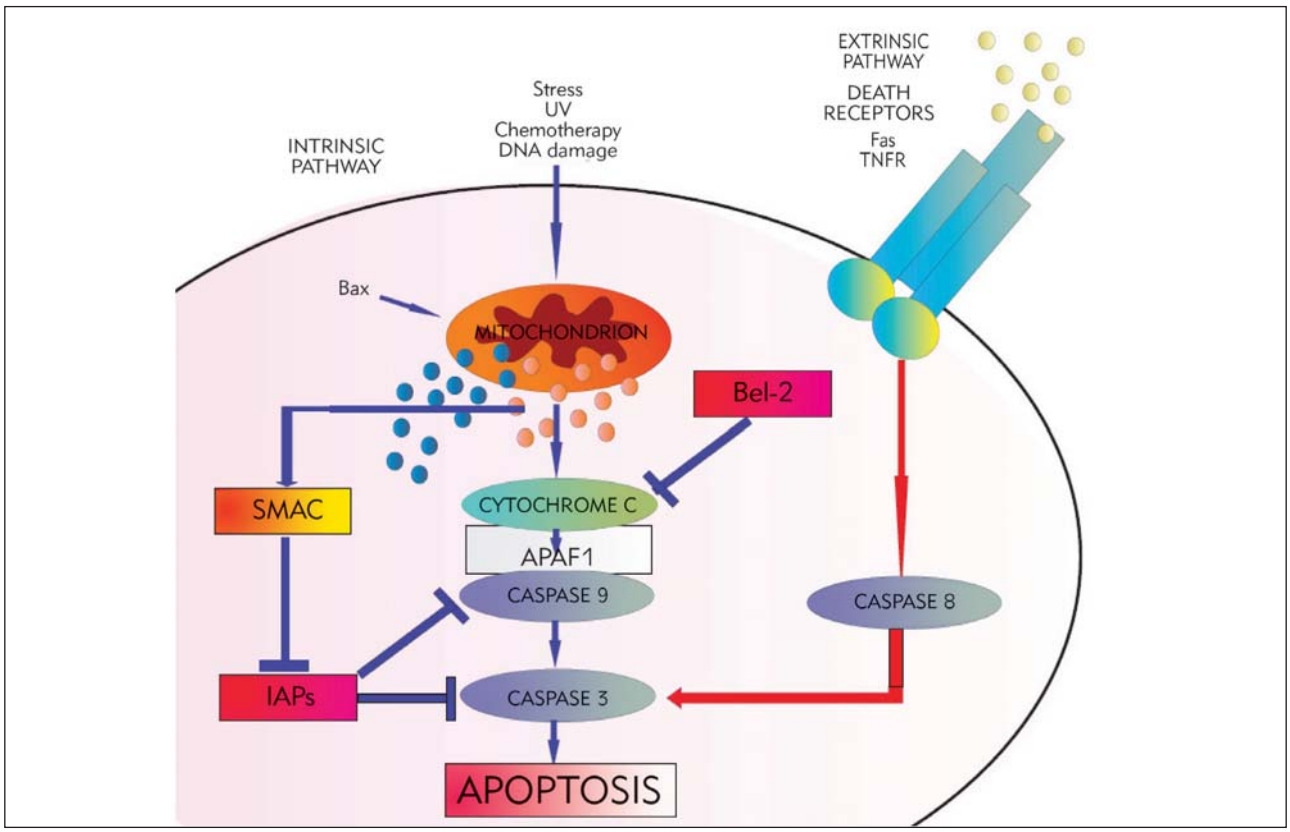

Figure 1 Mechanism of apoptosis and the way IAPs can inhibit this process (author Danica Marković).

lar and intracellular signals that induce the apoptotic process. After the activation of effector caspases, they degrade structural proteins of the cell and its vital elements (actin, proteins that build nuclear lamine, regulator proteins, deoxyribonuclease inhibitors (DFF45, ICAD) as well as other proapoptotic proteins and caspases). Antiapoptotic control relies on antiapoptotic proteins activation (Bcl 2, Bcl XL) and IAPs (c-IAP-1, SURVIVIN, LIVIN, XIAP, etc.) (4, 10). There are certain proteins in the cell that inhibit initiator caspases, but IAPs are the only known endogenous proteins that regulate the activity of both initiator and effector caspases (11). The specific position and function of IAPs in apoptosis can be seen in *Figure 1*.

IAP Family

IAPs include a family of proteins which contain one or more BIR domain in their structure and have the function of an intrinsic regulator of the caspase cascade (*Table I*). In modern medicine, IAPs are considered to be potential target molecules for the therapy of many human diseases. Their potential lies in the fact that if they are overexpressed, a cell may become resistant to apoptotic signals (therapy of neurodegeneration), and if they are overinhibited, an increased activation of cell death (therapy of tumors) will appear. They are also considered to be the only defence against activated caspases and the only factors in the saving of cells that have already entered apoptosis (3, 7, 8, 12, 13). However, there is a new question: Should we »rescue« a cell which is damaged to such an extent that it started the apoptotic process?

Table I List of all the IAPs along with all the abbreviations used in scientific literature and the specific caspases they inhibit.

Inhibitor of Apoptosis Protein	Synonyms	Caspases they bind to and inhibit
XIAP	API3; BIRC4; IAP-3; ILP1; MIHA; XLP2; hIAP-3	Caspase 3 Caspase 7 Caspase 9
cIAP-1	BIRC2; API1; hIAP-2; MIHB; RNF48	Caspase 9
cIAP-2	BIRC3; AIP1; API2; HAIP1; HIAP1; MALT2; MIHC; RNF49	Caspase 9
NAIP	BIRC1; NLRB1; psiNAIP	Caspase 1
Survivin	BIRC5; API4; EPR-1	Caspase 3 Caspase7
Livin	BIRC7; KIAP; ML-IAP; MLIAP; RNF50	Caspase 3 Caspase 7 Caspase 9
TsIAP	BIRC8; ILP2; hILP2	Caspase 9

The gene that encodes IAP was firstly identified in the baculovirus genome and its transcriptome function was to protect the infected cell from death and thereby maintain virus replication inside the organism. Later studies in the field of biology have shown that IAP genes are found in cells of many organisms at different evolution stages. All IAPs contain one to three BIR (Baillovirus IAP Repeats) domains, each of which consists of approximately 70–80 amino acid residues (3, 9, 13).

The first identified IAP homologue in mammals was Neuronal Apoptosis Inhibitory Protein (NAIP), which contains three BIR domains and a carboxyterminal RING zinc-finger domain (RZF). The NAIP encoding gene was isolated during the study of spinal muscular atrophy etiopathogenesis and the genes that cause this disease. Although it has not been proven as directly responsible, it appears that NAIP still has an impact on the development of the disease. After the NAIP discovery, other family members were identified and are represented in the Table I: cellular IAP1 (cIAP1), cIAP2, X chromosome linked IAP (XIAP), Survivin, Livin, Testis specific IAP (TsIAP) (3, 7, 14).

After their identification, cell culture experiments showed that IAPs suppress cell death by binding to caspases and that they prevent apoptosis caused by both external and internal signals (7). Later, it was shown that the biological activity of these proteins in the cell is far more complex and includes: binding to caspases and apoptosis inhibition, cell cycle regulation and signal transduction modulation mediated by receptors such as TNFR 2 (Tumor Necrosis Factor Receptor 2) and NFkB (Nuclear Factor kB) (3, 12, 15).

IAP Structure

There are four domains in the IAP structure: BIR, RZF, CARD (Caspase Recruitment Domain) and NOD (Nucleotide-binding and Oligomerisation domain) (8). All members of the IAP family have a BIR domain in their structure, while other domains are present only in some proteins. NAIP, c-IAP1, c-IAP2 and XIAP have only three BIR and one RZF domain. Survivin contains one BIR and one carboxy terminal »coiled coil« domain, while Livin and Ts-IAP contain one BIR and one RZF domain (3, 7, 13, 16).

BIR domain

BIR domain represents a functional unit of IAPs which has been most examined and its characteristic

is binding of the zinc ion. This domain contains a globular head and a tail of undefined structure that develops out of an amino-terminal linker region located upstream of the BIR domain in the IAP gene. Also, the BIR domain is responsible for most IAP functions in the cell. Many hydrophobic regions and amino acids can be found on the BIR domain surface and they are well preserved in every molecule. This domain is, thereby, considered to be actually responsible for IAPs interaction and binding to other proteins. Of course, there are certain structural differences between the BIR domains of different IAP family members (6, 7, 12, 17).

In general, the rule is this: if an IAP contains more than one BIR domain, the third BIR domain has the function of caspase 9 inhibition while the second BIR domain inhibits caspases 3 and 7 (3). In the case of XIAP, which contains three BIR domains, the researches have shown that only the second BIR domain is responsible for this protein's binding to caspase and later deactivation of the same molecule. BIR3-RING fragment of this protein binds and inhibits caspase 9, while the BIR 1 domain function is not yet known (3, 6, 7, 11, 12). IAPs that contain only one BIR domain use this domain for their basic function. For example, TsIAP (ILP 2) inhibits caspase 9 with its BIR domain, while Survivin's BIR domain inhibits caspases 3 and 8. The interesting fact is that one BIR domain of the Livin protein inhibits caspases 3, 7 and 9 and in this way its BIR domain has greater function than any other (3, 6, 7, 12, 14).

RZF domain

RING zinc-finger domains are a subclass of zinc-finger domains which bind two zinc ions. A protein which contains RZF in its structure acts as an adapter for the recruitment of target proteins, which leads to the multicomponent complex formation and proteosomal degradation (3, 13, 17). The function of RZF domain in the IAP structure is not completely understood, but since its discovery several theories, based on scientific researches, have been set. Studies indicate that an RZF domain on XIAP and c-IAP1 provokes ubiquitination and degradation of IAPs in response to apoptotic stimuli. Another explanation is that IAPs actually trigger the ubiquitination process of caspase 3 and 7 in the proteosome by the RZF domain. It is also believed that proteins which contain RZF ubiquitinate secondary mitochondrial caspase activators, the antagonists of IAP function, with the same mechanism. This then activates cell survival and inhibition of apoptosis. It is expected that future research will discover the real function of the RZF domain within IAPs (3, 11, 13).

CARD and NOD domains

CARD domain takes part in the oligomerisation process with other proteins which also contain CARD in their structure and activates homodimerization. The CARD domains of cIAP1 and cIAP2 proteins are located between the BIR and carboxy terminal RZF domain. Except the activation of the homodimerization process, other specific functions of the CARD domain in cIAP1 and 2 have not been determined yet (3, 11, 13).

NOD domain is characteristic for NAIP. In the organisms of lower developmental stadium, only NAIP has a role in the cellular response to bacterial infection. It is assumed that during this response oligomerisation of the NOD domain and exposure/activation of the BIR domain are initiated. In this way, NAIP prevents cell apoptosis by the inhibition of caspase 1, which is activated during the inflammatory process (3, 11, 13).

Mechanism of Caspases Inhibition

A caspase is a tetramer that consists of two larger (α) and two smaller (β) subunits. It is made up of two homodimers. A loop bundle includes L2 (intersubunits linker), L4 (Loop-3) and L29 (symmetry-associated intersubunit linker). This protein's active site is located on the C-terminal end of parallel β chain. Caspase specificity is determined by the so-called pockets: S1 (accommodate aspartate side chain), S2 (accommodate small aliphatic residues), S3 (engaged in the main-chain hydrogen bonds with the P3 residue), S4 (provide major specificity-conferring elements to the different subclasses), S5 (specific for caspase 2) and S1 pocket (still needs to be explored).

The mechanism of caspase 3 and 7 inhibition was discovered by the combination of structural and biochemical analyses. XIAP is the most potent inhibitor of these caspases in *in vitro* conditions, while cIAP1 and 2 have about a hundred times weaker inhibitory effects when compared to XIAP. XIAP binds to caspase 3 and 7 by its BIR2 domain which has a function to block the active caspase locus (13, 14, 17). It has been shown that Asp148 of XIAP protein, which binds to the S4 caspase pocket with the same mechanism as it binds to the P4 residue of covalent peptide inhibitors, is critical for achieving caspase 3 inhibition. Val 146 binds with strong van der Waals's forces to the surrounding caspase residues including P2. However, in this contact, the S1 caspase pocket, which is responsible for caspase substrate selectivity, remains free. Studies have shown that the linker region between the BIR1 and BIR2 domain in the XIAP protein has no function in caspase 3 and 7 inhibition as it was previously thought (7, 13, 17, 18).

Only XIAP inhibition of caspase 9 has been proved *in vitro*. Thereby, the mechanism of caspase 9 inhibition by XIAP is the most explored and it differs from the mechanisms of caspase 3 and 7 inhibition (3).

Procaspase 9 is activated after the release of cytochrome c from mitochondria. Cytochrome c binds to Apaf1 (Apoptosis Protease-Activating Factor-1) in the cytosol and causes its oligomerisation or apoptosome formation after attracting procaspase 9 and its autoactivation. Caspase 9 is activated by forming a homodimer and then it activates downstream caspases. Caspase 9 can also undergo self-degradation in the linker region between p20 and p10 subunits on Asp315 but this process may also lead to caspase 9 activation. This protein contains the internal IAP-binding tetrapeptide motif (Ala-Thr-Pro-Phe). In the absence of proteolytical processing, caspase 9 is not able to form a stable complex with IAP because the tetrapeptide motif does not have an exposed N terminal. By the processing of procaspase 9 on Asp315 the internal tetrapeptide motif is exposed, which initiates XIAP inhibition of caspase 9 (13, 18).

Caspase 9 inhibition by XIAP requires a preserved surface and structure of the BIR3 domain in the XIAP protein and the preserved IAP-binding tetrapeptide motif on caspase 9 (14). The point of mutations (e.g. His343) on the BIR 3 domain can induce a significant decrease in the level of XIAP caspase 9 binding (19). Recent research has also pointed out that the preservation of the other binding sites, besides the tetrapeptide motif in caspase 9 and BIR3 domain in XIAP, is essential for the binding of these two proteins. The mechanism of inhibition lies in the formation of the XIAP caspase 9 heterodimer which prevents the formation of an active caspase homodimer. If the heterodimer of caspase 9 is formed, there is no possibility of forming a supportive sequential element (L2 loop) which is a characteristic of homodimerisation and is thereby inactive. It is interesting that cIAP1 and cIAP2 cannot inhibit caspase 9 by preventing homodimerisation as XIAP can, because they do not contain the special sequence of four amino acids (12, 13, 18).

In the case of caspase 9 self-activation by degradation, the BIR3 domain of XIAP binds to a newly exposed protein's amino terminal. This interaction is further stabilized by the contacts of caspase 9 and XIAP. When Apaf1 and cytochrome c are excluded from the cell, this interaction prevents the homodimerisation of caspase 9 and stabilizes this enzyme in an inactive state, which is similar to its monomer form (12, 13). Proteins XIAP, cIAP1 and cIAP2 can directly bind to the activated caspases 3 and 7 and inhibit their further activities. The research has also shown that these three proteins can inhibit caspase 9 as well and prevent its activation by apoptotic stimuli (12, 13).

IAPs AS Caspase Substrates

Previous experiments demonstrated that XIAP and cIAP1 could serve as the caspase substrates. *In vitro* studies suggest that caspase 3, 6, 7 and 8 can degrade the XIAP molecule. The significance of this process is not known. Even in spite of molecule degradation, the BIR3-RING fragment of XIAP protein seems long-lived and keeps the ability to inhibit caspase 9 and Bax-induced apoptosis. Some believe that the degradation of the XIAP molecule results in the separation of two functional regions of the protein which can independently attack the caspases. However, it is more likely that XIAP protein degradation is a characteristic of the cell death rather than a characteristic of its defense. cIAP1 protein can also be a substrate for caspase 3 and thereby a carboxy terminal fragment (CARD and RING finger domain) and an amino terminal fragment which contains three BIR domains become apparent. The amino terminal end degrades rapidly, while the carboxy terminal end starts to act as a proapoptotic protein (7, 8).

Negative Regulators of IAP Function

There are three proteins which bind to IAPs and suppress their activity: XIAP-associated factor 1 (XAF1), Smac and Omi (3).

The most important inhibitor of IAP function is Smac. The newly synthesized Smac protein consists of 239 amino acids. During the protein maturation, removal of the mitochondrial target sequence appears and four hydrophobic amino acids (Ala-Val-Pro-Ile) are exposed on the N terminal end. Such an amino acid tetrade in the mature Smac molecule represents the IAP binding motif in mammals and fruit flies (13). Further analyses have shown that the amino acid alanine is the most responsible for this connection. Smac is present in the mitochondrion of a healthy cell and is released in the middle of apoptotic stress at a similar rate as cytochrome c. The mechanism of Smac molecule release from the mitochondrion is not yet fully understood, however, it is believed that, as a small molecule, Smac can pass through the mitochondrial pores previously made by Bax or Bak. Smac binds to all the members of the IAP family and inhibits their function. This allows reactivation of the apoptotic process as well as the potentiation of caspase function. It is interesting that the same motif in the IAP molecule causes a potentiation or an inhibition of these proteins' function whether it binds to the tetrapeptide sequence of Smac or the same sequence of caspase 9. Experiments have shown that, although Smac is able to prevent the inhibition of IAP (XIAP) function on caspase 9, it has no ability to effectively and equally inhibit the same function of XIAP on caspases 3 and 7. The tetrapeptide domain on the Smac molecule fully corresponds to the only BIR domain of XIAP, but it is not completely specific for the BIR2 domain. BIR2 domain is responsible for the inhibition of caspases 3 and 7. However, inhibition of caspase 3 by the XIAP molecule is possible if the BIR2 domain sequences, which remain free due

to incomplete specific binding, are covered with the rest of the Smac molecules (3, 8, 11).

In vitro experiments have shown that it is possible for XAF1 to directly bind to XIAP and thus interfere with caspase 3 inhibition. Cell culture studies have shown that XAF1 interferes with XIAP-mediated protection against chemotherapeutic drugs (etoposide, cisplatin). XAF1 is located in the nucleus, while XIAP is located predominantly in the cytosol. However, XAF1 can cause a transfer of XIAP from the cytosol to the nucleus and enable their interaction. XAF1 protein is normally expressed in healthy cells, but in extremely small quantities (3).

Up to now, another IAP inhibitor has been identified and has been labeled as Omi (HtrA2, High Temperature Requirement). Omi is released from the mitochondrion at the same time as the Smac/DIABLO molecule. It is known that Omi plays a major role in regulating the mitochondrial homeostasis, but its target molecule and the molecules with which it can interact are not yet defined. Omi binds to IAPs with its N-terminal motif. It can cause caspase-independent apoptosis through its protease activity as well as caspase-dependent apoptosis through its ability to interfere with the interaction between caspases and IAPs (3, 8, 11, 20).

Control Points of Apoptosis

Apoptotic stress causes the activation of the Bcl2 protein family members. This family contains both pro- and antiapoptotic members. The balance of proapoptotic (Bax, Bak) and antiapoptotic (Bcl 2, Bcl XL, Mcl 1) Bcl 2 proteins represents the first control point of apoptosis. If the signals leading to apoptosis are too strong, proapoptotic Bcl2 proteins cause the release of cytochrome c through pores formed in the mitochondrial membrane (3, 21). The release of cytochrome c is the second control point at which the levels of IAP and XAF1 determine the outcome. If the IAP suppression and caspase activation occur simultaneously, the permeability of mitochondrial membrane increases which makes possible the release of apoptosis inducing factor (AIF), Smac and Omi. AIF enters the nucleus where it can indicate chromatin condensation, while Smac and Omi bind to IAP and inhibit their function. Also, IAPs could be degraded by caspases or directed so as to activate continuous release of the proapoptotic fragments (cIAP1). However, if the IAP activation prevails, caspases could be inactivated and therefore apoptosis might be stopped (3).

Conclusion

A large number of laboratory and research methods have been developed with the aim of detecting the aberrant IAP expression. It is important to link specific polymorphisms with the possible onset of certain diseases for the purpose of discovering new drugs (22). It is also important to provide further research in the field of apoptosis regulation through the interaction of caspases and IAPs. As the IAPs can inhibit caspases and stop or slow down the apoptotic process, these proteins are considered to be target proteins in the therapy of many diseases associated with an increased level of apoptosis (3, 23).

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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