Caspase Family Proteases and Apoptosis

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Abstract Apoptosis, or programmed cell death, is an essential physiological process that plays a critical role in development and tissue homeostasis. The progress of apoptosis is regulated in an orderly way by a series of signal cascades under certain circumstances. The caspase-cascade system plays vital roles in the induction, transduction and amplification of intracellular apoptotic signals. Caspases, closely associated with apoptosis, are aspartate-specific cysteine proteases and members of the interleukin-1β-converting enzyme family. The activation and function of caspases, involved in the delicate caspase-cascade system, are regulated by various kinds of molecules, such as the inhibitor of apoptosis protein, Bcl-2 family proteins, calpain, and Ca2+. Based on the latest research, the members of the caspase family, caspase-cascade system and caspase-regulating molecules involved in apoptosis are reviewed.

Key words caspase; apoptosis; interleukin-1β-converting enzyme family; inhibitor of apoptosis protein; Bcl-2 family

Molecular Properties of Caspases

Caspases, the interleukin–1β-converting enzyme family proteases, are highly homologous to Caenorhabditis elegans cell death gene CED-3. Fourteen caspases have been identified so far, all of which share some common properties: they are all aspartate-specific cysteine proteases; they all have a conservative pentapeptide active site ‘QACXG’ (X can be R, Q or D); their precursors are all zymogens known as procaspases. The N-terminal of the prodomain in procaspases contains a highly diverse structure required for caspase activation; and they all have a conservative pentapeptide active site ‘QACXG’ (X can be R, Q or D); their precursors are all zymogens known as procaspases. The N-terminal of the prodomain in procaspases contains a highly diverse structure required for caspase activation; and they all have a conservative pentapeptide active site ‘QACXG’ (X can be R, Q or D); their precursors are all zymogens known as procaspases.

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mediator caspases and apoptosis activator caspases all have long prodomains in procaspases [2,3]. The long prodomain contains the death effector domain (DED) in procaspase-8 and -10, or the caspase recruitment domain (CARD) in procaspase-2 and procaspase-9. DED and CARD, the death domain family members, are involved in procaspase activation and downstream caspase-cascade regulation through protein-protein interactions. A similar pyrin domain was found in the prodomain of zebra fish procaspase. The three domains all contain a common 3-D structure known as the death domain fold, composed of six antiparallel \( \alpha \)-helices arranged in a Greek key conformation. However, the shorter prodomains in the procaspases of apoptosis executioner caspases are not involved in protein-protein interactions [3].

### Procaspase Activation

Generally, there are two pathways through which the caspase family proteases can be activated: one is the death signal-induced, death receptor-mediated pathway; the other is the stress-induced, mitochondrion-mediated pathway (i.e. a caspase-9-dependent pathway).

#### Death receptor-mediated procaspase-activation pathway

*Death receptor-dependent procaspase-activation pathway of caspase-8/caspase-10*  
Cell death signals, such as Fas ligand (FasL) and tumor necrosis factor (TNF)-2, can be specifically recognized by their corresponding death receptors, such as Fas or TNF receptor (TNFR)-1, in the plasma membrane. Their binding will in turn activate the death receptors. Fas can bind to the Fas-associated death domain (FADD) (or TNFR-associated death domain, TRADD) and cause FADD aggregation and the emergence of DEDs. These exposed DEDs interact with the DEDs in the prodomain of procaspase-8, which will induce the oligomerization of procaspase-8 localized on the cytosolic side of the plasma membrane. Then a massive molecule complex known as the death-inducing signal complex (DISC) is formed. In DISC, two linear subunits of procaspase-8 compact to each other followed by procaspase-8 autoactivation to caspase-8. The activation of the downstream pathways of caspase-8 varies with different cell types (Fig. 1). In Type I cells (cells of some lymphoid cell lines), caspase-8 is vigorously activated and can directly activate the downstream procaspases (e.g. procaspase-3). In Type II cells (other than Type I cells), caspase-8 is only mildly activated and unable to activate procaspase-3 directly. However, it can activate the mitochondrion-mediated pathway by truncating Bid (a pro-apoptotic Bcl-2 family member), a kind of proapoptotic protein in the cytosol, into its active form, tBid. tBid will trigger the activation of the mitochondrion pathway: cytochrome c, apoptosis-inducing factor (AIF) and other molecules are released from mitochondria, and apoptosis will be induced [4–7].

**Table 1**  
Subfamily members of caspase family

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**Fig. 1**  
Caspase-8/caspase-10-dependent procaspase-activation pathway

AIF, apoptosis-inducing factor; Apaf-1, apoptotic protease activation factor-1; Cyto c, cytochrome c; FADD, Fas-associated death domain; TNF, tumor necrosis factor; TNFR, TNF receptor; TRADD, TNFR-associated death domain.

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The activation pathway mediated by procaspase-10, with a DED-containing prodomain, is similar to that mediated by procaspase-8. Caspase-10 functions mainly in the apoptosis of lymphoid cells [8]. It can function independently of caspase-8 in initiating Fas- and TNF-related apoptosis. Moreover, Fas crosslinking in primary human T cells leads to the recruitment and activation of procaspase-10.

Although caspase-8 and caspase-10 both interact with the DED of FADD in death receptor signaling, they may have different apoptosis substrates and therefore potentially function distinctly in death receptor signaling or other cellular processes [8,9].

Death receptor-dependent procaspase-activation pathway of caspase-2 Once death signals bind to their corresponding death receptors on the plasma membrane, death receptors will be activated. The activated receptors recruit procaspase-2 by adaptors, such as receptor-interacting protein (RIP), RIP-associated ICH-1/CED-3 homologous protein with a death domain and TRADD, by means of the prodomain of procaspase-2. Procaspase-2 is activated after the recruitment (Fig. 2). Very little has been understood so far concerning the downstream substrates of caspase-2 [10].

Mitochondrion-mediated procaspase-activation pathway

Mitochondrion-mediated procaspase-activation pathway of caspase-8 Apart from being recruited to form a DISC complex after autoactivation, procaspase-8 could also be activated through a cytochrome c-dependent pathway.

After cytochrome c is released from mitochondria to the cytosol, caspase-6 is the only cytosolic caspase with the ability to activate procaspase-8, which depends solely on procaspase-6 activation by prodomain cleaving. It means that, in the cytochrome c-dependent pathway, the activation of procaspase-8 requires neither the interaction with FADD nor the formation of a DISC complex [9].

Mitochondrion-mediated procaspase-activation pathway of caspase-9 When cellular stress (e.g. DNA damage) occurs, proapoptotic proteins in the cytosol will be activated, which will in turn induce the opening of mitochondrial permeability transition pores (MPTPs). As a result, cytochrome c localized in mitochondria will be released to the cytosol. With the presence of cytosolic dATP (deoxyadenosine triphosphate) or ATP, apoptotic protease activation factor-1 (Apaf-1) oligomerizes. Together with cytosolic procaspase-9, dATP and cytochrome c, oligomerized Apaf-1 can result in the formation of a massive complex known as apoptosome. The N-terminal of Apaf-1 and the prodomain of procaspase-9 both have CARDs, with complementary shapes and opposite charges. They interact with each other by CARDs and form a complex in the proportion of 1:1 [5,11]. Activated caspase-9 can in turn activate procaspase-3 and procaspase-7. The activated caspase-3 will then activate procaspase-9 and form a positive feedback activation pathway (Fig. 3).

Fig. 2 Caspase-2-dependent procaspase-activation pathway
RIP, receptor-interacting protein; TNF, tumour necrosis factor; TNFR, TNF receptor; TRADD, TNFR-associated death domain.

Fig. 3 Typical mitochondrion-mediated and caspase-dependent pathway
Apaf-1, apoptotic protease activation factor-1; Cyto c, cytochrome c; FADD, Fas-associated death domain; TRADD, tumour necrosis factor receptor-associated death domain.
In the mitochondrion-mediated activation pathway, Apaf-1 is a central component of the apoptosome. Apaf-1 has three distinct domains: an N-terminal CARD, a nucleotide-binding domain and 12–13 repeats of WD40 near its C-terminal. At least four different isoforms of Apaf-1 have been found, all of which contain the three domains resulted from the alternative splicing of Apaf-1 pre-mRNA. CARD is responsible for binding the prodomain of procaspase-9, thus it is important in procaspase-9 recruitment and activation. The sequence of the nucleotide-binding domain is very similar to CED-4 in C. elegans. For this reason, the domain is also referred to as the CED-4-homologous domain. This domain is responsible for Apaf-1 oligomerization in the presence of cytochrome c and dATP. The dATP-binding ability of Apaf-1 alone is poor, but with cytochrome c it can be greatly enhanced. Procaspase-9 also has a synergic promotion to the binding [12]. WD40 repeats are involved in the interaction of Apaf-1 and cytochrome c [13,14].

Recently, there have been many reports concerning the activation of caspase-9, which have challenged traditional ideas. Under normal physiological conditions, inactive caspase-9 exists in the form of a monomer. When caspase-9 is artificially crystallized or is recruited by Apaf-1 caspase-9 exists in the form of a monomer. When caspase-9 is artificially crystallized or is recruited by Apaf-1 in vivo, the formation of a caspase-9 dimer results in the activation of caspase-9 [15]. In murine embryonic fibroblast cells, the activation of procaspase-9 was independent of cytochrome c release, the presence of Apaf-1 or reactive oxygen intermediates in apoptosis triggered by Sendai virus infection [16]. Costantini et al. [17] reported both procaspase-9 and caspase-9 exist in mitochondria isolated from liver, brain, kidney, spleen and heart. Procaspase-9 translocated from mitochondria to the cytosol and the nucleus in apoptosis because of changes in the permeability of the mitochondrial membrane [17].

According to these new results, alternative ideas have been brought forward about how procaspase-9 is activated and what molecules are required during the activation. One view generally held is that, although the prodomain of procaspase-9 is cleaved, the formation of the caspase-9 (or procaspase-9) dimer, rather than the cleavage, is essential to the activation of caspase-9. However, under some circumstances, the activation of procaspase-9 may be independent of mitochondrial factors, such as cytochrome c.

**Downstream Substrates of Caspases**

Once activated, apoptosis activator caspases such as caspase-2, -8 and/or -10 will activate other downstream apoptosis executioner caspases including caspase-3, -6, and -7. Furthermore, active caspase 8 can cleave BID to tBid, which translocates to the mitochondrial membrane and triggers cytochrome c release and activation of the mitochondrial apoptotic pathway [18]. The activated executioner caspases can subsequently cleave distinct cellular proteins such as PARP [poly(ADP-ribose) polymerase], lamin, fodrin, and also Bcl-2, leading to the characteristic morphological changes. The downstream substrates of inflammatory mediator caspases, such as caspase-1, -4 and -5, include pro-IL-1β, pro-IL-18, IL-1F7b and NOD-LRR (nucleotide-binding oligomerization domain-leucine-rich repeat) members such as Ipaf (interleukin-1β-converting enzyme protease-activating factor), LRR and pyrin proteins, etc. [19,20].

**Caspase-3, caspase-6 and caspase-7**

Caspase-3, a key factor in apoptosis execution, is the active form of procaspase-3. The latter can be activated by caspase-3, caspase-8, caspase-9, caspase-10, CPP32 activating protease, granzyme B (Gran B), and others. The downstream substrates of caspase-3 include procaspase-3, procaspase-6, procaspase-9, DNA-PK, PKCγ, PARP, D4-GDI (D4 GDP-dissociation inhibitor), steroid response element-binding protein, U1-70kD, inhibitor of caspase-activated deoxyribonuclease (ICAD) and so on. Except for α-fodrin and topoisomerase I, all of the substrates can be cleaved during the apoptosis in caspase-3− cells, from which we can see that caspase-3 is not the only apoptosis executioner caspase [3]. Because all substrates of caspase-3 contain DEVD sequences in common, artificially synthesized tetra peptides Ac-DEVE-AMC and Ac-DEVE-CHO are usually used as the specific substrate and inhibitor of caspase-3, respectively.

Through alternative splicing, caspase-3 pre-mRNA can be translated into a short caspase-3 (caspase-3S), which lacks the conservative ‘QACXG’ sequence in the catalyzing site, and is co-expressed with caspase-3 in all human tissues. In HEK293 cells, overexpressed caspase-3S could protect cells from apoptosis induced by proteosome inhibition [3].

Caspase-6 and caspase-7 are highly homologous to caspase-3. Procaspase-6 can be activated by caspase-3 but not Gran B. Caspase-6 can also activate procaspase-3 by a positive feedback pathway. The substrates of caspase-6 include PARP, lamin and procaspase-3. Procaspase-7, whose substrates include PARP, procaspase-6 and steroid response element-binding protein, can be activated by Gran B [9,21].
Other downstream substrates of caspases

The downstream substrates of caspases, such as PARP, DNA-PK and U1-70kD, are also involved in DNA repair. Once these substrates have been inactivated by the cleavage of caspases, DNA degradation will ensue.

Caspase-activated deoxyribonuclease (CAD) is a kind of constitutive, magnesium-dependent endonuclease that can be activated by caspases. CAD plays an important role in DNA degradation in the apoptosis of mammals. In normal cells, CAD resides in the nucleus, binding with its specific inhibitor, ICAD, to form a complex. ICAD is not only the inhibitor but also the molecular chaperone of CAD, essential for the proper folding of CAD. In apoptosis, caspase-9 damages the nuclear pores in an unknown fashion so that caspase-3 can enter the nucleus to cleave ICAD. This releases the CAD from the complex, which can result in DNA degradation (Fig. 4).

Lamin A and fodrin are essential components of the nuclear skeleton and cytosolic skeleton, respectively. The cleavage of lamin by caspases in apoptosis can lead to the condensation of chromatins and the decomposition of the nuclear membrane. The cleavage of fodrin by caspases in apoptosis can result in apoptotic body formation.

When all kinds of caspase substrates are activated, the cell will go through a series of changes, including the activation of related genes, a decrease in DNA damage repair ability, the activation of zymogens or inactivation of enzymes, cytoskeleton disassembly, and chromatin fragmentation. The cell inevitably undergoes apoptosis.

Functions of Caspase-2

Caspase-2 is the earliest identified caspase in mammals. This enzyme is unique for its features of both initiator and effector caspases. Caspase-2 appears to be necessary for the onset of apoptosis triggered by several insults, including DNA damage, administration of TNF, and different pathogens and viruses [22]. Both caspase-2 and caspase-9 are similar to CED-3 in *C. elegans*, all of them with a CARD. Caspase-2 widely distributes in most tissues and cell types. It can be found in the nucleus as well as the cytoplasm, with a considerable portion in the Golgi complex.

Many studies have shown that caspase-2 serves as an apoptosis inducer in some types of cells. Read et al. [10] reported the spontaneous recruitment of procaspase-2 into a protein complex without cytochrome c or Apaf-1 in some cells. The complex formed through the recruitment was enough to activate procaspase-2. In this case, procaspase-2 might be activated upstream of procaspase-9 activation, the release of cytochrome c and other apoptosis factors inside the mitochondria [10]. In the same year, the research results of Paroni et al. [23] showed that in the early phase of apoptosis, caspase-2 inside the nucleus could cause mitochondrial dysfunction without entering the cytosol. The release of cytochrome c was not accompanied by any obvious alteration in nuclear pores. Only in the late phase of apoptosis, caspase-2 entered the cytosol because of an increase in the diffusion limits of the nuclear pores. Guo et al. [24] reported that purified caspase-2 at physiological levels could cleave cytosolic Bid into tBid, which could induce the release of mitochondrial cytochrome c. Furthermore, caspase-2 could induce the release of cytochrome c, AIF and second mitochondrial activators of caspases/direct IAP binding protein with low pI (Smac/DIABLO) from mitochondria, independent of Bid or other cytosolic factors [6]. Mitochondrial cytochrome c released by caspase-2 was sufficient to activate apoptosome in vitro [24]. In 2002, Lassus et al. [25] found that in caspase-2-deficient cells, the translocation of Bax from the cytosol to mitochondria,
induced by etoposide, was inhibited. The reports cited above put forward a new question: In the mitochondrion-mediated activation pathway of apoptosis, which caspase is the first to be activated, caspase-2 or caspase-9? These new results also gave rise to the new proposal that Bcl-2 may act as CED-9, inhibiting apoptosis through inhibiting the activation of procaspase-2 rather than, as previously known, through inhibiting the release of mitochondrial proapoptotic factors and maintaining the normal MPTPs [26,27]. In addition, it was found that not only was caspase-2 associated with the activation of procaspase-9, but caspase-2L could also promote the formation of DISC to help with the activation of procaspase-8 in Fas-mediated apoptosis [28].

In 2002, Mendelsohn et al. [29] found that cyclin D3, a positive cell cycle regulator, could interact with caspase-2 and stabilize it. The interaction implies the important roles that cyclin D3 and caspase-2 may play in coordinating the balance of cell division and apoptosis.

**Caspase-12 and Endoplasmic Reticulum (ER) Stress-induced Apoptosis**

Caspase-1, caspase-4, caspase-5, caspase-11 and caspase-12 are highly homologous [30,31].

Caspase-12 localizes in ER and mediates apoptosis under ER stress. It plays a key role in many nervous system diseases, such as Alzheimer’s disease. ER stress is mainly caused by the accumulation of proteins, particularly unfolded and malfolded ones, in ER lumen and/or the perturbation of calcium ion homeostasis. Thapsigargin, tunicamycin, calcium ionophores, brefeldin-A and cisplatin can all induce ER stress.

It has been proved in some cell types that ER stress can lead to apoptosis in which caspase-12 is involved. In apoptosis caused by tunicamycin, the processing of procaspase-12 at its N-terminus was necessary not only for the translocation of active caspase-12 into the nucleus but also for cell apoptosis. Under ER stress, the activation of procaspase-12 could be induced by other caspases. The stress inducers can lead to the translocation of caspase-7 from the cytosol to the ER surface. Caspase-7 activates procaspase-12 by exsecting its prodomain through interaction. This activation manner may be employed in all prolonged apoptosis caused by ER stress [32]. The functions of mitochondria in this type of apoptosis varied with different reports. Morishima et al. [31] reported that procaspase-12 was specifically activated as an inducer caspase in apoptosis triggered by ER stress in murine myoblast cell line C2C12. The activated caspase-12 then activates procaspase-9, and the activated caspase-9 in turn activates procaspase-3, -6 and -7 (Fig. 5). In these newly-found caspase-activation pathways, no cytochrome c was found to be released from mitochondria, which implies that cytochrome c is not involved in the activation of procaspase-9, and, in this case, procaspase-9 is the downstream substrate of caspase-12 [31].

**Fig. 5** Caspase-12 involved in apoptosis triggered by ER stress

Apaf-1, apoptotic protease activation factor-1; ER, endoplasmic reticulum; FADD, Fas-associated death domain; TRADD, tumour necrosis factor receptor-associated death domain.

**Caspase Family Protease Regulating Factors**

The activation and inactivation of caspases are regulated by various proteins, ions and other factors, such as IAP, Bcl-2 family proteins, calpain, Ca²⁺, Gran B and cytokine response modifier A (Crm A).

**IAP**

IAP was first identified in insect cells infected by the baculovirus. Encoded by a viral gene, IAP can inhibit infected host cells from executing the apoptotic program. So far, in humans, the identified members of the IAP family include cIAP1, cIAP2, XIAP (X-linked mammalian inhibitor of apoptosis protein), NAIP (neuronal apoptosis inhibitory protein), survivin and livin. All members of the family contain 1–3 N-terminal baculovirus IAP repeat
(BIR) domains and one conservative C-terminal RING (really interesting new gene) domain. The BIR domains are zinc finger-like structures that can chelate zinc ions. These zinc fingers can bind to the surface of caspases so that the amino acid sequences, or linkers, between BIR domains can block the catalyzing grooves of caspases. As a result, IAP can protect a cell from apoptosis by inhibiting the activity of caspases. However, not all BIR-containing proteins are inhibitors of apoptosis. Survivin, for example, containing only one BIR domain, may act as a regulator of mitosis rather than apoptosis. The RING domain has the catalyzing activity of ubiquitin ligase E3. It can catalyze the connection of ubiquitin with the RING domain or with other proteins. It can be hypothesized that the RING domain may facilitate the degradation of caspases that bind to IAP [34].

The activity of mammalian IAP can be inhibited by Smac/DIABLO released from mitochondria. As the four-residue sequence (Ala1-Val2-Pro3-Ile4) in the newly-formed N-terminus of Smac/DIABLO can recognize and bind to the caspase-9-binding site of XIAP, so that XIAP will be inactivated, its inhibiting effect on caspase-9 will in turn be relieved [17]. IAP family proteins may also have other functions besides caspase inhibition. As reported by Uren et al., IAP family members in yeast could neither unite caspases nor induce apoptosis [35].

Bcl-2 family proteins

The members of the Bcl-2 family are a group of crucial regulatory factors in apoptosis. According to functional and structural criteria, the members can be divided into two groups. Group I proteins are all anti-apoptotic proteins, including A1/Bfl1, Bcl-2, Bcl-w, Bcl-xL, Boo/Diva, Mcl-1, NR-13 and Nrf3 in mammalians, BHRF-1, E1B19K, Ks-Bel-2, LMW5-HL and ORF16 in bacteria, and Ced-9 in C. elegans [7,36,37]. They all have four short Bcl-2 homology (BH) domains: BH1, BH2, BH3 and BH4. The most overt mechanism of their anti-apoptotic functions is inhibiting proapoptotic proteins of the Bcl-2 family by binding to them. Group II proteins are all proapoptotic proteins, including Bad, Bak, Bax, Bel-rambo, Bel-xS, Bid, Bik, Bim, Bik, BNIP3, Bok/Mtd, Hrk and Nip3 in mammalians, and Egl-1 in C. elegans [36]. Bax and Bak, originally localized in the cytoplasm, can translocate to the mitochondrial outer membrane after an apoptotic program starts. Following the translocation, they will undergo conformation changes, oligomerization and insertion into the mitochondrial outer membrane to elevate the permeability of MPTPs. Group I proteins can bind selectively to the active conformation of Bax to prevent it from inserting into the mitochondrial outer membrane to maintain the normal permeability of MPTPs, and prevent the release of mitochondrial proapoptotic factors, such as cytochrome c, AIF and Smac/DIABLO [6,11]. Through cytochrome c, AIF, and others, Bcl-2 family proteins can indirectly regulate the activity of caspases in related apoptotic pathways [11].

Calpain and calcium ion

Calpain is a kind of Ca2+-dependent cysteine protease of the papainase family. It is generally believed that calpain is activated in both necrosis and apoptosis. Calpain and caspase-3 share many common substrates, including fodrin, Ca2+-dependent protein kinase and ADP-ribosyltransferase/PARP [38]. In apoptosis induced by ER stress, calpain’s functions are particularly salient because of the perturbed Ca2+ homeostasis. In the brain cells of rats suffering from unilateral hypoxia-ischemia, m-calpain first cleaved procaspase-3 into 29 kDa fragments to facilitate its further cleavage and activation [39]. Cisplatin, a kind of anticancer agent, can cause ER stress and apoptosis. During this process, the activation of procaspase-12 by cisplatin is dependent on Ca2+ and calpain [40]. In addition, calpain can also cleave Bcl-xL in its loop region, which will convert Bcl-xL to a proapoptotic molecule from an anti-apoptotic one [41].

Gran B, CrmA and p35

Gran B is a kind of serine protease with an important role in apoptosis in cytotoxic T cells. Gran B can activate various procaspases, such as procaspase-3, procaspase-7, procaspase-8, procaspase-9 and procaspase-10, to initiate apoptosis [42]. In 2000, Barry et al. found that Gran B could cleave Bid to initiate the mitochondrion-mediated activation pathway [43].

The activity of Gran B can be inhibited by CrmA, a kind of serpin from the vaccinia virus. CrmA, a strong inhibitor of caspase-1 and caspase-8, and a weak inhibitor of caspase-3 and caspase-6, can prevent the cross-link of Fas and inactivate Gran B (Fig. 6).

Baculovirus p35, with the ability of binding to caspases to cleave and inactivate them, is an effective inhibitor of caspases from caspase-1 to caspase-8 [44].

However, the mechanisms through which the members of the caspase family interact with each other, and how they interact with other proapoptotic and antiapoptotic factors, are still uncertain. Studies on these problems in apoptosis research are quite intense, and continual advances in this field will give us further understanding about the caspase family and apoptosis. Apoptosis is vital in normal embryonic genesis and development, the differentiation of

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immune cells, autoimmunity, tumorigenesis and nervous system injuries. Caspase family proteases are key factors in apoptosis, and the related research can help us to obtain the essence of the above phenomena at the molecular level and enable us to make breakthroughs in the therapy of tumors, immune system diseases and nervous system diseases using the artificial control of apoptosis.

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