ISSN (Online) 2287-3406
Journal of Life Science **2021** Vol. 31. No. 10. 954~959 DOI : https://doi.org/10.5352/JLS.2021.31.10.954

- Review -

Structural and Functional Roles of Caspase-8 in Extrinsic Apoptosis

Min Seon Ha[1], Mi Suk Jeong[2] and Se Bok Jang[1]*

[1]*Department of Molecular Biology, College of Natural Sciences, Pusan National University, Jangjeon-dong, Geumjeong-gu, Busan 46241, Korea*
[2]*Institute for Plastic Information and Energy Materials and Sustainable Utilization of Photovoltaic Energy Research Center, Pusan National University, Jangjeon-dong, Geumjeong-gu, Busan 46241, Korea*

Received September 24, 2021 /Revised October 5, 2021 /Accepted October 21, 2021

Apoptosis is an important mechanism that regulates cellular populations to maintain homeostasis, and the caspases, a family of cysteine proteases, are key mediators of the apoptosis pathway. Caspase-8 is an initiator caspase of the extrinsic apoptotic pathway, which is initiated by extracellular stimuli. Caspase-8 have two conserved domains, N-terminal tandem death effector domains (DED) and C-terminal two catalytic domain, which are important for this extrinsic apoptosis pathway. In extrinsic apoptosis pathway, death receptors which members of TNF superfamily are activated by binding of death receptor specific ligands from cell outside. After the activated death receptors recruit adaptor protein Fas-associated death domain protein (FADD), death domains (DD) of death receptor and FADD bind to each other and FADD combined with death receptor recruits procaspase-8, a precursor form of caspase-8. The DED of FADD and procaspase-8 bind to one another and FADD-bound procaspase-8 is activated by cleavage of the prodomain. This death receptor-FADD-caspase-8 complex called death inducing signaling complex (DISC). Cellular FLICE-inhibitory proteins (c-FLIPs) regulate caspase-8 activation by acting both anti- and pro-apoptotically, and caspase-8 activation initiates the activation of executioner caspases such as caspase-3. Finally activated executioner caspases complete the apoptosis by acting critically DNA degradation, nuclear condensation, plasma membrane blebbing, and the proteolysis of certain caspase substrates.

Key words : Caspase-8, DISC, extrinsic apoptosis, FADD, FLIP

Extrinsic apoptosis pathway

The term apoptosis was first proposed by Kerr, Wyllie, and Currie in 1972, who suggested a mechanism of programmed cell deletion complementary to mitosis that regulates animal cell cell populations [19, 20]. Since then, several other types of programmed cell deaths such as pyroptosis and necroptosis have been defined [7, 44]. However, apoptosis is the most studied type of programmed cell death.

Apoptosis is important for maintaining cellular homeostasis and plays critically important roles during developmental and disease processes, especially in cancer and neurodegenerative diseases. Apoptosis occurs via two pathways, that is intrinsic and extrinsic pathways [41]. Intrinsic apoptosis is initiated by cellular stress, such as that caused by critical DNA damage, and occurs via the mitochondrial pathway, whereas extrinsic apoptosis is initiated by extracellular death signals and does not require mitochondrial pathway activation [17].

Extrinsic apoptosis is triggered when death receptors are bound by specific ligands. These receptors are members of the tumor necrosis factor (TNF) receptor superfamily, which contains tumor necrosis factor (TNF) receptor-1, CD95 (Apo-1 and Fas), DR4, and DR5 (TRAIL-R1 and -R2) and are characterized by a similar cytokine-rich extracellular domain. One example of the ligand binding death receptors is provided by binding between Fas ligands and Fas receptors. Examples of FasL/FasR and TNF-α/TNFR1 pathways are provided in Fig. 1 [1, 38, 43]. This ligand binding at death receptors leads to caspase activation, which eventually leads to apoptosis [41].

Features of Caspase-8

Caspases are a family of cysteine proteases, which cleave substrates at aspartic acid residues, from which the term "caspase" was derived [33]. Caspases are divided into inflammatory caspases which include caspase-1, -4, and -5, and apoptotic caspases like caspase-2, -3, -6, -7, -8, -9, and -10

***Corresponding author**
Tel : +82-51-510-2523, Fax : +82-51-581-2544
E-mail : sbjang@pusan.ac.kr

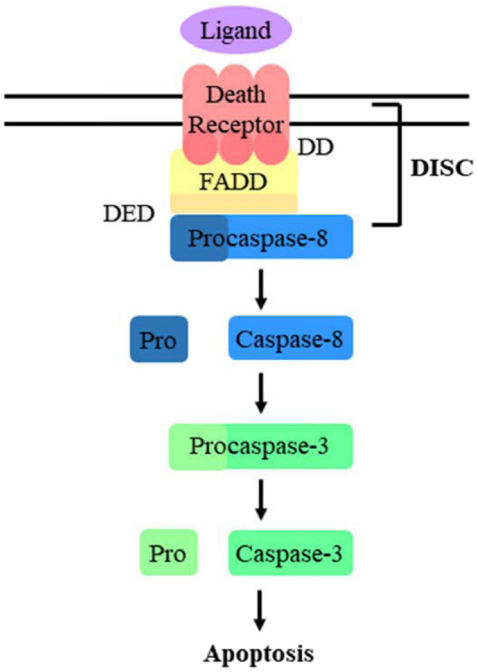

Fig. 1. Extrinsic apoptosis signaling pathway. In this schematic, the death receptor is Fas or TRAIL receptor. The ligands of Fas and TRAIL receptor are Fas ligand and TRAIL. Other death receptors follow more complex pathways. Ligands bind to death receptor and the cytosolic death domain of death receptor binds to the death domain of FADD. The death effector domain of FADD then interacts with the death effector domain of procaspase-8, and FADD bound procaspase-8 is processed by autoproteolysis to activated caspase-8, which activates procaspase-3 and leads to apoptosis.

Table 1. Classification of caspases

Apoptosis		Inflammation
Initiator	Executioner	
Caspase-2 Caspase-8 Caspase-9 Caspase-10	Caspase-3 Caspase-6 Caspase-7	Caspase-1 Caspase-4 Caspase-5 Caspase-12

Depending on function, caspases are classified apoptosis caspases and inflammation caspases. And Apoptosis caspases divided two types: Initiator caspases and Executioner caspases. Initiator caspases can activate executioner caspases. All caspases entered are human caspases.

(Table 1) [5, 28]. The apoptotic caspases are vital mediators of apoptosis and are classified as initiator or executioner caspases. Caspase-8 (also known as FLICE) is an initiator caspase [2, 7], and when active activates effector caspases. Caspase-8 functions primarily in the extrinsic apoptotic pathway [39] but has also been shown to play roles in several non-apoptotic processes [27].

As its name implies, procaspase-8 is a precursor of caspase-8, and is 55 kDa long and possesses two DEDs which are pro-domain at its N-terminal and C-terminal two proteolytic domains. And two proteolytic domains are composed of large subunit p18 and small subunit p12 [26](Fig. 2A). Caspase-8 is complexed with zymogen in cytosol [22], but during apoptosis, caspase-8 is sequentially activated by proteolysis at aspartic acid residues.

Mature caspase-8 is a heterotetramer consisting of two large subunits and two small subunits generated from two separate procaspase-8 molecules. Activation of procaspase-8 is initiated by its separation into large and small subunits, which is followed by separation of the large subunit and its prodomain [3, 46].

Structure analysis DISC formation

Extrinsic apoptosis is initiated by the formation of death receptor-FADD-caspase-8 complex (DISC) as a result of extracellular stimulation (Fig. 1), and all three of these components of DISC are essential for its activity [30]. Although DISC formation also depends on death receptor, in this review we describe the FasL/FasR and TNF-α/TNFR1 models [31].

The first step of DISC formation involves death receptor activation, which is induced by its binding a receptor-specific ligand. After ligand binding, activated death receptor recruits other death receptors to form a homotrimer.

In the second step, the trimerized death receptors recruit the adapter protein FADD, which is a cytosolic adaptor protein essential for apoptotic signaling by death receptors. FADD has two highly conserved domains, that is, an N-terminal DED and a C-terminal DD [2](Fig. 2A). The DDs of death receptors and FADD are homotypic proteins that bind together in cytosol. The DDs of death receptor are cytoplasmic domains composed of about 80 amino acids that play key roles in the transmission of death signals from cell surfaces to intracellular signaling pathways [7]. When FADD binds to trimerized death receptor it causes a conformational change that exposes its DED, which binds caspase-8 [14, 23].

The third step involves the recruitment of procaspase-8 by the DED of FADD and their interaction. Procaspase-8 binds to the exposed DED of death receptor-associated FADD through a pocket in its first DED to form DISC. Oligomerization then ensues via an interaction between a

pocket in the second DED of the first caspase-8 and the first DED of the second caspase-8 molecule. This process continues with successive interactions to produce filaments [6, 10]. Finally, cleavage of these filaments stabilizes and releases active caspase-8 dimers into the cytosol, which initiate apoptosis by processing target proteins [18, 42].

During the process of procaspases dimerization, procaspase-8 undergoes a conformational change and forms an active center of procaspase-8a/b, which is auto-catalytically cleaved by proteolysis to produce the active caspase-8 heterotetramer 2p10 and 2p18 [12].

In an investigation of the structure of the tandem DED of caspase-8, researchers demonstrated the dimeric structure of two caspase-8 tandem DED domains (Fig. 2B). The DEDs of the caspase-8 N-terminal were found to compose an α helical fold, in which they were closely associated with each other to form a dumbbell-shaped structure. The crystal structure of caspase-8 DEDs was solved as a dimer in the asymmetric unit. The proteolytic domain of the C-terminal of caspase-8 is composed of six β strands and five α helices [35] (Fig. 2C).

Therefore, in extrinsic apoptosis pathway, procaspase-8 dimerization and filamentation are important process to progress the apoptotic pathway. Thus, mutation of DEDs of procaspase-8 can affect procaspase-8 dimerization and formation of filament. Mutations inhibiting the dimerization of the DEDs such as F122A/I128D or F122A/N168R mutations prevent the dimerization and formation of cellular death effector filaments (DEFs) and the induced apoptosis by overexpressed DEDs. In addition, these mutations also hinder the activation of the procaspase-8 and the downstream apoptosis cascade [34].

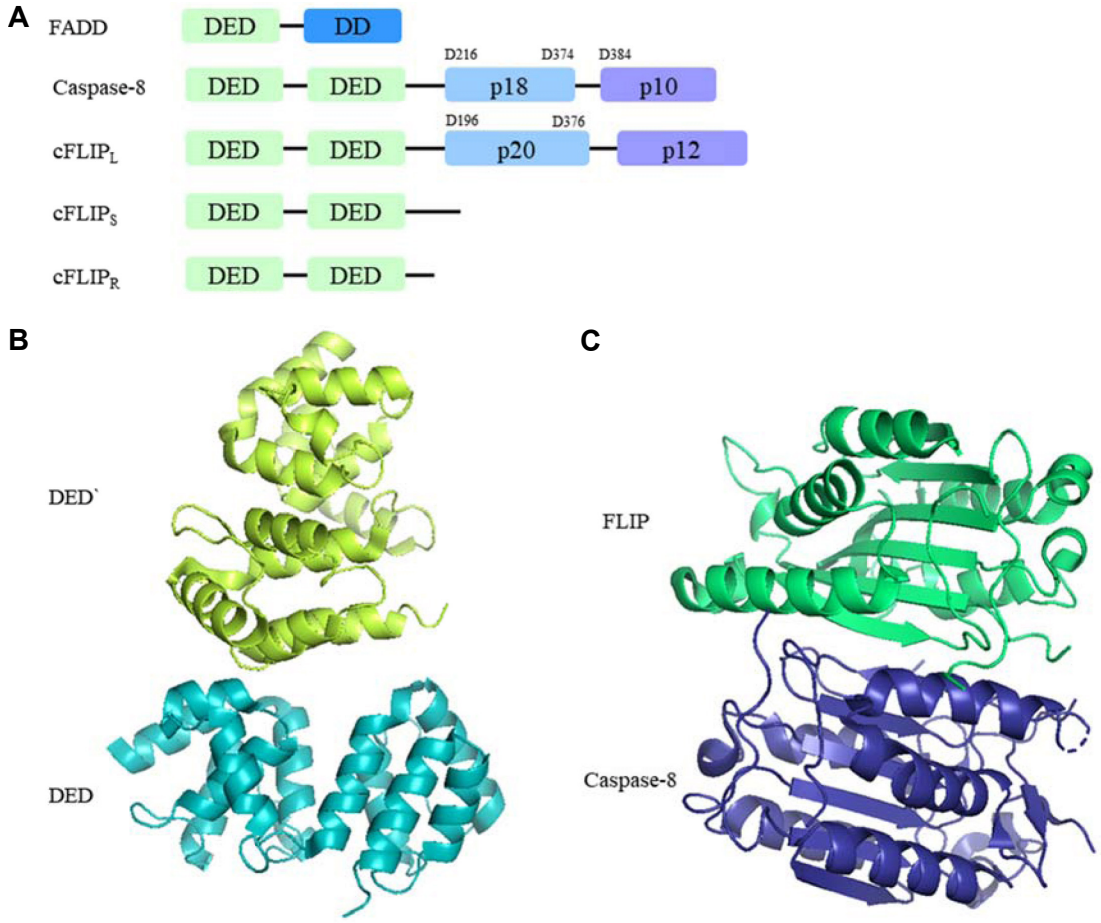

Fig. 2. Structural analysis of FADD, caspase-8, and c-FLIP. Domain structures of FADD, caspase-8, c-FLIP$_L$, c-FLIP$_s$, and c-FLIP$_R$. FADD consists of DED and DD. (A) Caspase-8 and c-FLIP$_L$ each possess tandem DEDs and two catalytic domains. c-FLIP$_S$ and c-FLIP$_R$ both consist of a tandem DED and a short tail domain. (B) The dimeric structure of the tandem DED of caspase-8 (residues 1-188; PDB ID: 4ZBW). (C) The interaction between c-FLIPL and caspase-8. The two proteins bind each other's catalytic domains (residues c-FLIPL: 209-480, caspase-8: 217-479; PDB ID: 3H11).

c-FLIP regulates caspase-8 activation

c-FLIP is a central regulator of the extrinsic apoptosis pathway and determines the activity of caspase-8 [16, 32, 40]. c-FLIP has three splice forms: a long splice form $FLIP_L$ and two short splice forms $FLIP_S$ and $FLIP_R$. [11, 15]. The sizes of these proteins are 55 kDa for $FLIP_L$, 27 kDa for $FLIP_S$, and 25 kDa for $FLIP_R$. [29].

Caspase-8 and c-$FLIP_L$ have similar structures and domains, namely, two DEDs and two proteolytic domains [26] (Fig. 2A). The major difference between c-$FLIP_L$ and procaspase-8 is the lack of proteolytic activity of c-$FLIP_L$ due to the absence of a catalytic cysteine in its large subunit. The two short forms c-$FLIP_S$ and c-$FLIP_R$ only contain a tandem DED and a short C-terminal tail. Therefore, all c-FLIP isoforms contain tandem DED that is structurally similar to tandem DED of procaspase-8. Short form FLIPs do not have a proteolytic domain, and thus, lack proteolytic activity [41].

The functions of c-FLIP isoforms differ. Short form c-FLIPs block caspase-8 activation by inhibiting the procaspase-8 chains of DISC. These isoforms integrate into DED chains and block caspase-8 activation by forming inactive heterodimers [12]. On the other hand, c-$FLIP_L$ in DISC can act anti- or pro-apoptotically [4, 21]. c-FLIPL functions like c-$FLIP_S$ and $FLIP_R$ when expressed at high concentrations intracellularly but at moderate concentrations facilitates the activation of procaspase-8 in DISC [29]. When c-$FLIP_L$ acts pro-apoptotically, it is cleaved by procaspase-8 and processed caspase-8, and the then processed c-FLIP facilitates the activation of caspase-8 and enhances the heterodimerization of c-FLIP and caspase-8. The interaction between the catalytic domain of c-FLIPL and caspase-8 is shown in Fig. 2C [16, 24].

Recently, electron microscopy showed that when c-FLIPs is inserted into DISC, it inhibits caspase-8 activity due to steric hindrance of the canonical tandem DED Type I binding site. Thus, c-FLIPs prevents caspase-8 catalytic domain assembly and tandem DED helical filament elongation [8].

Active caspase-8 activates executioner caspases

Caspase-3 is the most important executioner caspase and is activated by any of the initiator caspases. Procaspase-3 exists dimeric in cytosol and have N-terminal short prodomain and C-terminal two catalytic domains. Caspase-8 can directly activate procaspase-3 by cleaving the prodomain of procaspase-3 [36]. These caspase cascades amplify apoptotic signaling and make the executioner caspase complete the apoptosis process [5]. Caspase-3 is important for DNA degradation, nuclear condensation, plasma membrane blebbing, and the proteolysis of certain caspase substrates [35]. Full activation of caspase-3 leads to cell death [17].

Non-apoptotic roles of caspase-8

Caspase-8 functions not only apoptosis but also other programmed cell death process such as necroptosis or pyroptosis. Many studies demonstrated that when the caspase-8 defective conditions, necroptosis and pyroptosis occur [9, 41]. In necroptosis, programmed necrotic cell death, caspase-8 hindered necroptosis by preventing assemble the necrosome [23]. Like extrinsic apoptosis, necroptosis can be initiated by receptors such as TNFR or Fas. Necroptosis can occur upon activation of death receptors by specific receptors in the absence of caspase-8 activation [12].

Pyroptosis is an inflammatory form of programmed cell death that relies on the enzymatic activity of caspase-1 [44]. In pyroptosis pathway, caspase-8 is also concerned with the process. Extrinsic apoptosis triggers can lead to GSDMD cleavage and subsequent pyroptosis-like cell death in macrophages of Murine, which is mediated by the caspase-8 [12].

Conclusion

The extrinsic apoptosis pathway is regulated by extracellular stimuli and consequent DISC formation. Caspase-8, an important mediator of extrinsic apoptosis, is a component of DISC, and its tandem DEDs are importantly required for this process. FADD recruits the DED of a caspase-8 molecule and the second DED of this molecule binds the first DED of a second caspase-8, and this oligomerization proceeds to form a filament structure. Activated caspase-8 converts other caspases and itself into executioner caspases.

c-FLIP can function in both anti- and pro-apoptotic ways. c-FLIPs and c-FLIPr block caspase-8 activation by interacting with the chains of procaspase-8, whereas c-FLIPL inhibits the activation of caspase-8 at high concentrations but facilitates its activation at moderate concentrations. When activated caspase-8 activates executioner caspases, cells are committed to apoptosis.

Acknowledgement

This work was supported by a 2-Year Research Grant from Pusan National University (2021-2022).

The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

References

1. Ashkenazi, A. and Dixit, V. M. 1998. Death receptors: signaling and modulation. *Science* **281**, 1305-1308.
2. Barnhart, B. C., Lee, J. C., Alappat, E. C. and Peter, M. E. 2003. The death effector domain protein family. *Oncogene* **22**, 8634-8644.
3. Chang, D. W., Xing, Z., Capacio, V. L., Peter, M. E. and Yang, X. 2003. Interdimer processing mechanism of procaspase-8 activation. *EMBO J.* **22**, 4132-4142.
4. Chang, D. W., Xing, Z., Pan, Y., Algeciras-Schimnich, A., Barnhart, B. C., Yaish-Ohad, S. and Yang, X. 2002. c-FLIPL is a dual function regulator for caspase-8 activation and CD95-mediated apoptosis. *EMBO J.* **21**, 3704-3714.
5. Degterev, A., Boyce, M. and Yuan, J. 2003. A decade of caspases. *Oncogene* **22**, 8543-8567.
6. Dickens, L. S., Boyd, R. S., Jukes-Jones, R., Hughes, M. A., Robinson, G. L., Fairall, L. and MacFarlane, M. 2012. A death effector domain chain DISC model reveals a crucial role for caspase-8 chain assembly in mediating apoptotic cell death. *Mol. Cell* **47**, 291-305.
7. Elmore, S. 2007. Apoptosis: a review of programmed cell death. *Toxicol. Pathol.* **35**, 495-516.
8. Fox, J. L., Hughes, M. A., Meng, X., Sarnowska, N. A., Powley, I. R., Jukes-Jones, R. and MacFarlane, M. 2021. Cryo-EM structural analysis of FADD: Caspase-8 complexes defines the catalytic dimer architecture for co-ordinated control of cell fate. *Nat. Commun.* **12**, 1-17.
9. Fritsch, M., Günther, S. D., Schwarzer, R., Albert, M. C., Schorn, F., Werthenbach, J. P. and Kashkar, H. 2019. Caspase-8 is the molecular switch for apoptosis, necroptosis and pyroptosis. *Nature* **575**, 683-687.
10. Fu, T. M., Li, Y., Lu, A., Li, Z., Vajjhala, P. R., Cruz, A. C. and Wu, H. 2016. Cryo-EM structure of caspase-8 tandem DED filament reveals assembly and regulation mechanisms of the death-inducing signaling complex. *Mol. Cell* **64**, 236-250.
11. Golks, A., Brenner, D., Fritsch, C., Krammer, P. H. and Lavrik, I. N. 2005. c-FLIPR, a new regulator of death receptor-induced apoptosis. *J. Biol. Chem.* **280**, 14507-14513.
12. Gram, A. M., Booty, L. M. and Bryant, C. E. 2019. Chopping GSDMD: caspase-8 has joined the team of pyroptosis-mediating caspases. *EMBO J.* **38**, e102065.
13. Hillert, L. K., Ivanisenko, N. V., Busse, D., Espe, J., König, C., Peltek, S. E. and Lavrik, I. N. 2020. Dissecting DISC regulation via pharmacological targeting of caspase-8/c-FLIP L heterodimer. *Cell Death Differ.* **27**, 2117-2130.
14. Hughes, M. A., Powley, I. R., Jukes-Jones, R., Horn, S., Feoktistova, M., Fairall, L. and MacFarlane, M. 2016. Co-operative and hierarchical binding of c-FLIP and caspase-8: a unified model defines how c-FLIP isoforms differentially control cell fate. *Mol. Cell* **61**, 834-849.
15. Irmler, M., Thome, M., Hahne, M., Schneider, P., Hofmann, K., Steiner, V. and Tschopp, J. 1997. Inhibition of death receptor signals by cellular FLIP. *Nature* **388**, 190-195.
16. Jong, W. Y., Jeffrey, P. D. and Shi, Y. 2009. Mechanism of procaspase-8 activation by c-FLIPL. *Proc. Natl. Acad. Sci. USA.* **106**, 8169-8174.
17. Kantari, C. and Walczak, H. 2011. Caspase-8 and bid: caught in the act between death receptors and mitochondria. *Biochim. Biophys. Acta Mol. Cell. Res.* **1813**, 558-563.
18. Keller, N., Mareš, J., Zerbe, O. and Grütter, M. G. 2009. Structural and biochemical studies on procaspase-8: new insights on initiator caspase activation. *Structure* **17**, 438-448.
19. Kerr, J. F. 2002. History of the events leading to the formulation of the apoptosis concept. *Toxicology* **181**, 471-474.
20. Kerr, J. F., Wyllie, A. H. and Currie, A. R. 1972. Apoptosis: a basic biological phenomenon with wideranging implications in tissue kinetics. *Br. J. Cancer* **26**, 239-257.
21. Krueger, A., Schmitz, I., Baumann, S., Krammer, P. H. and Kirchhoff, S. 2001. Cellular FLICE-inhibitory protein splice variants inhibit different steps of caspase-8 activation at the CD95 death-inducing signaling complex. *J. Biol. Chem.* **276**, 20633-20640.
22. Kruidering, M. and Evan, G. I. 2000. Caspase-8 in apoptosis: the beginning of "the end"? *IUBMB Life* **50**, 85-90.
23. Linkermann, A. and Green, D. R. 2014. Necroptosis. *N. Engl. J. Med.* **370**, 455-465.
24. Medema, J. P., Scaffidi, C., Kischkel, F. C., Shevchenko, A., Mann, M., Krammer, P. H. and Peter, M. E. 1997. FLICE is activated by association with the CD95 death-inducing signaling complex (DISC). *EMBO J.* **16**, 2794-2804.
25. Micheau, O., Thome, M., Schneider, P., Holler, N., Tschopp, J., Nicholson, D. W. and Grütter, M. G. 2002. The long form of FLIP is an activator of caspase-8 at the Fas death-inducing signaling complex. *J. Biol. Chem.* **277**, 45162-45171.
26. Muzio, M., Chinnaiyan, A. M., Kischkel, F. C., O'Rourke, K., Shevchenko, A., Ni, J. and Dixit, V. M. 1996. FLICE, a novel FADD-homologous ICE/CED-3–like protease, is recruited to the CD95 (Fas/APO-1) death-inducing signaling complex. *Cell* **85**, 817-827.
27. Oberst, A. and Green, D. R. 2011. It cuts both ways: reconciling the dual roles of caspase 8 in cell death and survival. *Nat. Rev. Mol. Cell Biol.* **12**, 757-763.
28. Orning, P. and Lien, E. 2021. Multiple roles of caspase-8 in cell death, inflammation, and innate immunity. *J. Leukoc. Biol.* **109**, 121-141.
29. Öztürk, S., Schleich, K. and Lavrik, I. N. 2012. Cellular FLICE-like inhibitory proteins (c-FLIPs): fine-tuners of life and death decisions. *Exp. Cell. Res.* **318**, 1324-1331.

30. Peter, M. E. 2000. The TRAIL DISCussion: It is FADD and caspase-8!. *Cell Death Differ.* **7**, 759-760.
31. Raducka-Jaszul, O., Bogusławska, D. M., Jędruchniewicz, N. and Sikorski, A. F. 2020. Role of extrinsic apoptotic signaling pathway during definitive erythropoiesis in normal patients and in patients with β-thalassemia. *Int. J. Mol. Sci.* **21**, 3325.
32. Schleich, K., Buchbinder, J. H., Pietkiewicz, S., Kähne, T., Warnken, U., Öztürk, S. and Lavrik, I. N. 2016. Molecular architecture of the DED chains at the DISC: regulation of procaspase-8 activation by short DED proteins c-FLIP and procaspase-8 prodomain. *Cell Death Differ.* **23**, 681-694.
33. Seaman, J. E., Julien, O., Lee, P. S., Rettenmaier, T. J., Thomsen, N. D. and Wells, J. A. 2016. Cacidases: caspases can cleave after aspartate, glutamate and phosphoserine residues. *Cell Death Differ.* **23**, 1717-1726.
34. Shen, C., Pei, J., Guo, X., Zhou, L., Li, Q. and Quan, J. 2018. Structural basis for dimerization of the death effector domain of the F122A mutant of Caspase-8. *Sci. Rep.* **8**, 1-10.
35. Shen, C., Yue, H., Pei, J., Guo, X., Wang, T. and Quan, J. M. 2015. Crystal structure of the death effector domains of caspase-8. *Biochem. Biophys. Res. Commun.* **463**, 297-302.
36. Slee, E. A., Adrain, C. and Martin, S. J. 2001. Executioner caspase-3,-6, and-7 perform distinct, non-redundant roles during the demolition phase of apoptosis. *J. Biol. Chem.* **276**, 7320-7326.
37. Stennicke, H. R., Jurgensmeier, J. M., Shin, H., Deveraux, Q., Wolf, B. B., Yang, X. and Salvesen, G. S. 1998. Pro-caspase-3 is a major physiologic target of caspase-8. *J. Biol. Chem.* **273**, 27084-27090.
38. Suliman, A., Lam, A., Datta, R. and Srivastava, R. K. 2001. Intracellular mechanisms of TRAIL: apoptosis through mitochondrial-dependent and-independent pathways. *Oncogene* **20**, 2122-2133.
39. Sun, S. Y. 2011. Understanding the role of the death receptor 5/FADD/caspase-8 death signaling in cancer metastasis. *Mol. Cell. Pharmacol.* **3**, 31.
40. Tsuchiya, Y., Nakabayashi, O. and Nakano, H. 2015. FLIP the Switch: Regulation of Apoptosis and Necroptosis by cFLIP. *Int. J. Mol. Sci.* **16**, 30321-30341.
41. Tummers, B. and Green, D. R. 2017. Caspase-8: regulating life and death. *Immunol. Rev.* **277**, 76-89.
42. Tummers, B., Mari, L., Guy, C. S., Heckmann, B. L., Rodriguez, D. A., Rühl, S. and Green, D. R. 2020. Caspase-8-dependent inflammatory responses are controlled by its adaptor, FADD, and necroptosis. *Immunity* **52**, 994-1006.
43. Wajant, H. 2002. The Fas signaling pathway: more than a paradigm. *Science* **296**, 1635-1636.
44. Walle, L. V. and Lamkanfi, M. 2016. Pyroptosis. *Curr. Biol.* **26**, R568-R572.
45. Yan, G., Elbadawi, M. and Efferth, T. 2020. Multiple cell death modalities and their key features. *World Acad. Sci. J.* **2**, 39-48.
46. Zhao, Y., Sui, X. and Ren, H. 2010. From procaspase-8 to caspase-8: Revisiting structural functions of caspase-8. *J. Cell. Physiol.* **225**, 316-320.

초록 : Apoptosis의 외인성 경로에서 caspase-8의 구조적 및 기능적 역할

하민선[1] · 정미숙[2] · 장세복[1]*

([1]부산대학교 자연과학대학 분자생물학과, [2]부산대학교 플라스틱 정보 및 에너지 재료 및 지속 가능한 활용 태양광 에너지 연구 센터)

세포 사멸은 항상성을 유지하기 위해 세포군을 조절하는 중요한 메커니즘이며 시스테인 단백질분해효소 중 하나인 카스파제는 세포 사멸 경로의 중요한 중재자이다. Caspase-8은 세포외 자극에 의해 시작되는 외인성 세포자멸 경로의 개시자 카스파제이다. Caspase-8에는 보존된 도메인인 N-말단의 두개의 죽음 이펙터 도메인(DED)과 C-말단의 2개의 촉매 도메인을 가지며, 이는 이러한 외인성 세포자멸 경로에 중요하게 작용한다. 외인성 세포멸사 경로에서, TNF 슈퍼패밀리인 죽음 수용체는 세포 외부로부터의 죽음 수용체 특이적 리간드의 결합에 의해 활성화된다. 활성화된 죽음 수용체가 어댑터 단백질인 Fas-associated death domain 단백질(FADD)을 모집한 후, 죽음 수용체와 FADD의 죽음 도메인(DD)이 서로 결합하고 죽음 수용체와 결합한 FADD가 caspase-8의 전구체 형태인 procaspase-8을 모집한다. FADD와 procaspase-8의 죽음 이펙터 도메인은 서로 결합하고 FADD에 결합된 procaspase-8은 prodomain의 절단에 의해 활성화된다. 이 죽음 수용체-FADD-caspase-8 복합체는 세포사멸 유도 신호 복합체(DISC)라고 한다. 세포 FLICE 억제 단백질(c-FLIPs)은 세포사멸을 억제하는 역할과 촉진하는 역할을 모두 수행하여 caspase-8의 활성화를 조절하고 caspase-8 활성화는 caspase-3와 같은 작동자 카스파제를 활성화를 시킨다. 마지막으로 활성화된 작동자 카스파제는 DNA 분해, 핵 응축, 세포막 수포 및 카스파제 기질의 단백질 분해에 작용하여 세포사멸을 완료한다.