Structures, Domains and Functions in Cell Death (DD, DED, CARD, PYD)

Hao Wu, *Weill Cornell Medical College, New York, USA*

Yu-Chih Lo, *Weill Cornell Medical College, New York, USA*

Advanced article

Article Contents

Online posting date: 15th December 2009

The death domain (DD), death effector domain (DED), caspase-recruitment domain (CARD) and pyrin domain (PYD) are subfamilies of the DD superfamily. By mediating homotypic interactions, these proteins play important roles in the assembly and activation of apoptotic signalling complexes. They are responsible for caspase recruitment and for formation of oligomeric platforms for signalling. DD superfamily proteins have a common six-helical bundle fold and show different surface features for each of the subfamilies. Most interestingly, the homotypic interactions within each subfamily are mostly mediated by asymmetric contacts, in which different surfaces of the interaction partners are adjacent to each other. The DD superfamily proteins appear to use three common types of asymmetric interactions to assemble into large oligomeric complexes.

Introduction

Apoptosis is an orderly cellular suicide programme, that is, critical for the development and homeostasis of a multicellular organism. Failure to control apoptosis can lead to serious diseases that threaten the existence of the organism (Rathmell and Thompson, 2002). Apoptosis proceeds through characteristic morphological changes that are dependent on caspase activities. Caspases are cysteine proteases that cleave specifically after aspartic acid residues (Riedl and Shi, 2004). Because caspases are the executioners of apoptosis, they are the key players in apoptotic cell death.

On a molecular level, the death domain (DD) superfamily members are involved in formation of oligomeric signalling complexes for caspase activation. A central paradigm in caspase activation is the assembly of oligomeric signalling complexes in response to internal or external stimuli. In a simplified view, these molecular complexes activate their effectors via 'proximity-induced autoactivation' such as dimerization and proteolytic autoprocessing (Salvesen and Dixit, 1999). The DD superfamily plays a critical role in this assembly by participating in both self-association and other protein:protein interactions.

The DD superfamily is one of the largest and most studied domain superfamilies (McEntyre and Gibson, 2004). It is currently composed of four subfamilies, the DD, the death effector domain (DED), the caspase recruitment domain (CARD) and the pyrin domain (PYD) subfamilies (Reed *et al*., 2004). DDs, DEDs, CARDs and PYDs are involved in both caspase activation and the related process of nuclear factor-κB (NFκB) activation in host defence. The DD superfamily proteins are evolutionarily conserved in many multicellular organisms such as mammals, *Drosophila* and *Caenorhabditis elegans*. Based on a genome analysis, there are 32 DDs, 7 DEDs, 28 CARDs and 19 PYDs in the human genome (Reed *et al*., 2004).

Deregulation of caspase activation is related to many human diseases. Most notably, defective receptor-mediated caspase activation and cell death underlies the human genetic disease autoimmune lymphoproliferative syndrome (ALPS) (Poppema *et al*., 2004; Rieux-Laucat *et al*., 2003b). When lymphocytes from patients with ALPS are cultured *in vitro*, they are resistant to apoptosis as compared to cells from healthy controls. Most patients with ALPS have mutations in the intracellular DD of the receptor (Rieux-Laucat *et al*., 2003a).

Functions of DDs, DEDs, CARDs and PYDs: Assembly of Caspase-activating Signalling Complexes

DDs, DEDs, CARDs and PYDs participate in homotypic interactions within the same subfamily. Many proteins involved in apoptosis contain these domains (**Figure 1**). Some examples of these important signalling complexes are presented in the next section.

ELS subject area: Genetics and Molecular Biology

How to cite:
Wu, Hao; and, Lo, Yu-Chih (December 2009) Structures, Domains and Functions in Cell Death (DD, DED, CARD, PYD). In: Encyclopedia of Life Sciences (ELS). John Wiley & Sons, Ltd: Chichester.
DOI: 10.1002/9780470015902.a0021579

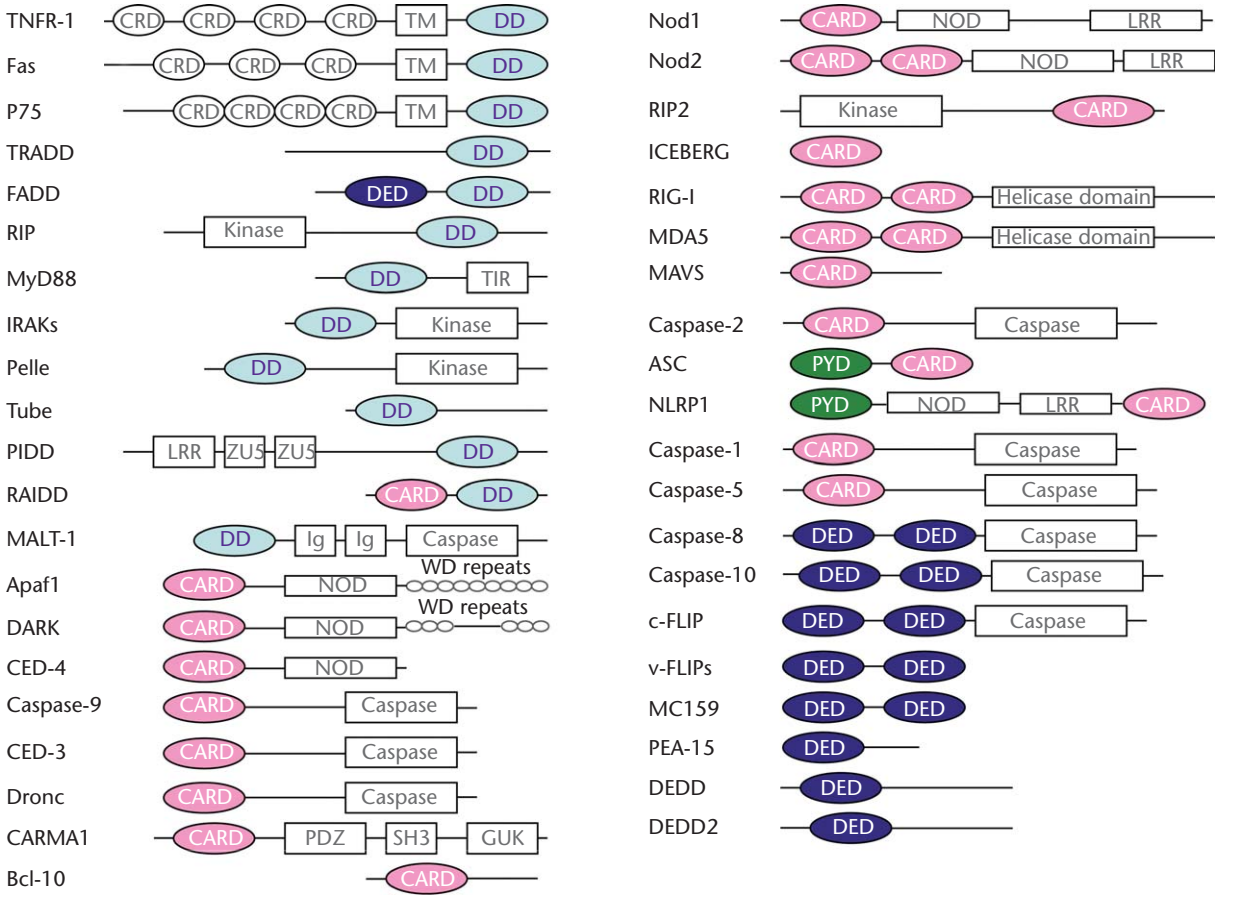

Figure 1 Domain organizations of selective proteins containing the DD superfamily domains. Abbreviations: CARD, caspase recruitment domain; CRD, cysteine-rich domain; DD, death domain; DED, death effector domain; GUK, guanylate kinase-like; LRR, leucine-rich repeat; NOD, nucleotide-binding oligomerization domain; PYD, pyrin domain; TIR, toll/interleukin 1 receptor and TM, transmembrane domain.

Death-inducing signalling complex for activation of caspase-8 and caspase-10 and its inhibition by FLIPs

Fas (also known as CD95) is a prototypical member of death receptors that form a subfamily of the tumour necrosis factor (TNF) receptor superfamily to mediate the extrinsic cell death pathway. Members of the TNF superfamily of ligands are mostly trimeric and activate the TNF receptor superfamily by ligand-induced receptor trimerization and higher order oligomerization (Kischkel *et al*., 1995). The intracellular regions of death receptors contain DDs (Tartaglia *et al*., 1993). For Fas, on ligand activation, its DD recruits the Fas-associated DD (FADD) adapter protein via a homotypic interaction with the *C*-terminal DD of FADD (Chinnaiyan *et al*., 1995; Kischkel *et al*., 1995). FADD also contains an *N*-terminal DED that interacts homotypically with the tandem DED in the prodomain of caspase-8 or -10 (Wajant, 2002). These interactions form the ternary death-inducing signalling complex (DISC)-containing Fas, FADD and caspase-8 or -10 (Wajant, 2002). Recruitment of pro-caspases into the DISC initiates caspase proteolytic auto-processing. This liberates active caspase-8 or -10 into the cytoplasm to cleave and activate effector caspases such as caspase-3 and caspase-7, leading to a cascade of events in apoptotic cell death.

Caspase activation by the DISC is inhibited by FLIPs, a family of cellular and viral tandem DED-containing proteins that interact with FADD (Thome and Tschopp, 2001). Cellular FLIPs (c-FLIPs), comprising the long and short isoforms, c-FLIP-L and c-FLIP-S, are tightly regulated in expression in T cells and may be involved in controlling both T-cell activation and death (Thome and Tschopp, 2001). v-FLIPs (viral FLIPs) appear to have evolved to inhibit apoptosis of virally infected host cells and are present in the poxvirus *Molluscum contagiosum virus* (MCV) as proteins MC159 and MC160 (Shisler and Moss, 2001) and in γ-herpesviruses (Thome and Tschopp, 2001).

Apoptosome for caspase-9 activation

The intrinsic pathway of apoptotic cell death is induced in a mitochondria-dependent manner in response to intracellular insults. A CARD-containing protein Apaf-1 (apoptosis-activating factor 1) forms the central platform of a molecular

complex known as the apoptosome for caspase activation in this pathway (Li *et al*., 1997). Apaf-1 is composed of an *N*-terminal CARD, a central nucleotide-binding oligomerization domain (NOD) and a *C*-terminal (Trp-Asp) WD repeat domain. On mitochondrial leakage, cytochrome *c*, which normally resides at the intermembrane space of the mitochondria, is released to the cytosol. The interaction of cytochrome *c* with the WD repeat domain of Apaf-1 presumably opens up the Apaf-1 structure, leading to an adenosine triphosphate (ATP)- or dATP-dependent oligomerization of Apaf-1 to form the apoptosome. The apoptosome then recruits caspase-9 via the CARD domain interaction between Apaf-1 and caspase-9.

PIDDosome for caspase-2 activation

In response to genotoxic stress, the DD-containing and p53-induced protein with a death domain (PIDD) mediates both caspase-2 and NFκB activation. Caspase-2 is an evolutionarily conserved initiator caspase with a CARD prodomain (Wang *et al*., 1994). The caspase-2 activation pathway involves the formation of a ternary complex known as the PIDDosome (Berube *et al*., 2005; Tinel and Tschopp, 2004), which comprises proteins PIDD (Lin *et al*., 2000), RAIDD (RIP-associated ICH-1 homologous protein with a death domain; Duan and Dixit, 1997) and caspase-2 and is assembled via the DD interaction between PIDD and RAIDD and the CARD interaction between RAIDD and caspase-2. Accumulating data have shown that caspase-2 acts upstream of the mitochondria to initiate apoptosis (Lassus *et al*., 2002).

Inflammasome for caspase-1 activation

Members of the Nod-like receptor (NLR) family, including NLRP1, NLRP3 and NLRC4, and the adaptor ASC (apoptosis-associated speck-like protein containing a CARD) are critical components of the inflammasome that link microbial and endogenous 'danger' signals to caspase-1 activation (Franchi *et al*., 2009). NLR family proteins are PYD- and NOD-containing proteins. For example, NLRP1 contains an *N*-terminal PYD, a central NOD for oligomerization, a leucine-rich repeat (LRR) region and a *C*-terminal CARD. ASC contains both a PYD and a CARD. Caspase-1 is recruited to the inflammasome either via ASC or directly to NLR proteins. Once activated, caspase-1 cleaves and activates the cytokine interleukin 1β (IL-1β), leading to recruitment of inflammatory cells to the site of infection and a specific form of cell death called 'pyroptosis'. Direct linkage between pathogen invasion and inflammasome formation has been obscure. A series of recent studies provided advancement in this regard by showing that a PYD-containing protein AIM2 (absent in melanoma 2) senses cytoplasmic foreign double-standard deoxyribonucleic acid (dsDNA) and interacts with ASC for caspase-1 activation (Burckstummer *et al*., 2009; Fernandes-Alnemri *et al*., 2009; Hornung *et al*., 2009; Roberts *et al*., 2009).

Structures of Isolated Domains and Their Surface Features

The unifying feature of the DD superfamily is the six-helical bundle structural fold as exemplified by structures of Fas DD (Huang *et al*., 1996; **Figure 2a**), FADD DED (Eberstadt *et al*., 1998; **Figure 2b**), Apaf-1 CARD (Qin *et al*., 1999; **Figure 2c**) and NLRP1 PYD (Hiller *et al*., 2003; **Figure 2d**). Although all members of the DD superfamily have this conserved structural fold, individual subfamilies also exhibit distinct structural and sequence characteristics not shared with other subfamilies. There are currently structures of seven DDs, four DEDs, five CARDs and five PYDs. Because many DDs seem to self-associate and have a tendency to aggregate, their structures were often determined under nonphysiological conditions such as extreme pH and/or with 'de-aggregating' mutations (Huang *et al*., 1996). Of the four DED structures, three are more similar to each other than to other members of the DD superfamily. In contrast, the MC159 DED1, which was solved in the context of a tandem DED, is structurally more divergent from the other known DED structures (Li *et al*., 2006; Yang *et al*., 2005). In particular, helix H3 is missing and replaced by a short loop connecting helices H2 and H4. Two additional helices are present, helix H0 at the *N*-terminus and helix H7 that brings the chain to the beginning of DED2. For CARDs, although their topology is identical with the conserved six-helical bundle fold of the DD superfamily, the structures are unique in that helix H1 tends to be either bent or broken into two closely separated H1a and H1b helices (**Figure 2c**). In addition, the orientations and lengths of several helices may be somewhat different among the different CARDs. The PYD structures are divergent among themselves in the H2 and H3 region (Hiller *et al*., 2003; Liepinsh *et al*., 2003; Natarajan *et al*., 2006). Although the PYD of NLRP1 has a completely disordered H3, both ASC and ASC2 PYDs have a formed H3 but a long loop between H2 and H3.

There seems to be limited structural plasticity of these domains. Superposition of the Apaf-1 CARD structures in isolation, in complex with caspase-9 CARD and in the context of its NOD domain shows lack of substantial conformational changes (Qin *et al*., 1999; Riedl *et al*., 2005). Similarly, superposition of RAIDD DD in isolation and in complex with PIDD DD showed that the structures are similar (Park *et al*., 2007b; Park and Wu, 2006).

Because of the low sequence homology among DDs, the surface features of these DDs are also entirely different, which may be responsible for their specificity in protein:-protein interactions (Park *et al*., 2007a). However, CARDs seem to be different in this regard. They are mostly polarized with both basic and acidic surfaces, which may be used for protein:protein interactions (**Figure 2e**). Similarly, PYDs seem to share the surface charge polarization of CARDs.

The few available DED structures seem to have most conserved surface features, which distinguish them from other members of the DD superfamily. The first feature is a conserved hydrogen-bonded charge triad revealed by the high-resolution structure of MC159 (Yang *et al*., 2005).

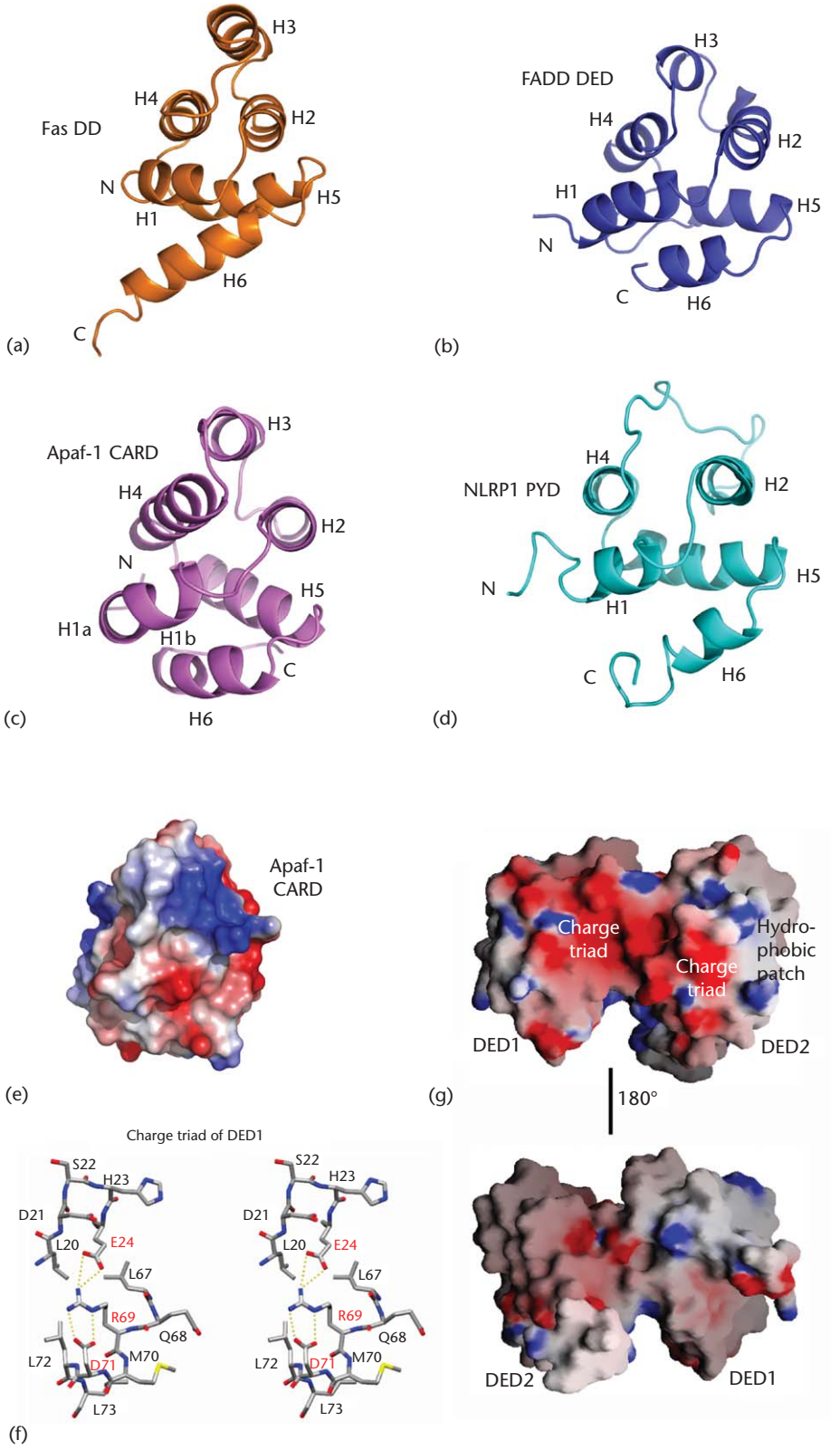

Figure 2 Ribbon diagrams for each subfamily of the DD superfamily: (a) Fas DD, (b) FADD DED, (c) Apaf-1 CARD and (d) NLRP1 PYD. (e) Electrostatic surface representation of Apaf-1 CARD. (f) Stick model for the hydrogen-bonding interactions in the charge triad of MC159 DED1. (g) Electrostatic surface representation of MC159 DED1 and DED2, showing the dumbbell-shaped structure, the rich charges on one face and the location of the hydrophobic patch. Panels (f) and (g) are taken from Yang *et al.* (2005).

The charge triad is formed by the E/D-RxDL (E is Glu, D is Asp, R is Arg, L is Leu and x is any residue) motif and involves the Arg and Asp residues in the RxDL motif in helix H6 and the preceding loop, and an acidic residue in helix H2. Extensive hydrogen-bonding interactions are observed among the charged side chains with the Arg residue situated in between the two acidic residues (**Figure 2f**). The second surface feature is the conserved hydrophobic patch formed mostly by residues on H2 (**Figure 2g**). This was first observed in the nuclear magnetic resonance (NMR) structure of FADD DED (Eberstadt *et al*., 1998) and later shown to be conserved in most tandem DEDs as well (Yang *et al*., 2005). Both surface features appear to be used for protein:protein interactions.

Interactions in the DD Superfamily

DD:DD interaction in the Pelle:Tube complex

The crystal structure of the monomeric Pelle DD:Tube DD complex is the first structure of a complex in the DD superfamily (Xiao *et al*., 1999; **Figure 3a**). The biggest surprise from the structure is perhaps the asymmetry of the interaction, considering that symmetric interactions are often expected for homotypic interactions. The first interface between Pelle and Tube involves the H4 helix and the following loop of Pelle and the H1–H2 corner, H6 and the preceding loop in Tube. Most strikingly, the *C*-terminal tail of Tube wraps around a groove formed by the H4–H5 and H2–H3 hairpins of Pelle to form the second interface and contributes significantly to the interaction (Xiao *et al*., 1999). Though many charged residues at the first interface are involved in the interaction, three large hydrophobic residues on the *C*-terminal tail of Tube dominate the second interface.

CARD:CARD interaction in the Apaf1:procaspase-9 complex

The only structure of a CARD:CARD complex is provided by the crystal structure of the complex between Apaf-1 CARD and procaspase-9 CARD (Qin *et al*., 1999; **Figure 3b**). The interaction is mediated by the mutual recognition of the slightly concave surface of procaspase-9 CARD formed by the positively charged H1a, H1b and H4 helices and the convex surface of Apaf-1 CARD formed by the negatively charged H2 and H3 helices. Three positively charged residues in procaspase-9 CARD and two negatively charged in Apaf-1 CARD are crucial for this interaction (Qin *et al*., 1999). This study confirmed the ionic nature of the Apaf-1 CARD:procaspase-9 CARD interaction.

DED:DED interaction in the tandem DED structure of MC159 v-FLIP

The structure of MC159 revealed the first glimpse of a DED:DED interaction (Li *et al*., 2006; Yang *et al*., 2005; **Figure 3c**). Instead of beads on a string, DED1 and DED2 interact with each other intimately to form a rigid, dumbbell-shaped structure. The two DEDs are related approximately by a translation across the contact interface so that one side of DED1 is contacting the equivalently opposite side of DED2. The translational relationship between DED1 and DED2 is made possible by helix H7 of DED1. The interaction at the DED1:DED2 interface is mostly hydrophobic, mediated by helices H2 and H5 of DED1 and helices H1 and H4 of DED2. There are a total of 195 interfacial atomic contacts, among which 117 are between nonpolar atoms. The interfacial residues, especially those that are completely buried at the DED1:DED2 interface and contribute large surface areas are mostly conserved in tandem DEDs. This suggests that all known tandem DEDs form a similar rigid compact structure as MC159. This interaction between DED1 and DED2 shows some orientational similarity in the Apaf-1 CARD:procaspase-9 CARD interaction.

Asymmetric oligomeric DD:DD interaction in the PIDD:RAIDD complex

The PIDD DD and RAIDD DD complex forms the core of the caspase-2-activating complex PIDDosome. Its structure represents the first glimpse of an oligomeric complex in the DD superfamily (Park *et al*., 2007b). Although RAIDD DD and PIDD DD are monomers, they assemble into a complex that is consistent with a total of 12 DDs. The structure of the complex revealed an entirely asymmetric arrangement that comprises seven RAIDD DDs and five PIDD DDs (**Figure 3d**). Despite the asymmetry, all DDs in the complex are in quasi-equivalent environments. The structure provided eight unique asymmetric interfaces, which can be classified into three types (**Figure 3e**). On each DD, these three types of interactions together cover a majority of its surface.

In the type I interaction, residues at H1 and H4 of the first DD (type Ia surface) interact with residues at H2 and H3 of the second DD (type Ib surface). This type of interaction is similar to the Apaf-1 CARD:procaspase-9 CARD interaction, although slight orientational adjustment is observed. In the type II interaction, residues at the H4 helix and the H4–H5 loop of the first DD (type IIa surface) and residues at the H5–H6 loop and H6 helix of the second DD (type IIb surface) mediate this interaction. This type of interaction resembles the Pelle DD:Tube DD complex. In comparison with the type I interaction, the type II buries a smaller surface area. In the Pelle DD:Tube DD complex, this interaction is strengthened by an additional interaction between a long tail of Tube and the H2–H3 and H4–H5 region of Pelle. In the type III interaction, residues at H3 of the first DD (type IIIa) interact with residues near the H1–H2 and the H3–H4 loops of the second DD (type IIIb).

Oligomeric DD:DD interaction in the Fas:FADD complex

The Fas DD and FADD DD complex is the core of the DISC in death receptor signalling. A structure of the complex, which was crystallized at pH 4.0, showed a

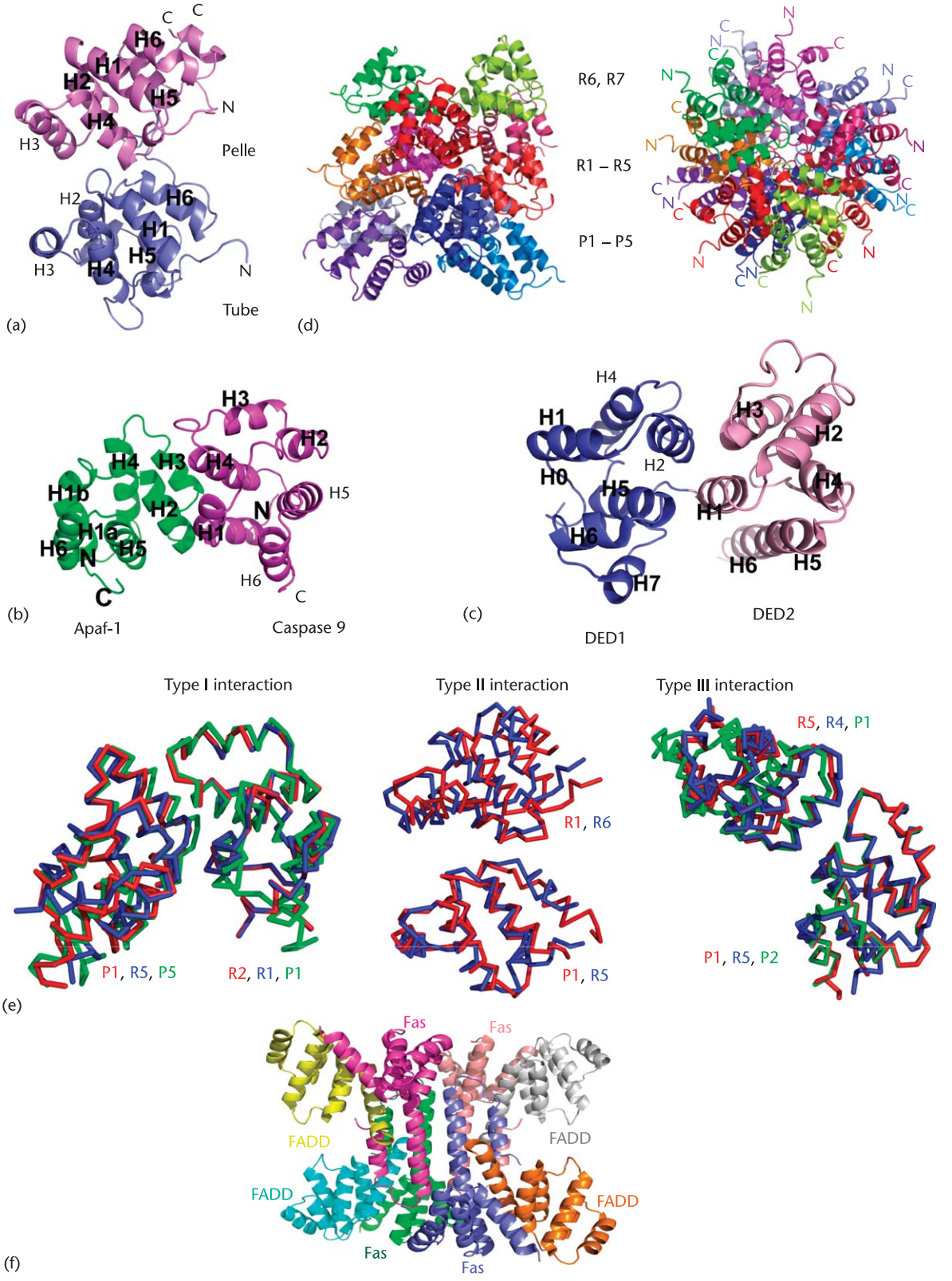

Figure 3 Structural features of interactions in the DD superfamily. (a) Pelle DD:Tube DD complex, as a type II interaction. (b) Apaf-1 CARD:procaspase-9 CARD complex, as a type I interaction. (c) MC159 DED1:DED2 interaction, as a type I interaction. (d) Overview of the PIDD DD:RAIDD DD complex in two orthogonal orientations. (e) Superposition of the eight unique interactions in the PIDD DD:RAIDD DD complex. R:RAIDD DD; P:PIDD DD. There are three type I interactions, two type II interactions and three type III interactions. (f) Tetrameric Fas DD:FADD DD complex. Panels (d) and (e) are taken from Park *et al.* (2007b).

striking, tetrameric arrangement of four FADD DDs bound to four Fas DDs (Scott *et al*., 2009; **Figure 3f**). A conformational opening of the Fas DD exposes the FADD DD binding site and simultaneously generates an Fas:Fas interface. Surprisingly, most natural mutations of Fas that cause the human disease ALPS did not map to its interface with FADD DD, raising the possibility that the observed interfaces at pH 4.0 do not represent the physiological interactions.

Preferred Modes among the Homotypic Interactions

There may be preferred modes of interactions among the DD superfamily fold. First of all, almost all structures of DD superfamily complexes are asymmetric, suggesting this to be a preferred means that DDs, DEDs, CARDs and PYDs interact with each other. Secondly, all the observed asymmetric pairs of interactions may be classified into one of the three types of interactions in the PIDD DD:RAIDD DD complex. The Apaf-1 CARD:procaspase-9 CARD interaction and the DED1:DED2 interaction in MC159 may be considered type I whereas the Pelle DD:Tube DD interaction is similar to the type II interaction. In addition, prediction by surface electrostatics has implicated a mode of PYD interaction similar to the observed type I interaction (Liepinsh *et al*., 2003). Therefore, the observed three types of asymmetric interactions may represent preferred modes of interactions for the entire DD superfamily.

Summary

The DD superfamily is one of the largest and most widely distributed domain superfamily. One important function of these domains is to participate in homotypic protein:-protein interactions in the assembly of oligomeric signalling complexes in apoptosis. Evolutionarily, it seems that the ever-expanding DD superfamily may have evolved by inserting into various signal transduction proteins such as caspases, kinases and adapter proteins. In this regard, it is amazing that almost all oligomeric signalling complexes in apoptosis contain domains of the DD superfamily. Through self-associations and homotypic interactions with other members of each of the subfamilies, these proteins often form the platform of these oligomeric assemblies to allow 'proximity' induced caspase and kinase activation.

Many biochemical and structural studies have been performed on these domains. These studies have revealed a conserved six-helical bundle fold of the DD superfamily. Almost all known protein:protein interactions in the superfamily are either self-association or homotypic interactions with other members of the same subfamily. This is somewhat surprising given the structural similarity among the different subfamilies, but may reflect evolutionary circumstances.

Acknowledgement

This work was supported by the National Institute of Health (AI50872 and AI76927). We apologize to all whose work has not been appropriately reviewed or cited due to space limitations.

References

Berube C, Boucher LM, Ma W *et al*. (2005) Apoptosis caused by p53-induced protein with death domain (PIDD) depends on the death adapter protein RAIDD. *Proceedings of the National Academy of Sciences of the USA* **102**: 14314–14320.

Burckstummer T, Baumann C, Bluml S *et al*. (2009) An orthogonal proteomic-genomic screen identifies AIM2 as a cytoplasmic DNA sensor for the inflammasome. *Nature Immunology* **10**: 266–272.

Chinnaiyan AM, O'Rourke K, Tewari M and Dixit VM (1995) FADD, a novel death domain-containing protein, interacts with the death domain of Fas and initiates apoptosis. *Cell* **81**: 505–512.

Duan H and Dixit VM (1997) RAIDD is a new 'death' adaptor molecule. *Nature* **385**: 86–89.

Eberstadt M, Huang B, Chen Z *et al*. (1998) NMR structure and mutagenesis of the FADD (Mort1) death-effector domain. *Nature* **392**: 941–945.

Fernandes-Alnemri T, Yu JW, Datta P, Wu J and Alnemri ES (2009) AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA. *Nature* **458**: 509–513.

Franchi L, Eigenbrod T, Munoz-Planillo R and Nunez G (2009) The inflammasome: a caspase-1-activation platform that regulates immune responses and disease pathogenesis. *Nature Immunology* **10**: 241–247.

Hiller S, Kohl A, Fiorito F *et al*. (2003) NMR structure of the apoptosis- and inflammation-related NALP1 pyrin domain. *Structure* **11**: 1199–1205.

Hornung V, Ablasser A, Charrel-Dennis M *et al*. (2009) AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. *Nature* **458**: 514–518.

Huang B, Eberstadt M, Olejniczak ET, Meadows RP and Fesik SW (1996) NMR structure and mutagenesis of the Fas (APO-1/CD95) death domain. *Nature* **384**: 638–641.

Kischkel FC, Hellbardt S, Behrmann I *et al*. (1995) Cytotoxicity-dependent APO-1 (Fas/CD95)-associated proteins form a death-inducing signaling complex (DISC) with the receptor. *EMBO Journal* **14**: 5579–5588.

Lassus P, Opitz-Araya X and Lazebnik Y (2002) Requirement for caspase-2 in stress-induced apoptosis before mitochondrial permeabilization. *Science* **297**: 1352–1354.

Li FY, Jeffrey PD, Yu JW and Shi Y (2006) Crystal structure of a viral FLIP: insights into FLIP-mediated inhibition of death receptor signaling. *Journal of Biological Chemistry* **281**: 2960–2968.

Li P, Nijhawan D, Budihardjo I *et al*. (1997) Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade. *Cell* **91**: 479–489.

Liepinsh E, Barbals R, Dahl E *et al*. (2003) The death-domain fold of the ASC PYRIN domain, presenting a basis for PYRIN/PYRIN recognition. *Journal of Molecular Biology* **332**: 1155–1163.

Lin Y, Ma W and Benchimol S (2000) Pidd, a new death-domain-containing protein, is induced by p53 and promotes apoptosis. *Nature Genetics* **26**: 122–127.

McEntyre JR and Gibson TJ (2004) Patterns and clusters within the PSM column in TiBS, 1992–2004. *Trends in Biochemical Science* **29**: 627–633.

Natarajan A, Ghose R and Hill JM (2006) Structure and dynamics of ASC2, a pyrin domain-only protein that regulates inflammatory signaling. *Journal of Biological Chemistry* **281**: 31863–31875.

Park HH and Wu H (2006) Crystal structure of RAIDD death domain implicates potential mechanism of PIDDosome assembly. *Journal of Molecular Biology* **357**: 358–364.

Park HH, Lo YC, Lin SC *et al*. (2007a) The death domain superfamily in intracellular signaling of apoptosis and inflammation. *Annual Review of Immunology* **25**: 561–586.

Park HH, Logette E, Rauser S *et al*. (2007b) Death domain assembly mechanism revealed by crystal structure of the oligomeric PIDDosome core complex. *Cell* **128**: 533–546.

Poppema S, Maggio E and van den Berg A (2004) Development of lymphoma in autoimmune lymphoproliferative syndrome (ALPS) and its relationship to Fas gene mutations. *Leukemia & Lymphoma* **45**: 423–431.

Qin H, Srinivasula SM, Wu G *et al*. (1999) Structural basis of procaspase-9 recruitment by the apoptotic protease-activating factor 1. *Nature* **399**: 549–557.

Rathmell JC and Thompson CB (2002) Pathways of apoptosis in lymphocyte development, homeostasis, and disease. *Cell* **109**(suppl.): S97–S107.

Reed JC, Doctor KS and Godzik A (2004) The domains of apoptosis: a genomics perspective. *Science's STKE* **2004**: re9.

Riedl SJ and Shi Y (2004) Molecular mechanisms of caspase regulation during apoptosis. *Nature Reviews. Molecular Cell Biology* **5**: 897–907.

Riedl SJ, Li W, Chao Y, Schwarzenbacher R and Shi Y (2005) Structure of the apoptotic protease-activating factor 1 bound to ADP. *Nature* **434**: 926–933.

Rieux-Laucat F, Fischer A and Deist FL (2003a) Cell-death signaling and human disease. *Current Opinion in Immunology* **15**: 325–331.

Rieux-Laucat F, Le Deist F and Fischer A (2003b) Autoimmune lymphoproliferative syndromes: genetic defects of apoptosis pathways. *Cell Death and Differentiation* **10**: 124–133.

Roberts TL, Idris A, Dunn JA *et al*. (2009) HIN-200 proteins regulate caspase activation in response to foreign cytoplasmic DNA. *Science* **323**: 1057–1060.

Salvesen GS and Dixit VM (1999) Caspase activation: the induced-proximity model. *Proceedings of the National Academy of Sciences of the USA* **96**: 10964–10967.

Scott FL, Stec B, Pop C *et al*. (2009) The Fas-FADD death domain complex structure unravels signalling by receptor clustering. *Nature* **457**: 1019–1022.

Shisler JL and Moss B (2001) *Molluscum contagiosum virus* inhibitors of apoptosis: the MC159 v-FLIP protein blocks Fas-induced activation of procaspases and degradation of the related MC160 protein. *Virology* **282**: 14–25.

Tartaglia LA, Ayres TM, Wong GH and Goeddel DV (1993) A novel domain within the 55 kd TNF receptor signals cell death. *Cell* **74**: 845–853.

Thome M and Tschopp J (2001) Regulation of lymphocyte proliferation and death by FLIP. *Nature Reviews. Immunology* **1**: 50–58.

Tinel A and Tschopp J (2004) The PIDDosome, a protein complex implicated in activation of caspase-2 in response to genotoxic stress. *Science* **304**: 843–846.

Wajant H (2002) The Fas signaling pathway: more than a paradigm. *Science* **296**: 1635–1636.

Wang L, Miura M, Bergeron L, Zhu H and Yuan J (1994) Ich-1, an Ice/ced-3-related gene, encodes both positive and negative regulators of programmed cell death. *Cell* **78**: 739–750.

Xiao T, Towb P, Wasserman SA and Sprang SR (1999) Three-dimensional structure of a complex between the death domains of Pelle and Tube. *Cell* **99**: 545–555.

Yang JK, Wang L, Zheng L *et al*. (2005) Crystal structure of MC159 reveals molecular mechanism of DISC assembly and FLIP inhibition. *Molecular Cell* **20**: 939–949.

Further Reading

Damiano JS and Reed JC (2004) CARD proteins as therapeutic targets in cancer. *Current Drug Targets* **5**: 367–374.

Hong GS and Jung YK (2002) Caspase recruitment domain (CARD) as a bi-functional switch of caspase regulation and NF-kappaB signals. *Journal of Biochemistry and Molecular Biology* **35**: 19–23.

Valmiki MG and Ramos JW (2009) Death effector domain-containing proteins. *Cell Mol Life Sci* **66**: 814–830.

Yu JW and Shi Y (2008) FLIP and the death effector domain family. *Oncogene* **27**: 6216–6227.