Death Receptors: Signaling and Modulation

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Science **281**, 1305 (1998);
DOI: 10.1126/science.281.5381.1305

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.

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REVIEW

Apoptosis is a cell suicide mechanism that enables metazoans to control cell number in tissues and to eliminate individual cells that threaten the animal's survival. Certain cells have unique sensors, termed death receptors, on their surface. Death receptors detect the presence of extracellular death signals and, in response, they rapidly ignite the cell's intrinsic apoptosis machinery.

Apoptosis plays a central role both in development and in homeostasis of metazoans (*1*). Cells die by apoptosis in the developing embryo during morphogenesis or synaptogenesis and in the adult animal during tissue turnover or at the end of an immune response. Because the physiological role of apoptosis is crucial, aberration of this process can be detrimental. Thus, unscheduled apoptosis of certain brain neurons contributes to disorders such as Alzheimer's and Parkinson's diseases, whereas the failure of dividing cells to initiate apoptosis after sustaining severe DNA damage contributes to cancer (*2*).

The Basic Apoptosis Machinery

Metazoan cells contain a similar enzymatic apparatus that initiates apoptosis upon activation (*1*). The nematode *Caenorhabditis elegans* has been a good model organism for studying the core components of the cell death machinery. Three *C. elegans* gene products are essential for apoptosis: CED-3 and CED-4 promote apoptosis, whereas CED-9 inhibits apoptosis (*3*). CED-3 is a caspase, that is, a cysteine protease that cleaves certain proteins after specific aspartic acid residues; it exists as a zymogen, which is activated through self-cleavage (*4*). CED-4 binds to CED-3 and promotes CED-3 activation, whereas CED-9 binds to CED-4 and prevents it from activating CED-3 (*5*). Normally, CED-9 is complexed with CED-4 and CED-3, keeping CED-3 inactive. Apoptosis stimuli cause CED-9 dissociation, allowing CED-3 activation and thereby committing the cell to die by apoptosis. Vertebrates have evolved entire gene families that resemble *C. elegans* cell death genes. Mammalian caspases are similar to CED-3 (*4*). Apaf-1 is the only mammalian CED-4 homolog known so far (*6*). The products of the mammalian *Bcl-2* gene family are related to CED-9 but include two subgroups of proteins that either inhibit or promote apoptosis (*7*).

Death Receptors Have Direct Access to the Apoptotic Machinery

Survival signals from the cell's environment and internal sensors for cellular integrity normally keep a cell's apoptotic machinery in check. In the event that a cell loses contact with its surroundings or sustains irreparable internal damage, the cell initiates apoptosis. A cell that simultaneously receives conflicting signals driving or attenuating its division cycle also triggers apoptosis (*8*). Mammals have evolved yet another mechanism that enables the organism actively to direct individual cells to self-destruct. This kind of "instructive" apoptosis is important especially in the immune system (*9*). Death receptors—cell surface receptors that transmit apoptosis signals initiated by specific "death ligands"—play a central role in instructive apoptosis. These receptors can activate death caspases within seconds of ligand binding, causing an apoptotic demise of the cell within hours.

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Death receptors belong to the tumor necrosis factor (TNF) receptor gene superfamily, which is defined by similar, cysteine-rich extracellular domains (*10*). The death receptors contain in addition a homologous cytoplasmic sequence termed the "death domain" (*11*, *12*). Death domains typically enable death receptors to engage the cell's apoptotic machinery, but in some instances they mediate functions that are distinct from or even counteract apoptosis. Some molecules that transmit signals from death receptors contain death domains themselves.

The best characterized death receptors are CD95 (also called Fas or Apo1) and TNFR1 (also called p55 or CD120a) (*10, 12*). Additional death receptors are avian CAR1 (*13*); death receptor 3 (DR3; also called Apo3, WSL-1, TRAMP, or LARD) (*14*); DR4 (*15*); and DR5 (also called Apo2, TRAIL-R2, TRICK 2, or KILLER) (*16–21*). The p75 nerve growth factor (NGF) receptor also contains a death domain (*22*). The ligands that activate these receptors, with the exception of NGF, are structurally related molecules that belong to the TNF gene superfamily (*10*). CD95 ligand (CD95L) binds to CD95; TNF and lymphotoxin α bind to TNFR1; Apo3 ligand (Apo3L, also called TWEAK) (*23, 24*) binds to DR3 (*24*); and Apo2 ligand (Apo2L, also called TRAIL) (*25, 26*) binds to DR4 (*15*) and DR5 (*16–21*). The ligand for CAR1 is unknown.

Signaling by CD95

CD95 and CD95L play an important role mainly in three types of physiologic apoptosis (*12*): (i) peripheral deletion of activated mature T cells at the end of an immune response; (ii) killing of targets such as virus-infected cells or cancer cells by cytotoxic T cells and by natural killer cells; and (iii) killing of inflammatory cells at "immune-privileged" sites such as the eye. Evidence for the biological role of CD95 comes from certain mouse strains and from human patients who have defective genes for CD95 or CD95L (*12*). Such mutations can lead to accumulation of peripheral lymphoid cells and to a fatal autoimmune syndrome characterized by massive enlargement of lymph nodes. CD95 and CD95L are implicated also in pathological suppression of immune surveillance, namely, elimination of tumor-reactive immune cells by certain tumors that constitutively express CD95L (*27*).

Like other TNF family members, CD95L is a homotrimeric molecule. The crystal structure of lymphotoxin α in complex with TNFR1 suggests by analogy that each CD95L trimer binds three CD95 molecules (*10, 12*). Because death domains have a propensity to associate with one another, CD95 ligation leads to clustering of the receptors' death domains (Fig. 1); this is supported by nuclear magnetic resonance structure analysis and mutagenesis studies (*28*). An adapter protein called FADD (Fas-associated death domain; also called Mort 1) (*29*) then binds through its own death domain to the clustered receptor death domains. FADD also contains a "death effector domain" that binds to an analogous domain repeated in tandem within the zymogen form of caspase-8 (also called FLICE, or MACH) (*30*). The death effector domain is a specific example of a more global homophilic interaction domain termed CARD (caspase recruitment domain), which is found in several caspases with large prodomains, including caspases-2, -8, -9, and -10 (*31*). Upon recruitment by FADD, caspase-8 oligomerization drives its activation through self-cleavage (*32*). Caspase-8 then activates downstream effector caspases such as caspase-9—the mammalian functional homolog of CED-3—committing the cell to apoptosis. Studies with

FADD gene knockout mice (*33*) and with transgenic mice expressing a dominant negative mutant of FADD (FADD-DN) in T cells (*34*) establish that FADD is essential for apoptosis induction by CD95. Surprisingly, these mice display reduced proliferation of mature T cells in response to antigenic stimulation; moreover, FADD deletion causes embryonic lethality (*33, 34*). These results are consistent with FADD having other critical signaling functions besides coupling CD95 to caspase-8.

A family of viral proteins called vFLIPs and a related cellular protein called cFLIP (also called Casper, I-FLICE, FLAME, or CASH) (*35*) contain a death effector domain that is similar to the corresponding segment in FADD and caspase-8. The role of FLIP is controversial, as FLIP overexpression either inhibits or activates apoptosis (*35*). Several other cytoplasmic proteins besides FADD can bind to CD95 (*12*), including Daxx, which recognizes the CD95 death domain (*36*). Daxx can activate a FADD-independent death pathway that involves the stress-activated c-Jun NH_2-terminal kinase (JNK). As several types of FADD-deficient cells show complete resistance to CD95-induced apoptosis (*33*), it appears that at least in some cell types, Daxx does not couple CD95 to apoptosis.

Signaling by TNFR1

TNF is produced mainly by activated macrophages and T cells in response to infection (*37*). By engaging TNFR1, TNF activates the transcription factors NF-κB and AP-1, leading to induction of proinflammatory and immunomodulatory genes (*37*). In some cell types, TNF also induces apoptosis through TNFR1. Unlike CD95L, however, TNF rarely triggers apoptosis unless protein synthesis is blocked, which suggests the preexistence of cellular factors that can suppress the apoptotic stimulus generated by TNF. Expression of these suppressive proteins probably is controlled through NF-κB and JNK/AP-1, as inhibition of either pathway sensitizes cells to apoptosis induction by TNF (*38*).

TNF trimerizes TNFR1 upon binding (*10*), inducing association of the receptors' death domains (Fig. 2). Subsequently, an adapter termed TRADD (TNFR-associated death domain) (*39*) binds through its own death domain to the clustered receptor death domains. TRADD functions as a platform adapter that recruits several signaling molecules to the activated receptor: TNFR-associated factor–2 (TRAF2) (*40, 41*) and receptor-interacting protein (RIP) (*42*) stimulate pathways leading to activation of NF-κB and of JNK/AP-1, whereas FADD mediates activation of apoptosis (*41, 43*). Of these, only RIP has enzymatic activity, namely that of a serine-threonine kinase; however, a role for RIP's kinase activity in the activation of NF-κB or JNK/AP-1 has yet to be established.

TRAF2 and RIP activate the NF-κB–inducing kinase (NIK), which in turn activates the inhibitor of κB (I-κB) kinase complex, IKK (*44*). IKK phosphorylates I-κB, leading to I-κB degradation and allowing NF-κB to move to the nucleus to activate transcription. The pathway from TRAF2 and RIP to JNK involves a cascade that includes the mitogen-activated protein (MAP) kinases MEKK1 (MAP/Erk kinase kinase–1), JNKK (JNK kinase), and JNK (*45*). MEKK1 is related to NIK, and it is implicated in the pathway because kinase-inactive MEKK1 mutants block JNK activation by TNF; however, MEKK1 does not bind to TRAF2 (*46*), suggesting that another TRAF2-binding kinase acts upstream or instead of MEKK1.

Cells from TRAF2 gene knockout mice or from transgenic mice expressing a dominant negative TRAF2 mutant have only a slight defect in their NF-κB response to TNF (*47*). Thus, TRAF2 may not be essential for NF-κB activation by TNF; alternatively, there may be another TRAF family member that binds to TRADD and NIK and substitutes for TRAF2. TRAF2-deficient cells are totally lacking in

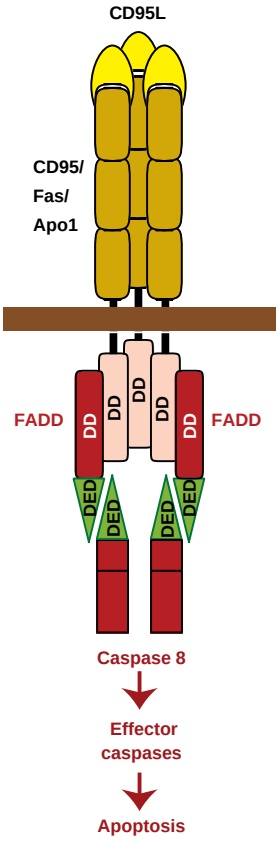

Fig. 1. Apoptosis signaling by CD95. DD, death domain; DED, death effector domain.

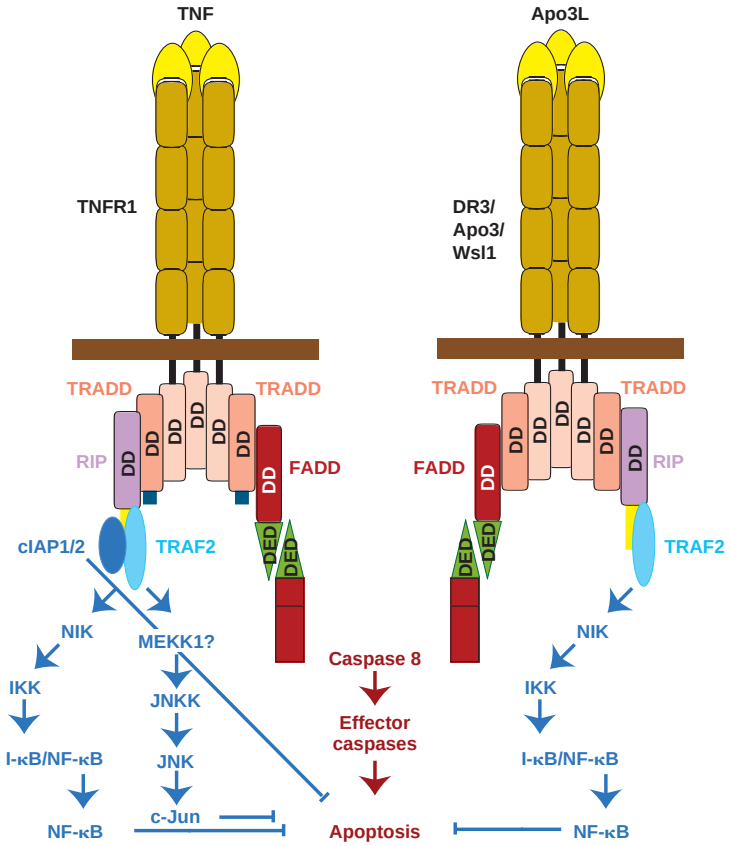

Fig. 2. Proapoptotic and antiapoptotic signaling by TNFR1 and DR3.

JNK activation in response to TNF, demonstrating a critical role for TRAF2 in this response. The picture emerging from RIP-deficient cells is the inverse: NF-κB activation in response to TNF is absent, whereas JNK activation is intact (*48*). Hence, RIP is required for coupling TNFR1 to NF-κB, but it may not be crucial for coupling TNFR1 to JNK. Both TRAF2 and RIP knockout mice have pathologies that cannot be ascribed to defects in TNF signaling, which suggests that each of these proteins has additional functions. TRAF2 also binds to cIAP1 and cIAP2 (cellular inhibitor of apoptosis-1 and -2) (*49*), which belong to a family of mammalian and viral proteins with anti-apoptotic activity.

FADD couples the TNFR1-TRADD complex to activation of caspase-8, thereby initiating apoptosis (*41, 43*). Cells from FADD knockout mice are resistant to TNF-induced apoptosis, demonstrating an obligatory role of FADD in this response (*33*). Besides FADD, TNFR1 can engage an adapter called RAIDD or CRADD (*50*). RAIDD binds through a death domain to the death domain of RIP and through a CARD motif to a similar sequence in the death effector caspase-2, thereby inducing apoptosis.

Signaling by DR3

DR3 shows close sequence similarity to TNFR1 (*14*). Upon overexpression, DR3 triggers responses that resemble those of TNFR1, namely, NF-κB activation and apoptosis. Like TNFR1, DR3 activates NF-κB through TRADD, TRAF2, and RIP and apoptosis through TRADD, FADD, and caspase-8 (Fig. 2). DR3 binds to Apo3L, which is related most closely to TNF (*24*). Apo3L activates NF-κB through TRADD, TRAF2, RIP, and NIK and triggers apoptosis through TRADD and FADD, consistent with signaling through DR3. Thus, with respect to the regulation of NF-κB and apoptosis, Apo3L closely resembles TNF. There are notable differences, however, in the expression of these ligands and receptors. TNF expression occurs mainly in activated macrophages and lymphocytes (*37*), whereas Apo3L messenger RNA is expressed constitutively in many tissues (*23, 24*). Conversely, TNFR1 is expressed ubiquitously (*37*), whereas DR3 transcripts are present mainly in spleen, thymus, and peripheral blood and are induced by activation in T cells (*14*). Hence, despite overlapping signaling mechanisms, Apo3L-DR3 and TNF-TNFR1 interactions probably have distinct biological roles.

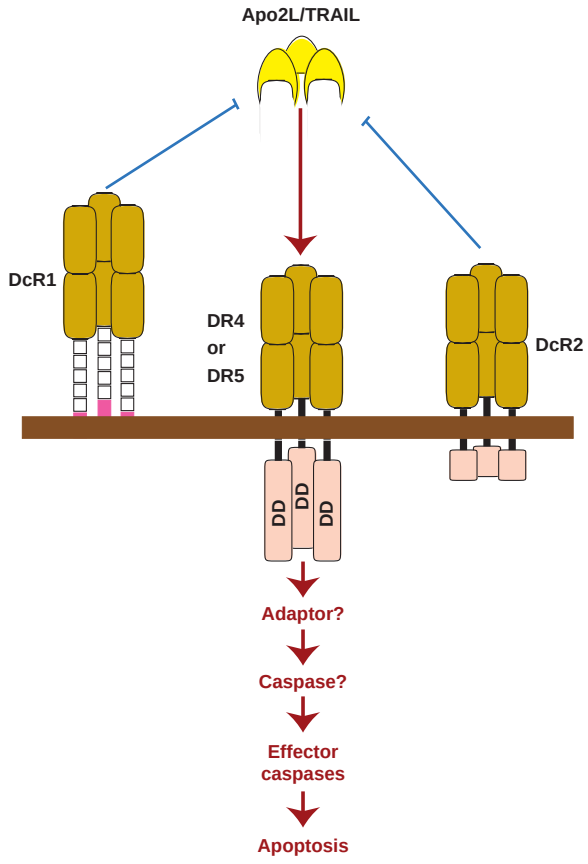

Fig. 3. Apoptosis signaling by DR4 and DR5 and its modulation by decoy receptors.

Signaling by DR4 and DR5 and Modulation by Decoy Receptors

A TNF family member that shows the most similarity to CD95L was identified independently by two groups who named it TRAIL or Apo2L (*25*). Similar to CD95L, Apo2L triggers rapid apoptosis in many tumor cell lines (*25, 26, 51*). Unlike expression of CD95L, which is restricted mainly to activated T cells and NK cells, and to immune-privileged sites (*12*), Apo2L messenger RNA expression is constitutive in many tissues (*25*); however, like CD95L, Apo2L transcription is elevated upon stimulation in peripheral blood T cells (*19, 52, 53*). A subset of mature T cells acquires sensitivity to Apo2L-induced apoptosis after stimulation by interleukin-2, suggesting that Apo2L may play some role in peripheral T cell deletion (*26, 52*). In addition, T cells from human immunodeficiency virus–infected individuals show increased sensitivity to Apo2L, implicating this ligand in the killing of virus-infected cells (*53*).

Apoptosis induction by Apo2L requires caspase activity (*26, 51, 52*). Surprisingly, ectopic expression of FADD-DN in amounts sufficient to block CD95-induced cell death did not block apoptosis induction by Apo2L, which suggests that a FADD-independent pathway links Apo2L to caspases (*26*). Overexpression of DR4 (*15*) or DR5 (*16–21*), which bind to Apo2L, triggers apoptosis; however, there are conflicting reports on the effect of FADD-DN transfection on this response: Some investigators observed no effect (*15–17*), whereas others observed inhibition (*18, 21*). The disagreement extends also to the ability of DR4 and DR5 to bind to known adapters: Some experiments show no such interaction (*15, 16*), whereas others show binding to TRADD, FADD, TRAF2, and RIP (*18, 21*). Because the interactions were observed in cotransfection experiments, it is possible that the abnormally high amounts of receptors and adapters led to promiscuous homophilic association between domains that do not physiologically interact. Cells from FADD-deficient mice, which are resistant to apoptosis induction by CD95, TNFR1, and DR3, show full responsiveness to DR4, confirming the existence of a FADD-independent pathway that couples Apo2L to caspases (*33*) (Fig. 3).

Like the Apo2L mRNA, DR4 and DR5 transcripts are expressed in several tissues, suggesting that there may be mechanisms that protect cells from apoptosis induction by Apo2L. One type of protection is based on a unique set of decoy receptors (DcRs), which compete with DR4 and DR5 for binding to Apo2L (*54*). DcR1 (also called TRID, TRAIL-R3, or LIT) (*16, 17, 20, 21, 55, 56*) is a glycosyl phosphatidylinositol (GPI)–anchored cell surface protein that resembles DR4 and DR5, but lacks a cytoplasmic tail. DcR1 binds to Apo2L, and its transfection into Apo2L-sensitive cells substantially reduces responsiveness to the ligand (*16, 17, 56*). Treatment of DcR1-bearing cells with a phospholipase that cleaves the GPI anchor results in marked sensitization to Apo2L-induced apoptosis (*17*). Thus, DcR1 appears to function as a decoy that prevents Apo2L from binding to its death receptors (Fig. 3). DcR2 (also called TRAIL-R4 or TRUNDD) (*57–59*) is another receptor that resembles DR4 and DR5, but it has a substantially truncated cytoplasmic death domain. Four out of six amino acid positions that are critical for apoptosis and NF-κB activation by TNFR1 (*11*) are absent in DcR2. DcR2 transfection inhibits apoptosis induction by Apo2L (*57–59*); deletion of the DcR2 cytoplasmic region does not abrogate the inhibitory activity (*57*), indicating that this receptor acts as a decoy that competes with DR4 and DR5

for binding to Apo2L (Fig. 3). Overexpression of DcR2 activated NF-κB in one study (*58*), but not in another study (*56*); whether the ligand itself stimulates NF-κB through DcR2 is yet to be investigated. The genes encoding DR4, DR5, DcR1, and DcR2 map together to human chromosome 8p21-22, suggesting that they arose from a common ancestral gene (*57, 58*). It has been reported that a secreted TNFR homolog called osteoprotegerin, which maps to chromosome 8q23-24 and is not closely related to the latter four receptors, binds to Apo2L and inhibits Apo2L function (*60*); however, this interaction was seen in one study, but not in another (*61*).

The idea of targeting specific death receptors to induce apoptosis in tumors is attractive, because death receptors have direct access to the caspase machinery. Moreover, unlike many chemotherapeutic agents or radiation therapy, death receptors initiate apoptosis independently of the p53 tumor suppressor gene, which is inactivated by mutation in more than half of human cancers. Despite these advantages, the clinical utility of both TNF and CD95L has been hampered by toxic side effects. Systemic administration of certain TNF doses causes a severe inflammatory response syndrome that resembles septic shock; this is believed to be mediated mainly by induction of proinflammatory genes in macrophages and endothelial cells through NF-κB activation. Injection of agonistic antibody to CD95 in tumor-bearing mice can be lethal, apparently because of apoptosis induction in hepatocytes, which express abundant CD95 (*12*). Several differences between Apo2L and TNF or CD95L suggest that Apo2L may be a safer agent. First, although DR4 and DR5 can activate NF-κB upon overexpression (*17, 21*), Apo2L itself induces this response only weakly, and activation requires doses that are considerably higher than doses of TNF that activate a strong NF-κB response (*17*). Second, many tissues constitutively express the Apo2L mRNA. Third, DR4 and DR5 are expressed in normal tissues and in many types of tumor cells, whereas DcR1 and DcR2 are expressed frequently in normal tissues but infrequently in tumor cells. This differential expression of death and decoy receptors might enable Apo2L to induce apoptosis in tumors while sparing normal cells.

Future Prospects

Researchers have made substantial progress in delineating the signaling pathways that couple CD95 and TNFR1 to downstream cellular effectors. The same basic principles probably also apply to signaling by the more recently discovered DR3, DR4, and DR5. Indeed, the signaling elements used by DR3 and TNFR1 are similar; however, the pathway from DR4 and DR5 to caspases appears distinct, and its molecular components have yet to be identified in nontransfected cells. A number of interesting questions warrant further study: What are all of the biological roles of the newly identified death receptors and ligands? Do defects in these receptors and ligands contribute to disease? What roles does FADD have in embryonic development and in activation-induced T cell proliferation? It will be particularly intriguing to elucidate why a complex family of death and decoy receptors modulates Apo2L function.

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