Members of the tumor necrosis factor (TNF) superfamily of receptors induce apoptosis by recruiting adaptor molecules through death domain interactions. The central adaptor molecule for these receptors is the death domain-containing protein Fas-associated death domain (FADD). FADD binds a death domain on a receptor or additional adaptor and recruits caspases to the activated receptor. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) signals apoptosis through two receptors, DR4 and DR5. Although there is much interest in TRAIL, the mechanism by which FADD is recruited to the TRAIL receptors is not clear. Using a reverse two-hybrid system we previously identified mutations in the death effector domain of FADD that prevented binding to Fas/CD95. Here we show that these mutations also prevent binding to DR5. FADD-deficient Jurkat cells stably expressing these FADD mutations did not transduce TRAIL or Fas/CD95 signaling. Second site compensating mutations that restore binding to and signaling through Fas/CD95 and DR5 were also in the death effector domain. We conclude that in contrast to current models where the death domain of FADD functions independently of the death effector domain, the death effector domain of FADD comes into direct contact with both TRAIL and Fas/CD95 receptors.

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mutations in the FADD DED could prevent binding to Fas/CD95 (22). This suggests that the FADD DED contributes to the interaction with the Fas/CD95 receptor and that the DED and DD of FADD do not function independently as suggested in previous models. Here we show that mutations in the DED of FADD also prevent binding of FADD to DR5 and are unable to rescue TRAIL signaling in FADD-deficient cells. Compensating second-site mutations that restore binding of such a FADD mutation to DR5 were identified in the DED of FADD and restore TRAIL-induced activation of caspases, further indicating a role for the DED in coordinating the FADD-DR5 interaction. Using a reverse two-hybrid approach we were able to identify only one mutation in the FADD DD that showed differential binding between Fas/CD95 and DR5. These data suggest that the same residues in both the DED and DD of FADD regulate binding of FADD to Fas/CD95 and DR5.

MATERIALS AND METHODS

Reagents—Antibodies and reagents were purchased from the following sources: caspase-8 and caspase-3 (Cell Signaling, Beverly, MA), anti-FADD (Transduction Labs, Lexington, KY), anti-GFP (Chemicon, Temecula, CA), anti-actin and anti-FLAG (Sigma), FasL (Upstate, Charlotteville, VA), recombinant human TRAIL and anti-His6 antibody (R & D Systems, Minneapolis, MN).

Plasmids—pGB14 was made by cloning the ADH1 promoter, Gal4 DNA-binding domain, multiple cloning site, ADH1 terminator cassette from pGBKT7 into the KpnI and SacI sites of pBS314. DR5 (amino acids 209–412), Fas (amino acids 177–335), and full-length catalytically inactive caspase-8 were made by PCR on the corresponding cDNA (23) and by cloning the product into pGB14. Full-length TRADD was cloned into pBTM-1 and pcDNA-Puro plasmids and have been described previously (22). Full-length FADD and FADD-DD (amino acids 79–412) were cloned into pEGFP-C2 or pAC3. The cytoplasmic domains of DR5 (amino acids 209–412) or Fas (amino acids 177–335) were cloned into pHFpGFP-C2. Amino acids 1–298 of FADD or 272–469 of DR5 were cloned C-terminally to FLAG. A more complete description of plasmids, maps, and sequences are available upon request.

Cell Lines—HeLa cells were maintained in Dulbecco’s modified Eagle’s medium with 10% fetal bovine serum. Jurkat cells were maintained in RPMI 1640 with 10% fetal bovine serum. FADD-deficient Jurkat cells (24) stably expressing FADD mutations were made by electroporating pcDNA3.1-Puro constructs and selecting for stable transformants as previously described (22).

Immunoprecipitation—HeLa cells were transfected with 2 μg of pEGFP construct plus 2 μg of FLAG or FLAG-FADD using FuGENE 6 (Roche Applied Science) in a 10-cm plate. After 18 h the cells were lysed in Trizion X-100 lysis buffer (50 mM Tris, pH 8.0, 150 mM NaCl, 5 mM EDTA, 1% Triton X-100) and the soluble fraction was separated with 30 μl of M2-agarose (Sigma) for 4 h at 4 °C. The beads were washed twice in Tris-buffered saline, and precipitated GFP fusions were detected by immunoblot.

DISC Immunoprecipitation—20 x 10^6 BJAB cells were treated with 1.0 μg/ml non specific mouse IgG (Sigma) or monoclonal antibody 631 (R & D Systems, Minneapolis, MN) cross-linked with an equal amount of anti-mouse Fc (Sigma) for 30 min. The precipitations were carried out using protein A-G-agarose beads essentially as described (19), and the bound proteins were detected by immunoblot.

Two-hybrid Assays—Strains Y190 (MATa his3 ade2 trp1 leu2 gal4 gal80 cyh2, LYS2 Gal4-1 HIS3 URA3 Gal1-1 LacZ), DY6877 (MATa ade2 can1 his3 leu2 lys2 trp1 URA3 2-38 LexA-LacZ), and LY26 (MATa can1 his3 leu2 met15 trp1 ura3 gal4:hisG8:hisH8:lys2:LexA(op)-HIS3 TetO-ADH2 hox:KanMX::GAL1-TetR) were used for directed two-hybrid assays and reverse two-hybrid screens essentially as described (22). Strain Y190 was used for quantitative β-galactosidase assays as previously described (20).

Caspase Activation—Jurkat cells were seeded at a density of 1.0 x 10^6 cells/ml in growth medium + 1 μg/ml cycloheximide. The cells were incubated for 6 h with FasL (2 ng/ml) or TRAIL (50 ng/ml) cross-linked with an equal amount of anti-His6, washed once with phosphate-buffered saline, and then harvested in Triton X-100 lysis buffer then analyzed by immunoblot.

Modelling of FADD Mutations—Free energies were obtained by using the thermodynamic cycle of (wild type protein – mutant protein) – (wild type residues – mutant residues). To determine the free energy for each mutant state and the wild types, the solvated energy was computed from snapshots taken from a 500 ps Molecular Dynamics simulation (one for each mutant/wild type) and averaged over each trajectory. Residue energies were obtained by taking the protein simulations, deleting all of the protein except the mutated residue(s) and computing the solvated energy for each snapshot. The generalized born molecular volume with surface area (26, 27) approach was used to obtain the solvated energy and added to the CHARMm22 (28) force field energy to obtain the solvated energy for each snapshot.

RESULTS

FADD Binds Directly to DR5—We performed DR5 DISC immunoprecipitations to see whether FADD precipitated in the endogenous DR5 DISC. BJAB cells were stimulated for 30 min with either non specific IgG or an agonistic DR5 antibody (αDR5), and the endogenous DR5 DISC was precipitated. Both FADD and processed caspase-8 co-precipitate in cells stimulated with αDR5 but not in cells stimulated with IgG. B, the cytoplasmic domains of Fas/CD95 and DR5 fused to the Gal4 DNA-binding domain were tested for interaction with FADD in a directed two-hybrid assay. A color change indicates that FADD is able to interact with both Fas/CD95 and DR5 in yeast. C, immunoprecipitation (IP) experiments were performed to test for interaction between FADD and DR5 or Fas/CD95 in vivo. Both Fas/CD95 and GFP-Fas were precipitated with FLAG-FADD, indicating a direct interaction. Whole cell lysates were blotted with anti-FLAG and anti-GFP to show equal transfection.

Although it has been suggested that FADD binds directly to DR5 (21), other reports indicate that an adaptor protein such as TRADD (29) or DAP3 (23) might be involved in recruiting FADD to the DR5 DISC. We therefore used a yeast two-hybrid assay to test for interaction between the cytoplasmic domain of DR5 and full-length FADD. Fas/CD95 was used as a positive control because it is known to interact directly with FADD (30). Both Fas/CD95 and DR5 interacted with FADD in yeast, suggesting that DR5 is recruited directly to the activated TRAIL receptor complex (Fig. 1B). To test whether FADD could bind directly to DR5 in mammalian cells, we performed immunoprecipitation experiments with full-length FADD and the cytoplasmic domains of DR5 and Fas/CD95. Empty FLAG vector or FLAG-tagged FADD was transfected into HeLa cells with GFP-tagged Fas/CD95 or DR5 cytoplasmic domains. FLAG complexes were immunoprecipitated, and interaction was detected by immunoblotting for GFP. As shown in Fig. 1C, both Fas/CD95 and DR5 co-precipitated with FLAG-FADD but not with empty vector. We also observed a modest decrease in the amount of GFP-DR5 remaining in the lysate after immunoprecipitation. We conclude that similar to the Fas/CD95 model, FADD binds directly to DR5.

The Death Effector Domain of FADD Modulates Binding to DR5—Using a reverse two-hybrid strategy, we previously identified mutations in the DED of FADD that prevent binding to Fas/CD95 (22). These mutations do not disrupt overall protein
structure because the mutated proteins still bind both TRADD and caspase-8 and are able to transduce caspase signaling in response to TNFα in mammalian cells (22). Using a directed yeast two-hybrid assay, we tested these FADD mutations to see whether they affected binding to DR5. A mutation in FADD at arginine 71, which is located in the loop between helices 5 and 6 of the DED (31), to either alanine or tryptophan prevented interaction with both DR5 and Fas/CD95 as measured in a directed yeast two-hybrid assay. B, FADD expression in cells stably transfected with the second site FADD mutations was determined by immunoblot. Jurkat cells expressing the second site FADD mutations were treated with TRAIL (C) or FasL (D), and caspase-8 and caspase-3 processing was detected by immunoblot. Each of the second site mutations rescued DR5 and Fas/CD95-induced caspase processing.

![Fig. 2. The DED of FADD regulates binding to DR5. A](#) a directed yeast two-hybrid assay was used to test for interaction of DR5, Fas, TRADD, and caspase-8 with empty vector (pACT3), wild type FADD, or FADD DED mutations. Changes in arginine 71 to either alanine or tryptophan prevented interaction with both DR5 and Fas/CD95 while retaining interaction with TRADD and caspase-8. B, FADD-deficient Jurkat cells were stably transfected with GFP vector, wild type FADD, or FADD mutants. The level of FADD protein was determined by immunoblot. C, stable Jurkat cells were left untreated or stimulated with TRAIL, and caspase-8 and caspase-3 processing was measured by immunoblot. Only cells expressing wild type FADD showed any processing, indicating that arginine 71 is required for FADD binding to DR5.]

![Fig. 3. Helix 5 of the DED regulates binding of FADD to DR5 and Fas/CD95. A](#) second site mutations in FADD R71A of glutamates 61 to lysine (R71A E61K), leucine 62 to phenylalanine (R71A L62F), and glutamate 65 to lysine (R71A E65K) restore binding to both DR5 and Fas/CD95 as measured in a directed yeast two-hybrid assay. B, FADD expression in cells stably transfected with the second site FADD mutations was determined by immunoblot. Jurkat cells expressing the second site FADD mutations were treated with TRAIL (C) or FasL (D), and caspase-8 and caspase-3 processing was detected by immunoblot. Each of the second site mutations rescued DR5 and Fas/CD95-induced caspase processing.

Mutations That Restore Binding to DR5 Are Located in the DED of FADD—We next sought to identify secondary compensating mutations that would restore binding of FADD DED mutations to DR5. Using a forward two-hybrid approach, we performed a second round of random mutagenesis on FADD (R71A) and screened for second site mutations that restore the binding activity of FADD (R71A) (22). The second site mutations were located in helix 5 of the FADD DED: glutamate 61 to lysine, leucine 62 to phenylalanine, and glutamate 65 to lysine. These mutations restored binding of FADD (R71A) to both DR5 and Fas/CD95 (Fig. 3A).

We introduced FADD molecules with these double mutations into FADD-deficient Jurkat cells (Fig. 3B) and measured caspase processing after treatment with TRAIL. Cells expressing FADD (R71A) did not show caspase-8 or caspase-3 processing when treated with TRAIL, whereas cells expressing FADD (R71A) along with a second site compensating mutation in the DED showed strong TRAIL-induced caspase cleavage (Fig. 3C). Thus, DR5-induced processing of caspase-8 and caspase-3 is prevented by mutations in the DED of FADD and second site mutations that are also in the DED restored processing. Further experiments are required to determine whether the FADD DED helix 5 mutations identified here promote interaction of FADD with TRAIL receptors in other cell types, as has been observed for Fas/CD95 (31).
thermore caspase processing occurs only in response to treatment with the ligand, indicating that it is in response to receptor activation. The same second site mutations also restored Fas/CD95-induced caspase cleavage (Fig. 3D). These data suggest that FADD uses the same surface of the DED, specifically helix 5, to bind both DR5 and Fas/CD95.

Full-length FADD Binds Better to DR5 than the Death Domain Alone—Dominant negative FADD, which consists of the DD alone, can inhibit signaling through TRAIL, indicating that the DD is sufficient for binding to DR5 when overexpressed (14). Because the DED is important for the interaction between DR5 and FADD, we reasoned that full-length FADD might bind better than the DD alone. Constructs expressing either the FADD-DD or full-length FADD were tested for interaction with DR5 in yeast. To measure this interaction we used β-galactosidase assays, which allow us to quantitate each interaction. We observed about a 20% increase in binding of DR5 to full-length FADD compared with the DD alone (Fig. 4A). We performed immunoprecipitation experiments with FLAG-tagged DR5 and GFP-tagged FADD or FADD-DD to measure this interaction in mammalian cells. Full-length FADD co-precipitated with DR5 to a much greater extent than the death domain alone (Fig. 4B). Thus, both the DD and the DED of FADD contribute to the interaction with DR5.

The Death Domain of FADD Can Discriminate between DR5 and Fas/CD95—Because all of our data indicate that binding of FADD to DR5 and Fas/CD95 is very similar, we attempted to identify residues in FADD that are required for binding to one receptor but not the other. We performed a reverse two-hybrid screen to identify mutations in FADD that prevent binding to Fas/CD95 but retain binding to DR5. We screened more than 10 million randomly mutated FADD molecules but were able to identify only a single mutation that discriminated between Fas/CD95 and DR5 binding. A change in valine 108 to glutamate (V108E) in the DD of FADD prevents binding to Fas/CD95 but does not alter binding to DR5, TRADD, or caspase-8 (Fig. 5A). We also screened for mutations in FADD that prevent binding to DR5 but retain interaction with Fas/CD95 but were unable to find such a mutation. This implies that other than valine 108, the same residues that are required for FADD binding to DR5 are also required for Fas/CD95 binding.

To determine whether FADD (V108E) rescues signaling in response to activation of DR5 or Fas/CD95 in mammalian cells, we introduced this FADD mutation into FADD-deficient Jurkat cells. The expression level of FADD (V108E) alone with cells expressing wild type FADD or GFP is shown in Fig. 5B. These cells were treated with TRAIL or FasL, and caspase processing was measured by immunoblot. GFP cells did not show caspase processing when treated with TRAIL or FasL, whereas cells expressing FADD showed both caspase-8 and caspase-3 processing (Fig. 5C). Cells expressing FADD (V108E) underwent caspase processing in response to TRAIL but not when treated with FasL (Fig. 5C). Thus, FADD (V108E) is able to bind DR5 and transduce TRAIL signaling but is unable to bind Fas/CD95 or transduce signaling through FasL.

**DISCUSSION**

We and others have reported that the DED of death domain proteins can regulate binding of the DD (22, 32). Previously we identified mutations in the DED of FADD that prevent binding to Fas/CD95. These FADD mutations did not cause gross conformational changes because binding to TRADD and caspase-8 was still intact. Here we show that mutations in the DED of FADD also prevent binding to DR5. Cells expressing FADD with a mutation in the DED were unable to transduce TRAIL signaling, whereas second site compensating mutations within the DED were able to restore FADD binding to DR5 and rescue TRAIL signaling. Computer modeling indicates that these mutations do not disrupt the overall protein structure because the effect on free energy for most mutations was small (Fig. 6A). FADD R71A L62F is the only mutation with a significant change in free energy, but this mutation actually leads to a more stable structure. Interestingly the second site mutations in FADD that rescued binding to DR5 also rescued binding to Fas/CD95, suggesting that FADD uses the same surface of the DED for binding to both receptors.

Both immunoprecipitation and two-hybrid experiments indi-
helix 5 of the DED (Fig. 6B). Had the effects of the DED on binding to DR5 been allosteric, we would have expected to find compensating mutations in the DD. In addition, we show that DR5 binds more efficiently to full-length FADD than it does to the FADD DD alone. We therefore suggest that in the context of the full-length FADD, helix 5 of the DED comes into direct contact with the receptor.

Although the requirements for FADD binding to DR5 and Fas/CD95 are very similar with regards to the DED, we identified valine 108 in helix 2 of the DD as necessary for binding to Fas/CD95 but dispensable for binding to DR5, TRADD and caspase-8 (Fig. 6C). Because we were unable to identify any other mutations in FADD that could discriminate between DR5 and Fas/CD95, we reason that FADD uses the same surface to bind both receptors. Berglund et al. (33) identified a patch of charged residues on the surface of FADD that was necessary for binding to Fas/CD95. Valine 108 is near this patch, suggesting that the Fas/CD95-binding surface of FADD is larger than the binding surface for DR5. Taken together, our data indicate that FADD uses the same surface of the DED for binding to DR5 and Fas/CD95, whereas regions within the DD can confer specificity for each receptor.

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Direct Binding of Fas-associated Death Domain (FADD) to the Tumor Necrosis Factor-related Apoptosis-inducing Ligand Receptor DR5 Is Regulated by the Death Effector Domain of FADD

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