TRAIL Receptor-Selective Mutants Signal to Apoptosis via TRAIL-R1 in Primary Lymphoid Malignancies

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Abstract

Tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) and its agonistic antibodies, which are currently in early clinical trials for treating various malignancies, induce apoptosis through triggering of either TRAIL-R1 or TRAIL-R2. Based on studies using agonistic monoclonal antibodies, we recently proposed that primary chronic lymphocytic leukemic cells seem to signal apoptosis primarily through TRAIL-R1. We have now synthesized mutant forms of TRAIL specific for TRAIL-R1 or TRAIL-R2. The selectivity of these mutants to induce apoptosis in cell lines is due to selective binding to their cognate receptors resulting in apoptosis via formation of a death-inducing signaling complex. Using these mutants, we now unequivocally show that primary cells from patients with chronic lymphocytic leukemia and mantle cell lymphoma signal to apoptosis almost exclusively through TRAIL-R1. Thus, no significant therapeutic benefit can be anticipated from treating such patients with agents currently in clinical trials that signal predominantly through TRAIL-R2, such as HGS-ETR2 or Apo2L/TRAIL. Our study highlights the necessity to determine whether primary cells from a particular tumor signal via TRAIL-R1 or TRAIL-R2. Such information will provide a rational approach to optimize TRAIL therapy.

Introduction

Tumor necrosis factor–related apoptosis inducing ligand (TRAIL) induces apoptosis by binding to two membrane-bound receptors, TRAIL-R1 (DR4) and TRAIL-R2 (DR5/TRICK2), which results in the recruitment of FADD/MORT1 and activation of caspase-8 within the death-inducing signaling complex (DISC; refs. 1–3). Due to the selective toxicity of TRAIL to tumor cells (4), clinical trials have been initiated with HGS-ETR1 and HGS-ETR2 (Human Genome Sciences, Rockville, MD), selective agonistic antibodies for TRAIL-R1 and TRAIL-R2, respectively (5), and with Apo2L/TRAIL. (Genentech, South San Francisco, CA). However, many primary cells from patients, such as those with chronic lymphocytic leukemia (CLL) and non–Hodgkin’s lymphoma, are resistant to TRAIL (6, 7). Consequently, combination treatments are used to sensitize resistant cells (8) and we have shown that histone deacetylase inhibitors (HDACi) can sensitize CLL cells to TRAIL (9, 10). Although TRAIL signals via TRAIL-R1 or TRAIL-R2, most studies suggest that TRAIL-R1 is the primary receptor leading to apoptosis (4, 8, 11, 12). However, based on indirect evidence, we proposed that CLL cells signal predominantly through TRAIL-R1 (10). To resolve this discrepancy, we have synthesized TRAIL mutants that bind selectively to either TRAIL-R1 or TRAIL-R2. TRAIL-R1-selective, but not TRAIL-R2-selective, mutants induced apoptosis in primary CLL cells, thereby conclusively demonstrating that these cells signal through TRAIL-R1 and not TRAIL-R2.

Materials and Methods

Ramos and Jurkat T cells (clone E6-1) were cultured as previously described (10). CLL and mantle cell lymphoma (MCL) cells were obtained, with patient consent and local ethical committee approval, and purified as described (7). Cells were incubated for 16 hours with desipramine (10 amol/L) and cultured a further 6 hours with HGS-ETR1 or HGS-ETR2 (Human Genome Sciences), His-TRAIL (13), a mutant form of His-TRAIL or His-TRAIL-LE (a recombinant TRAIL with low endotoxin; ref. 10). Samples were analyzed for apoptosis or Western blotting (7, 9, 10). Mutants of His-TRAIL (residues 95-281) were generated using the Quick-Change site-directed mutagenesis kit (Stratagene, La Jolla, CA), confirmed by DNA sequencing, expressed in Escherichia coli and purified as described (13). We modeled the TRAIL/TRAIR1 complex based on the crystal structure of the TRAIL/ TRAIL-R2 complex (14, 15). First, homology modeling (Modeller; ref. 16) was used to produce a structural model of TRAIL-R1 based on the structure of TRAIL-R2. The TRAIL/TRAIL-R1 complex was then modeled by superposing the backbone atoms of the TRAIL-R1 model onto the corresponding atoms of TRAIL-R2 in complex with TRAIL.

Results and Discussion

Apoptotic activity of TRAIL receptor–selective mutants. Recently, a novel phage display approach was used to select TRAIL mutants selective for binding to TRAIL-R1 or TRAIL-R2, based on their affinities for the appropriate receptor-Fc. Only mutants selective for binding to TRAIL-R2 induced apoptosis in several cell lines, leading the authors to conclude that signaling via TRAIL-R2 rather than TRAIL-R1 was more important for induction of apoptosis (12). However, we recently suggested that CLL cells signal almost entirely through TRAIL-R1 (10). To resolve this discrepancy, we synthesized two mutants, TRAIL-R1-6 and TRAIL-R2-6 (Table 1), reported to be selective for TRAIL-R1 or TRAIL-R2, respectively (12), and assessed their ability to induce apoptosis in Ramos and Jurkat cells, which signal predominantly through TRAIL-R1 and TRAIL-R2, respectively (10). HGS-ETR2 and TRAIL-R2-6 induced apoptosis in Jurkat but not in Ramos cells (Fig. 1A and B), supporting the conclusion that TRAIL-R2-6 (Table 1) is a selective TRAIL-R2 mutant. However, TRAIL-R1-6, the proposed TRAIL-R1-selective mutant (12), was inactive in Jurkat cells as expected but surprisingly was also largely inactive in Ramos cells (Fig. 1A and B). We predicted that this mutant would be active in Ramos cells, having reasoned that its observed
inactivity (12) was due to the use of cell lines that signaled primarily through TRAIL-R2 rather than TRAIL-R1. Clearly, the loss of activity was due to the substitution of some or all of the six amino acid residues in TRAIL-R1-6. To test this, we synthesized TRAIL mutants with intermediate substitutions between the wild-type protein and TRAIL-R1-6 (Table 1) and tested their activity in Ramos and Jurkat cells with the aim of obtaining mutants that selectively induce apoptosis in Ramos cells. Initially, we tested TRAIL-R1-2 as the amino acid substitutions, Tyr213Trp and Ser215Asp were included in all TRAIL-R1 mutants in the phage display library because they had a similar affinity to TRAIL-R1-Fc but a 10-fold lower affinity for TRAIL-R2-Fc (12). However, this mutant had a similar activity to wild-type TRAIL in both cell lines (Table 1), suggesting that it was neither specific for TRAIL-R1 nor TRAIL-R2. The TRAIL-R1-4 mutant induced similar levels of apoptosis to wild-type TRAIL in Ramos cells but exhibited a decreased activity in Jurkat cells (Table 1), suggesting a degree of selectivity for TRAIL-R1. An additional substitution at Tyr189Ala to yield TRAIL-R1-5a resulted in the loss of all activity to TRAIL-R2 and also much activity to TRAIL-R1, as determined by its complete inactivity on Jurkat cells and markedly diminished activity on Ramos cells (Table 1). This led us to examine the single amino acid substitution Tyr189Ala alone. Compared with wild-type TRAIL, TRAIL-R1-1 exerted a decreased ability to induce apoptosis in both Ramos and Jurkat cells (Table 1). As the Tyr189Ala substitution resulted in such a loss of activity, we omitted this substitution from TRAIL-R1-6. The resulting mutant, TRAIL-R1-5, retained most of the activity of wild-type TRAIL on Ramos cells but lost much activity on Jurkat cells (Table 1). This mutant also showed a similar concentration response to wild-type TRAIL in Ramos cells but was much less active than wild-type TRAIL in Jurkat cells (Fig. 1A and B). Thus, this mutant exhibited the requisite properties of inducing apoptosis primarily by signaling through TRAIL-R1. The specificity of the TRAIL-R1-5 mutant to signal through TRAIL-R1 in Ramos cells was confirmed by the ability of a blocking antibody specific to TRAIL-R1 but not to TRAIL-R2 to inhibit apoptosis (Fig. 1C). The TRAIL-R2 neutralizing antibody inhibited both TRAIL-R2-6 and HGS-ETR2-induced apoptosis in Jurkat cells (Fig. 1C). To confirm that the mutants were inducing apoptosis, we examined their effects on caspase processing. In Ramos cells, wild-type TRAIL, TRAIL-R1-5, and HGS-ETR1, but not TRAIL-R2-6 or HGS-ETR2, induced the processing of both caspase-8 and caspase-3 to their active large subunits (Fig. 1D). In Jurkat cells, wild-type TRAIL, TRAIL-R2-6, and HGS-ETR2 were the most potent at inducing both apoptosis (Table 1) and the processing of caspase-8 and caspase-3 (Fig. 1D, lanes 2, 3, and 6). Both TRAIL-R1-5 and HGS-ETR1 induced small amounts of caspase processing (Fig. 1D, lanes 4 and 5) commensurate with their ability to induce low levels of apoptosis in Jurkat cells (Fig. 1A) and compatible with there being a small amount of residual TRAIL-R1 signaling. Our finding that in Jurkat cells, the TRAIL-R1 blocking antibody blocked both the TRAIL-R1-5 and HGS-ETR1, but not TRAIL-R2-6 or HGS-ETR2-induced apoptosis, provided support for this notion (Fig. 1C). Taken together, these data show that TRAIL-R1-5 and TRAIL-R2-6 are relatively specific for TRAIL-R1 and TRAIL-R2, respectively.

**Death-inducing signaling complex formation induced by TRAIL mutant proteins.** As the formation of an active DISC is often rate-limiting in many forms of death receptor–induced apoptosis (17), we examined the abilities of the mutants to form a DISC. Biotinylated wild-type TRAIL bound both TRAIL-R1 and TRAIL-R2, and recruited FADD and caspase-8 to the DISC in Ramos cells and caspase-8 was processed (Fig. 2A, lane 2). Neither TRAIL-R1-6 nor TRAIL-R2-6 bound detectable amounts of TRAIL-R1 or TRAIL-R2 and consequently failed to recruit FADD or caspase-8 to the DISC (Fig. 2A, lanes 6 and 8), hence explaining their inability to induce apoptosis (Fig. 1; Table 1). However, TRAIL-R1-5, our selective TRAIL-R1 mutant (Fig. 1; Table 1), bound predominantly TRAIL-R1 together with a small amount of TRAIL-R2, and recruited FADD and caspase-8, which was processed to its p43/41 forms (Fig. 2A, lane 4). In contrast with Jurkat cells, wild-type TRAIL, and TRAIL-R2-6 bound TRAIL-R2 extensively in the DISC and recruited FADD and activated caspase-8 (Fig. 2B, lanes 2 and 8). TRAIL-R1-6 bound neither TRAIL-R1 nor TRAIL-R2 and did not recruit FADD or caspase-8 to

### Table 1. Apoptosis-inducing abilities of various TRAIL mutants

<table>
<thead>
<tr>
<th>His-TRAIL*</th>
<th>Amino acid changes</th>
<th>PS+ cells (b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Tyr189 Arg191 Gln193 Arg199 Lys201 Tyr213 Ser215 Arg267</td>
<td>Ramos 5.7 ± 0.4 Jurkat 5.7 ± 0.4</td>
</tr>
<tr>
<td>Wild-type</td>
<td>Tyr189 Arg191 Gln193 Arg199 Lys201 Tyr213 Ser215 Arg267</td>
<td>Ramos 45.5 ± 4.1 Jurkat 45.5 ± 4.1</td>
</tr>
<tr>
<td>TRAIL-R1-6</td>
<td>Ala — Ser Val Arg Trp Asp — — —</td>
<td>Ramos 41.8 ± 5.2 Jurkat 41.8 ± 5.2</td>
</tr>
<tr>
<td>TRAIL-R1-2</td>
<td>— — — — — — — — — — — — —</td>
<td>Ramos 13.7 ± 1.3 Jurkat 13.7 ± 1.3</td>
</tr>
<tr>
<td>TRAIL-R1-4</td>
<td>— — — — Ser Val Arg Trp Asp — — —</td>
<td>Ramos 42.2 ± 3.1 Jurkat 42.2 ± 3.1</td>
</tr>
<tr>
<td>TRAIL-R1-5a</td>
<td>Ala — — — Ser Val Arg Trp Asp — — —</td>
<td>Ramos 43.5 ± 2.5 Jurkat 43.5 ± 2.5</td>
</tr>
<tr>
<td>TRAIL-R1-1</td>
<td>Ala — — — — — — — — — — — — —</td>
<td>Ramos 46.6 ± 3.1 Jurkat 46.6 ± 3.1</td>
</tr>
<tr>
<td>TRAIL-R1-5</td>
<td>— — — — — — — — — — — — —</td>
<td>Ramos 24.9 ± 2.2 Jurkat 24.9 ± 2.2</td>
</tr>
<tr>
<td>TRAIL-R1-6</td>
<td>Gln Lys Arg — — — — — — — — — —</td>
<td>Ramos 20.0 ± 2.3 Jurkat 20.0 ± 2.3</td>
</tr>
</tbody>
</table>

*Mutants were produced from His-tagged TRAIL (95-281). Labeling of the mutant as R1 or R2 indicates that it was synthesized with specificity for TRAIL-R1 or TRAIL-R2, respectively. The last number of the mutant indicates the number of amino acid substitutions compared with wild-type TRAIL.

1Amino acid changes relative to the wild-type TRAIL are shown in boldface. The dash indicates no change in amino acid from wild-type TRAIL.
the DISC (Fig. 2B, lane 6). TRAIL.R1-5 bound small amounts of both TRAIL-R1 and TRAIL-R2 as well as some FADD within the DISC together with a small amount of caspase-8, which was partially processed (Fig. 2B, lane 4). Taken together, these data show the critical importance of the formation of a DISC containing primarily TRAIL-R1 or TRAIL-R2 in Ramos and Jurkat cells, respectively. Thus, small structural changes in TRAIL permit its preferential binding to TRAIL-R1 or TRAIL-R2, thereby determining its ability to form a DISC and induce apoptosis in an appropriate target cell.

Effect of substitutions on the interaction of TRAIL with TRAIL-R1. To gain insight into the effect of TRAIL mutations on the binding of TRAIL to TRAIL-R1 (Table 1), we produced a structural model of the TRAIL/TRAIL-R1 complex and compared it with the crystal structure of the TRAIL/TRAIL-R2 complex (14, 15). The comparison was facilitated by the sequence similarity between the two proteins (TRAIL-R1 and TRAIL-R2 share 64% amino acid sequence identity in their extracellular domains; Fig. 3A). As previously observed (14, 15), the TRAIL/TRAIL-R2 interaction occurs through two main interaction patches containing residues important for high-affinity binding. The first interaction patch is a hydrophobic area near the top of the TRAIL/TRAIL-R2 complex, referred to as the 50s loop, and is conserved in many tumor necrosis factor superfamily members. The second patch is an area, referred to as the receptor loop, close to the bottom of the complex near the cell membrane, which contains features specific for each individual family member and controls receptor selectivity (Fig. 3A; refs. 14, 15).

**Figure 1.** Cell type specific induction of apoptosis by TRAIL receptor–selective mutants. Jurkat (A) and Ramos (B) cells were cultured for 4 hours with the indicated concentrations of wild-type TRAIL (○), TRAIL.R1-5 (□), TRAIL.R2-6 (▲), and TRAIL.R1-6 (●); apoptosis was measured. Cells were also exposed to HGS-ETR1 or HGS-ETR2 (1 lg/mL). C, Ramos or Jurkat cells were preincubated for 30 minutes either alone or with TRAIL-R1 blocking antibody (Alexis) or TRAIL-R2 neutralizing antibody (R&D systems; 5 lg/mL). Ramos cells were then exposed for 4 hours to either wild-type TRAIL, TRAIL.R1-5 (500 ng/mL), or HGS-ETR1 (1 lg/mL); Jurkat cells were exposed to TRAIL.R2-6 (250 ng/mL), TRAIL.R1-5 (1 lg/mL), or HGS-ETR1 and ETR2 (1 lg/mL), and apoptosis was assessed. D, Ramos and Jurkat cells were exposed to wild-type TRAIL or TRAIL mutants as described above, and processing of caspase-3 and caspase-8 was determined by Western blot analysis. Caspase-8 was processed to its p43/41 forms and its p18 large subunit and caspase-3 to its p19/17 large subunit. *, nonspecific band. The bottom portion of the blot for detection of the caspase-8 p18 subunit was exposed twice as long as the top portion. Apoptosis was assessed by phosphatidylserine externalization and results expressed as the mean ± SE of at least three separate determinations.
loop, containing residues 91 to 104, interacts with a cluster of residues around Gln205 in TRAIL near the bottom of the trimer complex (Fig. 3B). Compared with wild-type TRAIL, the substitutions, Tyr213Trp and Ser215Asp, in TRAIL.R1-2 did not show any differential effects on Ramos or Jurkat cells (Table 1). However, two further substitutions, Asn199Val and Lys201Arg, resulted in the mutant TRAIL.R1-4, which retained the activity of wild-type TRAIL to Ramos cells but lost some activity on Jurkat cells (Table 1), thereby showing some selectivity for signaling through TRAIL-R1 compared with TRAIL-R2. Analysis of the

**Figure 2.** TRAIL mutants selectively induce DISC formation in different cell types. Ramos (A) and Jurkat (B) cells (5 × 10^6 cells per treatment) were exposed for 30 minutes to 500 ng mL^-1 of the biotinylated forms of wild-type TRAIL (His-TRAIL), TRAIL.R1-5, the TRAIL-R1-selective mutant, TRAIL.R2-6, the TRAIL-R2-selective mutant, and TRAIL.R1-6, a related but inactive mutant. After exposure of the cells for 30 minutes, DISC complexes were isolated and analyzed for the indicated proteins by Western blotting (7). To provide an unstimulated receptor control (u/s), biotinylated wild-type or mutant TRAIL was added to lysate from untreated cells. C, freshly isolated cells from patients with CLL were incubated for 16 hours either alone or in the presence of depsipeptide (10 nmol/L). Cells were then exposed for a further 6 hours to wild-type TRAIL (100 ng mL^-1) or TRAIL.R1-5, TRAIL.R2-6, HGS-ETR1 (ETR1), or HGS-ETR2 (ETR2) at 1 μg mL^-1 and apoptosis assessed. Virtually identical results were obtained with TRAIL.R1-5 or TRAIL.R2-6 (100 ng mL^-1) but the higher concentration shows the lack of activity of TRAIL.R2-6. Different symbols, data from six individual patients; solid line, mean. For clarity, data from another patient with a high level of spontaneous apoptosis is omitted but showed the same trend.
Asn199 (Fig. 3a, much shorter Ser residue, which cannot hydrogen bond to R2, corresponding to Glu98 in TRAIL-R2. The substitution hydrogen bond to a conserved Glu in both TRAIL-R1 and TRAIL-R2, this substitution is predicted to cause the loss of TRAIL/TRAIL-R1 because in TRAIL-R1, the equivalent to Arg104 is Arg(Ser)104 (red star) are discussed in the text. B, sequence and crystallographic secondary structure (blue) of TRAIL, indicating the position of TRAIL-R1 (red down arrow) and TRAIL-R2 (blue up arrow) substitutions. C, role of TRAIL Asn199 in TRAIL (yellow)/TRAIL-R1 (cyan)/R2 (green) interactions. Hydrogen bond present with both TRAIL-R1 and TRAIL-R2 (black dashed line), and that present with only TRAIL-R2 (red dashed line). The loss of these hydrogen bonds with the TRAIL substitution N199V is also illustrated. D, role of TRAIL Tyr189 in TRAIL (yellow)/TRAIL-R1/R2 (green) interactions. Hydrogen bond from this tyrosine to the conserved glutamate in TRAIL-R1/R2 (dashed line). Residues in TRAIL involved in hydrophobic interactions with Tyr189—in interactions lost in Y189A-substituted TRAIL—are also shown: (A) and (B) were generated using ESPript (19); (C) and (D) using PyMol (20).

TRAIL/TRAIL-R1 (our model) and the TRAIL/TRAIL-R2 (14, 15) interface suggests that this small increase in TRAIL-R1 selectivity may be due to the substitution Asn199Val (but not Lys201Arg). In TRAIL/TRA1-R2, this substitution is predicted to cause the loss of two hydrogen bonds (to the side chain of Arg104 and to the main chain carbonyl of Cys125). In contrast, the Asn199Val substitution would result in the loss of only one interprotein hydrogen bond in TRAIL/TRAIL-R1 because in TRAIL-R1, the equivalent to Arg104 is a much shorter Ser residue, which cannot hydrogen bond to Asn199 (Fig. 3a and C). The Tyr189Ala substitution was present in two TRAIL mutants, TRAIL.R1-6 and TRAIL.R1-5a, which both exhibited a marked loss of activity (Table 1). The importance of Tyr189 in the binding of TRAIL-R1 and TRAIL-R2 could be rationalized through direct and indirect effects. Tyr189 forms a hydrogen bond to a conserved Glu in both TRAIL-R1 and TRAIL-R2, corresponding to Glu98 in TRAIL-R2. The substitution Tyr189Ala removes this hydrogen bond in both the TRAIL/TRAIL-R1 and TRAIL-R2 complexes (Fig. 3D). Substitution of Tyr189Ala also results in the removal of hydrophobic interactions to Arg191, Asp267, Ala272, and Lys233 close to the surface of TRAIL (Fig. 3D). Thus, this substitution may indirectly affect ligand binding by distorting the surface of TRAIL.

TRAIL-R1 selective mutants induce apoptosis in chronic lymphocytic leukemia cells. Previously, we suggested that TRAIL induced apoptosis in CLL cells by signaling through TRAIL-R1 but not TRAIL-R2 (10). Synthesis of TRAIL receptor–selective mutants enabled us to show this point unequivocally. Depsipeptide, an HDACi, sensitized CLL cells to TRAIL and HGS-ETR1 but not to HGS-ETR2-induced apoptosis (Fig. 2C) in agreement with our previous findings (10). Importantly depsipeptide also sensitized CLL cells to TRAIL-R1-5, the TRAIL-R1-selective mutant, but not to TRAIL-R2-6, the TRAIL-R2-selective mutant (Fig. 2C). We also obtained three samples from patients with MCL, an incurable aggressive disease, with a poor prognosis particularly for the blastoid variant (18). MCL cells were isolated, exposed for 16 hours to depsipeptide (5 nmol/L), and then to different forms of TRAIL. MCL and CLL cells gave similar results. Spontaneous apoptosis (23.4 ± 2.9%) was not increased by wild-type TRAIL (25.5 ± 3.8%) but was increased by depsipeptide (35.4 ± 5%). Depsipeptide sensitized MCL cells to HGS-ETR1 (68.2 ± 6.1%) and TRAIL-R1-5 (54.3 ± 9.1%) but not to HGS-ETR2 (38.3 ± 4.3%) or TRAIL-R2-6 (35.5 ± 3.1%). Taken together, these data show unequivocally that TRAIL signals apoptosis primarily by activating TRAIL-R1 but not TRAIL-R2 in both CLL and MCL cells.

By using receptor-selective mutants, we now unequivocally show that CLL and MCL cells signal apoptosis almost exclusively via TRAIL-R1 and not TRAIL-R2. The discrepancy between our studies showing that leukemic cells signal primarily through TRAIL-R1, whereas tumor cell lines derived from colon and breast signal primarily though TRAIL-R2 (12), may be entirely due to cell type specificity or may also be due in part to the use of cell lines rather than using primary tumor tissue obtained from patients. Our results have significant implications for rational therapy with TRAIL or its agonistic antibodies. If tumors, such as CLL or MCL,
signal primarily through TRAIL-R1, then it is difficult to conceive any justifiable rationale in exposing such individuals to preparations that signal almost exclusively through TRAIL-R2, such as HGS-ETR2 (Human Genome Sciences) or Apo2L/TRAIL (Genentech; refs. 10, 12). Thus, prior to initiating therapy, it is critical to determine whether primary tumor cells signal via TRAIL-R1 or TRAIL-R2. Furthermore, our data show that small structural changes in TRAIL can allow preferential binding to either TRAIL-R1 or TRAIL-R2 with subsequent formation of a TRAIL-R1 or TRAIL-R2 DISC followed by recruitment of FADD and caspase-8. Significantly, such TRAIL mutants may also be of therapeutic value.

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