Formyl peptide receptor-like 1–mediated endogenous *TRAIL* gene expression with tumoricidal activity

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Abstract

Formyl peptide receptor-like 1 (FPRL1), which is a G protein–coupled receptor of chemoattractant subfamily, plays an important role in the regulation of host defense against pathogenic infection and the chemotactic and activating effects of $A\beta_{42}$ on mononuclear phagocytes as well as in the elimination of damaged or pathogen-infected cells. In the present study, we showed that stimulation of FPRL1 agonist ligands (W peptide from a synthetic peptide library, N36 peptide from HIV-1 gp41, and F peptide from HIV-1 envelope protein gp120) elevated endogenous tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) expression in human THP-1 monocytes, primary neutrophils, and mouse leukocytes. Activation of nuclear factor κB was required by the FPRL1-mediated TRAIL expression in the human THP-1 cells and primary neutrophils. The increased TRAIL expression in the mice significantly suppressed the growth of transplanted mouse liver tumor cells by inducing apoptotic cell death. Together, these data provide novel evidence for the physiologic role of FPRL1 and TRAIL in tumor immune surveillance and innate immunity, and implicate a novel strategy for cancer therapy by triggering the endogenous TRAIL expression via stimulation of G protein–coupled receptor FPRL1. [Mol Cancer Ther 2007;6(10):2618–25]

Introduction

Formyl peptide receptor-like 1 (FPRL1), which is a G protein–coupled receptor, interacts with a variety of exogenous and host-derived agonists such as the peptides of invading pathogens, W peptide (WKYMVm) from random peptide library, F peptide corresponding to the amino acid residues 414 to 434 in the V4-C4 region of HIV-1 gp120, N36 peptide corresponding to the amino acid residues 546 to 581 in the NH_2-terminal region of HIV-1 gp41, and the endogenous peptides of ruptured host cells, such as amyloid β42, lipid metabolite lipoxin A4, mitochondrial peptide (MYFINILTL), and prion protein fragments (1–5). FPRL1 is expressed in a great variety of cells including T lymphocytes, monocytes, neutrophils, and macrophages (4, 6). Binding of FPRL1 by the agonists results in a cascade of G protein–mediated signaling events leading to chemotaxis, phagocytic cell adhesion, enhanced phagocytosis, release of oxygen intermediate, bacterial killing, mitogen-activated protein kinase activation, and gene transcription (7). As more FPRL1 binding partners were recently identified, additional roles of FPRL1 have been proposed, involving FPRL1 in the host defense against pathogenic infection, in the clearance of damaged cells, as well as in various diseases such as amyloidosis, Alzheimer's disease, prion disease, and AIDS (2, 8, 9). However, the molecular mechanisms of the involvement of FPRL1 in physiologic processes remain to be clarified.

Tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) is a type II membrane protein (10) that could be cleaved from the membrane by cysteine protease to generate a soluble form (sTRAIL) through enzymatic shedding or released in association with microvesicles (11, 12). The most notable characteristic of TRAIL is its ability to induce apoptosis in transformed or cancer cells but not in normal cells (13, 14). Preclinical studies in nonhuman vertebrates have shown that administration of the recombinant soluble TRAIL (rsTRAIL) or adenovirus- and adeno-associated virus-mediated *TRAIL* gene therapy suppressed the formation and growth of TRAIL-sensitive human tumor xenografts with no apparent systemic toxicity (15–17).

TRAIL is expressed in various normal tissues such as liver, brain, kidney, heart, colon, lung, and testis (10). It is reported that a physiologic role of TRAIL is as a natural suppressor of metastasis in liver and chemically induced or spontaneous tumor development (18). TRAIL mRNA expression in the lung of influenza virus–infected mice and TRAIL protein expression in natural killer and T cells were increased (19). A number of experiments showed that TRAIL is crucial in the induction of autoimmune diseases (20, 21). The data accumulated thus far suggest that TRAIL may play an important role in host tumor surveillance, innate immunity against virus infection, and maintenance of immune homeostasis. However, the molecular mechanisms involved in the physiologic functions of TRAIL are far from clarified.

TRAIL receptors, DR4 or DR5, are indispensable for the initiation of intracellular signaling cascade leading to cell

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death (22). DR4- or DR5-mediated signaling includes the activation of apoptotic caspase cascade, c-Jun NH_2-terminal kinase, p38 mitogen-activated protein kinase, and nuclear factor κB (NF-κB; ref. 23). In a previous study, we showed by using the yeast two-hybrid screening technology that FPRL1 could bind with DR4 specifically (18). In the present study, we further showed that FPRL1 agonists could up-regulate endogenous TRAIL expression with tumoricidal activity, indicating that FPRL1 activation may endue the function of TRAIL against cancer and pathogen infection in host innate immunity.

Materials and Methods

Materials

W peptide (Trp-Lys-Tyr-Val-D-Met, or WKYMVm; ref. 24) from a synthetic peptide library, F peptide (EGSDTITLP-CRIKQFINMWQE) corresponding to the amino acid residues 414 to 434 in the V4-C4 region of HIV-1 gp120 (25), N36 peptide (SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQL-QARIL) corresponding to the amino acid residues 546 to 581 in the NH_2-terminal region of HIV-1 gp41 (2), and the random synthetic peptide (AKERLEAKHRERMSQVM; designated as R peptide) were purchased from Langene Company. rsTRAIL (amino acids 95–281, nontagged) was prepared as previously reported (26). Antibodies against TRAIL, IκBα, phosphorylated IκBα (p-IκBα), and β-actin were purchased from Santa Cruz Biotechnology, Inc. NF-κB activation inhibitor *N*-acetyl-Leu-Leu-norleucinal (LLnL), FPRL1 antagonist pertussis toxin, which could block FPRL1-mediated signal transduction, and anti–β-actin antibody were purchased from Sigma. The horseradish peroxidase–conjugated antimouse immunoglobulin G (IgG) complex, antirabbit IgG, and antigoat IgG antibodies were purchased from Zhongshan Co.

Cell Culture

The human acute monocyte leukemia cell line (THP-1) was purchased from American Type Culture Collection. The cells were cultured in RPMI 1640 (Life Technologies, Inc.) supplemented with 10% FCS (Hyclone), 100 units/mL penicillin, 100 μg/mL streptomycin, and 2 mmol/L glutamine at 37°C in a 5% CO_2 incubator. The human neutrophils were isolated from the peripheral blood of healthy volunteers by 4% dextran T500 (Amersham Pharmacia) sedimentation and purified on Percoll (Amersham Pharmacia) density gradients. The primary neutrophils with a purity of >98% were either used immediately or cultured in a humidified 5% CO_2 incubator. H22 murine hepatoma cell line (syngeneic to the Kunming strain of mice) was provided by Prof. Xiaoguang Chen (Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing, China) and passaged *in vivo* in the Kunming mice with ascitic fluid (27, 28).

Analysis of Endogenous TRAIL Expression in Human THP-1 Monocytes, Primary Neutrophils, and Mice

The human THP-1 cells and freshly isolated primary neutrophils were pretreated with or without pertussis toxin (200 ng/mL) for 2 h followed by treatment with or without W peptide (0.1 μmol/L), F peptide (50 μmol/L), and N36 peptide (10 μmol/L) for 0, 6, and 12 h, respectively. The cells were lysed and subjected to SDS-PAGE followed by Western blot analysis with specific antibody against TRAIL.

All the animal experiments were approved by the Institute's Animal Care and Use Committee. Kunming mice were originated from outbred group of Swiss mice and introduced to Kunming, capital of Yunnan Province, China, from Indian Haffkine Institute in 1964, which have become one of the most important strains of mice widely used in medical research (27, 28). Six-week-old female Kunming mice (provided by the Institute of Animal Sciences, Chinese Academy of Medical Sciences, Beijing, China) were randomized into two groups ($n = 3$) and were given W peptide (0.43 mg/kg, 100 μmol/L W peptide, 100 μL) or PBS by i.p. injection once a day for 3 days. The mice were sacrificed on the 4th day; $\sim 2 \times 10^6$ leukocytes were isolated, lysed, and subjected to SDS-PAGE followed by Western blot analysis with specific antibody against TRAIL.

Western Blot Analysis

The cell lysates were subjected to SDS-PAGE and the proteins in the gel were transferred onto polyvinylidene difluoride membranes (Amersham Biosciences). The membrane was blocked with 5% nonfat dry milk in TBS-T [20 mmol/L Tris-HCl (pH 8.0), 8 g/L NaCl, and 0.1% Tween 20] for 1 h at room temperature and then incubated with the indicated primary antibodies in TBS-T containing 5% nonfat dry milk at 4°C overnight, followed by horseradish peroxidase–conjugated secondary antibodies. The specific proteins were visualized with the ECL plus Western Blotting Detection System according to the manufacturer's instructions (Amersham Biosciences).

Analysis of Tumoricidal Activity of the Endogenous TRAIL

The mice were inoculated s.c. with murine hepatoma H22 cells (5×10^6) into the left flanks (29). When the tumor size reached ~ 50 mm^3, the animals were randomized into six groups ($n = 16$) and given 100 μL of PBS, W peptide (0.43 mg/kg), R peptide (1.05 mg/kg), rsTRAIL (5.00 mg/kg), W peptide (0.43 mg/kg) plus anti-TRAIL IgG (1.25 mg/kg), and W peptide (0.43 mg/kg) plus normal rabbit IgG (1.25 mg/kg) once a day for 7 days by i.p. injection. Some of the mice were sacrificed on the 8th day and tumor growth was measured by the tumor mass ($n = 6$). The survival time was observed in the remainder of mice ($n = 10$). The animals were euthanized when gross ascites, palpable tumors >5 cm, dehydration, emaciation, or weight loss >20% of initial body weight developed. Survival is presented as a Kaplan-Meier plot.

ELISA

Concentrations of soluble TRAIL in the sera of experimental animals were measured with commercial ELISA kits (TRAIL ELISA Set, BD Bioscience) according to the manufacturer's instructions.

In situ Analysis of Apoptotic Cells

Mouse tumor tissues at injection sites were surgically excised, fixed for 12 to 24 h in 4% paraformaldehyde,

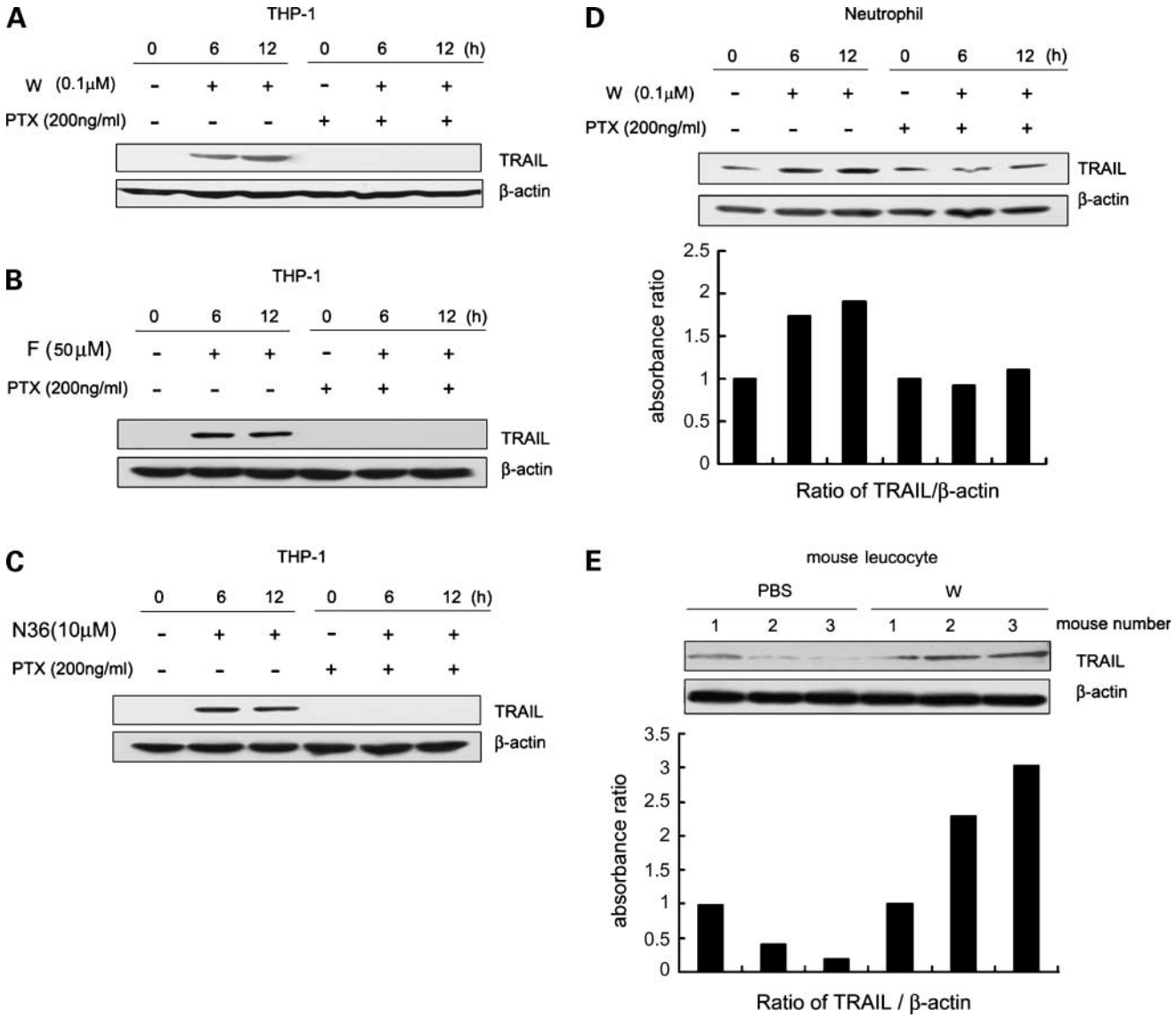

Figure 1. FPRL1 agonists enhance endogenous TRAIL expression both *in vitro* and *in vivo*. THP-1 cells were pretreated with or without pertussis toxin (*PTX*; 200 ng/mL) for 2 h followed by treatment with or without 0.1 μmol/L W peptide for 6 or 12 h (**A**) or with F peptide (50 μmol/L; **B**) or N36 peptide (10 μmol/L; **C**) for 6 or 12 h. Human primary neutrophils were pretreated with or without pertussis toxin (200 ng/mL) for 2 h followed by treatment with or without 0.1 μmol/L W peptide for 6 or 12 h (**D**). TRAIL expression was determined by Western blot analysis with anti-TRAIL antibody. Six-week-old female Kunming mice (**E**) were randomized into two groups ($n = 3$) and given W peptide (0.43 mg/kg) or PBS by i.p. injection once a day for 3 consecutive days. The mouse leukocytes were isolated from the peripheral blood on the 4th day and TRAIL expression was determined by Western blot analysis with anti-TRAIL antibody. β-Actin was used as the internal control. Representative of three independent experiments.

embedded in paraffin, and serially sectioned. Apoptotic cells were detected by terminal deoxyribonucleotidyl transferase–mediated dUTP nick end labeling assay with an *in situ* cell death detection kit (Roche Molecular Biochemicals) according to the manufacturer's instructions.

Statistical Analysis

Results were depicted as mean ± SD and Student's t test was used to evaluate statistical significance. $P < 0.05$ was considered significant.

Results

FPRL1 Agonists Enhanced Endogenous TRAIL Expression Both *In vitro* and *In vivo*

It was reported that binding of FPRL1 by the agonists results in a cascade of G protein–coupled receptor–mediated signaling events leading to the release of the proinflammatory cytokines interleukin-8 and tumor necrosis factor α in human neutrophils (30). Because TRAIL is one member of tumor necrosis factor superfamily, we first investigated whether FPRL1 agonists could stimulate

TRAIL expression in human monocytes and neutrophils, which might throw light on the physiologic functions of TRAIL *in vivo*. The human acute monocyte leukemia cells (THP-1) were stimulated with the FPRL1 agonist W peptide for a time course, and TRAIL expression in the cells was determined by Western blot assay with specific antibody against TRAIL. As shown in Fig. 1A, TRAIL expression was enhanced by W peptide (0.1 μmol/L) in THP-1 cells and completely abolished by pretreatment with pertussis toxin (200 ng/mL), an FPRL1 antagonist that blocks FPRL1-mediated signal transduction. The stimulatory effect on TRAIL expression was not limited to W peptide, as two other FPRL1 agonists, F peptide and N36 peptide, also caused the elevation of TRAIL protein level in THP-1 cells (Fig. 1B and C). The W peptide–dependent and pertussis toxin–sensitive TRAIL up-regulation was also observed in freshly isolated normal human neutrophils (Fig. 1D). The augmented TRAIL expression was also observed in the leukocytes of mice given W peptide via i.p. injection (0.43 mg/kg; Fig. 1E). Together, these data suggest that the FPRL1 activation by the agonists may provide a novel mechanism of TRAIL up-regulation.

W Peptide–Enhanced TRAIL Expression Requires NF-κB Activation

It is reported that FPRL1 could be activated by a number of synthetic peptides and lead to pertussis toxin–sensitive G protein–coupled receptor signaling events including the activation of NF-κB (30, 31). To explore the mechanism of FPRL1-mediated endogenous TRAIL expression in THP-1 monocytes, the cells were treated with or without W peptide for a time course in the presence or absence of NF-κB inhibitor LLnL. NF-κB activation, represented by IκBα phosphorylation and TRAIL expression, was examined by Western blot analysis. As shown in Fig. 2A, IκBα was phosphorylated in the cells treated with W peptide (0.1 μmol/L) for 1 min, which reached a maximum at

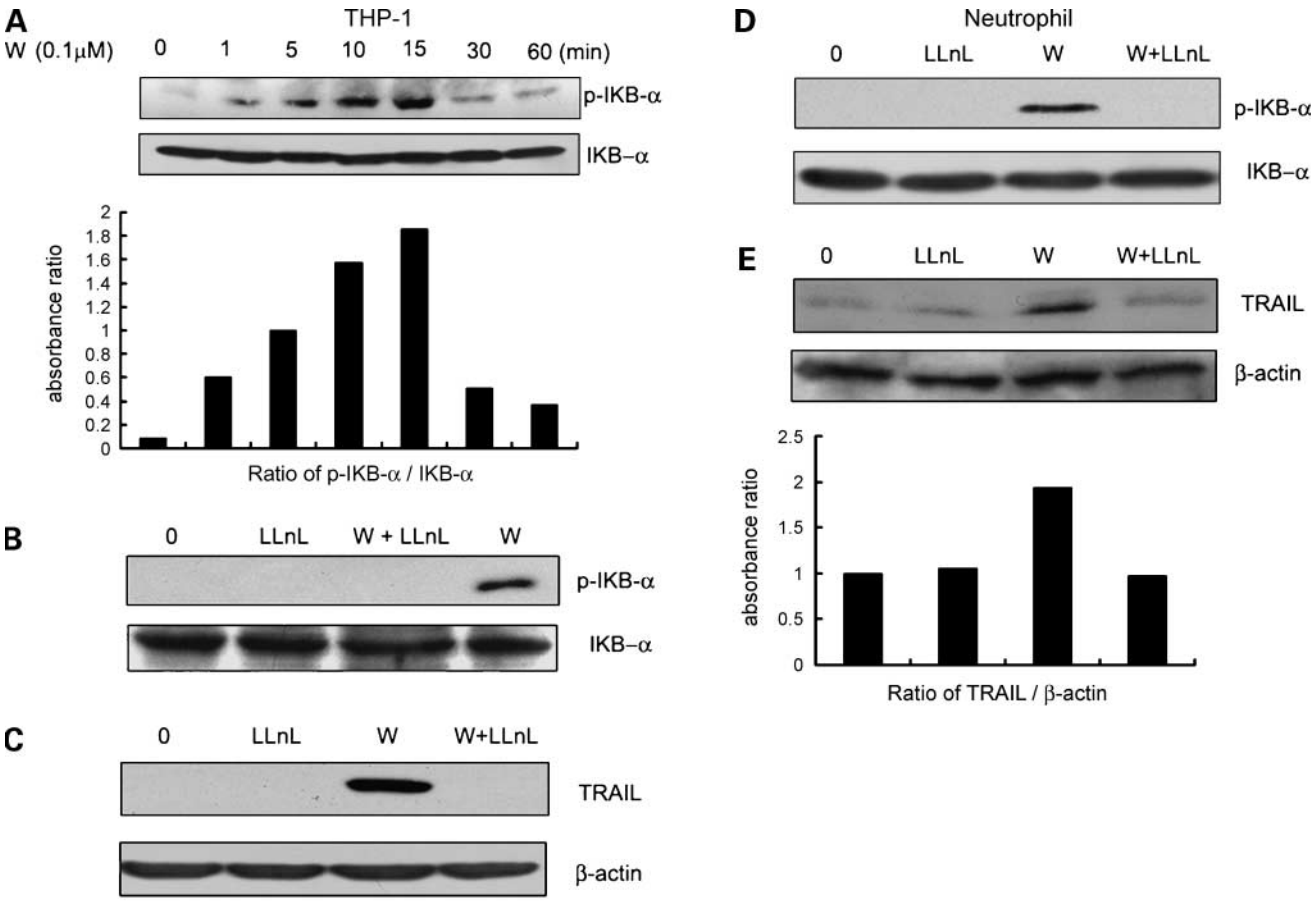

Figure 2. W peptide–enhanced TRAIL expression was regulated by NF-κB activation. **A,** THP-1 cells were treated with 0.1 μmol/L W peptide at the indicated time points. **B,** THP-1 cells were pretreated with or without NF-κB inhibitor LLnL (5 μmol/L) for 60 min followed by treatment with or without W peptide for 15 min. The cell lysates were subjected to SDS-PAGE followed by Western blot with anti-IκBα and anti–p-IκBα. **C,** THP-1 cells were pretreated with or without LLnL (5 μmol/L) for 1 h followed by treatment with or without W peptide for 12 h. The cell lysates were subjected to SDS-PAGE and Western blot with anti-TRAIL antibody. β-Actin was used as the internal control. **D,** normal human primary neutrophils were pretreated with or without NF-κB inhibitor LLnL (5 μmol/L) for 60 min followed by treatment with or without W peptide for 15 min. **E,** normal human primary neutrophils were pretreated with or without LLnL (5 μmol/L) for 1 h followed by treatment with or without W peptide for 12 h. Representative of three independent experiments.

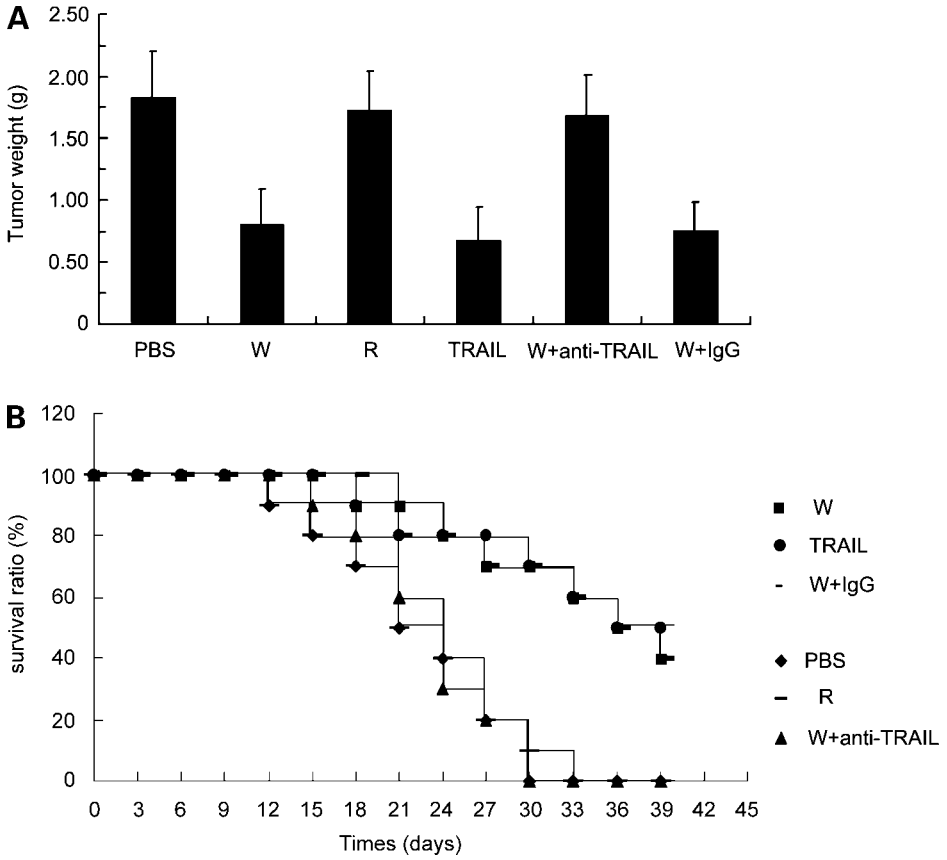

Figure 3. W peptide enhances TRAIL expression with tumoricidal activity. **A,** Kunming mice were inoculated s.c. with murine hepatoma H22 cells. When the tumor size reached ~50 mm^3, the mice were given 100 μL of PBS, W peptide (0.43 mg/kg), R peptide (1.05 mg/kg), rsTRAIL (5.00 mg/kg), W peptide (0.43 mg/kg) plus anti-TRAIL IgG (1.25 mg/kg), and W peptide (0.43 mg/kg) plus normal rabbit IgG (1.25 mg/kg) by i.p. injection once a day for 7 d. The mice were sacrificed on the 8th day and the tumoricidal activities were depicted by the tumor mass (n = 6). **B,** the treated animals were also monitored for the survival time (n = 10). The days represent mouse survival time after tumor inoculation at day 0. Survival is presented as a Kaplan-Meier plot. Representative of two independent experiments.

15 min; however, both IκBα phosphorylation (Fig. 2B) and TRAIL expression (Fig. 2C) were inhibited when the cells were pretreated with LLnL (5 mmol/L) for 1 h. This phenomenon was also observed in normal human primary neutrophils (Fig. 2D and E), indicating that FPRL1-mediated endogenous TRAIL expression is regulated in a NF-κB activation–dependent manner.

W Peptide–Enhanced TRAIL Expression Suppressed Tumor Growth and Prolonged Survival of the Tumor-Bearing Mice

FPRL1 agonists triggering TRAIL expression in the THP-1 cells and the mice led us to propose the tumoricidal activity of W peptide–enhanced TRAIL expression. To address this hypothesis, an animal model was established by s.c. inoculation of murine hepatoma H22 cells. When tumor size reached ~50 mm^3 (~4 days post-inoculation), the animals were randomized into six groups (n = 16) and W peptide was administered by i.p. injection once a day for 7 consecutive days. Then, the six mice in each group were sacrificed and tumoricidal activity was depicted by the tumor mass. As shown in Fig. 3A, administration of W peptide alone reduced tumor weights by ~50% as compared with PBS treatment ($P < 0.05$). The extent of tumor suppression by W peptide was similar to that of TRAIL administration ($P < 0.05$), but the irrelevant peptide R peptide as negative control could not induce tumor regression. The W peptide–induced tumor suppression was partially blocked by anti-TRAIL antibodies but was not inhibited by normal rabbit IgG, showing that W peptide–enhanced TRAIL expression suppressed tumor growth.

The survival of the tumor-bearing mice (n = 10) was also observed after treatment. As shown in Fig. 3B, 40% of mice treated with W peptide survived for 40 days, whereas mice treated with PBS or polyclonal rabbit anti-TRAIL IgG died within 29 days, indicating that W peptide prolonged the survival of the tumor-bearing mice significantly.

TRAIL Expression Was Up-Regulated in the W Peptide–Administered Mice

To determine whether TRAIL expression was up-regulated in the W peptide–administered mice, the expression level of membrane-bound TRAIL in the leukocytes and that of soluble TRAIL in the sera of the mice were analyzed by Western blot and ELISA, respectively. As shown in Fig. 4A, the membrane-bound TRAIL in the leukocytes was dramatically augmented. The soluble TRAIL in the sera of the mice given W peptide was 2,099 ± 983 pg/mL; PBS treatment, 412 ± 231 pg/mL; the irrelevant R peptide treatment, 336 ± 220 pg/mL; the anti-TRAIL plus W peptide treatment, 36.7 ± 25.6 pg/mL; and the normal rabbit IgG plus W peptide treatment, 2,076 ± 632 pg/mL (Fig. 4B), indicating that the soluble TRAIL in the sera of

the mice treated with W peptide was also markedly increased. These data showed that W peptide–induced TRAIL up-regulation in the mice is responsible for the *in vivo* tumoricidal activity.

W Peptide–Enhanced TRAIL Expression Suppressed Tumor Growth by Apoptosis

To further explore the mechanism of tumor growth suppression by W peptide, the tumor tissue sections were prepared from the mice and subjected to *in situ* terminal deoxyribonucleotidyl transferase–mediated dUTP nick end labeling assay. As shown in Fig. 5, W peptide–enhanced TRAIL expression in the mice suppressed tumor growth by apoptosis (brown color), which was abolished by the treatment with anti-TRAIL antibody. These data show that endogenous TRAIL expression in the animals is enhanced by the administration of FPRL1 agonist W peptide and, consequently, the up-regulated TRAIL inhibits the transplanted tumor growth by apoptosis.

Discussion

In the present study, we have shown for the first time that FPRL1 agonists, W peptide, F peptide, and N36 peptide, enhanced endogenous TRAIL expression in human monocytes, human primary neutrophils, as well as in mouse in a NF-κB activation–dependent manner. The W peptide, a more specific FPRL1 ligand, suppressed transplanted liver tumor growth in mice via up-regulation of TRAIL expression and induction of apoptosis. This study showed a novel mechanism for the G protein–coupled receptor FPRL1 playing a role in tumor immune surveillance.

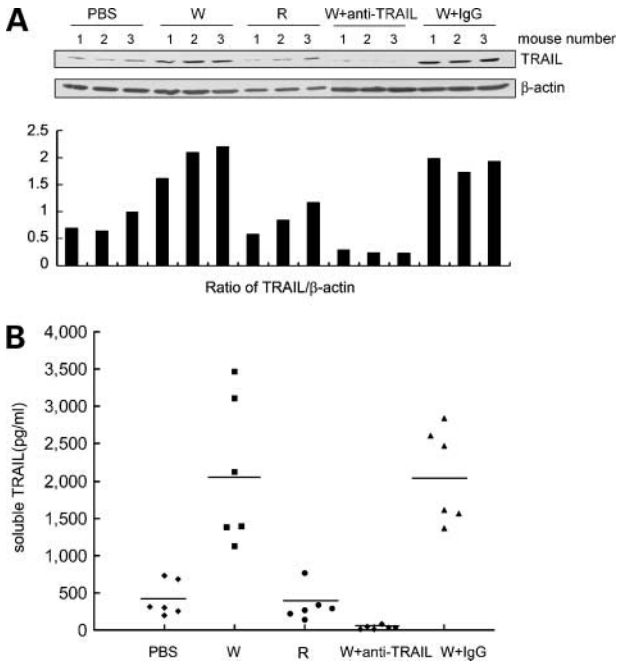

Figure 4. TRAIL expression in leukocytes and sera of mice. **A,** the leukocytes isolated from the mice (n = 3) treated as described in Fig. 3 were lysed. The lysates were subjected to SDS-PAGE followed by Western blot analysis with specific antibody against TRAIL. β-Actin was used as the internal control. **B,** TRAIL expression in the sera isolated from the mice treated as described above was analyzed by ELISA. Representative of three independent experiments.

TRAIL is known as a novel potential anticancer agent because it kills various cancer cells selectively but not normal cells (13, 14). The safety of TRAIL *in vivo* has been investigated extensively. The major controversy is whether TRAIL could induce normal hepatic cell death (32, 33). It is worthy to note that studies showing hepatotoxicity were all either with the full-length membrane-bound form of the protein (33) or with the soluble form fused with exogenous sequence tags (32). It is reported that histidine-tagged TRAIL has an altered protein conformation, reduced stability, decreased solubility, and liver toxicity; however, the soluble form of native TRAIL without tags is able to kill cancer cells with little or no evidence of toxicity to primary human hepatocytes *in vitro* (34). We previously proved that the recombinant soluble form of native TRAIL (rsTRAIL) produced in our laboratory was safe both *in vivo* and *in vitro* (14, 17, 26). In the present study, we observed that W peptide–enhanced endogenous TRAIL expression suppressed the growth of transplanted mouse liver tumor cells without toxicity to lung, liver, spleen, and kidney (data no shown). The efficacy of tumor suppression by W peptide–enhanced soluble TRAIL was similar to that of rsTRAIL, suggesting a novel strategy for cancer therapy by up-regulating the endogenous TRAIL expression via FPRL1 stimulation.

Stimulation of FPRL1 by the various agonists results in a cascade of G protein–coupled receptor–mediated signaling events (4, 6), indicating that FPRL1 is a promiscuous receptor involved in the host immune defense against pathogenic infection, clearance of damaged cells, as well as various diseases. The FPRL1 agonist ligand W peptide is known as a very potent activator of leukocyte and has functions in chemotaxis, Ca^{2+} flux, and activation of the NADPH oxidase. We showed that FPRL1 agonists, W peptides as well as F and N36 peptides derived from HIV, enhanced the TRAIL expression in monocytes, primary neutrophils, and mouse. Interestingly, pertussis toxin completely blocked TRAIL expression in THP-1 cells but only partially suppressed TRAIL expression in human primary neutrophils (Fig. 1), suggesting that W peptide–activated TRAIL expression might be cell type specific, or pertussis toxin inhibited not only FPRL1 but also other G protein–coupled receptor signaling pathways. Further investigation on the molecular mechanisms involved in FPRL1-mediated TRAIL expression showed that the TRAIL expression in THP-1 monocytes and neutrophils enhanced by W, F, and N36 peptides was dependent on NF-κB activation. These data are consistent with the reports that TRAIL expression was dramatically down-regulated by inhibition of NF-κB activity in Jurkat and primary T lymphocytes (35) and induced by influenza A virus infection in a NF-κB–dependent manner (36). Because the activation of NF-κB is usually involved in cell activation and

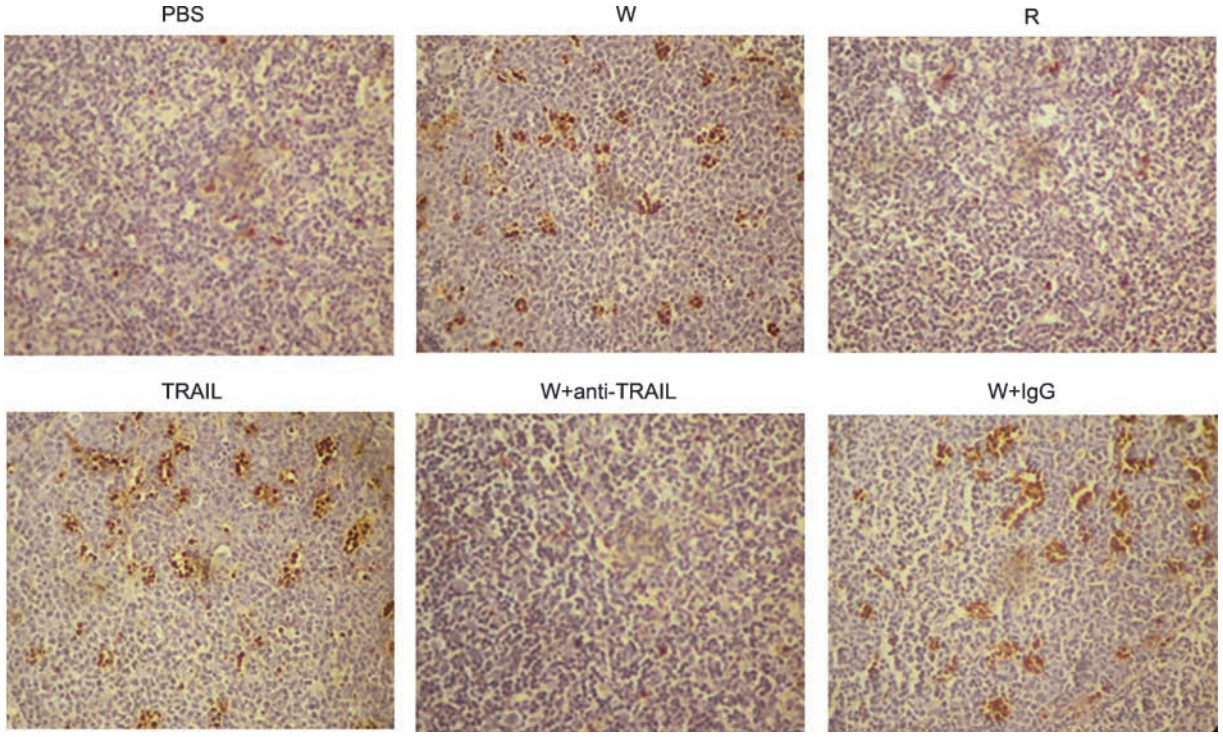

Figure 5. Up-regulated TRAIL expression suppressed tumor growth by apoptosis. Mouse tumor tissues at injection sites were surgically excised and serially sectioned. Apoptotic cells (*brown-colored cells*) were detected by terminal deoxyribonucleotidyl transferase–mediated dUTP nick end labeling assay. Representative images of multiple microscopic fields observed in six mice per group (magnification, ×200).

proliferation, FPRL1-mediated TRAIL expression in a NF-κB activation–dependent manner in monocytes and neutrophils suggests that while the pathogens, such as HIV or influenza A virus, invade the host, TRAIL expression could be up-regulated; on one hand, therefore, host immune surveillance is elicited to kill any transformed or infected cells, and NF-κB is activated, and on the other hand, monocytes and neutrophils could be activated to trigger host innate immunity against microbe invaders. W peptide–enhanced TRAIL expression and NF-κB activation implicated that FPRL1 might be involved in the clearance of tumor cells and the activation of monocytes and neutrophils. The data from TRAIL knockout mice showed that TRAIL-deficient mice are hypersensitive to collagen-induced arthritis and streptozotocin-induced diabetes and develop heightened autoimmune responses (20), indicating that TRAIL does play an important role in immune surveillance within the body in the innate immune response against both tumors and pathogen-infected cells. Our data provide novel evidence for the immunologic function of TRAIL *in vivo*. However, although TRAIL kills transformed cells *in vitro*, TRAIL knockout mice did not spontaneously develop overt tumors at an early age (37), suggesting that distinct physiologic functions of TRAIL might require different priming (38) to trigger various downstream regulating molecules. We further showed that W peptide enhanced suppression of tumor growth in the mouse model by inducing tumor cell apoptosis. This result implicates a novel strategy for cancer therapy by triggering the endogenous TRAIL expression via stimulation of the G protein–coupled receptor FPRL1.

Acknowledgments

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