Review

Current Understanding on the Immunological Functions of Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand

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Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) selectively induces apoptosis in various tumor cells and virus-infected cells, but rarely in normal cells. The killing specificity of TRAIL has brought great interests to develop a novel apoptosis-based anti-tumor agent for clinical application. TRAIL is expressed in many normal tissues and cells, such as liver, brain, kidney, heart, colon, lung, and testis. However, immunological and physiological functions of TRAIL *in vivo* have not been understood well. In the present paper we summarized the progress in the research on immunological functions of TRAIL. *Cellular & Molecular Immunology*. 2005;2(4): 265-269.

Key Words: TRAIL, immune surveillance, autoimmune disease, innate immunity

Introduction

Tumor necrosis factor (TNF)-related apoptosis–inducing ligand (TRAIL), which is also known as apoptosis ligand 2 (Apo2L), is a member of TNF family and discovered by Wiley et al. in 1995 by searching homologues of the TNF family proteins in EST database (1). TRAIL is a type II membrane protein on surfaces of the cells, which are mostly in immune system, including T lymphocytes (2, 3), monocytes (4), dendritic cells (5), natural killer (NK) cells (6, 7), and neutrophils (8). There are two forms of TRAIL molecules, i.e., membrane-bound form and soluble form. Five receptors for TRAIL have been identified in human. DR4 (death receptor 4 or TRAIL-R1) and DR5 (death receptor 5, TRAIL-R2) contain a conservative death domain in cytoplasma tail, which mediates cell death signals. DcR1 (decoy receptor 1, TRAIL-R3) and DcR2 (decoy receptor 2, TRAIL-R4) have close homology to the extracellular domains of DR4 and DR5, but a defective death domain, so that unable to transmit apoptotic signals. Osteoprotegerin (OPG) is a secreted receptor with lower affinity at physiological conditions (9, 10) and competes with the other TRAIL receptors.

Specific killing activity of TRAIL to various tumor cells has brought great interests to develop a novel apoptosis-based anti-tumor agent for clinical application. However, immunological functions of TRAIL *in vivo* have not been understood well. In the present paper we summarized the progress in the immunological functions of TRAIL.

Critical role of TRAIL in tumor immune surveillance

Natural killer (NK) cells have long been implicated in innate immunity against tumors and pathogens. Reports by Takeda et al. showed that TRAIL was constitutively expressed on murine NK cells in liver and acted as a natural suppressor of spontaneous tumor development and metastasis in an IFN-γ dependent manner (11). The onset of tumor in $p53^{+/-}$ mice induced by chemical carcinogen methylcholanthrene (MCA) or spontaneous tumor development could be protected by TRAIL. These functions were partly mediated by NK cells and totally depended on IFN-γ expression (12). In addition, Seki et al. showed that TRAIL, mostly from the NK cells in the liver, partially limited the hepatic metastases of various mouse tumors (13). Smyth et al. reported that anti-metastatic effect of TRAIL was mediated by IFN-γ and IL-12, and lung tumor metastases were also suppressed in a TRAIL-dependent fashion (14). Cretney et al. showed that TRAIL gene knockout mice with defective in TRAIL expression and TRAIL-mediated cytotoxicity in liver and spleen mononuclear cells were more susceptible to experimental and spontaneous tumor metastasis (15). Sova et al. successfully

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eliminated liver metastases in the majority of tumor-bearing mice by intravenous injection of recombinant adenovirus Ad5/35 encoding for the pro-apoptotic TRAIL expressed in tumor specifically (16). TRAIL is predominantly expressed in immature NK cells of human fetus and neonatal mice, but not in the maturated granular NK cells (6, 17). Therefore, it is deducible that TRAIL constitutively expressed on mouse liver NK cells represent a distinct immature subset or stage of NK cell differentiation (6), and it is believable that TRAIL in NK cells of fetus possesses the cytotoxic activity and exerts an anti-tumor surveillance function (17). These data suggested that TRAIL appeared to be a key effector molecule in tumor immune surveillance.

Kamohara et al. reported that TRAIL is also constitutively expressed on the surfaces of freshly isolated neutrophils, while TNF-α is a down-regulator and IFN-γ an up-regulator of TRAIL mRNA expression (8). This result is conflict to the report by Stephen et al. that IFN-γ does not up-regulate the expression of TRAIL (18). Neutrophils are abundant in circulating blood leukocytes, provide the first-line defense against infection, and are potent effectors of inflammation. Furthermore, neutrophils have a short lifespan with survival limited by a constitutive program of apoptosis. Some investigations demonstrated that neutrophil-derived TRAIL/TRAIL receptor system may play a role in neutrophil apoptosis (18) and immune surveillance (7). Hara et al. showed that neutrophils also played a key role in all of the cytokine-induced tumor rejection in co-operation with $CD8^+$ T cells (19). TRAIL is expected to be applied to the treatment of inflammatory of neutrophils, unlike Fas ligand (FasL), it does not induce a chemotactic response and provide a mechanism for clearance of neutrophils from the sites of inflammations (18). Chou et al. reported that TRAIL in combination with anti-CD3 monoclonal antibody could augment IFN-γ secretion in human lymphocytes *in vitro*, suggesting that there might be an amplification loop (20), whereby neutrophil-derived TRAIL stimulates lymphocytes to secrete IFN-γ, which further up-regulates TRAIL release and enhances TRAIL killing activity to tumor cells (8). In contrast, Pekarek et al. reported that elimination of granulocytes *in vivo* in nude mice by a specific anti-granulocyte antibody inhibited growth of variant cancers, indicating that tumor requires granulocytes for rapid growth, suggesting that the function of neutrophils in killing tumor cells needs to be clarified extensively (21).

Griffith et al. reported that TRAIL, but not Fas ligand or TNF, was rapidly expressed in human monocytes stimulated with IFN-γ or IFN-α, and the cells acquire the ability to kill tumor cells (4). Monocyte-mediated tumor cell apoptosis was TRAIL specific as it could be inhibited by expression of the soluble TRAIL receptor. Moreover, IFN stimulation caused a concomitant loss of TRAIL receptor DR5, which was kept pace with resistance acquisition of monocytes to TRAIL-mediated apoptosis. These results define a novel mechanism of monocyte-induced cytotoxicity that requires TRAIL. Fanger et al. in the same group showed in another paper that TRAIL is also expressed in human blood $CD11c^+$ dendritic cells (DCs) stimulated with either IFN-γ or -α and the cells acquire the ability to kill TRAIL-sensitive tumor cells, but not TRAIL-resistant tumor or normal cells (5). These results indicate that TRAIL may serve as an innate effector molecule on $CD11c^+$ DCs for the elimination of spontaneously arising tumor cells and suggest a means by which TRAIL-expressing DCs may regulate or eliminate T cell response to antigen presented by the DCs, and TRAIL is a key immune regulation effector molecule in anti-tumor activity *in vivo*.

From the data above, we could understand that IFN-γ played a critical role in the TRAIL-induced apoptosis. IFN-γ, regulated by IL-12 and α-galactosylceramide, is a potential inducer to mediate TRAIL expression on NK cells and neutrophils (14). It is reported that IFN-γ not only up-regulates the expression of TRAIL or its receptors, but also sensitizes tumor cells to TRAIL-mediated cytotoxicity by up-regulating the expression of caspases and adhesion molecules, as well as down-regulating the expression of FILP, which is known as the inhibitor of caspase 8 (12). Park et al. explored the mechanism of IFN-γ action on TRAIL-induced apoptosis in A549 tumor cells and showed that IFN-γ dramatically increased protein levels of interferon regulatory factor (IRF)-1, but not TRAIL receptors (DR4 and DR5), pro-apoptotic (FADD and Bax), and anti-apoptotic factors (Bcl-2, Bcl-XL, cIAP-1, cIAP-2 and XIAP) (22). IRF-1 overexpression minimally increased apoptotic cell death, but significantly enhanced apoptotic cell death induced by TRAIL, indicating that IFN-γ enhances TRAIL-induced apoptosis through IRF-1. Shankaran et al. demonstrated that IFN-γ could administrate adaptive immunity *via* $CD8^+$ T cells by up-regulation of MHC class I primarily on tumor cells (23). These results suggested a probably substantial role of TRAIL in natural protection from infection and tumor development. Administration of the recombinant adeno-associated virus 2/5 (rAAV2/5) encoding for extracellular domain of TRAIL by intratumor injection resulted in a statistically significant reduction in tumor size and no toxicity to normal tissues was detected (24). Recombinant soluble TRAIL has been applied in nude and SCID mice and nonhuman primate against human tumor xenografts and primary tumors development successfully without apparent systemic toxicity (25, 26). The phase I clinical trial against human cancers is now in progress. However, further studies are needed to explore the effect of TRAIL on tumor surveillance and anti-infection in mouse and human.

Role of TRAIL in innate immunity

It is reported that although normal colonic epithelial cells express TRAIL, TRAIL-R1, TRAIL-R2, and TRAIL-R4, they are completely resistant to TRAIL-induced apoptosis *in vitro* (27). But if the colonic epithelial cells infected with human cytomegalovirus or productive adenovirus, apoptosis of the cells could be induced by up-regulating TRAIL, TRAIL-R1, and TRAIL-R2 on the cell surfaces, indicating

that TRAIL could eliminated early-virus-infected epithelial cells.

Ishikawa et al. investigated the expression of TRAIL in lungs of the influenza virus-infected mice and the function of TRAIL in the immune response to the infection and found that influenza virus infection increased TRAIL mRNA expression in the lungs and TRAIL protein expression in NK and T cells, suggesting that TRAIL may play an important role in the host innate immunity against virus infection (28).

Herbeuval et al. demonstrated that higher TRAIL concentration in the plasma of HIV-1 patients than that of healthy donors and the patients received anti-retroviral therapy (ART) (29). *In vitro* experiments, exposure to infectious HIV-1 results in the production of sTRAIL and membrane bound TRAIL (mTRAIL) in monocytes and monocyte-derived dendritic cells, but not in macrophages or $CD4^+$ or $CD8^+$ T cells. There are two apoptosis models for the depletion of the $CD4^+$ T cells. HIV virus encoded proteins Tat, Nef, Vpr (30), and HIV protease (31) mediate direct cell apoptosis pathway, and Tat (32) and TRAIL (29) proteins mediate indirect apoptosis pathway. Reports showed that the secretion of sTRAIL was initiated by CD4-gp120 interaction (29) and Tat protein activation (33). The Tat and TRAIL secreted by HIV infected cells interact with uninfected $CD4^+$ T cells and therefore cause apoptosis of the cells. The indirect pathway principally involved in the apoptosis of HIV-uninfected cells. This mechanism could well explain why the apoptotic infectious cells are only a small fraction in the total depleted cells. Badley et al. proposed that it was the cytotoxic ligands or viral proteins produced by HIV-infected macrophages, B cells, and $CD8^+$ T cells killed uninfected $CD4^+$ T cells (31). Miura et al. demonstrated that TRAIL induced apoptosis of uninfected $CD4^+$ cells in a model of HIV-1-infected human peripheral blood lymphocyte-transplanted non-obese diabetic severe combined immunodeficient (hu-PBL-NOD-SCID) mice (34). These data proved that TRAIL was involved in depletion of $CD4^+$ cells during the infection of HIV-1. As for why HIV-infected $CD4^+$ T cells become sensitive to TRAIL is still unclear. Maybe HIV infection could result in the up-regulation of TRAIL and TRAIL-R expression in $CD4^+$ T cells, and therefore it satisfies the threshold which is required by $CD4^+$ T cells or some unknown cytokines enhance the interaction between TRAIL and TRAIL receptors.

Moreover, Badley et al. indicated that HIV infection might not induce apoptosis in resting T cells and macrophages, and it might be a critical step in the development of HIV reservoirs (31). LUM et al. reported that lymphocytes and monocyte-derived macrophages (MDM) from HIV-uninfected donors do not die following treatment with either leucine zipper human TRAIL (LZhuTRAIL) or agonistic anti-TRAIL receptor antibodies (35). By contrast, such treatment induces apoptosis *in vitro* of HIV-infected MDM as well as peripheral blood lymphocytes from HIV-infected patients, including $CD4^+CD45RO^+HLA\text{-}DR^-$ lymphocytes. In addition, LZhuTRAIL-treated cells produce less viral RNA and p24 antigen than untreated controls. Whereas untreated cultures produced large amounts of HIV RNA and p24 antigen, of seven treated $CD4^+CD45RO^+HLA\text{-}DR^-$ cell cultures, viral RNA production was undetectable in all, p24 antigen was undetectable in six, and proviral DNA was undetectable in four. These data demonstrate that TRAIL or anti-TRAIL receptor antibody could induce apoptosis of the cells from HIV-infected patients, including cell types which harbor latent HIV reservoirs, so that TRAIL or anti-TRAIL receptor antibody-based apoptosis-inducing therapy might throw some light on eradication of HIV infection.

Besides the functions mentioned above, Cantarella et al. showed that TRAIL contributed substantially to amyloid-induced neurotoxicity in human SHSY5Y neuronal cells (36). As we know that the deposit of β-amyloid protein (βAP) in the brain parenchyma appears to be a crucial factor in the onset of Alzheimer's disease (AD). Treatment of SHSY5Y cells with βAP_{25-35} up-regulated the gene expression of TRAIL and DR5, and the increased expression of TRAIL and its receptor mediated neuronal cell death. Interestingly, Gretchen et al. reported that TRAIL receptor knockout mice ($TRAIL\text{-}R^{-/-}$) developed normal lymphocyte populations, but possessed enhanced innate immune responses in the context of both *ex vivo* and *in vivo* challenges, suggesting that TRAIL-R signaling contributed to the negative regulation of cytokine production in macrophages and dendritic cells (37). The immediate-early Toll-like receptor (TLR) signaling events in macrophages and dendritic cells from the $TRAIL\text{-}R^{-/-}$ mice are normal, but IκB-α homeostatic regulation and NF-κB activity at later time points are perturbed. Although TRAIL is one of the TNF family members and is commonly regarded as an apoptosis inducer, TRAIL can also promote survival and proliferation of endothelial and vascular smooth muscle cells by activating Akt and ERK pathways (38), and regulate the maturation of erythroid and monocytes (39, 40).

Regulatory role of TRAIL in autoimmune diseases

The more and more reports support that TRAIL plays an important role in the induction of autoimmune diseases (41). TRAIL is regarded to maintain immune homeostasis and down-regulate immune responses *in vivo*, including auto-immune responses. The mechanism of this function could be that TRAIL blocks the effect of G1 to S phase progression in cell cycle (42) or induces apoptosis of inflammatory cells (41).

Hilliard et al. showed that chronic TRAIL blockade in mice exacerbated experimental autoimmune encephalo-myelitis (EAE) induced by myelin oligodendrocyte glycoprotein (43). They claimed that TRAIL inhibits autoimmune encephalomyelitis and prevents activation of autoreactive T cells. However, Aktas et al. reported recently that clinical severity and neuronal apoptosis in brainstem motor areas were substantially reduced upon brain-specific blockade of TRAIL after induction of EAE by adoptive transfer of encephalitogenic T cells, which are supposed to kill neurons by secreting TRAIL (44). Giuliani et al. confirmed that these T cells are toxic to neurons *in vitro* (45).

Rheumatoid arthritis (RA) is a serious autoimmune disease. The hallmark of RA is pseudo-tumoral expansion of fibroblast-like synoviocytes (FLSs). The FLS from patients of RA has therefore been proposed as a therapeutic target. A previous study analyzed the effect of TRAIL on RA FLS, the cells were treated for a shorter time, i.e., up to 24 h *in vitro*, and found that apoptosis of the FLS was induced (46). However, Morel et al. reported that TRAIL induced proliferation of RA FLS in a dose-dependent manner in a longer culture time, i.e., 72 h (47). Myashita et al. reported that TRAIL activated ERK1/2 and Akt in RA FLS and prevented these cells from undergoing apoptosis, suggesting that TRAIL induces RA FLS proliferation by activating ERK, p38, PI3 kinase/Akt, and MAP kinase signaling pathway (48).

Systemic lupus erythematosus (SLE) is another autoimmune disease and one characteristic feature of SLE pathophysiology is increased apoptosis in neutrophils, monocytes, and lymphocytes. Hooge et al. demonstrated that soluble TRAIL (sTRAIL) concentrations in serum of SLE patients were higher than those patients with rheumatoid arthritis or Wegener's granulomatosis, suggesting that TRAIL could be another target molecule for the SLE therapy (49).

Moreover, intrathymic negative selection is a very important event for T lymphocyte function and greatly related to various autoimmune diseases. There are controversial opinions on the function of TRAIL in the intrathymic negative selection. Lamhamedi-Cherradi et al. reported that negative selection was at least partially impaired in TRAIL-deficient mice or in the absence of soluble TRAIL receptor DR5 (41). However, Cretney et al. showed that TRAIL was not critical for intrathymic negative selection in their four experimental models (50). Katharina et al. ruled out the possibility that TRAIL played a major role in antigen-induced deletion of thymocytes (51). They suggested that the negative selection could be a cooperative work of several TNF family members. Therefore, intensive investigation on TRAIL function in intrathymic negative selection is required.

In summary, TRAIL as a newly discovered TNF family member has multiple immunological functions. More investigation on understanding its immunological functions is needed intensively.

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