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The Biology of TRAIL and the Role of TRAIL-Based Therapeutics in Infectious Diseases

Brett D. Shepard and Andrew D. Badley*

Mayo Clinic College of Medicine, Division of Infectious Diseases, Rochester, MN, 55905, USA

Abstract

TNF-related apoptosis inducing ligand (TRAIL) is a key mediator of the innate immune response to infection. While TRAIL-mediated apoptosis plays an essential role in the clearance of virus-infected cells, its physiologic role also includes immunosurveillance for cancer cells. Therapeutics that induce TRAIL-mediated apoptosis in cancer cells remain a focus of ongoing investigation in clinical trials, and much has been learned from these studies regarding the efficacy and toxicity of these interventions. These data, combined with data from numerous preclinical studies that detail the important and multifaceted role of TRAIL during infection with human immunodeficiency virus and other viruses, suggest that therapeutic exploitation of TRAIL signaling offers a novel and efficacious strategy for the management of infectious diseases.

INTRODUCTION

Apoptosis, or programmed cell death, is an essential component of human physiology which facilitates tissue homeostasis through the removal of superfluous cells (such as in limb development) and diseased cells (such as infected or malignant cells). In contrast to necrosis which is mediated by tissue injury and causes subsequent inflammation, apoptosis in the normal host is an ordered and highly regulated process controlled by different networks of cellular proteins. However, all pathways to apoptosis lead to the same physiologic outcome: cell death characterized by nuclear disruption through DNA fragmentation and chromatin condensation, as well as cellular blebbing and shrinkage.

Apoptosis is regulated through the coordinated activity of several cysteine-dependent, aspartate-specific proteases (caspases), which participate as “initiators” and “effectors” in signaling cascades to transmit and amplify specific death signals. A key component of this regulation is the synthesis of caspases and their storage in the cytosol as inactive zymogens, or procaspases. Procaspases contain prodomains which facilitate their interaction with regulatory proteins, thus preventing unregulated cell death. However, specific death signals lead to the generation of intracellular protein complexes which cleave procaspase prodomains, leading to the sequential production and release of active initiator and effector caspases. Following activation by initiator caspases, the effector caspases promote apoptosis through activation of DNases and other cellular enzymes responsible for the characteristic apoptotic morphologies.

Death signals that cause apoptosis are delivered via either the intrinsic or extrinsic pathway. The intrinsic pathway is activated by DNA damage following exposure to agents of cellular stress, such as ultraviolet radiation, chemotherapy, hypoxia, starvation, and extremes of

temperature [1]. Activation of the intrinsic pathway leads to mitochondrial translocation of pro-apoptotic members of the Bcl-2 protein family and subsequent loss of mitochondrial transmembrane potential, which promotes release of cytochrome *c* and other mitochondrial factors into the cytosol [2]. These factors form a protein complex called the apoptosome, which leads to the generation of initiator and effector caspases and subsequent cell death. Activation of the extrinsic pathway is mediated by binding of extracellular ligands to death receptors, a subset of the tumor necrosis factor (TNF) receptor superfamily. Ligand binding to the cell-surface expressed death receptor leads to signal transduction through the formation of the death-inducing signaling complex (DISC). The DISC then mediates the subsequent generation of initiator and effector caspases. Unlike the intrinsic pathway, apoptosis via the extrinsic pathway does not always require mitochondria. Nonetheless, both pathways generate similar effector caspases that serve to amplify the initial death signal. Furthermore, specific molecular mechanisms allow the extrinsic pathway to activate the intrinsic pathway [3, 4]. Thus, despite functional distinction, there is molecular overlap and crosstalk between the two pathways. The remainder of this review will focus on the specific details of the extrinsic pathway of TRAIL-mediated apoptosis, its physiologic role, and its potential for therapeutic manipulation.

TRAIL ACTIVATION OF THE EXTRINSIC PATHWAY OF APOPTOSIS

TNF-Related Apoptosis Inducing Ligand

TNF-related apoptosis inducing ligand (TRAIL) is a type II transmembrane protein composed of 281 amino acids, which binds with its cognate receptors (discussed below), which are members of the TNF receptor superfamily to induce apoptosis. TRAIL was initially identified based on its sequence homology to TNF- α and Fas ligand (FasL). Similar to TNF- α , FasL, and other members of the TNF family, TRAIL contains a C-terminal extracellular domain which is conserved among TNF family members and mediates receptor binding. The extracellular domain is linked via a transmembrane helix to an N-terminal cytoplasmic domain, which is not conserved among TNF family members. In addition to its transmembrane form, TRAIL has also been found in vesicle-associated and soluble forms, the latter following proteolytic cleavage of the extracellular domain.

Unlike FasL, TRAIL mRNA and protein have been found in many different human tissues [5, 6], thus suggesting no *in vivo* cytotoxicity to normal tissues [2]. While most normal tissues are resistant to TRAIL-mediated apoptosis [2, 7–10], TRAIL has been shown in some studies to induce apoptosis in neural cells [11] and hepatocytes [12, 13]. However, these latter findings have been controversial for reasons which will be reviewed later. Although TRAIL mRNA and protein have been found in T cells, macrophages, dendritic cells, and natural killer (NK) cells [2, 5, 14, 15], TRAIL has not been found on the surface of resting cells from these subsets [1, 16]. However, most cells within these subsets express cell surface TRAIL after activation with proinflammatory cytokines (*e.g.*, IFN- α , IFN- β , IFN- γ , IL-2, TNF- α) [16–22] or lipopolysaccharide [23]. Additionally, fibroblasts have been shown to increase TRAIL expression in response to IFN- γ treatment or cytomegalovirus (CMV) infection [7], and hepatocytes increase TRAIL expression following infection with hepatitis C virus (HCV) [24] or adenovirus [25]. These data suggest an important role for TRAIL in innate immunity [1, 14, 26]. In support of this hypothesis, an early study demonstrated that CMV infection increased TRAIL expression by primary human fibroblasts, as did IFN- γ treatment of uninfected cells [7]. Furthermore, CMV infection and IFN- γ treatment decreased the expression of TRAIL receptors on neighboring uninfected fibroblasts, thus highlighting a dynamic mechanism by which infected cells become susceptible to TRAIL-induced apoptosis and normal cells remain resistant [7]. This study and others that investigated the physiologic role of TRAIL soon revealed the important role

of TRAIL in the innate immune response to infectious diseases, particularly to viral infections.

TRAIL Receptors

TRAIL can bind to four membrane-bound receptors and one soluble receptor [8, 27, 28]. Two receptors, TRAIL-R1 (DR4) and TRAIL-R2 (DR5), trigger activation of the extrinsic pathway of apoptosis upon binding of TRAIL at the cell surface [10, 29–32]. Transduction of the apoptotic signal is facilitated by a cytoplasmic death domain (DD) on each receptor which assists in the assembly of the DISC [29, 33, 34]. TRAIL can bind two additional membrane-bound receptors, TRAIL-R3 and TRAIL-R4 [34, 35]. However, TRAIL binding to each of these receptors fails to induce apoptosis [10, 35], due to the absence of a cytoplasmic DD in TRAIL-R3 and truncation of the cytoplasmic DD in TRAIL-R4 [10, 36]. Thus, TRAIL-R3 and TRAIL-R4 are also referred to as decoy receptor 1 (DcR1) and decoy receptor 2 (DcR2), respectively [1, 14, 34, 35]. Lastly, TRAIL can bind to a fifth receptor, soluble osteoprotegerin (OPG) [14, 28, 34], which contributes to activation of bone remodeling when bound by other members of the TNF family [37]. Given the low affinity of TRAIL binding to OPG [38] and the higher affinity between OPG and other TNF ligand family members, the physiologic role of TRAIL binding to OPG remains uncertain [28].

The expression and distribution of TRAIL receptors has been investigated as a mechanism by which normal tissues are resistant to TRAIL-mediated apoptosis, while diseased cells (*e.g.*, infected or transformed cells) are not. Initially, increased expression of TRAIL decoy receptors by normal tissues and TRAIL receptors by diseased cells was proposed as the mechanism for differential sensitivity to TRAIL-mediated apoptosis [8–10]. However, TRAIL decoy receptor expression did not correlate with the TRAIL susceptibility of several different cancer cell lines [39, 40]. Studies have shown increased expression of TRAIL-R1 and TRAIL-R2 in many tumors, with decreased expression of both in surrounding normal tissues [41]. Nonetheless, normal colonic tissue expressing TRAIL receptors remained TRAIL-resistant [42], suggesting that the mere presence of TRAIL receptors is not sufficient to confer sensitivity to TRAIL-mediated apoptosis. However, TRAIL sensitivity was induced following infection with either adenovirus or CMV which led to reciprocal alterations in TRAIL-R in infected and uninfected cells [42]. These data, combined with data showing that CMV infection increased TRAIL-R expression in infected fibroblasts and decreased TRAIL-R expression in uninfected fibroblasts [7], highlight a dynamic interplay between TRAIL-R expression and pathologic insults such as infection. Similar modulation of TRAIL-R expression has been seen in response to other viral infections. Increased hepatocyte expression of TRAIL-R in response to hepatitis B virus (HBV) infection has been measured [43], and HCV [24] and adenovirus [25, 42] infections have been shown to increase both TRAIL-R and TRAIL expression by infected hepatocytes. These dynamic changes in TRAIL-R expression, coupled with concomitant dynamic changes in TRAIL expression as a result of viral infection, further highlight a mechanism of differential TRAIL sensitivity and the important role of the TRAIL system in the innate immune response to viral infections.

Additional Proteins that Influence TRAIL Susceptibility

Dynamic changes in TRAIL and TRAIL-R expression are not the only factors that influence TRAIL susceptibility. While the details of other regulatory factors are beyond the scope of this review, they have been the subject of several recent reviews [34, 35, 44]. For example, members of the IAP (inhibitors of apoptosis) protein family bind directly to effector caspases such as caspase-3 and caspase-7, thus inhibiting their proapoptotic activity [45–47]. Downregulation of XIAP by RNA interference increased the susceptibility of pancreatic carcinoma cells to TRAIL-mediated apoptosis [48]. Members of the IAP family may in turn

be inhibited by the protein Smac/DIABLO, which binds directly to IAPs and prevents binding to effector caspases [49, 50], thus allowing apoptosis to proceed. A link to the regulation of TRAIL susceptibility was confirmed when synthetic Smac/DIABLO peptides were shown to increase susceptibility to TRAIL-mediated apoptosis [51, 52]. The FLICE-inhibitory proteins (FLIPs) are another family of proteins that can influence TRAIL susceptibility. These proteins inhibit TRAIL-induced apoptosis by preventing the activation of effector caspases at the DISC [53, 54]. Additionally, the anti-apoptotic proteins Bcl-2 and Mcl-1 play a role in modulating TRAIL susceptibility, as has been recently reviewed [34].

TRAIL Signal Transduction

Binding of TRAIL to a cell bearing either TRAIL-R1 or TRAIL-R2 leads to apoptosis through the extrinsic pathway. The interactions between TRAIL and the death receptors have been well characterized and provide insights for potential therapeutic exploitation. TRAIL binds as a homotrimer to either TRAIL-R1 or TRAIL-R2 [1], resulting in trimerization of the receptor on the cell surface [1, 34, 55]. Receptor trimerization results in recruitment of the cytoplasmic adaptor protein, Fas-associated death domain (FADD) [56–58]. FADD contains two functional domains essential for the transduction of the death signal. The death domain (DD) of FADD binds with the DD of either TRAIL-R1 or TRAIL-R2, completing the DISC formation [56–58]. This interaction exposes FADD's second functional domain, the death effector domain (DED), which recruits either procaspase-8 [56–58] or procaspase-10 [59] to the DISC. Next, caspase-8 and caspase-10 are formed through removal of their respective prodomains, possibly due to autocatalytic cleavage triggered by approximation of the procaspases at the DISC [60, 61], or by procaspase dimerization [62] or procaspase conformational stabilization [63]. Formation of the active initiator caspases triggers an intracellular signaling cascade through either direct activation of effector caspases (*e.g.*, caspase-3, -6, -7) or indirect effector caspase activation through mitochondria, which then mediate the final enzymatic activities that commit a cell to apoptosis [27, 64, 65].

Despite functional distinction between the two pathways of apoptosis, activation of the extrinsic pathway can activate the intrinsic pathway [66, 67]. Both caspase-8 and caspase-10 can cleave Bid, a pro-apoptotic Bcl-2 family member, to a truncated form (tBid) [3, 4]. tBid translocates to the mitochondria and activates Bax and Bak, both pro-apoptotic Bcl-2 family member, which trigger loss of mitochondrial transmembrane potential, release of cytochrome c, and apoptosis via the intrinsic pathway [68, 69].

THE PHYSIOLOGIC ROLE OF TRAIL

Tumor Immunosurveillance

Since the discovery of TRAIL and the elucidation of its mechanisms of apoptotic signal transduction, the physiologic role of TRAIL has been a focus of ongoing research. The discovery of inducible TRAIL expression upon activation of different immune cells suggested that the physiologic role of TRAIL is multifaceted [2], with the immune system as the common link. Because TNF- α and FasL induce apoptosis in cancer cells [70], the potential role of TRAIL in tumor immunosurveillance was investigated. An early study showed that soluble TRAIL induced apoptosis in transformed cells *in vitro* and in human tumor xenografts implanted in SCID mice [71]. Consistent with these data, treatment with TRAIL-neutralizing antibodies promoted tumor development in mice treated with the chemical carcinogen methylcholanthrene (MCA) [72] and increased liver metastases in mice inoculated with murine cancer cells [20, 73]. Subsequent experiments with TRAIL knockout mice, which develop normally [74, 75], yielded similar results. TRAIL-deficient mice demonstrated increased metastases following inoculation with murine lymphoma cells [75],

renal carcinoma cells [74], and mammary carcinoma cells [74], as well as increased tumorigenesis in response to MCA [74]. Conversely, experiments with TRAIL-neutralizing antibodies and TRAIL and TRAIL-R deficient mice have also yielded conflicting results which have not yet been completely resolved. For instance, deficiency of the single mouse TRAIL-R (a TRAIL-R2 homologue) [76] did not effect the development of intestinal adenomas in either mice carrying the adenomatous polyposis coli gene or p53-deficient mice [77]. Additionally, while TRAIL appears to inhibit metastasis of TRAIL-sensitive cancer cells, it appears to have no effect on the metastasis of TRAIL-resistant cancer cells [20, 73]. Lastly, although TRAIL-deficient mice do not spontaneously develop tumors at an early age [75], >25% of these mice develop lymphoid malignancies after 500 days of life [78].

Adaptive Immunity: Role in Autoimmunity

Another area of controversy regarding the physiologic role of TRAIL is the implication of TRAIL in negative selection. TRAIL knockout mice developed more severe and accelerated experimentally-induced autoimmune disease, such as streptozotocin-induced diabetes mellitus [79, 80] and collagen-induced arthritis [80]. Similarly, TRAIL blockade in nonobese diabetic (NOD) mice led to increased pancreatic islet inflammation and an accelerated disease course [79, 81]. However, other researchers were unable to identify a role for TRAIL in negative selection in several well-established *in vivo* and *in vitro* models of negative selection [82, 83]. Furthermore, mice deficient in TRAIL-R demonstrated normal negative selection [84]. These data were consistent with an earlier study that showed that negative selection in a murine model was not impaired by the absence of FADD, which is required for TRAIL signaling [85].

The discrepancy in the data regarding the role of TRAIL in negative selection may be related to the methodologies used in the different studies. Consistent with the preponderance of data that show TRAIL does not play a role in negative selection, mice deficient in either TRAIL or TRAIL-R do not develop *spontaneous* autoimmunity [14, 41], even with prolonged age [41]. However, deficiency or blockade of TRAIL appears to accelerate *experimentally-induced* autoimmunity, such as streptozotocin-induced diabetes mellitus [79, 80], collagen-induced arthritis [80], diabetes in NOD mice [79, 81], and experimental autoimmune encephalomyelitis (EAE) induced by myelin oligodendrocyte glycoprotein [86, 87]. Because other studies have shown that TRAIL does not play a role in negative selection, TRAIL may act by inhibiting cytokine production, antibody production, inflammation, or proliferation of autoreactive T cells in these models [41]. For example, in the EAE model systemic TRAIL blockade significantly enhanced the myelin oligodendrocyte glycoprotein-specific T_H1 and T_H2 cell responses, suggesting that TRAIL prevents activation of autoreactive T cells [87]. However, blockade of TRAIL specifically in the central nervous system prevented the pathologic changes of EAE [88]. Thus, while TRAIL may not play a direct role in negative selection and the prevention of spontaneous autoimmunity, TRAIL may modulate the activity of those autoreactive T cells that survive negative selection or develop secondary to physiologic perturbations. Furthermore, while TRAIL may promote peripheral tolerance, it may also play a dual role by contributing to the pathologic damage associated with autoimmune disease in the central nervous system.

Innate Immunity: Role in Infectious Diseases

Consistent with data showing a dynamic interplay between TRAIL and cytokine production during experimentally-induced autoimmunity, TRAIL and TRAIL receptors have emerged as mediators of the innate immune response to viral infection (Table 1). As discussed previously, many cells that mediate innate immunity increase their expression of TRAIL upon activation by a variety of proinflammatory cytokines (*e.g.*, IFN- α , IFN- β , IFN- γ , IL-2, TNF- α) [16–22] that are produced during viral infection. Both the murine and human

TRAIL promoters are regulated by interferons, and the gene encoding TRAIL is one of the earliest induced by interferons [89, 90], suggesting that TRAIL-mediated apoptosis may play a role in the clearance of virus-infected cells. For instance, hepatitis B virus (HBV) infection increased expression of TRAIL-R1 by hepatocytes *in vitro* [43]. Increased expression of both TRAIL and TRAIL-R2 was measured in livers from patients with acute HBV-mediated liver failure [25]. These data suggest a role for TRAIL-mediated apoptosis in the removal of cells infected with HBV, and this hypothesis is supported by studies which showed that inhibition of TRAIL signaling through either knockdown of the pro-apoptotic protein Bax [91] or treatment with soluble TRAIL-R2 [92] prevented apoptosis of HBV-infected cells. Because increased levels of both TRAIL-R1 and TRAIL-R2 were measured in liver tissues from patients infected with hepatitis C virus (HCV) [24], TRAIL-mediated apoptosis may play a similar role during HCV infection [93]. Similar findings have been observed in the study of other viral infections. Respiratory syncytial virus (RSV) infection of several different respiratory cell lines increased the expression of both TRAIL and TRAIL receptors [94]. Epithelial cells infected with reovirus increased their release of soluble TRAIL and their expression of both TRAIL-R1 and TRAIL-R2, leading to enhanced apoptosis of reovirus-infected cells [95]. Inhibition of TRAIL activity with either anti-TRAIL antibody or soluble TRAIL receptor blocked reovirus-induced apoptosis, as did treatment with inhibitors of either FADD or caspase 8 [95]. Enhanced PBMC expression of TRAIL and release of soluble TRAIL was seen in patients with Hantaan virus hemorrhagic fever with renal syndrome compared to healthy controls [96]. Similarly, IFN- α/β -induced modulation of the TRAIL/ TRAIL-R system enhanced the NK cell-mediated apoptotic killing of murine cells infected with encephalomyocarditis virus [90].

Although TRAIL-mediated apoptosis of virus infected cells is protective to the host in certain situations, some viruses have evolved mechanisms which activate the TRAIL system (Table 1). Several viral proteins sensitize cells to TRAIL-mediated apoptosis, including adenovirus E1A [97], human papilloma virus E7 [98], and the human T-cell leukemia virus Tax oncoprotein [99]. These proteins may aid in the release and dissemination of the virus through activation of TRAIL-mediated apoptosis. Indeed, infection with influenza virus has been shown to promote NF- κ B induction of TRAIL, which enhances efficient influenza virus dissemination through autocrine and paracrine proapoptotic activity [100].

In addition to the direct effects on virus-infected cells, TRAIL-mediated apoptosis has been linked to the pathogenesis of several different viruses through effects on uninfected cells. As shown during CMV infection, interferons dynamically modulate TRAIL receptor expression in both infected and uninfected cells [7, 101]. Similar observations have been made in the study of other viral infections. Measles virus infection of human monocyte-derived dendritic cells induced TRAIL expression and subsequent TRAIL-mediated cytolytic activity in infected cells [102]. Moreover, uninfected peripheral blood mononuclear cells (PBMC) from patients with acute measles expressed high levels of TRAIL receptors and apoptosis [103], suggesting that the profound lymphopenia and immunosuppression in measles patients is in part due to TRAIL-mediated apoptosis of uninfected cells [104, 105]. Consistent with this observation, uninfected CD4⁺ and CD8⁺ lymphocytes collected from patients with acute RSV bronchiolitis showed increased expression of TRAIL receptors. Because this coincided with a decline in the absolute number of CD4⁺ and CD8⁺ lymphocytes, increased TRAIL-mediated apoptosis may be the mechanism for the lymphopenia often seen during the illness [106]. Increased TRAIL expression by uninfected CD4⁺ and CD8⁺ lymphocytes and subsequent massive lymphocyte apoptosis have been shown in response to Ebola infection of nonhuman primates [107, 108], which may explain the poor antibody response to infection [107].

The role of TRAIL during human immunodeficiency virus (HIV) infection remains controversial, yet particularly intriguing given that the HIV envelope protein gp120 promotes acquired sensitivity to TRAIL-mediated apoptosis in T cells through upregulation of TRAIL-R1 and TRAIL-R2 [109] (Fig. 1). Furthermore, higher levels of soluble TRAIL were measured in plasma from HIV-infected patients compared to uninfected patients, and the level of soluble TRAIL was directly proportional to the HIV viral load [110] (Fig. 1). Thus, as will be discussed in a later section, exploitation of TRAIL signaling to promote TRAIL-induced apoptosis may have therapeutic value in the treatment of HIV infection by promoting the death of cells which harbor latent HIV reservoirs. However, apoptotic death of uninfected cells has been observed during HIV infection, in which TRAIL may contribute to T cell death [111, 112] via enhanced susceptibility of CD4⁺ and CD8⁺ T cells to TRAIL-mediated apoptosis [109, 113, 114]. Following HIV infection of mice transplanted with human peripheral blood lymphocytes, massive apoptosis of uninfected CD4⁺ T cells was observed in the spleens of infected mice, and these apoptotic cells co-localized with TRAIL-expressing CD3⁺CD4⁺ human T cells [115]. Treatment of infected mice with anti-TRAIL antibody inhibited apoptosis of uninfected CD4⁺ T cells [115], suggesting that TRAIL may play an important role in the bystander killing of uninfected T cells during HIV infection. Subsequent work showed that treatment of uninfected primary human macrophages with the HIV-1 Tat protein, induced TRAIL expression to levels comparable to those seen following HIV infection of macrophages [116]. Thus, the researchers proposed a model in which extracellular Tat produced by HIV-infected cells, induces TRAIL expression in uninfected macrophages and subsequent TRAIL-mediated apoptosis in uninfected bystander T cells [116] (Fig. 2).

An alternative, and perhaps complementary, model for TRAIL-mediated apoptotic death of bystander T cells has been suggested by several recent studies. Noninfectious HIV inactivated by treatment with aldrithiol-2 retains an intact viral envelope and antigenic integrity [117]. Both infectious and noninfectious HIV induced TRAIL and TRAIL-R2 expression by CD4⁺ T-cells, leading to apoptosis of CD4⁺ cells [118]. Because it is estimated that more than 99% of plasma HIV particles are noninfectious [119, 120], this is consistent with dogma that most apoptotic cells in the lymph nodes of HIV patients are not productively infected [121] and that the number of infected cells is too low to account for the degree of CD4⁺ T-cell loss during HIV infection [122]. HIV-induced expression of TRAIL subsequently was shown to be dependent on IFN- α [118], which is produced primarily by plasmacytoid dendritic cells (pDC) [123]. Furthermore, increased levels of mRNA for IFN- α , TRAIL, and TRAIL-R2 were measured in the tonsils of patients with progressive HIV disease compared to those with nonprogressive disease, while tonsils from uninfected patients did not contain TRAIL or TRAIL-R2 mRNA [124]. Based on these data a model has been proposed in which infectious or non-infectious HIV binds to pDC, leading to production of IFN- α by dendritic cells [125]. IFN- α then induces expression of TRAIL by uninfected CD4⁺ T cells [125]. Subsequent binding of either infectious or noninfectious HIV to these CD4⁺ T cells induces expression of TRAIL-R2, leading to apoptosis of the cells and their neighbors via “bystander death” [125] (Fig. 2).

The mechanisms of CD4⁺ T-cell death have not been definitively proven. Indeed, many more models of CD4⁺ T-cell death that do not require TRAIL-mediated apoptosis have been proposed and are beyond the scope of this review. Moreover, new data raise uncertainty about the two models detailed above. For instance, recent data demonstrated that HIV Tat increases c-FLIP and downregulates caspase-10 in T cells [126] and increases Bcl-2 in monocytes [127], each leading to inhibition of TRAIL-mediated apoptosis in each cell type. Furthermore, in HIV-infected human lymphocyte aggregate cultures containing pDC, antagonistic anti-TRAIL antibodies did not alter uninfected CD4⁺ T-cell death [128], thereby raising questions as to the true relevance of TRAIL in bystander killing. Lastly, a

potential role for TRAIL causing immune cell depletion is further argued against by the recent finding that HIV-infected macrophages upregulate Bfl-1 and Mcl-1 as a counter-regulatory mechanism to resist the cytotoxic effects of TRAIL [129].

Regardless of whether one model of bystander T-cell death during HIV infection proves to be more physiologic relevant than the other, each of the two models detailed above is consistent with clinical data that suggest a role for TRAIL-mediated apoptosis in HIV pathogenesis. Higher levels of soluble TRAIL were measured in plasma from HIV-infected patients compared to uninfected patients, and the level of soluble TRAIL was directly proportional to the HIV viral load [110]. Moreover, HIV viral load and levels of soluble TRAIL decreased in patients receiving effective highly-active antiretroviral therapy (HAART) [130]. Patients receiving effective HAART demonstrated increased CD4+ T-cell counts, which corresponded to decreased expression of TRAIL-R2 by the CD4+ T cells [130].

The induction of TRAIL-mediated bystander death of uninfected CD4+ T cells has been also been suggested as a mechanism of immune evasion by human herpesvirus 7 (HHV-7) [131]. Additional mechanisms of TRAIL-based immune escape have been reported. A recent report demonstrated that TRAIL resistance is acquired in certain cells during HIV infection. HIV infection of macrophages induced production of macrophage colony-stimulating factor (M-CSF), which was shown to be dependent on the viral envelope [129]. M-CSF decreased TRAIL-R1 by macrophages and induced the expression of the anti-apoptotic proteins Bfl-1 and Mcl-1, thus providing a potential mechanism for viral persistence [129]. Likewise, a similar mechanism of immune evasion may play a role in the persistence of HHV-7 infection, which was also shown to decrease TRAIL-R1 expression in infected cells [131]. Modulation of TRAIL-mediated apoptosis as a mechanism of immune evasion and viral persistence has been demonstrated in response to other viral infections. The Epstein-Barr virus (EBV) protein BHRF1 acts downstream of Bid cleavage and upstream of mitochondrial damage to inhibit TRAIL-mediated apoptosis [132]. EBV+ lymphoma cell lines derived from patients with post-transplant lymphoproliferative diseases are resistant to TRAIL-induced apoptosis despite abundant expression of TRAIL receptors [133], and resistance is due in part to EBV LMP-1-mediated NF- κ B activation and subsequent upregulation of the anti-apoptotic protein cFLIP [134]. Lastly, interaction of adenovirus protein E3-6.7K with adenovirus proteins E3/10.4K or E3/14.5K induces the internalization and degradation of TRAIL-R1 [135] and TRAIL-R2 [135, 136] in infected cells, and has been identified as key mechanism of adenoviral immune evasion and subsequent propagation [137, 138].

Modulation of the TRAIL/TRAIL-R system also occurs in prokaryotic infections. Lipopolysaccharide (LPS) increased the expression of surface-bound and soluble TRAIL by monocytes and macrophages *in vitro* [23]. LPS treatment also enhanced the cytotoxicity of monocytes and macrophages against two different TRAIL-sensitive cell lines, and this effect was significantly inhibited by treatment with the TRAIL decoy receptor DcR1 [23]. In human subjects, soluble TRAIL levels in plasma increased 10-fold 2.5 hours following the intravenous administration of endotoxin [139].

A complete understanding of the precise role of the TRAIL/TRAIL-R system in the immune response to infectious diseases has been confounded by a recent report, which may ultimately provide additional insight into this complex interaction. Whereas data cited above suggests that the TRAIL/TRAIL-R system enhances the immune response to cancer and infectious diseases, one study showed that TRAIL-R may negatively regulate innate immune responses. TRAIL-R-deficient mice were observed to have enhanced clearance of murine cytomegalovirus that correlated with increased levels of IFN- α , IFN- γ , and IL-12 [84].

Additionally, macrophages from these mice demonstrated increased TRAIL, TNF- α , and IL-12 expression after stimulation with mycobacteria and Toll-like receptor ligands [84]. The strength of these associations is uncertain, because the TRAIL-R-deficient mice showed no difference in their clearance of other pathogens such as encephalomyocarditis virus, bacillus Calmette-Guerin, *Salmonella typhimurium*, *Mycobacterium bovis*, and *Listeria monocytogenes* when compared to wild-type mice [84]. Furthermore, with respect to *L. monocytogenes*, the results contrast with another study that showed TRAIL-deficient mice are resistant to primary listeriosis when compared to wild-type mice [140]. Nonetheless, increased cytokine production in the TRAIL-R-deficient mice is intriguing and may relate to TRAIL/TRAIL-R activating other regulatory pathways, including NF- κ B [34]. Indeed, although the immediate-early Toll-like receptor response in macrophages and dendritic cells from TRAIL-R-deficient mice was normal, NF- κ B and I κ B activity at later time points was abnormal [84].

THERAPEUTIC USES OF TRAIL

With the development of a detailed understanding of the TRAIL apoptotic pathway and its physiologic role, research has begun to focus on the therapeutic exploitation of TRAIL signaling. Because of the initial focus on the role of TRAIL in cancer immunosurveillance, most all of the preclinical and clinical trials have studied the use of TRAIL agonists as cancer therapeutics [14]. Such trials have been of particular interest and focus, because TRAIL induces apoptosis in cancer cells independent of p53 [35], thus providing a potentially important therapeutic option for the approximately 50% of human cancers that have p53 mutations [44]. Despite their focus on cancer therapy, these studies have yielded important observations regarding efficacy and toxicity that will help guide future studies of TRAIL-targeted therapeutics in other disease states. Several methods for the manipulation of TRAIL signaling have been investigated to varying degrees, but most advances have been made in the study of soluble TRAIL and agonistic monoclonal antibodies against TRAIL-R receptors. Although TRAIL-based gene therapy is a promising cancer therapeutic [141–143], the role of gene therapy in infectious disease treatment is likely limited and thus will not be discussed. For similar reasons, the use of soluble TRAIL or agonistic anti-TRAIL-R antibodies in combination with traditional cancer chemotherapeutics (*e.g.*, irradiation, vincristin, cisplatin, etoposide, methotrexate, cyclophosphamide, etc.) [41, 55] will not be discussed.

Soluble TRAIL

Unlike TNF- α and Fas agonists, which cause severe hepatotoxicity *in vivo*, soluble TRAIL treatment of SCID mice with transplanted human mammary adenocarcinoma cells caused no toxicity to normal cells [71]. Additional work with xenograft murine models showed that soluble TRAIL induced apoptosis of transplanted human cancer cells from diverse lineages, such as colon carcinoma [144, 145], pancreatic adenocarcinoma [146], cholangiocarcinoma [147], multiple myeloma [148], and glioma cells [149, 150]. Furthermore, each of these studies was notable for the absence of toxicity to normal tissues in the murine models [144–150].

In effort to maximize the efficacy and efficiency of TRAIL-induced apoptosis in diseased cells while minimizing toxicity to normal tissues [35, 151], several versions of soluble TRAIL have been developed and tested using *in vitro* and *in vivo* models [8, 71, 144, 152–155], and in phase I clinical trials [14]. Four recombinant versions of soluble TRAIL contain exogenous sequences tags that have been shown to enhance the prerequisite homotrimerization of TRAIL and subsequent binding to TRAIL-R. In the first, an amino-terminal polyhistidine tag is fused to TRAIL amino acids 114–281 [152]. In the other three versions, the amino-terminal end of amino acids 95–281 is fused with either a Flag epitope

tag [153, 156], a modified yeast Gal-4 leucine zipper [71], or an isoleucine zipper [157]. Another version of soluble TRAIL contains amino acids 114-281 in their native sequence without the addition of exogenous tags [1, 8]. For reasons that will be detailed in a later section, this version of soluble TRAIL has emerged as the preferred form for future clinical use [35, 41]. While each of these versions of soluble TRAIL can bind to either TRAIL-R1 or TRAIL-R2, new derivatives of soluble TRAIL that are selective for either receptor were recently described [158]. As emerging data suggest that certain cancers predominantly express one receptor versus another [158], these new derivatives of soluble TRAIL may prove useful for enhancing the specificity and reducing the potential for toxicity.

Structural studies of biologically-active, homotrimeric TRAIL were performed to 1.3 Å resolution, and alanine-scanning mutagenesis was used to map the receptor-binding site [159]. The studies revealed a zinc ion in the receptor-binding domain at the interface between TRAIL monomers, which is coordinated by a single unpaired cysteine residue at amino acid 230 [Cys(230)] in each monomer [153, 159]. Site-directed mutagenesis of Cys(230) to alanine or serine reduced the stability of TRAIL homotrimers and decreased receptor binding by 200-fold, showing that the biological activity of both full-length TRAIL and its recombinant soluble forms is dependent on Cys(230) [153]. Because structural studies revealed that zinc was required for maintenance of the native structure and stability of the TRAIL homotrimer [159], it was presumed that the biologic activity of TRAIL was itself zinc-dependent. This was confirmed by demonstrating that in biologically active TRAIL Cys(230) chelates one zinc ion per TRAIL homotrimer, whereas in the absence of zinc an inactive form of TRAIL is produced by participation of Cys(230) in interchain disulfide bridge formation [153]. Thus, addition of zinc and reducing agents to cell culture media and extraction buffers has optimized the production of recombinant soluble TRAIL with biologic activity against many types of tumor cells [1, 144, 154, 155].

Agonistic anti-TRAIL-R Antibodies

As an alternative to activation of TRAIL-induced apoptosis through therapeutic use of soluble TRAIL, the efficacy of agonistic anti-TRAIL-R antibodies has been investigated. Agonistic anti-TRAIL-R antibodies may provide greater therapeutic benefit than soluble TRAIL. Some cancers have been shown to express increased levels of TRAIL decoy receptors that can bind soluble TRAIL and prevent delivery of the apoptotic signal [41, 55]. Agonistic antibodies specific to either TRAIL-R1 or TRAIL-R2 do not bind to the decoy receptors, thus circumventing this potential resistance mechanism in some cancers [41]. Additional therapeutic benefit may be provided by the prolonged plasma half-life of agonistic anti-TRAIL-R antibodies compared to soluble TRAIL, approximately 14–21 days versus 30 min, respectively [1, 14, 55, 160].

While several agonistic anti-TRAIL-R antibodies have been developed, a few fully humanized monoclonal antibodies emerged from preclinical studies after demonstration that each induced apoptotic death in a wide variety of cancer cell lines *in vitro* and in xenograft mouse models [161–163]. These agonistic antibodies have been or are being investigated in phase I and phase II clinical trials conducted by sponsors including Human Genome Sciences (Rockville, MD, USA), Amgen (Thousand Oaks, CA, USA), and San-kyo (Tokyo, Japan) [14, 55, 164]. Antibodies under investigation include HGS-ETR1 (mapatumumab), an agonistic antibody specific to TRAIL-R1; as well as HGS-ETR2 (lexatumumab), HGS-TR2J, TRA-8, and AMG 655, each specific to TRAIL-R2 [14, 55, 164].

Clinical trials have shown that treatment with agonistic anti-TRAIL-R antibodies is associated with disease regression or stability in several different types of cancer and has been well tolerated across a broad range of doses. For instance, in a phase I trial in patients with advanced solid tumors treated with HGS-ETR1, 19 of 40 patients developed stable

disease [160]. Plasma concentrations of HGS-ETR1 that were active in preclinical trials could be achieved with intravenous administration of 10 mg/kg every 14 days, with only mild (grade 1 or 2) non-hematologic adverse events [160]. Similar findings from phase II trials with HGS-ETR1 have been reported as abstracts at recent international meetings and have been reviewed elsewhere [1, 14]. HGS-ETR1 treatment (either 3 or 10 mg/kg IV every 21 days) was associated with partial or complete response in 8% and disease stability in 30% of patients with relapsed or refractory non-Hodgkin's lymphoma, with minimal toxicity [1]. In treatment-experienced patients with relapsed or refractory non-small cell lung cancer, treatment with HGS-ETR1 (10 mg/kg IV every 21 days) was associated with disease stability in 29% [1, 14]. Lastly, 32% of patients with relapsed or refractory colorectal cancer achieved disease stability following treatment with HGS-ETR1 (20 mg/kg IV every 14 days for 2 cycles, followed by 10 mg/kg IV every 14 days for 4 cycles [1, 14]. In each of these phase II trials no dose-limiting toxicities were observed, even with repetitive dosing, and the maximum tolerated dose was not achieved [1, 14]. Two separate phase I trials with HGS-ETR2 yielded similar outcomes, with treatment leading to disease stability in 32.3% and 29.7% of patients with advanced solid tumors receiving 0.1–10 mg/kg IV every 14 days or up to 20 mg/kg IV every 21 days, respectively [1]. Data from phase I trials of HGS-TR2J and AMG 655 have not been reported, and patient recruitment has not been begun for a phase I trial of TRA-8 [14].

A Role for Therapeutic Exploitation of TRAIL Signalling in the Management of Infectious Diseases?

Soluble TRAIL and agonistic anti-TRAIL-R antibodies hold promise as cancer therapeutics. Even though neither has been used in a clinical trial investigating their potential as therapeutics in the treatment of infectious diseases, the lessons learned from all types of clinical trials will undoubtedly provide useful data for the development of rational and safe trials in other settings. Additionally, data from preclinical research continues to provide general insights into the biologic activity of soluble TRAIL and agonistic anti-TRAIL-R antibodies, which may lead to new trials investigating novel uses of both. For example, the results from two recent studies suggest that agonistic anti-TRAIL-R antibodies facilitate recruitment of immune effector cells. An agonistic antibody specific for mouse TRAIL-R2 induced apoptosis in TRAIL-resistant cancer cells by recruitment of FcR-expressing cells (*e.g.*, macrophages, dendritic cells, NK cells) that mediate innate immunity through the processing and presentation of antigens to cytotoxic lymphocytes [165]. A similar interplay between agonistic anti-TRAIL-R antibodies and the immune system was highlighted in a second study. Mice with chemically-induced TRAIL-resistant tumors were treated with an agonistic antibody specific for the mouse TRAIL-R2 homologue as well as agonistic antibodies specific for CD40 and CD137, the latter provided to enhance T-cell activation [166]. The combinatorial treatment rapidly induced tumor-specific CD8⁺ T cells producing INF- γ in the tumor-draining lymph node [166]. As the tumors in each study were TRAIL-resistant, the specific immunity induced by treatment was the mechanism of tumor clearance, rather than apoptosis through TRAIL-R activation [165, 166]. These studies suggest that induction of antigen-specific T-cell memory through strategies employing agonistic anti-TRAIL-R antibodies may have broader utility for priming specific immunity in the management of other diseases, such as infectious diseases.

With respect to the potential use of TRAIL-based therapeutics in the treatment of infectious diseases, the vast majority of data has been developed from the preclinical studies of viral infections that were reviewed in an earlier section. While some have shown that TRAIL-mediated apoptosis plays an important role in the clearance of certain virally-infected cells, other studies have shown that TRAIL-mediated apoptosis itself may contribute to the pathogenesis and propagation of the viral infection. Thus, in some viral infections

therapeutic treatments to enhance TRAIL-mediated apoptotic clearance of virus-infected cells may be beneficial, such as through the use of soluble TRAIL and agonistic anti-TRAIL-R antibodies. However, in viral infections in which pathogenesis and propagation are enhanced by apoptosis, downregulation of TRAIL-mediated apoptosis may be the therapeutic goal. With respect to the latter, soluble TRAIL-R2 has been shown to block TRAIL-mediated apoptosis of HBV-transfected hepatocytes, which may alleviate the liver damage associated with HBV infection [92]. Furthermore, as this review has discussed, TRAIL-mediated death in uninfected bystander cells accounts for a significant amount of pathology in many viral infections. Thus, the use of targeted therapeutics for the inhibition of TRAIL-mediated apoptosis in both infected and uninfected cells has been suggested as a novel strategy for limiting tissue damage during viral infection [25, 92, 95, 108, 121]. However, while inhibition of TRAIL-mediated apoptotic clearance of virally infected cells may decrease pathology, it could concomitantly promote persistence of viral infection through establishment of viral reservoirs.

Exploitation of TRAIL Signaling in HIV Treatment?

Exploitation of TRAIL signaling to promote TRAIL-induced apoptosis may have therapeutic value in the treatment of HIV infection by promoting the death of cells which harbor latent HIV reservoirs. Indeed, leucine-zipper TRAIL and agonistic anti-TRAIL antibodies [114] or autologous activated NK cells expressing TRAIL [167] induced *in vitro* apoptosis of macrophages and lymphocytes from HIV-infected patients, resulting in reduced viral burden following limiting dilution microculture. In all cases tested TRAIL treatment of cells led to reduced viral burden, even to undetectable levels, whereas untreated cells produced large amounts of both HIV RNA and p24 antigen [114, 167].

We recently completed a study in which recombinant TRAIL reduced HIV viral burden, even in lymphocytes collected from HIV-infected patients with a suppressed viral load. Moreover, treatment with recombinant TRAIL had no adverse effect on either the quantity or function of immune cells from these patients, suggesting that there is not a significant level of bystander death in uninfected cells. These data suggest that TRAIL treatment may be an important adjunct to antiretroviral therapy, perhaps by inducing apoptosis in cells with latent HIV reservoirs. The results of our quantitative and functional assays in lymphocytes from infected patients supplement an earlier observation that treatment with recombinant TRAIL did not induce apoptosis in macrophages and peripheral blood lymphocytes collected from uninfected donors [114]. Furthermore, these results are consistent with a growing body of preclinical data which have not shown significant toxicity with use of recombinant untagged TRAIL, as discussed in the next section.

These data challenge suggested models that TRAIL promotes bystander death of uninfected cells in HIV-infected patients, which have not yet been definitively tested with antagonistic anti-TRAIL antibodies to show that TRAIL inhibition abrogates apoptosis in uninfected cells. Nonetheless, such models are not mutually exclusive with our new data and previous observation that uninfected macrophages and lymphocytes do not die following treatment with leucine-zipper TRAIL [114]. Although TRAIL may account for a degree of bystander killing of uninfected CD4⁺ T cells in patients with unsuppressed replication, it does not preclude a therapeutic role for TRAIL in patients with suppressed viral replication. The HIV envelope protein gp120 promotes acquired sensitivity to TRAIL-mediated apoptosis in T cells through upregulation of TRAIL-R1 and TRAIL-R2 [109]. Since infected cells have necessarily contacted gp120, all such cells would be predicted to have enhanced TRAIL sensitivity. In the setting of suppressed viral replication, very few uninfected cells should maintain TRAIL sensitivity due to an absence of ongoing gp120 induction of TRAIL-R1 and TRAIL-R2. Consequently, exogenous TRAIL might selectively target and kill those infected cells which harbor latent HIV reservoirs. Minimal bystander death may still occur,

not unlike that which occurs as a side effect from cancer chemotherapy, which if proven negligible in preclinical and clinical trials would not be expected to limit the therapeutic potential of TRAIL in the treatment of HIV infection.

TOXICITY OF TRAIL-BASED THERAPEUTICS

As summarized above, the clinical trials with agonistic anti-TRAIL-R antibodies demonstrated that treatment is well tolerated with mild side effects in a minority of patients. A phase I clinical trial with HGS-ETR1 documented only mild (grade 1 or 2) adverse events such as fatigue, fever, and myalgia and no clinically significant hematologic toxicity [160]. Moreover, minimal toxicity was measured in subsequent phase II trials with HGS-ETR1 [1, 41]. Clinical trials with HGS-ETR2 have documented limited toxicity at a lower dose (10 mg/kg IV every 21 days), but more significant toxicity at higher doses (20 mg/kg IV every 21 days) [1]. One patient receiving the higher dose developed transaminitis (grade 4), and hyperbilirubinemia (grade 4) probably related to HGS-ETR2, before death from acute renal failure which was considered as possibly related to the treatment [1]. However, the patient also developed sepsis (considered unrelated to HGS-ETR2) which may have exacerbated the severity of the acute renal failure [1]. Three additional patients receiving the higher dose of HGS-ETR2 developed transaminitis (grade 4) or hyperamylasemia (grade 3) [1, 41].

Studies regarding the toxicity to normal tissues following treatment with soluble TRAIL have been a source of great debate, which warrants review of preclinical and clinical trials of TRAIL in this section. The issue itself was rigorously reviewed, with the authors concluding that given the limitations of data on TRAIL toxicity, “it is also important that preclinical and clinical development of this agent not be abandoned prematurely” [151]. Early preclinical investigation with soluble TRAIL was promising. In contrast to hepatotoxicity following treatment with either TNF- α [168] or agonistic antibodies to the FasL receptor [169], no toxic effects to normal tissue were measured following administration of soluble TRAIL in murine models [71]. Moreover, administration of soluble TRAIL to nonhuman primates produced no toxicity in either cynomolgus macaques or chimpanzees [144, 154, 155], which share 84–99% and 97–99% extracellular protein sequence identity in TRAIL-R between humans, respectively [1].

The initial excitement regarding the limited toxicity of soluble TRAIL to normal tissues was tempered by a study which showed that more than 60% of human primary hepatocytes undergo apoptosis within 10 hours of treatment with polyhistidine-tagged soluble TRAIL [12]. Moreover, the findings confirmed previous studies by showing that treatment with polyhistidine-tagged soluble TRAIL was not toxic to hepatocytes from mice or nonhuman primates, suggesting that preclinical studies with such models may be inadequate due to the unique sensitivity of human hepatocytes [12, 151].

Since the report of toxicity to primary human hepatocytes (PHH) following treatment with polyhistidine-tagged soluble TRAIL, further insight into this troublesome finding has been gained through the study of alternative versions of soluble TRAIL. Polyhistidine-tagged soluble TRAIL is unable to bind zinc, leading to production of an inactive form of TRAIL through formation of disulfide bonds between monomers in the TRAIL homotrimer [154]. However, untagged, zinc-replete soluble TRAIL was not toxic *in vitro* to hepatocytes from cynomolgus monkeys or humans [154]. This was confirmed *in vivo* by the absence of toxicity to transplanted human hepatocytes in a mouse xenograft model following treatment with untagged soluble TRAIL [170]. A subsequent study confirmed a relationship between exogenous sequence tags and soluble TRAIL toxicity, showing that three tagged versions of TRAIL were toxic to PHH, whereas untagged TRAIL was not [157]. Similar toxicity following treatment with tagged versions of soluble TRAIL, but not untagged versions, has

also been observed in human keratinocytes [171, 172] and human astrocytes [11, 155, 173]. Excessive oligomerization of soluble TRAIL due to sequence tags and poor zinc optimization, rather than the sequence tags alone, may account for the toxicity of tagged soluble TRAIL to normal tissues [154, 157]. Indeed, the addition of 5 mM dithiotreitol to the protein purification protocol, resulted in the oligomerization of untagged soluble TRAIL into hexamers and monomers which were toxic to human esophageal epithelial cells [174]. Based on these studies it is now widely hypothesized that tagged versions of soluble TRAIL more readily form highly-oligomerized aggregates which enhance toxicity to normal tissues through enhanced multimerization of TRAIL-R, thus surpassing a higher threshold for apoptosis activation in normal cells [1, 35, 44, 55, 154]. For these reasons, as well as the concern that tagged versions of soluble TRAIL are more likely to be immunogenic in patients [35], untagged soluble TRAIL has emerged as the favored version for clinical trials [35, 151] which are currently in progress [1, 14, 175].

Certain issues regarding the use of soluble TRAIL in preclinical and clinical trials continue to require further investigation. First, an important point for consideration in the design of future studies relates to selection of appropriate *in vitro* and *in vivo* models. Despite being toxic to cultured PHH, polyhistidine-tagged soluble TRAIL was not toxic to hepatocytes from rats, mice, and nonhuman primates [12, 155]. Making the situation more complicated, normal human cells express variable levels of TRAIL sensitivity. For instance, PHH are sensitive to tagged versions of TRAIL at day 1 of *in vitro* culture, but become resistant to TRAIL at day 4 of culture [157]. Additionally, fetal astrocytes are TRAIL-resistant [176, 177], but adult astrocytes are TRAIL-sensitive [11, 173]. To avoid additional confusion and limits to progression of the field, model systems will need to be carefully considered in the context of these and similar issues. Second, therapeutic manipulation of TRAIL signaling may have toxicities that have not yet been fully described. Of potential concern, treatment with TRAIL has been shown in one study to induce survival and proliferation of TRAIL-resistant cancer cells [178]. In TRAIL-resistant cells, the predominant effect of TRAIL receptor engagement may be activation of NF- κ B which promotes tumor invasion and metastases [179]. Furthermore, TRAIL has also been shown to promote the proliferation and migration of normal cells such as vascular smooth muscle [180] and endothelial cells [181]. Thus, while the fear of TRAIL's potential hepatotoxicity has largely subsided as the result of further investigation, much work remains for identifying and circumventing other undesired effects of therapeutic manipulation of TRAIL signaling.

CONCLUSION

The complete and precise physiologic role of TRAIL has been and continues to be a source of fruitful investigation and debate. However, the preponderance of data shows that TRAIL plays an essential role in the innate immune response to viral infection, our knowledge of which continues to expand and evolve in new directions. Much has been learned regarding the efficacy and toxicity of TRAIL-based therapeutics as novel treatments for cancer, and data from these studies will hopefully accelerate the deployment of novel, TRAIL-based therapeutics in the management of infectious diseases. Additionally, given the multifaceted role of TRAIL in viral infectious diseases, further preclinical studies are required in order to best determine if the therapeutic goal is induction or downregulation of TRAIL-mediated apoptosis for optimal management of any given viral infection. Given the diverse physiologic role of TRAIL and the experience from its use as a cancer therapeutic, clinical trials exploring TRAIL-based therapeutics will need to be cautiously and meticulously designed. However, despite this caution, the clear physiologic importance of TRAIL in the innate immune response to viral infection mandates further specific clinical investigation of this role.

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Fig. 1.
Apoptotic death of cells infected with HIV.

Fig. 2.
Model of HIV-induced bystander death of uninfected cells.

Table 1

The Role of TRAIL in the Immune Response to Viral Infection and in Viral Pathogenesis

Protective Role of TRAIL-mediated Apoptosis Through the Clearance of Infected Cells		
Pathogen	Mechanism	References
Human immunodeficiency virus	Increased expression of TRAIL-R1, TRAIL-R2, and soluble TRAIL	109, 110
Cytomegalovirus	Increased expression of TRAIL-R1 and TRAIL-R2	7, 101
Hepatitis B virus	Increased expression of TRAIL-R1, TRAIL-R2, and TRAIL	25, 43
Hepatitis C virus	Increased expression of TRAIL-R1 and TRAIL-R2	24, 93
Respiratory syncytial virus	Increased expression of TRAIL-R1, TRAIL-R2, and TRAIL	94, 106
Reovirus	Increased expression TRAIL-R1, TRAIL-R2, and soluble TRAIL	95
Hantaan virus	Increased expression of TRAIL and soluble TRAIL	96
Encephalomyocarditis virus	Increased expression of TRAIL	90
Measles virus	Increased expression of TRAIL	102, 103
Ebola virus	Increased expression of TRAIL	107, 108
Pathogenic Role of TRAIL-mediated Apoptosis in Viral Dissemination and Immune Escape		
Pathogen	Mechanism	References
Adenovirus	Adenovirus E1A protein sensitizes cells to TRAIL-mediated apoptosis	97
Human papilloma virus (HPV)	HPV E7 protein sensitizes cells to TRAIL-mediated apoptosis	98
Human T-cell leukemia virus (HTLV)	HTLV Tax oncoprotein sensitizes cells to TRAIL-mediated apoptosis	99
Influenza virus	Promotes NF- κ B induction of TRAIL	100