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Regulation of the human TRAIL gene

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TRAIL is a member of the TNF superfamily that induces tumor-selective cell death by engaging the pro-apoptotic death receptors DR4 and DR5. The antitumor potential of the TRAIL pathway has been targeted by several therapeutic approaches including recombinant TRAIL and TRAIL-receptor agonist antibodies among others. Interest in sensitizing tumor cells to TRAIL-mediated apoptosis has driven investigations of TRAIL-receptor gene regulation, though regulation of the TRAIL gene has been less studied. Physiologically, TRAIL serves as a pro-apoptotic effector molecule in the immune surveillance of cancer that is conditionally expressed by immune cells upon stimulation via an interferon-response element that was identified in early studies of the TRAIL gene promoter. Here, we map the TRAIL gene promoter and review studies of TRAIL gene regulation that involve several modalities of gene regulation including transcription factors, epigenetics, single-nucleotide polymorphisms and functionally distinct isoforms.

Introduction

TNF-related apoptosis-inducing ligand (TRAIL) was initially identified by its sequence homology with other tumor necrosis factor (TNF) family members.[1,2] TRAIL has received considerable attention, primarily due to its tumor-selective apoptosis-inducing capability demonstrated in several human cancer cell lines.[3] TRAIL is expressed in a variety of human fetal and adult tissues including the spleen, thymus, prostate, small intestine and placenta.[1] Contrary to other TNF-family members, membrane-bound TRAIL is conditionally expressed in immune cells such as natural killer (NK) cells, B cells, monocytes and dendritic cells following cytokine stimulation.[4-7] Intracellular stores of TRAIL have also been found in polymorphonuclear neutrophils[8-12] that are released after a variety of stimuli.[9,13,14]

At physiological conditions, TRAIL is capable of binding to four distinct transmembrane receptors in humans: the proapoptotic death receptors DR4 and DR5 or the two decoy receptors DcR1 and DcR2. Both TRAIL and its receptors form homotrimers in a binary complex upon ligand binding.[15,16] In mice, TRAIL-R is the only cognate death receptor.[17] TRAIL binds to two decoy receptors, DcR1[18-20] that lacks an intracellular domain and DcR2[21-23] that contains a truncated intracellular domain. The two decoy receptors compete for TRAIL binding with the death receptors at similar binding affinities.[19,23] Additionally, TRAIL binds the soluble receptor osteoprotegerin that negatively regulates osteoclastogenesis and bone resorption, though the interaction is much weaker than that of the other TRAIL receptors.[24] The X-ray crystallographic structures of trimeric soluble TRAIL reveal a single zinc atom bound between the three monomers that is important for the integrity and activity of TRAIL (**Fig. 1**).[15,16,25-27] Upon binding TRAIL, the two human proapoptotic death receptors DR4[18] and DR5[3,21,28-30] initiate cell death signaling through colocalization of their intracellular death domains (DD) that occurs after ligand binding (**Fig. 2**).[31]

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TRAIL Signaling

Apoptotic signaling. Upon binding to TRAIL, the colocalized DDs of DR4 or DR5 recruit Fas-associated death domain (FADD) and procaspase-8 to form the death inducing signaling complex (DISC). Capase-10 is also recruited to this DISC and is activated at the same rate as caspase-8.[32-34] Mice lack a homolog of caspase-10, suggesting that capase-8 and caspase-10 may be functionally redundant. However, the ability of these two caspases to substitute for each other in TRAIL-mediated apoptosis in mammalian cells is unclear due to conflicting reports. The anti-apoptotic protein cellular FLICE-like inhibitory protein (c-FLIP) can also be recruited to DISC to inhibit binding activation of capase-8 and -10 by directly competing for binding to FADD.[35,36]

At the DISC, procaspase-8 is activated by autocatalytic cleavage to yield caspase-8, which can cleave the effector caspases-3, -6 and -7 to induce apoptosis by the intrinsic death pathway. Cells that undergo cell death via this pathway are known as type I cells. Activation of caspase-8 in type II cells, however, is not sufficient to trigger the caspase cascade. In type II cells, caspase-8 cleaves Bid to form tBid, which primarily interacts with Bax and Bak at the mitochondrial membrane to promote cytochrome c release.[37,38] In the cytosol, cytochrome c binds to apoptotic peptidase activating factor 1 (Apaf-1) and caspase-9 to form the apoptosome, which initiates the caspase cascade. Permeabilization of the mitochondrial membrane also releases Smac/DIABLO, which inhibits X-linked inhibitor of apoptosis protein (XIAP) to allow for complete activation of the effector caspases.[39-42]

Physiological Roles for TRAIL

TRAIL is expressed on the surface of immune effector cells such as natural killer cells, macrophages, dendritic cells and cytotoxic

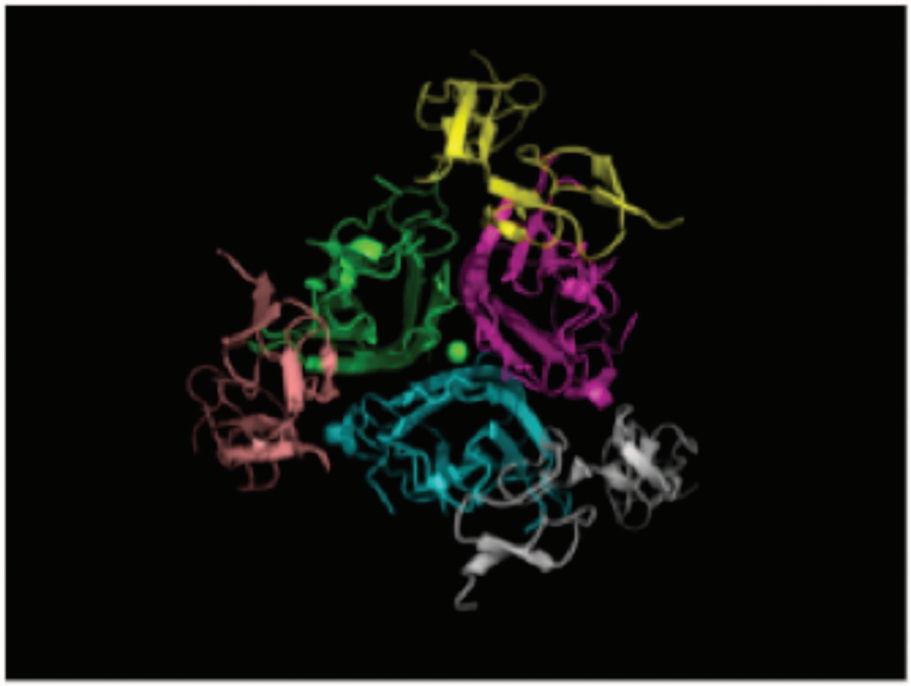


Figure 1. Crystal structure of TRAIL:DR5 complex. Homotrimeric DR5 (gray, light pink,and yellow) bound to homotrimeric TRAIL (cyan, green and magenta). A single zinc atom (green) is found in the center of the complex. The figure was generated using PyMOL software with Protein Data Bank (PBD) accession number 1D4V.[26]

T cells in response to cytokines, particularly interferon-gamma that possesses a response element in the TRAIL gene promoter.[43] TRAIL-knockout mice or zebrafish do not display any gross developmental defects,[25,44] though the mice are more susceptible to carcinogen-induced sarcomas and metastasis.[44] TRAIL-R knockout mice develop normally but have an enlarged thymus and decreased radiation-induced apoptosis in several tissues.[45] TRAIL-knockout mice also do not induce thymocyte apoptosis, which is deregulated in autoimmune diseases.[46] Clinical observations have also suggested a role for TRAIL in autoimmune diseases as patients with systemic lupus erythmatosus or multiple sclerosis have elevated serum levels of soluble TRAIL.[47,48] TRAIL has also been implicated in cardiovascular problems such as atherosclerosis[49,50] and diabetes.[51]

Regulation of the Human TRAIL Gene

The human TRAIL gene is tightly regulated, potentially due to its considerable apoptotic potential and its involvement in some immune responses. The first report to clone the TRAIL gene promoter characterized a ~1.6 kB promoter region, which is 97 bp upstream of the start of translation.[52] This report identified several putative transcription factor binding sites in the TRAIL gene promoter: NHF3, GKLF, AP-1, CEBP, NFAT, GATA and interferon-γ-activated sequence (GAS), GSP1, GSP2 and GSP4. Sequential deletions of the human TRAIL gene promoter driving luciferase reporters in Caco-2 cells suggested that the regions between -1371 to -819 and -165 to -35 contain critical elements that are responsible for basal TRAIL gene transcription. Increased TRAIL gene transcription has been reported in response to several cytokines and in some cases have been ascribed to transcription factors (**Fig. 3**) with consensus binding sequences found in the TRAIL gene promoter (**Fig. 4**).

Interferons. Interferons are cytokines that are intimately involved in the immune response in a variety of response by causing immune cell recruitment and/or activation by several mechanisms. Luciferase reporter experiments found that interferon-γ (IFN-γ) was capable of upregulating TRAIL gene promoter activity by 2-fold in a region between -165 and -35,[52] which provided a molecular explanation for a previous report that found rapid induction of TRAIL following incubation with IFN-γ.[5] STAT1 and IRF1 are thought to directly mediate the effects of IFN-γ on the TRAIL promoter. IFN-γ has also been shown to induce FasL- and TRAIL-dependent apoptosis in lung cancer cells[53] and is responsible for IL18- and TLR3-induced TRAIL expression in NK cells.[54]

There are reports that suggest type I interferons (IFN-α and -β) induce the TRAIL gene more strongly that IFN-γ.[43] IFN-α and -β potently induce TRAIL in $CD4^+$ and $CD8^+$ peripheral blood T cells following CD3-stimulation as well as Jurkat T cells.[55] IFN-α has also been shown to induce TRAIL in macrophages[56] and in lymphoma cells in a JNK-dependent manner.[57] IFN-β induces TRAIL in colorectal cancer cell lines by a Stat-1-dependent mechanism.[58] Taking the evidence together, IFN- α, -β, -γ have been shown to induce TRAIL gene transcription, though the robustness of TRAIL induction among them seems to be context-dependent.

NFAT. The human TRAIL gene is also positively regulated by the transcription factor NFAT, which is activated by calcineurin-mediated dephosphorylation that occurs during T-cell activation. Wang et al. investigated the role of NFAT regulation of the TRAIL gene promoter due to the two putative binding sites they previously noted along with three other newly found potential NFAT binding sites.[52,59] Among the five NFAT family members, NFATc1 was by far the most potent positive regulator of TRAIL gene transcription. Interestingly, NFAT-dependent TRAIL gene upregulation was not affected by deletion of their putative binding sites in TRAIL gene promoter luciferase reporters but instead was abrogated by deletion of the -165 to -35 region. Chromatin-immunoprecipitation and electrophoretic mobility shift assay (EMSA) experiments revealed that NFATc1 antagonizes SP-1 binding to the TRAIL gene promoter. This reports highlights a mechanism that immune cells such as cytotoxic T cells might

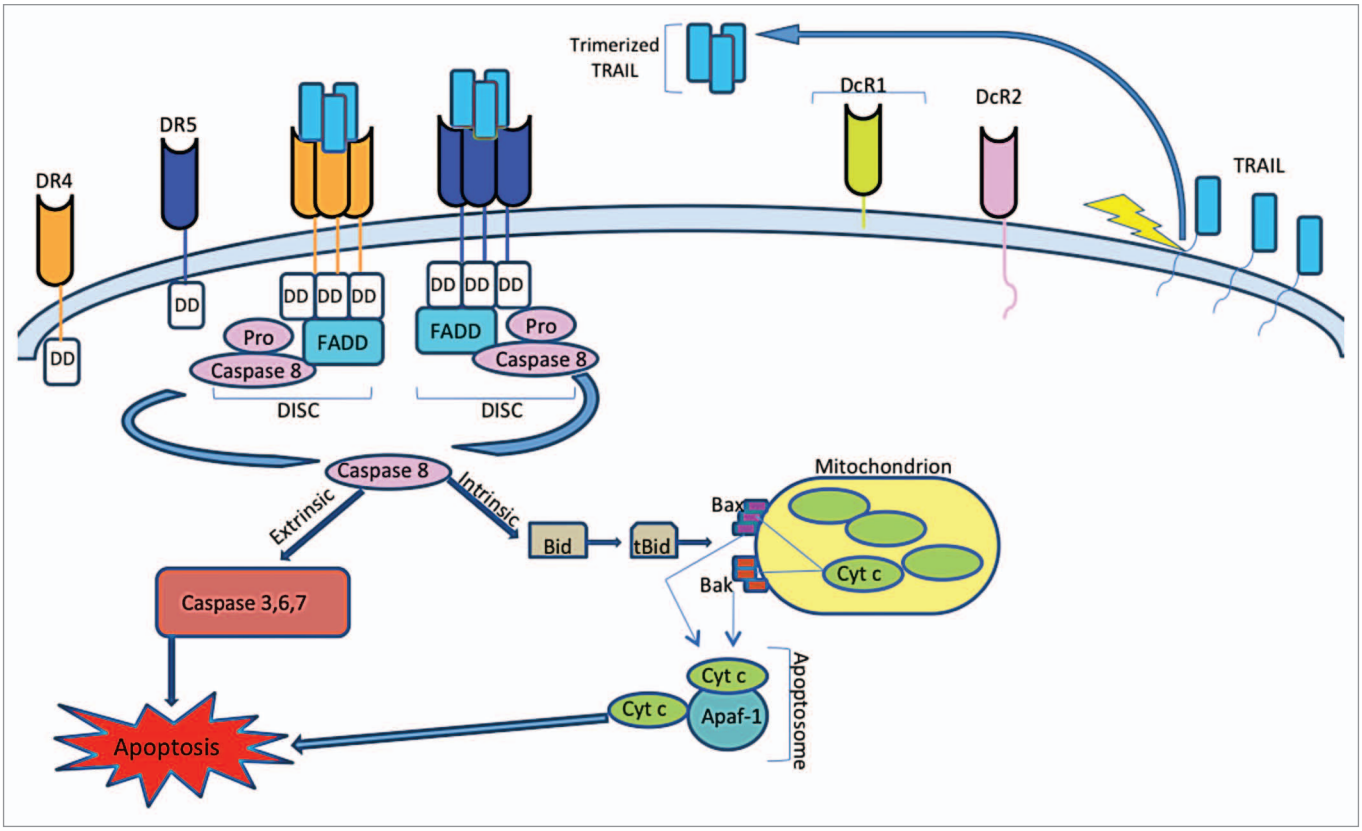


Figure 2. Apoptotic signaling induced by TRAIL. TRAIL initiates cell death by binding to the proapoptotic death receptors DR4 or DR5 that colocalizes their intracellular death domains. This clustering recruits the Fas-associated death domain (FADD) and pro-caspase-8 that results in its activation through autocatalytic cleavage. In type I cells, activate caspase-8 directly activates caspases-3, -6 and -7 to trigger the extrinsic cell death pathway. In type II cells, active caspase-8 cleaves Bid to a truncated form, tBid, which subsequently interacts with proapoptotic Bcl-2 family members Bax and Bak. This interaction leads to permeabilization of the mitochondrial membrane and release of cytochrome c. Cytosolic cytochrome c then combines with Apaf-1 and ATP to form the apoptosome that activates caspase-9 to trigger apoptosis through the caspase cascade.

utilize to upregulate TRAIL and underscores the need to directly test binding sites to accurately delineate transcriptional regulation. These observations also suggested that SP-1 might negatively regulate the TRAIL gene promoter.

SP-1. The study that described NFAT-mediated regulation of the TRAIL promoter also found that SP-1 represses TRAIL gene transcription, at least in human intestinal cells.[59] However, a recent study reported a positive regulation of TRAIL gene transcription by SP-1 in vascular smooth muscle cells that appears to involve SP-1 phosphorylated at Thr453.[60] Interestingly, phosphorylation of SP-1 at Thr453 and Thr739 by p38 mitogen-activated protein kinase appears to be essential for its positive regulation of the VEGF gene.[61] Future studies need to further examine if these differences are due to the difference in cell type or if this phosphorylation event modulates SP-1-mediated TRAIL gene regulation. The mechanism of HDACi-induced upregulation of TRAIL gene transcription appeared to involve SP-3.[62]

NFκB. Inhibition of the prosurvival transcription factor NFκB in Jurkat T cells and primary T lymphocytes revealed that NFκB positively regulates TRAIL gene expression in a manner that depends on the NFκB binding site 1[63] (**Fig. 4**). NFκB also upregulates FasL and together, these proapoptotic ligands may be responsible for tumor-cell elimination in immune surveillance and/or attenuation of T-cell activation to prevent autoimmunity. NFκB is also responsible for constitutive TRAIL expression in human T-cell leukemia virus type I (HTLV-1)-induced leukemia, though other concomitant effects of NFκB seem to cause resistance to TRAIL-mediated apoptosis.[64] In accordance with a positive regulatory role for NFκB with respect to the TRAIL gene, the prostaglandin 15d-PGJ2 represses TRAIL gene transcription by inhibiting the binding of NFκB to the NFκB binding site 1 (**Fig. 4**). This study also identified the transcription factor HSF-1 as a negative regulator of the TRAIL gene that is involved in 15d-PGJ2-induced repression of TRAIL gene transcription. This negative regulation of HSF-1 is completely dependent on its DNA binding domain and is in contrast to its positive regulation of the FasL gene.[65] Cnb, the regulatory subunit of calcineurin, was recently shown to active NFκB-mediated TRAIL expression through direct binding to the integrin CD11b.[66]

P53. Two potential p53 binding sites in the TRAIL gene promoter were identified following the observation that p53-inducing chemotherapies such as 5-fluorouracil and doxorubicin elevated TRAIL promoter activity.[67] One of these binding sites at the -630 position was shown to mediate p53-induced TRAIL promoter activity using luciferase reporter assays. Radiation has also been reported to induce TRAIL expression and it has

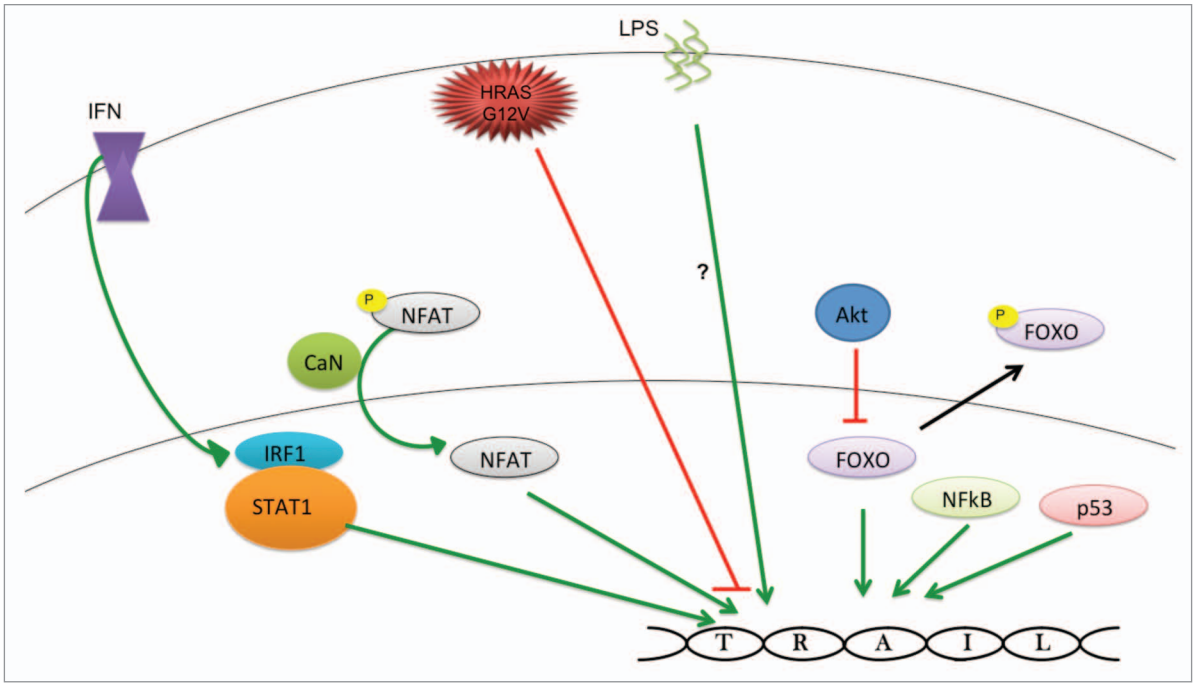


Figure 3. Molecules that alter human TRAIL gene transcription. Interferons (IFN) activate TRAIL gene transcription through ISRE and IRFE sequences in the promoter region. Mutant HRAS (G12V) silences TRAIL gene expression through hypermethylation of CpG islands in the TRAIL gene promoter. Green arrows indicate activating relationships and the red lines indicate inhibitory relationships.

been hypothesized that TRAIL mediates the bystander effects observed following radiation.[68,69] The role of p53 in radiation-induced TRAIL expression should be explored since it is well accepted that ionizing radiation robustly induces p53.

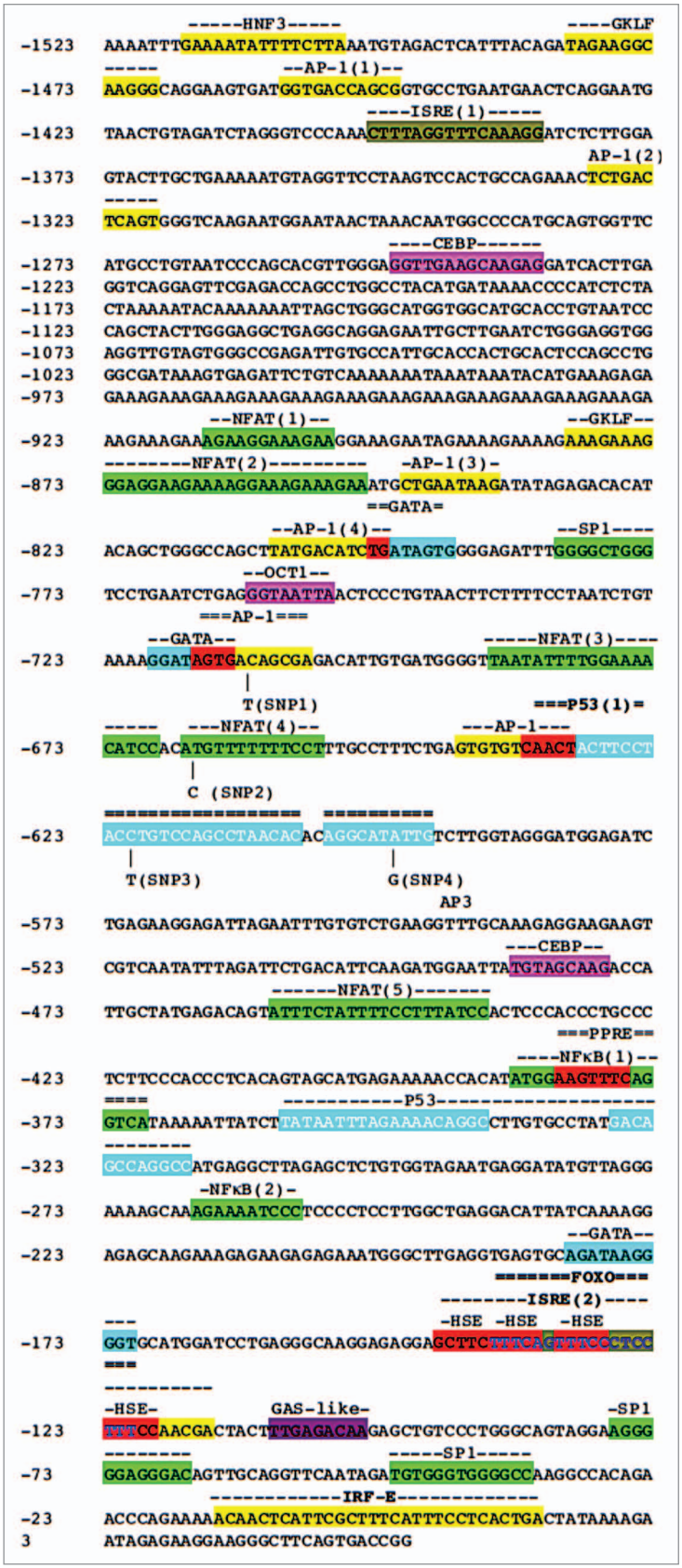
FOXO. Overexpression of Foxo3a in prostate cancer cells was found to induce TRAIL gene transcription by gene expression profiling.[70] In silico analysis revealed a binding site in the TRAIL gene promoter between -121 and -138 that was validated by luciferase reporter construct mutations and EMSAs to be completely responsible for Foxo3a-induced TRAIL gene promoter activity. This study also revealed that TRAIL expression is significantly decreased in metastatic prostate cancer. Foxo3a-dependent TRAIL upregulation has been recently described as the apoptotic mechanism responsible for memory B-cell loss that results from chronic HIV infection.[71]

Unexplored binding sites. Clearly there are several putative transcription factor-binding sites within the TRAIL gene promoter that have been unexplored. It is worth noting that only a few of the examined binding sites for a given transcription factor have turned out to be functionally important, as in the case of NFκB, AP-1 and SP-1, which have multiple putative binding sites in the TRAIL gene promoter. For example, Oct-1 is involved in regulating several housekeeping genes and has a putative binding site on the TRAIL promoter. Interestingly, HDACi have been found to induce Gadd45 expression through Oct-1.[72] This observation along with the report that HDACi induces TRAIL gene transcription suggests that the direct examination of Oct-1 binding to the TRAIL gene promoter may be worth further investigation. The role of the heat shock elements in the proximal region of the TRAIL gene promoter may also be worth investigation as heat shock has been linked to protection from TRAIL-mediated cell death.[73]

The MAPK pathway. Cells transformed with $HRAS_{G12V}$ were reported to have silenced expression of the TRAIL gene due to hypermethylation of CpG islands in the TRAIL gene promoter that lie ~2,000 bp upstream of the start of transcription.[74] Despite this silencing, TRAIL could still be induced by IFN-γ in these transformed cells and the silencing could be reversed with decitabine, a DNA methyltransferase inhibitor. Oncogenic mutations in KRAS during colon cancer progression are a common event in colon cancer.[75-77] This finding may explain the silencing of TRAIL expression that has been noted in colon cancer, particularly during the progression from adenoma to carcinoma.[78] Interestingly, oncogenic RAS sensitizes transformed cells to TRAIL-mediated apoptosis, potentially through MEK-dependent upregulation of DR4 and DR5.[79] Thus, concomitant silencing of TRAIL expression may be required to prevent induction of TRAIL-mediated apoptosis during Ras transformation that commonly occurs in tumorigenesis.

Other inducers. A recent report found that pigment epithelium-derived factor (PEDF) induced the expression of TRAIL on the surface of macrophages.[80] Further analysis revealed that PEGF also induces peroxisome proliferator-activated receptor-gamma (PPARγ), which binds to the TRAIL promoter to upregulate transcription at a PPAR-response element (PPRE). This represents yet another mechanism utilized by immune cells to induce the expression of TRAIL. Other molecules have been reported to induce TRAIL gene transcription but the underlying direct transcriptional mechanism has not been elucidated. Lipopolysaccharide (LPS), which is a component of

Figure 4. Sequence analysis of the human TRAIL gene promoter. Putative binding sites indicated by highlights above the appropriate sequences. Nucleotides contained in two or more putative binding sites are highlighted in red. Binding sites that have been empirically demonstrated to affect TRAIL promoter activity in experiment are bolded. Vertical lines below the sequence indicate SNPs. TRAIL sequence obtained from accession number AF178756.



gram-negative bacteria, has been reported to induce TRAIL gene transcription at higher concentrations,[81] though an early report did not observe TRAIL-induction by LPS at lower doses.[5]

Regulation of TRAIL activity by isoforms. The human TRAIL gene spans ~20 kb and contains five exons and four introns that contain typical splice acceptor-AG/GT-splice donor consensus sites at their boundaries.[43,82] The first exon encodes for the 21 amino acid transmembrane domain and the 17 amino acid cytoplasmic domain. Exons 4 and 5 encode for the amino acids in the extracellular domain that are responsible for the interaction of TRAIL with its receptors. Exon 5 also encodes for the C-terminal amino acids along with containing the 3'-UTR and poly-A tail.

TRAIL is well known for its potent and cancer-selective apoptotic activity. However, it seems that this activity is unique to only one specific isoform of TRAIL among the nine variants that have been reported to date (**Fig. 5**). The first report of TRAIL isoforms identified three variants that involved variable inclusion of exons 2 and 3: the full length TRAILα, TRAILβ that lacks exon 3, and TRAILγ that lacks exons 2 and 3.[83] Computational analysis of exons 2 and 3 revealed that both exons were flanked by consensus splice donor and splice acceptor sequences that are involved in post-translational alternative splicing. Interestingly, TRAILα and TRAILβ where localized to the cytoplasm whereas TRAILγ was associated with the nuclear and cell surface membrane. Sequence analysis of TRAIL mRNA in granulosa tumor cells identified TRAILδ, which lacks exons 3 and 4.[84] The truncated TRAIL isoforms do not induce apoptosis like the full-length TRAIL (TRAILα) and it has been suggested that these variants are negative regulators of their full-length counterpart. No TRAIL variants other than the full length TRAIL have been reported in murine cells.

Recently, seven alternatively spliced TRAIL truncated variants were identified that were incapable of potentiating apoptosis: AK, E2, E3, E4, DA, BX424 and BX439.[85] All of these isoforms contain common N-terminal sequences and possess the transmembrane helix but vary in the C-terminal region. The DA isoform lacks exon 3 and encodes for the same protein as TRAILβ and BX424 lacks exons 3 and 4, yielding the same protein as TRAILδ. BX439 completely lacks exons 2–4 but possesses the same exons 1 and 5 as the full length TRAIL. AK and DA contain a unique exon not shared by any other reported isoforms. E2, E3 and E4 contain exons 1–2, 1–3 and 1–4, respectively, with an extended sequence at C-terminus. All of these variants, however, activated NFκB and the authors note the possibility that truncated TRAIL may have intracellular activity. Future studies should directly

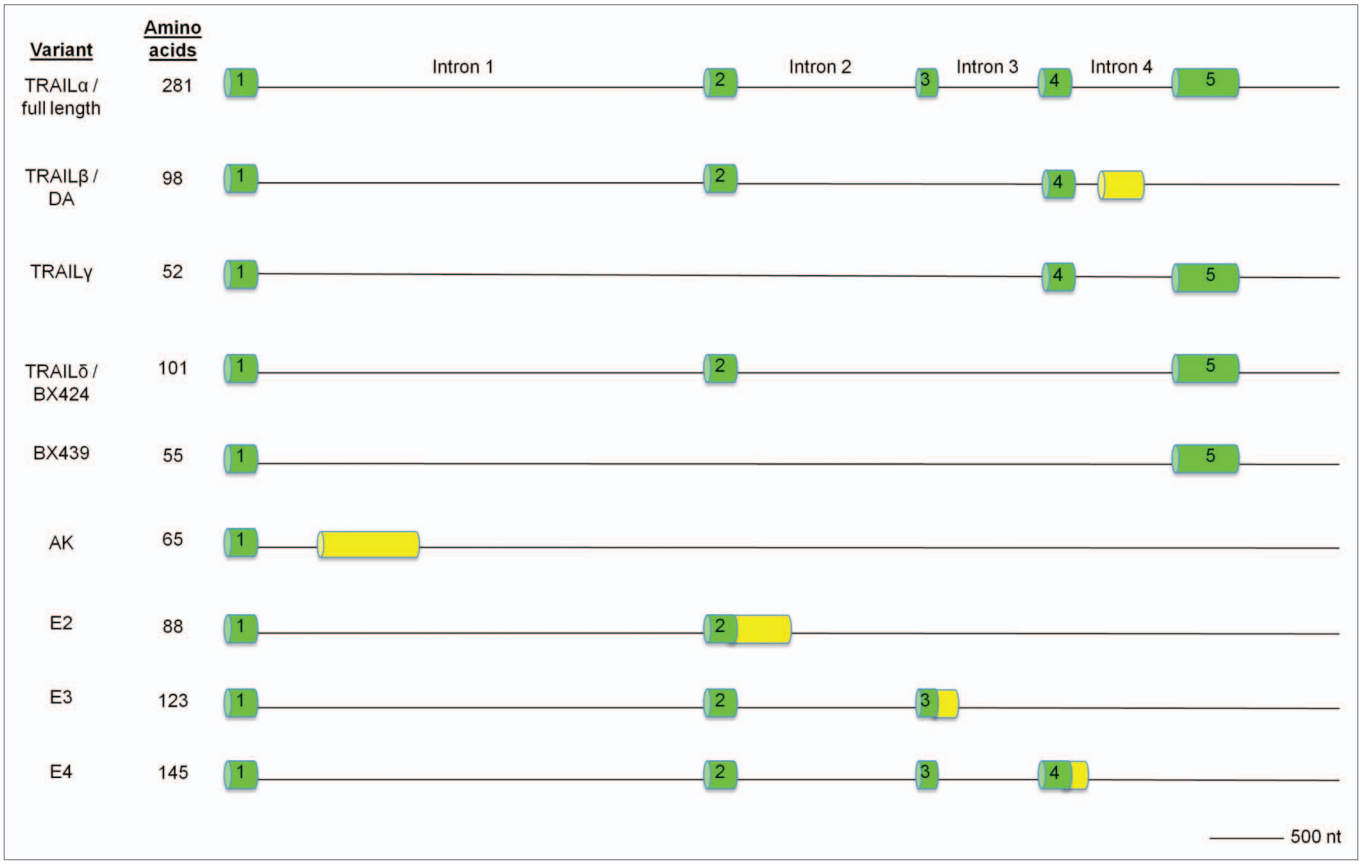


Figure 5. Genomic structure of human TRAIL variants. Exonic sequences of the full-length TRAIL are shown in green whereas novel sequences are shown in yellow.

examine the ability of these various TRAIL isoforms to bind to TRAIL receptors through in vitro studies.

The abundance of these isoforms varied significantly across the tested cancer cell lines with THP-1 human leukemia cell line and BT-325 human glioma cell line expressing most of these variants. A notable exception among the cell line panel was the human colon cancer cell line HCT116 that only expressed the full-length isoform.

SNPs in the TRAIL gene. Due to the altered expression of TRAIL in various disease settings, there have been multiple efforts to identify single nucleotide polymorphisms (SNPs) in various patient populations. SNP analysis of peripheral blood samples found that having a T instead of a C at position -723 was significantly associated with sporadic breast cancer and decreased TRAIL mRNA levels (SNP1)[86] (**Figs. 1–4**). Luciferase reporter assays in cell lines indicated that this mutation from C to T indeed repressed TRAIL transcriptional activity. In silico analysis found that this mutation is predicted to create an SP-1 binding site. The authors propose that SP3 is negatively regulating this SP1 site, though future studies will need to validate the mutation-induced putative binding site and directly evaluate this possibility.

Another SNP analysis of the TRAIL gene promoter revealed four SNPs that were highly polymorphic in healthy individuals.[87] However, these SNPs were not significantly associated with changes in TRAIL mRNA levels or with multiple sclerosis as a diagnostic or prognostic marker. The authors of the study note that SNP(1) is in an AP1 binding site, though they do not comment on other binding sites predicted at the other SNP sites. Interestingly, both SNP3 and SNP4 each lie in p53 response element half-sites that was previously shown to be important for TRAIL gene upregulation in response to chemotherapy.[67] While these SNPs were not associated with basal TRAIL levels in this population, it would be interesting to determine if these SNPs affect p53-induced TRAIL gene expression and response in chemotherapy-treated cancer patients.

A SNP at the -716 position of the TRAIL gene promoter was identified but not associated with prostate cancer. Other TRAIL gene promoter SNP associations have been identified in other disease settings but have not been evaluated for its functional effects on TRAIL gene transcription such as -1525/-1595 in fatty liver disease.[88] SNPs have been identified in coding regions such as position 1595 in exon 5 being linked with multiple sclerosis.[89] A small cohort study of healthy volunteers found five SNPs in TRAIL exons: three in the 3'-UTR at 1525, 1588 and 1595 whereas the other two were in in exon 1 and two at positions 192 and 912.[90] These two polymorphisms in the coding region do not alter the encoded amino acid sequence. Another SNP study in bronchial asthma patients found five SNPs in the TRAIL gene with one SNP being in a coding region at 825 and five SNPs

being in the 3'UTR at 1053, 1202, 1438, 1501 and 1508.[91] Future studies should further investigate the functional effects of identified SNPs on TRAIL gene transcription and therapeutic response to chemotherapies.

TRAIL expression in disease and physiology. Altered expression levels of TRAIL been noted in several diseases relative to healthy controls. For instance, TRAIL mRNA levels are elevated in patients with multiple sclerosis.[92] Patients with systemic lupus erythematous or multiple sclerosis have elevated serum levels of soluble TRAIL.[47,48] These clinical observations support a critical role for TRAIL in preventing autoimmune disorders, which is in line with the observation that TRAIL-knockout mice cannot induce thymocyte apoptosis.[46] Breast cancer patients with brain metastases have downregulated TRAIL mRNA levels.[93] TRAIL gene expression silencing has also been noted in metastatic prostate cancer[70] and colon cancer.[78] A role for TRAIL has been implicated in particular types of cellular differentiation such as colonic epithelial cells through a reciprocal expression relationship with PKCε.[94] TRAIL-receptor signaling has also been implicated in the DNA damage response to radiation as well as the late effects of radiation.[45,95]

Conclusion

The role of TRAIL as an effector molecule in the immune system and its apoptotic potential is reflected in the regulation of the TRAIL gene. Regulation of the TRAIL gene appears tightly controlled by transcriptional mechanisms that respond to interferon stimulation or are involved in immune cell activation as well as transcription factors that are tumor suppressors such as p53 and Foxo3a. Assimilating our current knowledge of TRAIL gene regulation, it is clear that the regulation is multimodal and can be highly context-dependent. The emerging evidence on TRAIL isoforms and TRAIL gene SNPs add other layers of complexity to how cells can tune the TRAIL gene to alter its effects. Mapping transcription factor binding sites and SNPs in the TRAIL gene promoter revealed several overlapping sites that should be examined in future studies. A detailed understanding of TRAIL gene upregulation will be better defined how TRAIL is utilized by the immune system and how it is altered in diseases. Such studies also have the potential to yield drug targets that can harness the antitumor potential of TRAIL.

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