The Role of TRAIL/DRs in the Modulation of Immune Cells and Responses

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Abstract: Expression of TRAIL (tumor necrosis factor–related apoptosis–inducing ligand) by immune cells can lead to the induction of apoptosis in tumor cells. However, it becomes increasingly clear that the interaction of TRAIL and its death receptors (DRs) can also directly impact immune cells and influence immune responses. Here, we review what is known about the role of TRAIL/DRs in immune cells and immune responses in general and in the tumor microenvironment in particular.

Keywords: apoptosis; immune regulation; tumor; myeloid cells; lymphoid cells

1. Introduction

The ‘Tumor Necrosis Factor-Related Apoptosis Inducing Ligand’ (TRAIL, CD253, TNFSF10) is a member of the ‘Tumor Necrosis Factor Superfamily’ (TNFSF), along with other closely related ligands, like TNF and CD178 (FasL, CD95L) [1–4]. Although, TRAIL is a type II transmembrane protein, protease cleavage at the membrane can generate a soluble version. In humans, five receptors for TRAIL are known. DR4 (CD261, TRAIL-R1, TNFRSF10A) and DR5 (CD262, TRAIL-R2, TNFRSF10B) contain a functional intracellular death domain (DD) required for signaling. Depending on the particular signaling pathway utilized, these signals can lead to three different outcomes [1,2,4]. On the one hand, cell death can be induced either via caspase 8- and caspase 3-dependent apoptosis or by necroptosis in a caspase-independent manner. On the other hand, DR4/DR5 signals can support survival, cell migration, and proliferation. Details on the respective signaling pathways have been reviewed previously [2,5–7]. The other three receptors described in humans lack a functional death domain and are, therefore, considered decoy receptors. These include the membrane-bound DcR1 (CD263, TRAIL-R3, TNFRSF10C) and DcR2 (CD264, TRAIL-R4, TNFRSF10D), and the soluble osteoprotegerin (OPG, TRAIL-R5, TNFRSF11B), which also can bind RANKL (TNFSF11) [8]. In contrast to humans, mice only express three receptors, DR5, DcR1 (Tnfrsf23), and DcR2 (Tnfrsf22) [1,4].

Early work indicated that particular tumor cells are highly susceptible towards TRAIL-induced apoptosis, with little harm to healthy cells [1–4]. Due to its great potential as anti-tumor drug, much work on TRAIL and its receptors has been and still is devoted on its development for anti-tumor therapy [1,4,9,10]. In addition to the cancer cells and their surrounding stroma, the tumor microenvironment contains innate and adaptive immune cells that can recognize and destroy tumors. TRAIL expression by immune cells is one major mean by which immune cells can induce apoptosis of tumor cells. However, it becomes increasingly clear that TRAIL/DRs interaction can also directly
impact the function of immune cells in many ways. In this review, we will first outline what role TRAIL and its receptors can play in immune cells in general (Section 2) and will discuss some open questions (Section 3). Then, we will outline how these and other findings are relevant for the anti-tumor responses (Section 4).

2. Expression and Function of TRAIL/DRs in Immune Cells

2.1. Myeloid Cells

2.1.1. Neutrophils

Human blood-derived neutrophils constitutively express mRNA for TRAIL [11–13]. However, how much of the TRAIL can be found on the cell surface, if any at all, seems to depend on the donor [11–13]. It was suggested that TRAIL is rather pre-stored intracellular in granules [14–16] and that some of this pre-stored TRAIL is in the cleaved soluble form which could facilitate secretion [14,16]. Indeed, upon activation, human neutrophils upregulate TRAIL and secrete functional soluble TRAIL. This was observed most potently with IFNα and IFNβ [14,15,17,18], but also, to a lesser extent [13], with IFNγ [11,13,15]. Several other pro-inflammatory stimuli, like fMLP, IL-8, Hsp96 [15]; IL-17 [19]; the CD184-ligand SDF1 [20]; and the TLR3-ligand Poly I:C [11,13,14,17]; were shown to boost the TRAIL-release by human neutrophils. In contrast, no impact on the TRAIL expression of human neutrophils was reported for IL-1, G-CSF, GM-CSF, TGFβ, and the TLR3-ligand Poly I:C [11,13,14,17]. Conflicting data were reported for TNF and the TLR4-ligand LPS, with some reports finding either a boost of TRAIL on neutrophils [14,15,18], no effect [13,17], or even a down-regulation of TRAIL [11]. In mice, TRAIL is not expressed by neutrophils [21,22], but can be upregulated following IFNβ stimulation [23]. Interestingly, stimulation of mouse neutrophils with IL-6 and G-CSF induced a tumor-promoting N2 phenotype, characterized by TRAIL down-regulation [24,25], but TRAIL expression could be rescued by IFNγ or TNF [26].

Most studies reported expression of DR5 [11,12,17,20] and DcR1 [11,12,20,27–29] on human neutrophils, and only two reports show DR4 and DcR2 expression [20,29]. Importantly, the expression of DR4/DR5 on neutrophils tended to be lower than the expression of the decoy receptors DcR1/DcR2 [11,12,17,28,29]. Activation of human neutrophils with TNF or SDF1 [11,20] or of mouse neutrophils with IFNβ [23] increased the expression of DR4/DR5. In contrast, TNF stimulation [11] or ER stress [30] down-regulated DcR1/DcR2 on human neutrophils. In mice, the expression of DR5 was observed on neutrophils [28,31–33], but DcR1 and DcR2 were not detected in the one study that tested their expression [34].

In line with the expression of death receptors, most [20,23,28,29] but not all [17] studies indicated that freshly isolated neutrophils are not sensitive towards TRAIL-induced apoptosis. However, the neutrophils became sensitive following activation [11,20,23,29] or after aging [12,20]. Interestingly, upon such aging, senescent neutrophils upregulated CD184/CXCR4 [35] and became receptive to SDF1, which increased TRAIL-sensitivity, via upregulation of DR4 and DR5 [20]. This aided the migration of the senescent neutrophils to the bone marrow for apoptotic removal in the mouse model [20].

Functionally, most reports are in line with the interpretation that TRAIL/DR-activity is involved in the apoptotic removal of activated, stressed, or aged neutrophils in vivo. As neutrophils are major drivers of inflammation [36–38], their elimination usually limits the inflammation and the resulting tissue damage and promotes the resolution of the inflammation. Therefore, TRAIL-deficient mice displayed reduced neutrophil apoptosis, leading to increased neutrophil numbers and inflammation. This was noted during TLR-ligands induced sepsis [39], in the bleomycin model of lung fibrosis [21], and following Streptococcus pneumoniae infection of the CNS [31]. Consequently, the administration of soluble TRAIL or agonistic αDR5-antibodies increased neutrophil apoptosis, leading to ameliorated inflammation following Streptococcus pneumoniae infection [31] and during sepsis induced by bacteria [32,34] or TLR-ligands [39]. It was also observed in other systems that blocking of neutrophil apoptosis augments inflammation and tissue damage [40]. However, the TRAIL-sensitivity of activated
neutrophils was not seen in all models, as, for examples, following S. pneumoniae infection of the lung neutrophil-apoptosis was unaffected by the absence of TRAIL [41].

Additionally, the TRAIL produced by activated human neutrophils themselves could mediate cytotoxicity of TRAIL-sensitive tumors [13,14,17,42,43]. However, blood-derived human neutrophils of some tumor patients (squamous cell carcinoma [44]; B cell chronic lymphocytic leukemia [45]) expressed less TRAIL than healthy donors and IFNα-therapy in vivo enhanced TRAIL expression on neutrophils of chronic myeloid leukemia (CML) patients [18]. Besides tumor cytotoxicity, neutrophil-derived TRAIL was also shown to be involved in the resolution of inflammations by targeting macrophages. Neutrophil-derived TRAIL could induce apoptosis of alveolar and lung macrophages in S. pneumoniae infected mice [41]. This apoptosis of S. pneumoniae-infected macrophages supported the bacterial clearance in the airways and limited the inflammation and the ensuing tissue damage [41].

2.1.2. Monocytes and Macrophages

Freshly purified human blood monocytes have a basal level of intracellular TRAIL expression [11,46]. Conflicting data were reported for the surface expression of TRAIL on human blood monocytes; with two studies reporting no TRAIL-expression [46,47] and two studies showing expression [11,48]. In vitro generated human monocyte-derived macrophages express high levels of TRAIL intracellularly, but low levels on the surface [48]. TRAIL expression can be rapidly induced in human monocytes via IFNα [47,49–52] and IFNβ [53]. Furthermore, secretion of soluble TRAIL after IFNα stimulation has been reported for human monocytes [17]. In addition, installation of the IFNα-inducer BCG into the bladder of bladder cancer patients led to an increase in TRAIL expression on tumor macrophages [54]. For the treatment of human blood monocytes with LPS, increased TRAIL surface expression was detected after 24 h incubation [48], but not after 12 h [47]. Apart from that, PEDF, an anti-angiogenic and anti-inflammatory agent widely used in clinical trials for cancer treatment [55], induces TRAIL production by human monocyte-derived macrophages [56]. In contrast, exposure of human CD14+ monocytes to C-reactive protein (CRP) led to a down-regulation of TRAIL [57]. In mice, approx. 25% of peritoneal macrophages express TRAIL [58]. TLR2 (lipoteichoic acid), TLR3 (poly I:C) and TLR4 (LPS) ligands, but not a TLR9 ligand (CpG), induced TRAIL expression in murine macrophages [59]. Moreover, murine bone-marrow derived macrophages (BMDMs) treated with PEDF in vitro or tumor infiltrating macrophages from PEDF-treated mice upregulated TRAIL expression [56]. Chemically induced ER stress also led to upregulation of soluble TRAIL in a murine monocytic cell line and in primary mouse peritoneal macrophages [60].

Human peripheral monocytes and monocyte-derived macrophages express functional DR4 and DR5, with DR5 being expressed usually higher than DR4 [28,47]. In contrast, tissue resident macrophages have very low DR5 expression [28]. Although one study demonstrated surface expression of DcR1 in human peripheral monocytes [47], other studies reported that decoy receptors are barely expressed by monocytes [28,52]. Macrophages tend to express higher level of DcR1 compared to monocytes [28]. However, macrophages are heterogeneous with several subpopulations displaying different functional activities. Macrophages can differentiate into two main types in the presence of certain polarization factors when recruited into peripheral tissues [61]. Pro-inflammatory signals, like LPS and IFNγ treatment, polarize macrophages towards M1 or classically activated macrophages, that are cytotoxic, pro-inflammatory, and are potent in fighting tumors and pathogens. In contrast, anti-inflammatory cytokines, like IL-4, IL-10, and IL-13, induce M2 or alternatively activated macrophage, that play a role in immune suppression, tumor promotion, angiogenesis, and tissue remodeling [61]. Death receptors are differentially expressed on M1 and M2 type macrophages. M2-like tumor associated macrophages (TAMs) and M2 polarized THP-1 macrophages express more DR5 than M1 macrophages [28,62,63]. Consistently, agents that support M2 polarization enhance DR4 and DR5 expression on human monocytes and monocyte-derived macrophages [28]. Furthermore, inflammatory mediators such as IFNγ [47] and IFNα [52] can downregulate surface expression of DR5 on human blood monocytes. In contrast, one study reported that LPS augments DR4 expression on human
monocytes [64]. Furthermore, M1 macrophages in the synovium of rheumatoid arthritis patients expressed higher levels of DR5 than M2 macrophages [65]. In mice, monocytes and macrophages express DR5 constitutively [28,62,65–68] and its expression can be augmented by the DNA-binder trabectedin [62].

Peripheral human monocytes are sensitive to TRAIL-induced apoptosis with 50% reduction in their survival 72 h after TRAIL treatment in vitro [28]. Furthermore, pre-treatment with the anti-inflammatory cytokines IL-4 or IL-10 seemed to sensitize monocytes towards TRAIL-mediated cell death [28,69]. TRAIL also induced apoptosis in the human macrophage cell line U937 [70] and in murine peritoneal macrophages [71]. M2 macrophages are more sensitive to TRAIL-induced apoptosis than M1 macrophages due to their higher DR5 surface expression [28] and due to the increased O-glycosylation of DR5, which augments receptor oligomerization [63]. Sensitivity of monocytes and macrophages to TRAIL-mediated apoptosis was also reported in disease models. In a mouse tumor model, TRAIL treatment in vivo was shown to suppress tumor growth by the elimination of monocytes and M2-like TAMs in the tumor [28,62]. In the atherosclerosis ApoE−/− mouse model, TRAIL treatment in vivo selectively induced apoptosis in vascular infiltrating inflammatory macrophages [66,67]. This may be due to the upregulation of DR5 on vascular macrophages by ER stress in advanced stages of atherogenesis [72]. In general, activated macrophages are sensitive to TRAIL-induced apoptosis and this is crucial for the regulation of homeostasis [58,71]. Besides inducing apoptosis, TRAIL-mediated signals can make monocytes and macrophages also anti-tumorigenic [17,47,50,52,53,73].

Apart from apoptotic effects, TRAIL/DR interaction can also impact monocytes and macrophages in other ways. For instance, TRAIL-treatment can enhance monocytic maturation of primary human CD34+ hematopoietic stem cells without inducing any cytotoxicity [74]. Furthermore, TRAIL-mediated DR4-triggering could induce migration of THP-1 monocytes and of LPS-activated primary human monocytes [64]. Moreover, treatment with soluble TRAIL induced the expression of pro-inflammatory cytokines in human monocyte-derived macrophages and in mouse peritoneal macrophages [75]. Similarly, in tumor-challenged nude mice injected with soluble TRAIL, TAMs were reported to exhibit increased expression of pro-inflammatory cytokines [75]. In contrast to these pro-inflammatory effects of TRAIL, one study reported an anti-inflammatory role. In a mice model of colitis-associated colorectal cancer (CAC), early treatment of TRAIL in vivo protected the mice by reducing the inflammation, probably by decreasing the levels of infiltrating macrophages and pro-inflammatory cytokines and increasing the percentage of M2 macrophages [76]. Additionally, after stimulation with LPS and TRAIL in vitro, the murine RAW264.7 macrophage cell line displayed a reduction in iNOS, IL-6, and TNF expression compared to LPS alone [76].

2.1.3. Dendritic Cells

Human dendritic cells (DCs), either isolated from blood or monocyte-derived, expressed no surface TRAIL in most [47,49,77–80] but not all [46,81] studies. However, TRAIL could be detected intracellular [46,77–80] and in the culture supernatant [79]. Similar to neutrophils, the activation of DCs by IFNα [49,77,82–88] or IFNβ [77,81,85] increases the levels of membrane-bound and soluble TRAIL. Known inducers of IFNα/IFNβ, like TLR-ligands [77,84,88–90] and virus particles [85,88,91–93], also induce TRAIL expression/secretion by human DCs. Conflicting results obtained with LPS could be due to the timing, as TRAIL induction was not observed after 12 h [49,81] but after 1-2 days [82,90] of incubation. Disagreement also exists about the impact of IFNγ on the TRAIL expression on human DCs [49,85]. Interestingly, it was suggested that CD40-ligation [77] or the action of regulatory T cells (Tregs) [94] could inhibit the upregulation of TRAIL on stimulated human DCs. Similar to humans, in mice, TRAIL was found to be upregulated on mouse DCs by IFNα and IFNβ directly [86] or indirectly [94–96]. Furthermore, IL-15 was suggested to be an inducer of TRAIL expression on mouse DCs [97,98].

With the exception of one report showing a weak staining for surface DR5 [90], most studies did not detect surface expression of DR4/DR5 [46,90,99,100] or DcR1/DcR2 [90,100] on human DCs.
However, DR4 and DR5 could be detected by mRNA [82,99] and intracellular staining [46]. The surface expression of DR4 and DR5 was upregulated after 2 days of stimulation with LPS in vitro [82]. However, in another study the incubation with LPS for 20 h resulted in a different outcome, with DR4 being unchanged and DR5 being down-regulated [90]. In the mouse system, DR5 surface expression was reported for bone-marrow derived DCs [101].

Surprisingly, little is known about the sensitivity of DCs towards TRAIL-induced apoptosis. Two studies, one on human monocyte-derived DCs [90] and one on mouse bone-marrow derived DCs [101], suggest that stimulated DCs are less sensitive towards TRAIL-induced apoptosis than immature DCs.

In contrast, many studies demonstrated that human DCs can exert TRAIL-dependent cytotoxic activity against various tumors cells. This was reported for unstimulated DCs [46,102], for IFNα/β stimulated monocyte-derived DCs [49,77,81–83,87,92,103,104], for pDCs [78,79], and for DCs stimulated with TLR-ligands [77,84,88] or virus particles [85,88,91,93,105]. Similar observations were made in the mouse system [86,95,96,98]. Interestingly, two studies suggest that TRAIL/DR interaction can also have a direct impact on the TRAIL+ DCs in an apoptosis-independent manner, although, they conflict in their implication. For human monocyte-derived DCs stimulated with LPS, TRAIL acted like a co-stimulatory molecule, as blocking TRAIL reduced the upregulation of activation markers and the production of cytokines by the DCs [90]. In contrast, in a mouse study, the engagement of DR5 on mouse DCs impaired the antigen-presenting functions of the DCs, leading to reduced priming of CD4+ and CD8+ T cells [106].

2.1.4. Other Myeloid Cells

Basophils and Mast Cells

Primary human blood-derived basophils expressed DR4 and DR5 in most but not all donors [107,108] and were resistant towards TRAIL-induced apoptosis [107]. In contrast, neoplastic basophils from chronic myeloid leukemia (CML) patients were TRAIL sensitive, despite lower expression of DR5 [107]. Human cord blood-derived mast cells (CBMCs) were reported to express only DR5 on the cell surface, although mRNA for DR4, DcR1, and DcR2 was detected in most of the donors [109]. These CBMCs were also sensitive towards TRAIL-induced apoptosis [109,110]. In contrast, primary human lung mast cells were reported to be negative for surface DR4 or DR5 expression [108].

Eosinophils

Human blood-derived eosinophils did not express surface TRAIL [111], but eosinophils upregulated TRAIL during inflammatory responses [111–113]. Eosinophils can express all four death receptors (DR4, DR5, DcR1, and DcR2), although the expression levels reported varied [29,113,114]. Interestingly, during inflammation, human eosinophils down-regulated the expression of the pro-apoptotic receptors (DR4, DR5) and up-regulated the expression of the decoy receptors (DcR1, DcR2). This was observed in asthmatic patients [113,114] and in patients with parasitic infections [114] or with Churg-Strauss syndrome, a disease characterized by eosinophilia [115]. Importantly, treatment with soluble TRAIL did not induce apoptosis in human eosinophils, but rather increased cell survival [29,113], although variability between donors was noted [29]. TRAIL was also shown to promote lung eosinophilia in an indirect fashion. Human and mouse bronchial epithelial cells incubated with soluble TRAIL produced CCL20 [116,117]. CCL20 caused the influx of IL-5-producing CD4+ T cells into the lung in mice [116] and IL-5 is an essential chemoattractant for eosinophils [118,119]. In line with the role of TRAIL in promoting eosinophilia and acute inflammation are animal studies on allergic asthma [116], rhinoviral infection [120], and eosinophilic esophagitis (EoE) [121]. However, one study probing the role of TRAIL late during the allergic asthma inflammation, suggested a protective role for TRAIL [122]. Furthermore, data on mouse models of chronic airway inflammation yielded
conflicting results [123,124]. These findings could suggest that the sensitivity of eosinophils towards TRAIL-induced apoptosis might differ during early and late stages of the inflammation.

Myeloid DerivedSuppressor Cells

Inhibitory myeloid derived suppressor cells (MDSCs), either derived from monocytes or granulocytes, are prevalent in the tumor microenvironment [125]. Their recruitment/induction can be promoted in mice by chemokines that tumor cells produce following treatment with soluble TRAIL [126]. Human and mouse MDSCs express DR5 [127] and, curiously, the tumor environment could cause an upregulation of DR5 on mouse MDSCs in vivo [127]. It was suggested that the increase of DR5 on MDSCs is a consequence of ER stress [62,127], which also led to a down-regulation of DcR1 and DcR2 on human MDSCs [127]. Consequently, human and mouse MDSCs are sensitive towards TRAIL-induced apoptosis [127], which was utilized already therapeutically to remove MDSCs in vivo in preclinical [62,127] and clinical settings [30]. However, another study found little DR5 expression on tumor-associated mouse MDSCs [28], suggesting that the TRAIL-sensitivity of MDSCs could vary depending on the tumor studied.

2.2. Lymphoid Cells

2.2.1. Conventional Natural Killer Cells and Innate Lymphoid Cells

Freshly purified Natural Killer (NK) cells (CD3\textsuperscript{neg} CD56\textsuperscript{+}) from human blood, either peripheral blood or umbilical cord blood, did in most reports not express membrane TRAIL [128–130]. Although one study suggested that TRAIL could be detected by intracellular staining [130], another one could not even detect expression of TRAIL mRNA in blood-derived NK cells [131], possibly reflecting donor differences. In those reports were a subset of blood-derived NK cells stained for surface TRAIL, it was found exclusively on the CD56\textsuperscript{bright} population [128,132] and large inter-individual variability was noted [132]. In contrast to the blood, most [128,133,134] but not all [135] studies demonstrated surface TRAIL expression on human liver CD56\textsuperscript{bright} NK cells. A similar expression profile was seen in mice, where only a subset of NK cells in the liver, but not in blood, spleen, or lung, constitutively expressed TRAIL [136–138]. In recent years it became clear, however, that these TRAIL\textsuperscript{+} CD56\textsuperscript{bright} cells are most likely not conventional NK (cNK) cells, but rather ILC1s, a related subset of innate lymphoid cells (ILCs) [139–141]. Indeed, TRAIL expression by ILC1s but not resting cNK cells seems to be a generic feature of these cells in humans [133] and in mice [142–150]. Interestingly, the expression of surface TRAIL on mouse cNK/ILC1s, but not on other cells, was dependent on CD335 (NKp46, Ncr1) [151–155] as in cells lacking CD335, TRAIL remained intracellular [151,153]. The distinction between cNK cells (CD11b\textsuperscript{+} CD49a\textsuperscript{−} CD49b\textsuperscript{−} Eomes\textsuperscript{−} TRAIL\textsuperscript{−}) and ILC1s (CD11b\textsuperscript{−} CD49a\textsuperscript{+} CD49b\textsuperscript{−} CD186\textsuperscript{−} Eomes\textsuperscript{−} TRAIL\textsuperscript{+}) is further complicated by the recent finding that mouse cNK cells can, under the influence of TGF\textbeta, convert into ILC1-like cells (CD49a\textsuperscript{+} CD49b\textsuperscript{−} TRAIL\textsuperscript{+}) [147,156,157]. This is, therefore, another example of the plasticity of innate lymphoid cells [141,158].

Nonetheless, both cNK cells and ILC1s can upregulate the expression of TRAIL following stimulation. This was seen with IL-2 [128,129,135,146,151,159–161], IL-15 [151,159–162], IFN\alpha/\beta [50,51,131,163–166], and IFN\gamma [136,137,167–170]. Upregulation of TRAIL on cNK/ILC1 was also seen in patients treated with IFN\alpha in vivo within 4–6 h [131,164,165,171–173], which negatively correlated with viral titers [131,172]. Given the prominent role of IFNs in anti-viral immune responses, it is not surprising that TRAIL upregulation was also seen following viral infections or stimulation with purified TLR3 or TLR9 ligands [51,148,166–169,174–177].

Little information is available on the expression of DRs on cNK/ILC1s. Whereas, resting human blood-derived NK cells were reported to express low levels of surface DcR2 [27], after in vitro activation only expression of DR5 and DcR2 was seen [160]. However, in vitro stimulated human NK cells were not sensitive towards TRAIL-induced apoptosis [160].
NK cells are prototypic cytotoxic cells, utilizing either soluble factors, like TNF, or granzymes and perforin stored in cytotoxic granules, or the death receptors CD178 (FasL, CD95L) and TRAIL to induce apoptosis in target cells [178,179]. The involvement of TRAIL+ cNK/ILC1s for anti-tumor response has been reviewed previously [179,180]. Importantly, cNK/ILC1s can also regulate and limit adaptive immune responses [158,181,182] and TRAIL-mediated cytotoxicity is one of several mechanisms to achieve this. In particular, activated but not resting T cells upregulate death receptors (see Section 2.2.2) and become sensitive towards apoptosis induced by TRAIL+ cNK/ILC1s. This was observed for CD4+ [177,183] and CD8+ [176] T cells and appears particularly important in the case of chronic virus infections, like MCMV in mice [177] and hepatitis B virus (HBV) [176]. By this TRAIL/DR-dependent removal of activated, antigen-specific T cells during the chronic MCMV infection, the cNK/ILC1s were able to restrain the T cell responses in mice and to limit tissue damage and the risk for autoimmunity [177]. Another TRAIL/DR-dependent means to limit T cell responses by mouse cNK/ILC1s was the induction of apoptosis in immature but not mature DC in vivo [101]. Interestingly, engaging DR5 on mouse DCs by TRAIL+ cNK/ILC1s was also reported to impair antigen-presenting functions of the DCs in an apoptosis-independent manner [106].

2.2.2. Conventional αβ T cells

Resting human and mouse T cells do not express TRAIL, but can upregulate it following TCR-mediated activation [58,160,184–191], although, in some reports, TCR-stimulation alone was not sufficient [59,192,193]. In general, this upregulation of TRAIL was stronger on CD4+ T cells than on CD8+ T cells [50,185–187]. Furthermore, in humans, a high degree of variability of TRAIL-upregulation on T cells between different donors was observed. In line with this, the degree of TRAIL-upregulation on mouse T cells was influenced by the genetic background [191]. In most studies, IFNα/IFNβ cytokines alone, similar to NK cells, could induce TRAIL expression on human T cells [50,51,185–187] and they could boost TCR-induced TRAIL expression [186,187,192,194].

Expression of all four TRAIL death receptors on naïve human [27,92,183] or mouse [32] T cells appears absent, with one study reporting DcR2 expression on human blood-derived CD8+ T cells but not CD4+ T cells [27]. Where changes following TCR-triggering were reported, the reports suggest an upregulation of all death receptors, however, at varying degrees [92,160,183,184,190,195]. Interestingly, TCR-mediated stimulation of human T cell lines led to a down-regulation of DR4 and DR5, without changes in DcR1 or DcR2 [184], suggesting that the regulation of the death receptors might differ between primary and secondary responses.

In line with the expression of death receptors, naïve or freshly stimulated human T cells were not sensitive towards TRAIL-induced apoptosis [160,184,196,197]. However, following repeated or chronic stimulation, T cells can become sensitive towards TRAIL-induced apoptosis. One important example for this is the elimination of antigen-specific T cells during viral infections by TRAIL+ cNK/ILC1s, as outlined above (see Section 2.2.1), and by TRAIL+ pDCs [92]. In a similar fashion, mouse Tregs upregulated membrane-bound TRAIL after TCR-mediated stimulation and induced apoptosis in effector T cells in vitro and in vivo [190]. Another example is the TRAIL-sensitivity of CD8+ T cells that have been primed without CD4+ T cell help [198,199], mediated by CD27/CD70 interaction [200], although, common γ-chain cytokines, like IL-2, IL-7, or IL-15, could substitute for CD4+ T cell help [199,201–203]. ‘Helpless’ CD8+ T cells expand normally during the primary response, but upon secondary stimulation undergo TRAIL-mediated ‘activation-induced cell death’ (AICD) [198,204]. Such ‘helpless’ CD8+ T cells could also release soluble TRAIL and induce fratricide [198] and their TRAIL-expression was implicated in their capability to transfer tolerance (infecious tolerance) [205,206]. Such ‘helpless’ CD8+ T cells were also detected in HIV patients with low peripheral CD4+ T cell numbers [207]. Interestingly, TRAIL-induced apoptosis also influenced, at least in mice, the balance of Th1- versus Th2-T cells. After TCR-driven in vitro stimulation, mouse Th2 cells expressed TRAIL, but were resistant towards TRAIL-driven apoptosis [191]. In contrast, Th1 cells did not express TRAIL, but were sensitive towards
TRAIL-induced apoptosis [191]. Due to this differential sensitivity, TRAIL/DR-engagement could impair Th1 and favor Th2 responses in vitro [191] and in vivo [59,195,208]. Importantly, TRAIL/DR expression on T cells serves also several non-apoptotic functions. The proliferation of human [196,197,209,210] and mouse [195,209,211–215] conventional, naïve T cells following TCR-mediated stimulation was impaired by concomitant TRAIL/DR-engagement. This inhibition was particularly strong with suboptimal TCR-stimulation [197,209] and both DR4 and DR5 were implicated [196,197,211,212]. Such DR-triggered signaling impaired proximal TCR-signals, Ca2+ influx, cell cycle progression, and subsequent cytokine production [196,197,209,212,213]. In contrast to naïve T cells, the proliferation of activated mouse CD4+ CD25+ Tregs was enhanced by TRAIL/DR-engagement in vitro and in vivo [195,216,217].

2.2.3. Innate-like T cells

Invariant Natural Killer T cells

Expression of functional TRAIL on human [218] and mouse [137,219,220] invariant Natural Killer T (iNKT) cells could be induced by antigenic stimulation, although IFNγ was suggested to be involved as well [137]. iNKT cells were discovered and studied extensively due to their anti-tumor activity [221,222]. Besides granzyme/perforin- [223,224] and CD178- [225,226] mediated cytotoxicity, TRAIL-dependent anti-tumor responses have been described for human [218,225,227] and mouse [219,228,229] iNKT cells.

γδ T cells

Expression of membrane bound and soluble TRAIL by human γδ T cells could be induced by TCR-triggering together with IL-2 [230–234] and/or by NKG2D-engagement [235,236]. TRAIL expression on blood-derived IL-17-producing Vγ9Vδ2 T cells was also noted during bacterial meningitis [237]. Furthermore, γδ T cell-agonists could augment serum levels of soluble TRAIL in vivo and this correlated positively with the clinical response in prostate cancer [230] but not in breast cancer [234] patients. Interestingly, the role of TRAIL in the cytotoxicity of the γδ T cells appears to be influenced by the mean by which the target cell is recognized. When the target cells were recognized via NKG2D-engagement, then the cytotoxicity of the γδ T cells was largely dependent on TRAIL [232,235,236]. In contrast, when the target recognition was TCR-driven, then TRAIL played a minor role and the cytotoxicity was largely dependent on perforin [231,233].

2.2.4. B cells

TRAIL expression on resting B cells was not observed in humans [53,238] but in mice on about 1/5th of splenic B cells [189]. Upregulation of TRAIL on human B cells was seen with IFNα and IFNα-inducers, like TLR9 ligands [51], but not following stimulation via the BCR, PHA/IL-2, or IFNβ [51,53]. Furthermore, naïve B cells expressed DR4 [27,239,240] and DR5 [32,239–241] and their expression levels increased upon stimulation [239,240,242]. Consequently, germinal center (GC) or memory B cells expressed higher levels of DR4 and DR5 than naïve cells [239,240]. However, conflicting data were reported for the expression of DcR1 and DcR2 on B cells [27,239,240].

Whereas naïve B cells are insensitive towards TRAIL-induced apoptosis, they develop sensitivity following activation [239,243]. In line with this, human CD5+ B cells [240] and human or mouse plasma cells [243] were reported to be particular sensitive towards TRAIL-induced apoptosis. The lack of protective CD40 ligation on plasma cells was suggested to be the reason for this sensitivity [243]. However, the impact of CD40 appears also dependent on the stage of B cell development or the type of stimulation. On the one hand, CD40 ligation concomitant to IFNα-mediated stimulation could boost TRAIL upregulation on naïve human B cells [51]. On the other hand, it was suggested that CD40 ligation could protect B cells from TRAIL-induced apoptosis early after BCR-mediated activation [240,244] but not 3–5 days later [239]. The connection between CD40 and TRAIL is complicated by two additional aspects. First, the hetero-oligomerization of CD40 and DR5 could dampen the activation of primary...
human B cells [242]. Second, CD40-ligation on B cells can induce expression of CD25 (IL-2Rα) [245] and IL-2 signaling was reported to cause down-regulation of TRAIL on B cells [246].

Importantly, the TRAIL/DR-interaction could influence the isotype of the antibodies produced by activated B cells. Data from in vivo experiments that either blocked TRAIL/DR-interaction [211,247] or triggered DRs with soluble TRAIL [247] indicated that TRAIL/DR-interaction impairs the production of IgG1 and, to a lesser extent, IgG2a antibodies.

3. Common Themes and Open Questions on the Role of TRAIL/DRs in Immune Cells

3.1. Regulation of TRAIL-Sensitivity

The sensitivity of immune cells towards TRAIL-induced apoptosis is regulated on several levels.

3.1.1. TRAIL Expression

As outlined above, the expression levels of TRAIL on immune cells can be influenced by intrinsic signals, like ER stress or senescence, as well as many extrinsic signals, like cytokines.

3.1.2. Membrane-Bound vs. Soluble TRAIL

Functional TRAIL can either be membrane-bound or soluble, after cleavage from the surface [1,5]. However, the bioactivity of membrane-bound and soluble TRAIL differs significantly. First, the cytotoxic potential of soluble TRAIL was suggested to be 100–1000-fold lower than that of membrane-bound TRAIL [248]. Second, soluble TRAIL, in contrast to the membrane-bound version, was not able to impair the activation of conventional T cells [197] or to promote the proliferation of Tregs [195]. Mechanistically, it was reported that soluble TRAIL could trigger only DR4, whereas membrane-bound TRAIL could trigger both DR4 and DR5 [249]. Given these distinctions, it is particular important to keep in mind that not all of the TRAIL-bioactivity found in cell culture supernatants or in body fluids stems solely from soluble TRAIL (see Section 3.2).

3.1.3. Expression Levels of the Death Receptors

Similar to TRAIL and as outlined in detail above, the expression levels of the death receptors on immune cells can be influenced by many intrinsic and extrinsic signals. The relative expression of these death receptors is relevant for two reasons. First, it was suggested that the affinity of DR4/DR5 towards TRAIL is higher than that of DcR1/DcR2 [250,251]. Second, it appears that the ratio of functional (DR4, DR5) vs. decoy receptors (DcR1, DcR2) can dictate the sensitivity towards TRAIL. Immune cells could become TRAIL-sensitive by upregulation of DR4/DR5 and/or by the down-regulation of DcR1/DcR2 [11,28,30]. In contrast, an inverse ratio predicts TRAIL-resistance [28,47,90,127]. Although, DR4 and DR5 appear on a first glance redundant, slight functional differences likely allow to fine-tune the response towards TRAIL. Such differences include, for example, the higher affinity of DR5 than DR4 for TRAIL [250,251], the inability of DR5 to bind soluble TRAIL [249], and the ability of DR5 to form hetero-oligomers [242,250]. However, other differences likely remain to be discovered.

3.1.4. Receptor Interactions

Besides the absolute expression levels of death receptors, their activity could also be influenced by the formation of hetero-oligomers. This has been suggested for DR5 and CD40, which reduced CD40-signaling [242], and for DR5 and DcR2, which reduced DR5-signaling [250].

3.1.5. Signaling Pathways

Finally, the outcome of DR-triggering is regulated on the level of the intracellular signaling pathways, which can lead to apoptosis, necroptosis, or increased survival and proliferation. The regulation of these pro- and anti-apoptotic signaling pathways are still poorly understood
and are discussed in detail elsewhere [2,5–7]. However, it is likely that these pathways contain several potential new drug targets to regulate the resolution phase of immune responses.

3.2. TRAIL on Exosomes

Most studies that investigated the TRAIL-activity in cell culture supernatants assumed that the activity is due to soluble TRAIL released from the cells in the culture. However, functional TRAIL could also be detected in exosomes released from various cells, including human T cells [252–254], human neutrophils [16], human placental explants [255], mouse bone-marrow-derived DC [256], and from various tumors [257–260]. Furthermore, TRAIL+ exosomes have been detected in sera of tumor patients [257] and in the synovial fluid of arthritis patients [261]. The TRAIL in these exosomes was the full-length, membrane-bound version and not the shorter version of soluble TRAIL [253,257]. Given that the bioactivity of soluble and membrane bound TRAIL are very different (see Section 3.1), it is important to know if the TRAIL-activity in the culture supernatant is due to soluble or exosome-bound TRAIL. However, few studies measured the molecular weight of the TRAIL recovered from the cell culture supernatants. Even transwell-studies could be misleading, as exosomes seem to move freely across pore sizes of 1 µm and can transmit 15–33% of the biological activity across 0.4 µm pores [262,263].

As most cells release exosome [264,265], a reasonable working hypothesis appears to be that all TRAIL+ immune cells are able to release TRAIL+ exosomes. How this, compared to soluble TRAIL, influences immune responses needs to be addressed in future studies.

3.3. TRAIL’s Role in the Resolution of Immune Responses

Looking at the findings outlined so far in a broad sense, it appears that one of the main roles of TRAIL/DRs in the immune system is during the resolution phase of immune responses. By removing senescent, chronically activated, or stressed immune cells at sites of inflammation, TRAIL/DRs regulate innate and adaptive immune responses by terminating the response and by limiting thereby tissue damage and the risk of autoimmunity.

3.3.1. Removing Effector Cells

Activated or senescent neutrophils become sensitive towards TRAIL-induced apoptosis [11,12,20,23,29]. As neutrophils are major drivers of inflammation [36–38], their TRAIL-dependent removal supported the resolution of the inflammation [21,23,31,32,34,39,41]. Furthermore, activated T cells are sensitive towards TRAIL-induced apoptosis [176,177,183,190]. Other immune effector cells known to be sensitive towards TRAIL-induced apoptosis are sub-optimal activated, ‘helpless’ CD8+ T cells upon secondary stimulation [198,204,207]; terminally differentiated cells, like T cell blasts [210,266]; plasma cells [243]; MDSCs [30,62,127]; and hematopoietic cancers (e.g., [100,188,238]). Activated immune cells greatly increase the synthesis of proteins, which can stress the endoplasmic reticulum (ER), leading to an ‘unfolded protein response’ (UPR) [267–269]. Similar, pathogens and chronic cell activation can cause ER stress [267,269,270]. Indeed, it was shown that ER stress increases the TRAIL-sensitivity of macrophages [271] and MDSCs [30,127]. Furthermore, Streptococcus pneumoniae infected alveolar macrophages were susceptible towards TRAIL-induced apoptosis [41]. However, beyond these two examples, the link between ER stress and TRAIL-sensitivity is not yet established. The two exceptions in the pattern of TRAIL-induced removal of effector cells, seem to be immature DCs and eosinophils. First, mouse cNK/ILC1s could induce apoptosis in immature but not mature DC in vivo in a TRAIL/DR-dependent manner [101]. Second, the survival and functions of eosinophils were reported to be augmented by TRAIL/DRs [116,120,121]. However, two studies that investigate the role of TRAIL either late during an allergic asthma inflammation [122] or during a chronic airway inflammation [123], suggested that TRAIL now induces apoptosis of eosinophils. These reports might indicate that the impact of TRAIL on eosinophil differs during early and late stages of the inflammation.
3.3.2. Impairing Effector Cells

Besides their direct apoptotic removal of effector cells, TRAIL/DR-activity can also impair the expansion/function of effector cells. Either directly, by impairing the activation and proliferation of pathogenic T cells, or indirectly, by augmenting the proliferation of inhibitory Tregs (see Section 2.2.2).

3.3.3. Limiting Tissue Damage

In line with the idea that the activity of TRAIL/DRs limits ongoing immune response and supports the transition into the resolution phase, is the fact that TRAIL-deficiency or TRAIL/DR-blockage exacerbates, whereas the injection of functional TRAIL ameliorates pathogen burden. This has been noted for Streptococcus pneumoniae infection of the CNS [31] or the lung [41], for systemic Listeria monocytogenes [33] or MCMV [177] infection, and for influenza vaccination [272] or infection [273]. At first, it might appear counterintuitive to curtail anti-pathogenic immune responses. However, this inhibition is likely aimed at limiting tissue damage. Without an efficient resolution in the absence of TRAIL/DRs, immune responses continue and could become damaging to the host tissue, which eventually could lead to autoimmunity. Indeed, augmented tissue damage and signs of autoimmunity in the absence of TRAIL were observed, for example, following influenza [22], MCMV [177], rhinovirus [120], Listeria monocytogenes [33], and Streptococcus pneumoniae [31] infections and during sepsis induced by bacteria [32,34] or TLR-ligands [39]. This probably also contributes to the increased susceptibility of TRAIL-deficient mice towards experimental autoimmune diseases, as reported for collagen-induced arthritis (CIA) [274], diabetes [67,274,275], and experimental autoimmune encephalomyelitis (EAE) [195,215].

3.3.4. Avoiding Autoimmunity

The idea that TRAIL/DR-activity limits tissue damage induced by unrestrained immune responses is also supported by the observation that TRAIL/DR-blockage exacerbates, whereas the injection of biologically active TRAIL ameliorates autoimmune diseases. This has been observed for colitis [214], collagen-induced arthritis (CIA) [211,276,277], diabetes [275,278], experimental autoimmune encephalomyelitis (EAE) [215,217,279–281], experimental autoimmune thyroiditis (EAT) [208,216], and systemic lupus erythematosus (SLE) [247].

4. TRAIL/DRs in the Tumor Microenvironment

4.1. Anti-Tumor Cytotoxicity of TRAIL+ Immune Cells

Many immune cells express TRAIL constitutively or following activation and thereby can be cytotoxic to TRAIL-sensitive tumor cells in vitro and in vivo. This has been reported for neutrophils [13,14,17,42,43], monocytes/macrophages [17,47,52,73], DCs [46,49,77–79,81–83,86,87,91,98,102–104], pDCs [84,85,88,91,93,95,96,105], cNK/ILC1s [134,136,137,163,228,282], iNKT cells [218,219,225,227,229], γδT cells [231,235], and conventional T cells [186,194,283–286].

4.2. TRAIL Susceptibility of Tumors and Immune-Surveillance

Malignant transformation of cells often leads to sensitivity towards TRAIL-induced apoptosis in a cell-autonomous manner [1,2]. As many activated immune cells express TRAIL, the selective pressure of the anti-tumor immune response forces the evolution of the tumor. This is best illustrated by TRAIL-deficient mice, which are more susceptible towards endogenous tumors developing either spontaneously [287] or induced by the chemical carcinogen methylcholanthrene (MCA) [228]. Furthermore, tumors in TRAIL−/− mice developed metastases more frequently [137,288]. Interestingly, this TRAIL-dependence of metastases was more prominent for some organs, like liver, than others, like lung [137,288], indicating organ differences of immune-surveillance mechanisms. The greater sensitivity towards MCA-induced tumors could also be mimicked by repeated injection
of a blocking anti-TRAIL-antibody [289]. Additionally, tumors developing in TRAIL−/− mice retained TRAIL-sensitivity, whereas tumors developing in TRAIL-proficient animals acquired TRAIL-resistance [289]. These reports demonstrate that TRAIL is an important mechanism, besides CD178 (FasL, CD95L) and perforin, in the tumor immune-surveillance. cNK/ILC1s [136,137,228,282,289] and iNKT cells [290–292] have been suggested to be major players in this tumor immune-surveillance. The presence of TRAIL+ ILC1s in the liver [139–141] might also explain some of the organ specificity of TRAIL-mediated immune-surveillance [137,288].

4.3. Tumor Mechanisms to Evade TRAIL-Mediated Cytotoxicity

The observation that tumors developing in TRAIL−/− but not in wild-type mice retained TRAIL-sensitivity [289] indicates that tumor cells can develop mechanisms to avoid TRAIL-mediated killing [1,2]. The tumor can achieve this by means that are not unique to TRAIL/DRs, like the upregulation of anti-apoptotic molecules [293] or an interference with general aspects of the death-receptor signaling, e.g., by mutating the death domain (DD) [294], by inactivating caspase-8 [295,296], or by overexpressing c-FLIP [297,298]. Several other tumor cell-intrinsic strategies were reported that limit the apoptotic-signals induced by DR4 or DR5 themselves. First, changes in glycosylation can alter the sensitivity of DR4/DR5 [299–302]. Second, the surface expression of DR4/DR5 can be reduced either by epigenetic changes in the respective genes [303,304], by autophagic removal [305], or by relocation to the nucleus [306]. Third, the tumor can upregulate the decoy receptor DcR1 and DcR2 [1,2,62], which reduces the TRAIL-binding to DR4 and DR5. Consequently, expression of DcR1/DcR2 correlated with poor prognosis for patients with breast cancer [307], prostate carcinoma [308], or acute myeloid leukemia (AML) [309,310]. In contrast, conflicting data have been reported for the correlation between DR4/DR5 expression and patient survival for renal cell carcinoma [311] and hepatocellular carcinoma (HCC) [304]. Furthermore, some single-nucleotide polymorphisms (SNPs) in TRAIL of HCC patients are correlated with overall patient survival [312]. In summary, these reports indicate that TRAIL/DRs are an important player in the anti-tumor response.

4.4. TRAIL/DR-Related Immune-Tumor Cross-Talk in the Tumor Microenvironment

The TRAIL-DR interaction does not only impact the tumor directly, but can also be utilized by the tumor to shape the tumor microenvironment. Treatment of TRAIL-resistant tumor cells with soluble TRAIL or agonistic αDR5-antibodies could promote tumor survival/proliferation [306,313], invasion and metastases [314–317], and cytokine production [126,316,318–321]. Such cytokines could induce chemotaxis and recruitment of various myeloid cells [126,318–320]. Many mechanisms have been described inside the tumor microenvironment that benefit the tumor [2,322–324]. In regard to TRAIL/DRs, several points can be mentioned. It was noted that neutrophils [18,44,45] and DCs [98,102] from the tumor itself or from blood of tumor patients express less TRAIL than cells from control tissue/donors. This reduction might be due to the proteolytic cleavage of TRAIL from the surface, as it was shown for CD178 [325–327]. Or the reduction could be a consequence of stimulation, as it was reported, for example, that mouse neutrophils stimulated with IL-6 and G-CSF lose TRAIL expression and their anti-tumor properties [24,25]. Furthermore, DR5-triggering of mouse DCs by TRAIL+ cNK/ILC1s reduced their cross-presentation and -priming capacity for tumor-antigens, leading to reduced anti-tumor T cell responses [106]. Finally, expression of DcR1/DcR2 by human stromal cells in the tumor microenvironment could reduce the ligation of DR4/DR5 on tumor cells [328]. All of these mechanisms would reduce the anti-tumor activity of the immune system directly, benefitting the tumor. Moreover, some other TRAIL/DR-dependent mechanisms promote tumor growth indirectly. TRAIL promoted the recruitment and polarization of immune-suppressive M2-like cells [126] and the proliferation of Tregs [190,195,216,217]. Furthermore, it is known that the tumor microenvironment triggers persistent ER stress in infiltrating immune cells and promotes immunosuppressive responses [329]. In regard to TRAIL/DRs, ER stress of myeloid cells has been linked to pro-inflammatory [271] but also anti-tumorigenic activities [30,127]. This latter point illustrates that
not all impacts of TRAIL/DRs would benefit TRAIL-resistant tumors. In line with the role of TRAIL/DRs in the elimination of stressed or senescent immune cells, some TRAIL/DR-actions could also suppress tumor growth. For example, the tumor environment induced upregulation of DR5 on mouse MDSCs in vivo for some [127] but not all [28] tumors. Furthermore, mouse and human MDSCs [127] and mouse TAMs [28,63] were shown to be sensitive to TRAIL-induced apoptosis. Consequently, treatment of head and neck cancer patients with agonistic αDR5-antibodies [30] or of tumor-bearing mice with soluble TRAIL [28,62] was able to limit tumor growth to some extent. Additionally, the endothelial cells of tumor-associated blood vessels of some [330] but not all [28] tumor-bearing mice upregulated DR5 and were TRAIL-sensitive, which led to blood vessels collapse and inhibited tumor growth [330].

An overview of the anti- and pro-tumorigenic activities of TRAIL/DRs in the tumor microenvironment is given in Figure 1.

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**Figure 1.** Anti- and pro-tumorigenic activities of TRAIL/DRs in the tumor micro-environment:

**A) Anti-tumorigenic**

1. TRAIL-induced cytotoxicity
2. Cytokine-induced cytotoxicity
3. TRAIL-sensitivity of ECs and myeloid cells
4. ER stress (increasing TRAIL-sensitivity of immune cells)

**B) Pro-tumorigenic**

5. Cytokines promote recruitment/polarization of suppressive myeloid cells and recruitment of Tregs
6. Proliferation of Tregs
7. TRAIL-induced cytokines
8. Impaired cross-priming of T cells by DCs
9. DcR1/DcR2 on stromal cells as TRAIL sink
10. Proteolytic cleavage of TRAIL?
11. TRAIL-induced cytotoxicity of effector cells?
12. DR4/DR5-mediated inhibition of T cells?

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**C) Tumor intrinsic TRAIL-desensitization**
recruitment of Tregs. (6) For Tregs it was shown that TRAIL-induced triggering of DR4/DR5 on Tregs can promote their proliferation. (7) TRAIL-induced cytokines, either produced by the tumor or immune cells, can promote tumor survival and proliferation directly or indirectly, e.g., by supporting neo-vascularization. (8) Triggering of DR4/DR5 on DCs by TRAIL- + cNK/ILC1s could suppress the cross-priming of tumor-specific T cells by the DCs. (9) Expression of DcR1 and DcR2 on tumor stroma cells can act as sink for TRAIL, reducing its availability to induce tumor cytotoxicity. (10–12) For several other mechanisms, an impact of TRAIL/DRs has not been demonstrated for the tumor microenvironment yet, but their role could be hypothesized based on published data in other contexts. (10) The tumor might promote the proteolytic cleavage of membrane TRAIL from immune cells. (11) TRAIL, either derived from immune cells or from the tumor itself, might promote cytotoxicity of TRAIL-sensitive immune effector cells. (12) TRAIL-mediated triggering of DR4/DR5 on recently activated T cells might inhibit their proliferation. (C) To support survival, the tumor can evolve several cell-intrinsic mechanisms to reduce its sensitivity towards TRAIL-induced cytotoxicity. These include the upregulation of anti-apoptotic molecules, the inactivation of signaling molecules, the upregulation of DcR1/DcR2, and changes in DR4/DR5 localization and glycosylation. Alternatively, the tumor can re-purpose the DR4/DR5-signals, for example, to support tumor survival and proliferation, to induce cytokine production by the tumor, and to promote tumor invasion and metastases.

5. Conclusions

The original observation that TRAIL preferentially induces apoptosis in tumor cells, while sparing healthy cells, initiated intense research on the development of TRAIL/DR-based anti-cancer therapies. Besides the tumor, innate and adaptive immune cells are a major constituent of the tumor microenvironment, where they can use TRAIL to fight the tumor by inducing apoptosis of tumor cells. However, it becomes increasingly clear that TRAIL/DRs interaction can also directly impact the function of immune cells in many ways. As outlined in this review, many relevant aspects are yet unclear. Therefore, a better understanding of how TRAIL/DRs influence both tumor and immune cells and their interaction within the tumor microenvironment will be essential for the development of successful TRAIL/DR-based anti-cancer therapies.

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Abbreviations

| Abbreviation | Meaning |
|--------------|---------|
| APC          | antigen presenting cell |
| AICD         | activation-induced cell death |
| AML          | acute myeloid leukemia |
| BCR          | B cell receptor |
| BM-DCs       | bone marrow-derived dendritic cells |
| BMDMs        | bone-marrow derived macrophages |
| CAC          | colitis-associated colorectal cancer |
| CBMCs        | cord blood-derived mast cells |
| CCL          | C-C motif chemokine ligand |
| CD           | cluster of differentiation |
| CIA          | collagen-induced arthritis |
| CML          | chronic myeloid leukemia |
| cNK          | conventional NK |
| CNS          | central nervous system |
| Abbreviation | Description |
|--------------|-------------|
| CRP          | C-reactive protein |
| CXCR         | C-X-C chemokine receptor |
| DC           | dendritic cell |
| DcR          | decoy receptor |
| DD           | death domain |
| DR           | death receptor |
| DTx          | diphtheria toxin |
| EAE          | experimental autoimmune encephalomyelitis |
| EAT          | experimental autoimmune thyroiditis |
| EoE          | eosinophilic esophagitis |
| Eomes        | eomesodermin |
| ER           | endoplasmic reticulum |
| fMLP         | N-Formylmethionyl-leucyl-phenylalanine |
| GC           | germinal center |
| G-CSF        | granulocyte-colony stimulating factor |
| GM-CSF       | granulocyte-macrophage colony-stimulating factor |
| HBV          | hepatitis B virus |
| HCC          | hepatocellular carcinoma |
| Hsp          | heat shock protein |
| IFN          | interferon |
| Ig           | immunoglobulin |
| IL           | interleukin |
| ILC          | innate lymphoid cell |
| LPS          | lipopolysaccharide |
| MCA          | methylcholanthrene |
| MCMV         | murine cytomegalovirus |
| MDSCs        | myeloid derived suppressor cells |
| mRNA         | messenger RNA |
| MSC          | mesenchymal stem cell |
| iNKT         | invariant Natural Killer T |
| NK           | Natural Killer |
| OPG          | osteoprotegerin |
| Pam3C         | tri-palmitoyl-S-glyceryl cysteine |
| pDC          | plasmacytoid dendritic cell |
| PEDF         | pigment epithelium derived factor |
| PHA          | phytohemagglutinin |
| Poly IC       | polyinosinic:polycytidylic acid |
| RANKL        | Receptor activator of nuclear factor kappa-B ligand |
| RNA          | ribonucleic acid |
| SDF1         | stromal cell-derived factor 1 |
| SLE          | systemic lupus erythematosus |
| TAMs         | tumor associated macrophages |
| TCR          | T cell receptor |
| TGF          | transforming growth factor |
| Th           | T helper type |
| TLR          | toll like receptor |
| TNF          | tumor necrosis factor |
| TNFRSF       | TNF receptor superfamily |
| TRAIL        | tumor necrosis factor–related apoptosis–inducing ligand |
| Treg         | regulatory T cell |
| UPR          | unfolded protein response. |
References

1. von Karstedt, S.; Montinaro, A.; Walczak, H. Exploring the TRAILs less travelled: TRAIL in cancer biology and therapy. Nat. Publ. Group 2017, 17, 352–366. [CrossRef]

2. O’Reilly, E.; Tirinisi, A.; Logue, S.E.; Szegedi, E. The Janus Face of Death Receptor Signaling during Tumor Immunoediting. Front. Immunol. 2016, 7, 273. [CrossRef] [PubMed]

3. Falschlehner, C.; Schaefer, U.; Walczak, H. Following TRAIL’s path in the immune system. Immunology 2009, 127, 145–154. [CrossRef] [PubMed]

4. Rossin, A.; Miloro, G.; Hueber, A.O. TRAIL and FasL Functions in Cancer and Autoimmune Diseases: Towards an Increasing Complexity. Cancers 2019, 11, 639. [CrossRef] [PubMed]

5. Naval, J.; de Miguel, D.; Gallego-Lleyda, A.; Anel, A.; Martinez-Lostao, L. Importance of TRAIL Molecular Anatomy in Receptor Oligomerization and Signaling. Implications for Cancer Therapy. Cancers 2019, 11, 444. [CrossRef]

6. Vanamee, É.S.; Faustman, D.L. Structural principles of tumor necrosis factor superfamily signaling. Sci. Signal. 2018, 11, eaao4910. [CrossRef] [PubMed]

7. Lafont, E.; Hartwig, T.; Walczak, H. Paving TRAIL’s Path with Ubiquitin. Trends Biochem. Sci. 2018, 43, 44–60. [CrossRef] [PubMed]

8. Emery, J.G.; McDonnell, P.; Burke, M.B.; Deen, K.C.; Lyn, S.; Silverman, C.; Dul, E.; Appelbaum, E.R.; Eichman, C.; DiPrinzio, R.; et al. Osteoprotegerin is a receptor for the cytotoxic ligand TRAIL. J. Biol. Chem. 1998, 273, 14363–14367. [CrossRef] [PubMed]

9. Dubuisson, A.; Micheau, O. Antibodies and Derivatives Targeting DR4 and DR5 for Cancer Therapy. Antibodies 2017, 6, 16. [CrossRef]

10. Kretz, A.L.; Trauzold, A.; Hillenbrand, A.; Knippschild, U.; Henne-Bruns, D.; von Karstedt, S.; Lemke, J. TRAILblazing Strategies for Cancer Treatment. Cancers 2019, 11, 456. [CrossRef] [PubMed]

11. Kamohara, H.; Matsuyama, W.; Shimozato, O.; Abe, K.; Galligan, C.; Dul, E.; Appelbaum, E.R.; Eichman, C.; DiPrinzio, R.; et al. Osteoprotegerin is a receptor for the cytotoxic ligand TRAIL. J. Biol. Chem. 1998, 273, 14363–14367. [CrossRef] [PubMed]

12. Renshaw, S.A.; Parmar, J.S.; Singleton, V.; Rowe, S.J.; Dockrell, D.H.; Dower, S.K.; Bingle, C.D.; Chilvers, E.R.; Whyte, M.K.B. Acceleration of Human Neutrophil Apoptosis by TRAIL. J. Immunol. 2003, 170, 1027–1033. [CrossRef] [PubMed]

13. Koga, Y.; Matsuzaki, A.; Suminoe, A.; Hattori, H.; Hara, T. Neutrophil-derived TNF-related apoptosis-inducing ligand (TRAIL): A novel mechanism of antitumor effect by neutrophils. Cancer Res. 2004, 64, 1037–1043. [CrossRef] [PubMed]

14. Kemp, T.J.; Ludwig, A.T.; Earel, J.K.; Moore, J.M.; Vanoosten, R.L.; Moses, B.; Leidal, K.; Nauseef, W.M.; Griffith, T.S. Neutrophil stimulation with Mycobacterium bovis bacillus Calmette-Guerin (BCG) results in the release of functional soluble TRAIL/Apo-2L. Blood 2005, 106, 3474–3482. [CrossRef] [PubMed]

15. Cassatella, M.A.; Huber, V.; Calzetti, F.; Margotto, D.; Tamassia, N.; Peri, G.; Mantovani, A.; Rivoltini, L.; Tecchio, C. Interferon-activated neutrophils store a TNF-related apoptosis-inducing ligand (TRAIL/Apo-2 ligand) intracellular pool that is readily mobilizable following exposure to proinflammatory mediators. J. Leukoc. Biol. 2006, 79, 123–132. [CrossRef] [PubMed]

16. Koga, Y.; Matsuzaki, A.; Suminoe, A.; Hattori, H.; Hara, T. Neutrophil-derived TNF-related apoptosis-inducing ligand (TRAIL): A novel mechanism of antitumor effect by neutrophils. Cancer Res. 2004, 64, 1037–1043. [CrossRef] [PubMed]

17. Tecchio, C.; Huber, V.; Scapini, P.; Calzetti, F.; Margotto, D.; Todeschini, G.; Pilla, L.; Martinelli, G.; Pizzolo, G.; Rivoltini, L.; et al. IFNalpha-stimulated neutrophils and monocytes release a soluble form of TNF-related apoptosis-inducing ligand (TRAIL/Apo-2 ligand) displaying apoptotic activity on leukemic cells. Blood 2004, 103, 3837–3844. [CrossRef]

18. Tanaka, H.; Ito, T.; Kyo, T.; Kimura, A. Treatment with IFNalpha in vivo up-regulates serum-soluble TNF-related apoptosis inducing ligand (sTRAIL) levels and TRAIL mRNA expressions in neutrophils in chronic myelogenous leukemia patients. Eur. J. Haematol. 2007, 78, 389–398. [CrossRef] [PubMed]

19. Chen, C.L.; Wang, Y.; Huang, C.Y.; Zhou, Z.Q.; Zhao, J.J.; Zhang, X.F.; Pan, Q.Z.; Wu, J.X.; Weng, D.S.; Tang, Y.; et al. IL-17 induces antitumor immunity by promoting beneficial neutrophil recruitment and activation in esophageal squamous cell carcinoma. Oncoimmunology 2017, 7, e1373234. [CrossRef] [PubMed]
20. Lum, J.J.; Bren, G.; McClure, R.; Badley, A.D. Elimination of Senescent Neutrophils by TNF-Related Apoptosis-Inducing Ligand. *J. Immunol.* **2005**, *175*, 1232–1238. [CrossRef] [PubMed]

21. McGrath, E.E.; Lawrie, A.; Marriott, H.M.; Mercer, P.; Cross, S.S.; Arnold, N.; Singleton, V.; Thompson, A.A.R.; Walmsley, S.R.; Renshaw, S.A.; et al. Deficiency of tumour necrosis factor-related apoptosis-inducing ligand exacerbates lung injury and fibrosis. *Thorax* **2012**, *67*, 796–803. [CrossRef] [PubMed]

22. Herold, S.; Steinmueller, M.; von Wulffen, W.; Cakarova, L.; Pinto, R.; Pleschka, S.; Mack, M.; Kuziel, W.A.; Corazza, N.; Brunner, T.; et al. Lung epithelial apoptosis in influenza virus pneumonia: The role of macrophage-expressed TNF-related apoptosis-inducing ligand. *J. Exp. Med.* **2008**, *205*, 3065–3077. [CrossRef] [PubMed]

23. Leu, S.W.; Shi, L.; Xu, C.; Zhao, Y.; Liu, B.; Li, Y.; Shiedlin, A.; Xiang, C.; Shen, H.; Quinn, D.A.; et al. TLR4 through IFN-beta Promotes Low Molecular Mass Hyaluronan-Induced Neutrophil Apoptosis. *J. Immunol.* **2011**, *186*, 556–562. [CrossRef] [PubMed]

24. Yan, B.; Wei, J.J.; Yuan, Y.; Sun, R.; Li, D.; Luo, J.; Liao, S.J.; Zhou, Y.H.; Shu, Y.; Wang, Q.; et al. IL-6 Cooperates with G-CSF To Induce Protumor Function of Neutrophils in Bone Marrow by Enhancing STAT3 Activation. *J. Immunol.* **2013**, *190*, 5882–5893. [CrossRef] [PubMed]

25. Zou, J.M.; Qin, J.; Li, Y.C.; Wang, Y.; Li, D.; Shu, Y.; Luo, C.; Wang, S.S.; Chi, G.; Guo, F.; et al. IL-35 induces N2 phenotype of neutrophils to promote tumor growth. *Oncotarget* **2017**, *8*, 33501–33514. [CrossRef]

26. Sun, R.; Luo, J.; Li, D.; Shu, Y.; Luo, C.; Wang, S.S.; Qin, J.; Zhang, G.M.; Feng, Z.H. Neutrophils with protumor potential could efficiently suppress tumor growth after cytokine priming and in presence of normal NK cells. *Oncotarget* **2014**, *5*, 12621–12634. [CrossRef]

27. Hasegawa, H.; Yamada, Y.; Harasawa, H.; Tsuji, T.; Murata, K.; Sugahara, K.; Tsuruda, K.; Masuda, M.; Takasu, N.; Kamihira, S. Restricted expression of tumor necrosis factor-related apoptosis-inducing ligand receptor 4 in human peripheral blood lymphocytes. *Cell. Immunol.* **2004**, *231*, 1–7. [CrossRef]

28. Ligouri, M.; Buracchi, C.; Pasqualini, F.; Bergomas, F.; Pesce, S.; Sironi, M.; Grizzi, F.; Mantovani, A.; Belgiojone, C.; Allavena, P. Functional TRAIL receptors in monocytes and tumor-associated macrophages: A possible targeting pathway in the tumor microenvironment. *Oncotarget* **2016**, *7*, 41662–41676. [CrossRef]

29. Daigle, I.; Simon, H.U. Alternative functions for TRAIL receptors in eosinophils and neutrophils. *Swiss Med. Wkly* **2001**, *131*, 231–237.

30. Domínguez, G.A.; Condamine, T.; Mony, S.; Hashimoto, A.; Wang, F.; Liu, Q.; Forero, A.; Bendell, J.; Witt, R.; Hockstein, N.; et al. Selective Targeting of Myeloid-Derived Suppressor Cells in Cancer Patients Using DS-8273a, an Agonistic TRAIL-R2 Antibody. *Clin. Cancer Res.* **2017**, *23*, 2942–2950. [CrossRef]

31. Hoffmann, O.; Priller, J.; Prozorovski, T.; Schulze-Topploff, U.; Baeva, N.; Lunemann, J.D.; Aktas, O.; Mahrhofer, C.; Stricker, S.; Zipp, F.; et al. TRAIL limits excessive host immune responses in bacterial meningitis. *J. Clin. Investig.* **2007**, *117*, 2004–2013. [CrossRef] [PubMed]

32. Beyer, K.; Poetschke, C.; Partecke, L.I.; von Bernstorff, W.; Maier, S.; Broeker, B.M.; Heidecke, C.D. TRAIL Induces Neutrophil Apoptosis and Dampens Sepsis-Induced Organ Injury in Murine Colon Ascendens Stent Peritonitis. *PLoS ONE* **2014**, *9*, e97451. [CrossRef] [PubMed]

33. Zheng, S.J.; Jiang, J.; Shen, H.; Chen, Y.H. Reduced Apoptosis and Ameliorated Listeriosis in TRAIL-Null Mice. *J. Immunol.* **2004**, *173*, 5652–5658. [CrossRef] [PubMed]

34. Cziupka, K.; Busemann, A.; Partecke, L.I.; Pötschke, C.; Rath, M.; Traeger, T.; Koerner, P.; von Bernstorff, W.; Kessler, W.; Diedrich, S.; et al. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) improves the innate immune response and enhances survival in murine polymicrobial sepsis. *Crit. Care Med.* **2010**, *38*, 2169–2174. [CrossRef] [PubMed]

35. Nagase, H.; Miyamasu, M.; Yamaguchi, M.; Imanishi, M.; Tsuno, N.H.; Matsushima, K.; Yamamoto, K.; Morita, Y.; Hirai, K. Cytokine-mediated regulation of CXCR4 expression in human neutrophils. *J. Leukoc. Biol.* **2002**, *71*, 711–717. [PubMed]

36. Liew, P.X.; Kubes, P. The Neutrophil’s Role During Health and Disease. *Physiol. Rev.* **2019**, *99*, 1223–1248. [CrossRef]

37. Vogt, K.L.; Summers, C.; Condiffe, A.M. The clinical consequences of neutrophil priming. *Curr. Opin. Hematol.* **2019**, *26*, 22–27. [CrossRef]

38. Wang, X.; Qiu, L.; Li, Z.; Wang, X.Y.; Yi, H. Understanding the Multifaceted Role of Neutrophils in Cancer and Autoimmune Diseases. *Front. Immunol.* **2018**, *9*, 2456. [CrossRef]
39. McGrath, E.E.; Marriott, H.M.; Lawrie, A.; Francis, S.E.; Sabroe, I.; Renshaw, S.A.; Dockrell, D.H.; Whyte, M.K.B. TNF-related apoptosis-inducing ligand (TRAIL) regulates inflammatory neutrophil apoptosis and enhances resolution of inflammation. *J. Leukoc. Biol.* **2011**, *90*, 855–865. [CrossRef]

40. Koedel, U.; Frankenberger, T.; Kirschnek, S.; Obermaier, B.; Häcker, H.; Paul, R.; Häcker, G. Apoptosis Is Essential for Neutrophil Functional Shutdown and Determines Tissue Damage in Experimental Pneumococcal Meningitis. *PLoS Pathog.* **2009**, *5*, e1000461. [CrossRef]

41. Steinwede, K.; Henken, S.; Bohling, J.; Maus, R.; Ueberberg, B.; Brumshagen, C.; Brincks, E.L.; Griffith, T.S.; Welte, T.; Maus, U.A. TNF-related apoptosis-inducing ligand (TRAIL) exerts therapeutic efficacy for the treatment of pneumococcal pneumonia in mice. *J. Exp. Med.* **2012**, *209*, 1937–1952. [CrossRef] [PubMed]

42. Shinnoh, M.; Horinaka, M.; Yasuda, T.; Yoshikawa, S.; Morita, M.; Yamada, T.; Miki, T.; Sakai, T. Clostridium butyricum MIYAIRI 588 shows antitumor effects by enhancing the release of TRAIL from neutrophils through MMP-8. *Int. J. Oncol.* **2013**, *42*, 903–911. [CrossRef] [PubMed]

43. Ludwig, A.T.; Moore, J.M.; Luo, Y.; Chen, X.; Saltsgaver, N.A.; O'Donnell, M.A.; Griffith, T.S. Tumor necrosis factor-related apoptosis-inducing ligand: A novel mechanism for Bacillus Calmette-Guérin-induced antitumor activity. *Cancer Res.* **2004**, *64*, 3386–3390. [CrossRef] [PubMed]

44. Jablonska, E.; Jablonski, J.; Marcinczyk, M.; Grabowska, Z.; Piotrowski, L. The release of soluble forms of TRAIL and DRS by neutrophils of oral cavity cancer patients. *Folia Histochem. Cytobiol.* **2008**, *46*, 177–183. [CrossRef] [PubMed]

45. Sawicka-Powierza, J.; Jablonska, E.; Kloczko, J.; Piszcz, J.; Garley, M.; Ratajczk-Wrona, W. Evaluation of TNF superfamily molecules release by neutrophils and B leukemic cells of patients with chronic B-Cell lymphocytic leukemia. *Neoplasma* **2011**, *58*, 45–50. [CrossRef] [PubMed]

46. Lu, G.; Janjic, B.M.; Janjic, J.; Whiteside, T.L.; Storkus, W.J.; Vujanovic, N.L. Innate Direct Anticancer Effector Function of Human Immature Dendritic Cells. II. Role of TNF, Lymphotoxin-α182, Fas Ligand, and TNF-Related Apoptosis-Inducing Ligand. *J. Immunol.* **2002**, *168*, 1831–1839. [CrossRef]

47. Griffith, T.S.; Wiley, S.R.; Kubin, M.Z.; Sedger, L.M.; Maliszewski, C.R.; Fanger, N.A. Monocyte-mediated Tumoricidal Activity via the Tumor Necrosis Factor-related Cytokine, TRAIL. *J. Exp. Med.* **1999**, *189*, 1343–1354. [CrossRef]

48. Halaas, O.; Vik, R.; Ashkenazi, A.; Espevik, T. Lipopolysaccharide induces expression of APO2 ligand/TRAIL in human monocytes and macrophages. *Scand. J. Immunol.* **2000**, *51*, 244–250. [CrossRef]

49. Fanger, N.A.; Maliszewski, C.R.; Schooley, K.; Griffith, T.S. Human Dendritic Cells Mediate Cellular Apoptosis via Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (Trail). *J. Exp. Med.* **1999**, *190*, 1155–1164. [CrossRef]

50. Yamamoto, T.; Nagano, H.; Sakon, M.; Wada, H.; Eguchi, H.; Kondo, M.; Damdinsuren, B.; Ota, H.; Nakamura, M.; Wada, H.; et al. Partial contribution of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)/TRAIL receptor pathway to antitumor effects of interferon-alpha/5-fluorouracil against Hepatocellular Carcinoma. *Clin. Cancer Res.* **2004**, *10*, 7884–7895. [CrossRef]

51. Kemp, T.J.; Moore, J.M.; Griffith, T.S. Human B Cells Express Functional TRAIL/Apo-2 Ligand after CpG-Containing Oligodeoxynucleotide Stimulation. *J. Immunol.* **2004**, *173*, 892–899. [CrossRef] [PubMed]

52. Washburn, B.; Weigand, M.A.; Grosse-Wilde, A.; Janke, M.; Stahl, H.; Rieser, E.; Sprick, M.R.; Schirmacher, V.; Walczak, H. TNF-Related Apoptosis-Inducing Ligand Mediates Tumoricidal Activity of Human Monocytes Stimulated by Newcastle Disease Virus. *J. Immunol.* **2003**, *170*, 1814–1821. [CrossRef]

53. Ehrlich, S.; Infante-Duarte, C.; Seeger, B.; Zipp, F. Regulation of soluble and surface-bound TRAIL in human T cells, B cells, and monocytes. *Cytokine* **2003**, *18*, 244–253. [CrossRef]

54. Mehmut, M.; Takeda, K.; Abe, M.; Ogata, H.; Hirose, S.; Okumura, K.; Fujime, M. Fas Ligand and TNF-Related Apoptosis-Inducing Ligand Induction on Infiltrating Lymphocytes in Bladder Carcinoma by Bacillus Calmette-Guérin Treatment. *Urol. Int.* **2005**, *75*, 80–87. [CrossRef] [PubMed]

55. Halin, S.; Rudolfsson, S.H.; Doll, I.A.; Crawford, S.E.; Wikström, P.; Bergh, A. Pigment Epithelium-Derived Factor Stimulates Tumor Macrophage Recruitment and Is Downregulated by the Prostate Tumor Microenvironment. *Neoplasia (New York)* **2010**, *12*, 336–345. [CrossRef]

56. Ho, T.C.; Chen, S.L.; Shih, S.C.; Chang, S.J.; Yang, S.L.; Hsieh, J.W.; Cheng, H.C.; Chen, L.J.; Tsao, Y.P. Pigment Epithelium-derived Factor (PEDF) Promotes Tumor Cell Death by Inducing Macrophage Membrane Tumor Necrosis Factor-related Apoptosis-inducing Ligand (TRAIL). *J. Biol. Chem.* **2011**, *286*, 35943–35954. [CrossRef]
57. Secchiero, P.; Rimondi, E.; di Iasio, M.G.; Agnoletto, C.; Melloni, E.; Volpi, I.; Zauli, G. C-Reactive Protein Downregulates TRAIL Expression in Human Peripheral Monocytes via an Egr-1-Dependent Pathway. *Clin. Cancer Res.* 2013, 19, 1949–1959. [CrossRef]  
58. Kaplan, M.J.; Ray, D.; Mo, R.R.; Yung, R.L.; Richardson, B.C. TRAIL (Apo2 Ligand) and TWEAK (Apo3 Ligand) Mediate CD4+ T Cell Killing of Antigen-Presenting Macrophages. *J. Immunol.* 2000, 164, 2897–2904. [CrossRef]  
59. Diehl, G.E.; Yue, H.H.; Hsieh, K.; Kuang, A.A.; Ho, M.; Morici, L.A.; Lenz, L.L.; Cado, D.; Riley, L.W.; Winoto, A. TRAIL-R as a negative regulator of innate immune cell responses. *Immunity* 2004, 21, 877–889. [CrossRef]  
60. Huang, Y.; Wang, Y.; Li, X.; Chen, Z.; Li, X.; Wang, H.; Ni, M.; Li, J. Molecular mechanism of ER stress-induced gene expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in macrophages. *F1000Prime Rep.* 2015, 282, 2361–2378. [CrossRef]  
61. Martinez, F.O.; Gordon, S. The M1 and M2 paradigm of macrophage activation: Time for reassessment. *F1000Prime Rep.* 2014, 6, 13. [CrossRef] [PubMed]  
62. Germano, G.; Frapolli, R.; Belgiovine, C.; Anselmo, A.; Pesce, S.; Liguori, M.; Erba, E.; Uboldi, S.; Zucchetti, M.; Pasqualini, F.; et al. Role of Macrophage Targeting in the Antitumor Activity of Trabectedin. *Cancer Cell* 2013, 23, 249–262. [CrossRef]  
63. Huang, Y.J.; Hsu, S.H. TRAIL-functionalized gold nanoparticles selectively trigger apoptosis in polarized macrophages. *Nanotheranostics* 2017, 1, 326–337. [CrossRef] [PubMed]  
64. Wei, W.; Wang, D.; Shi, J.; Xiang, Y.; Zhang, Y.; Liu, S.; Liu, Y.; Zheng, D. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) induces chemotactic migration of monocytes via a death receptor 4-mediated RhoGTPase pathway. *Mol. Immunol.* 2010, 47, 2475–2484. [CrossRef]  
65. Li, J.; Yang, P.; Wu, Q.; Li, H.; Ding, Y.; Hsu, H.C.; Spalding, D.M.; Mountz, J.D. Death receptor 5-targeted depletion of interleukin-23-producing macrophages, Th17, and Th1/17 associated with defective tyrosine phosphatase in mice and patients with rheumatoid arthritis. *Arthritis Rheum.* 2013, 65, 2594–2605. [CrossRef] [PubMed]  
66. Secchiero, P.; Candido, R.; Corallini, F.; Zacchigna, S.; Toffoli, B.; Rimondi, E.; Fabris, B.; Giaccia, M.; Zauli, G. Systemic Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Delivery Shows Antiatherosclerotic Activity in Apolipoprotein E-Null Diabetic Mice. *Circulation* 2006, 112, 1522–1530. [CrossRef]  
67. Di Bartolo, B.A.; Chan, J.; Bennett, M.R.; Cartland, S.; Bao, S.; Tuch, B.E.; Kavurma, M.M. TNF-related apoptosis-inducing ligand (TRAIL) protects against diabetes and atherosclerosis in Apoe<sup>−/−</sup> mice. *Diabetologia* 2011, 54, 3157–3167. [CrossRef]  
68. Li, J.; Hsu, H.C.; Yang, P.; Wu, Q.; Li, H.; Edgington, L.E.; Bogyo, M.; Kimberly, R.P.; Mountz, J.D. Treatment of arthritis by macrophage depletion and immunomodulation: Testing an apoptosis-mediated therapy in a humanized death receptor mouse model. *Arthritis Rheum.* 2012, 64, 1098–1109. [CrossRef] [PubMed]  
69. Zhang, S.; Li, Z.; Huang, W. Interleukin-4 Enhances the Sensitivity of Human Monocytes to Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Through Upregulation of Death Receptor 4. *J. Interferon Cytokine Res.* 2018, 38, 186–194. [CrossRef]  
70. Yao, Z.; Zhang, P.; Guo, H.; Shi, J.; Liu, S.; Liu, Y.; Zheng, D. RIP1 modulates death receptor mediated apoptosis and autophagy in macrophages. *Mol. Oncol.* 2014, 9, 806–817. [CrossRef] [PubMed]  
71. Strebel, A.; Bachmann, F.; Wernli, M.; Erb, P. Tumor necrosis factor-related, apoptosis-inducing ligand supports growth of mouse mastocytoma tumors by killing tumor-infiltrating macrophages. *Int. J. Cancer* 2002, 100, 627–634. [CrossRef] [PubMed]  
72. Liu, F.; Cheng, W.; Bi, X.; Zhang, Y.; Zhao, Y.; Jiang, F. Stage-dependent effects of exogenous TRAIL on atherogenesis: Role of ER stress-mediated sensitization of macrophage apoptosis. *Clin. Exp. Pharmacol. Physiol.* 2016, 43, 543–551. [CrossRef] [PubMed]  
73. Herbeuval, J.P.; Lambert, C.; Sabido, O.; Cottier, M.; Fournel, P.; Dy, M.; Genin, C. Macrophages from cancer patients: Analysis of TRAIL, TRAIL receptors, and colon tumor cell apoptosis. *J. Nat. Cancer Inst.* 2003, 95, 611–621. [CrossRef] [PubMed]  
74. Secchiero, P.; Gonelli, A.; Mirandola, P.; Melloni, E.; Zamai, L.; Celeghini, C.; Milani, D.; Zauli, G. Tumor necrosis factor-related apoptosis-inducing ligand induces monocytic maturation of leukemic and normal myeloid precursors through a caspase-dependent pathway. *Blood* 2002, 100, 2421–2429. [CrossRef] [PubMed]
75. Gao, J.; Wang, D.; Liu, D.; Liu, M.; Ge, Y.; Jiang, M.; Liu, Y.; Zheng, D. Tumor necrosis factor–related apoptosis-inducing ligand induces the expression of proinflammatory cytokines in macrophages and re-educates tumor-associated macrophages to an antitumor phenotype. *Mol. Biol. Cell* **2015**, *26*, 3178–3189. [CrossRef] [PubMed]

76. Kim, J.Y.; Kim, Y.M.; Park, J.M.; Han, Y.M.; Lee, K.C.; Hahm, K.B.; Hong, S. Cancer preventive effect of recombinant TRAIL by ablation of oncogenic inflammation in colitis-associated cancer rather than anticancer effect. *Onco Targets* **2018**, *9*, 1705–1716. [CrossRef] [PubMed]

77. Vidalain, P.O.; Azocar, O.; Yagita, H.; Rabourdin-Combe, C.; Servet-Delprat, C. Cytotoxic Activity of Human Dendritic Cells Is Differentially Regulated by Double-Stranded RNA and CD40 Ligand. *J. Immunol.* **2001**, *167*, 3765–3772. [CrossRef]

78. Shi, J.; Ikeda, K.; Maeda, Y.; Shinagawa, K.; Ohtsuka, A.; Yamamura, H.; Tanimoto, M. Identification of CD123+ myeloid dendritic cells as an early-stage immature subset with strong tumoristatic potential. *Cancer Lett.* **2008**, *270*, 19–29. [CrossRef] [PubMed]

79. Wang, M.; Shi, J.; Wan, Y.; Li, J.; Yuan, Y. A subset of myeloid dendritic cells derived from peripheral blood monocytes represented a predominant subset characterized by their potential tumor-inhibiting activity. *Vitr. Cell Dev. Biol. Anim.* **2009**, *45*, 398–404. [CrossRef]

80. Anguille, S.; Lion, E.; Tel, J.; de Vries, I.J.M.; Couturier, K.; Fromm, P.D.; Van Tendeloo, V.F.; Smits, E.L.; Berneman, Z.N. Interleukin-15-Induced CD56+ Myeloid Dendritic Cells Combine Potent Tumor Antigen Presentation with Direct Tumoral Potential. *PLoS ONE* **2012**, *7*, e51851. [CrossRef]

81. Liu, S.; Yu, Y.; Zhang, M.; Wang, W.; Cao, X. The Involvement of TNF-β-Related Apoptosis-Inducing Ligand in the Enhanced Cytotoxicity of IFN-α-Stimulated Human Dendritic Cells to Tumor Cells. *J. Immunol.* **2001**, *166*, 5407–5415. [CrossRef] [PubMed]

82. Santini, S.M.; Lapenta, C.; Logozzi, M.; Parlato, S.; Spada, M.; Di Pucchio, T.; Belardelli, F. Type I interferon as a powerful adjuvant for monocyte-derived dendritic cell development and activity in vitro and in Hu-PBL-SCID mice. *J. Exp. Med.* **2000**, *191*, 1777–1788. [CrossRef] [PubMed]

83. Korthals, M.; Safaian, N.; Kronenwett, R.; Maihöfer, D.; Schott, M.; Papewalis, C.; Diaz Blanco, E.; Winter, M.; Czibere, A.; Haas, R.; et al. Monocyte derived dendritic cells generated by IFN-α acquire mature dendritic and natural killer cell properties as shown by gene expression analysis. *J. Trans. Med.* **2007**, *5*, 46. [CrossRef] [PubMed]

84. Kalb, M.L.; Glaser, A.; Stary, G.; Koszik, F.; Stingl, G. TRAIL+ Human Plasmacytoid Dendritic Cells Kill Tumor Cells In Vitro: Mechanisms of Imiquimod- and IFN-α-Mediated Antitumor Reactivity. *J. Immunol.* **2012**, *188*, 1583–1591. [CrossRef] [PubMed]

85. Chaperot, L.; Blum, A.; Manches, O.; Lui, G.; Angel, J.; Molens, J.P.; Plumas, J. Virus or TLR Agonists Induce TRAIL-Mediated Cytotoxic Activity of Plasmacytoid Dendritic Cells. *J. Immunol.* **2005**, *176*, 248–255. [CrossRef] [PubMed]

86. Taieb, J.; Chaput, N.; Ménard, C.; Apetoh, L.; Ullrich, E.; Bonmort, M.; Péquignot, M.; Casares, N.; Termé, M.; Flamant, C.; et al. A novel dendritic cell subset involved in tumor immunosurveillance. *Nat. Med.* **2006**, *12*, 214–219. [CrossRef] [PubMed]

87. Papewalis, C.; Jacobs, B.; Wuttke, M.; Ullrich, E.; Baehring, T.; Fenk, R.; Willenberg, H.S.; Schinner, S.; Cohnen, M.; Seissler, J.; et al. IFN-alpha skew monocytes into CD56+ expressing dendritic cells with potent functional activities in vitro and in vivo. *J. Immunol.* **2008**, *180*, 1462–1470. [CrossRef] [PubMed]

88. Hardy, A.W.; Graham, D.R.; Shearer, G.M.; Herbeuval, J.P. HIV turns plasmacytoid dendritic cells (pDC) into TRAIL-expressing killer pDC and down-regulates HIV coreceptors by Toll-like receptor 7-induced IFN-alpha. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 17453–17458. [CrossRef] [PubMed]

89. Molenkamp, B.G.; van Leeuwen, P.A.M.; Meijer, S.; Sluijter, B.J.R.; Wijnands, P.G.J.T.B.; Baars, A.; van den Eertwegh, A.J.M.; Scheper, R.J.; de Gruijl, T.D. Intradermal CpG-B Activates Both Plasmacytoid and Myeloid Dendritic Cells in the Sentinel Lymph Node of Melanoma Patients. *Clin. Cancer Res.* **2007**, *13*, 2961–2969. [CrossRef] [PubMed]

90. Cho, Y.S.; Challa, S.; Clancy, L.; Chan, F.K.M. Lipopolysaccharide-induced expression of TRAIL promotes dendritic cell differentiation. *Immunology* **2010**, *130*, 504–515. [CrossRef] [PubMed]
Cancers 2019, 11, 1469

91. Achard, C.; Guillerme, J.B.; Bruni, D.; Boisgerault, N.; Combredet, C.; Tangy, F.; Jouvenet, N.; Grégoire, M.; Fonteneau, J.F. Oncolytic measles virus induces tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated cytotoxicity by human myeloid and plasmacytoid dendritic cells. *Oncoimmunology* 2017, 6, e1261240. [CrossRef] [PubMed]

92. Stary, G.; Klein, I.; Kohlhofer, S.; Koszik, F.; Scherzer, T.; Müllauer, L.; Quendler, H.; Kohrgruber, N.; Stingl, G. Plasmacytoid dendritic cells express TRAIL and induce CD4+ T-cell apoptosis in HIV-1 viremic patients. *Blood* 2009, 114, 3854–3863. [CrossRef] [PubMed]

93. Thomann, S.; Boscheinen, J.B.; Vogel, K.; Knipe, D.M.; DeLuca, N.; Gross, S.; Schulzer-Thurner, B.; Schuster, P.; Schmidt, B. Combined cytotoxic activity of an infectious, but non-replicative herpes simplex virus type 1 and plasmacytoid dendritic cells against tumour cells. *Immunology* 2015, 146, 327–338. [CrossRef] [PubMed]

94. Roux, S.; Apetoh, L.; Chalmin, F.; Ladoire, S.; Mignot, G.; Puig, P.E.; Lauvau, G.; Zitvogel, L.; Martin, F.; Chauffert, B.; et al. CD4+CD25+ Tregs control the TRAIL-dependent cytotoxicity of tumor-infiltrating DCs in rodent models of colon cancer. *J. Clin. Investig.* 2008, 118, 3751–3761. [CrossRef] [PubMed]

95. Drobits, B.; Holmann, M.; Amberg, N.; Sweicke, M.; Grundtner, R.; Hammer, M.; Colonna, M.; Sibilia, M. Imiquimod clears tumors in mice independent of adaptive immunity by converting pDCs into tumor-killing effector cells. *J. Clin. Investig.* 2012, 122, 575–585. [CrossRef]

96. Wu, J.; Li, S.; Yang, Y.; Zhu, S.; Zhang, M.; Qiao, Y.; Liu, Y.J.; Chen, J. TLR-activated plasmacytoid dendritic cells inhibit breast cancer cell growth in vitro and in vivo. *Oncotarget* 2017, 8, 11708–11718. [CrossRef] [PubMed]

97. Arina, A.; Murillo, O.; Dubrot, J.; Azpilikueta, A.; Gabari, I.; Perez-Gracia, J.L.; Alfaro, C.; Berasain, C.; Prieto, J.; Ferrini, S.; et al. Interleukin-15 liver gene transfer increases the number and function of iDCs and NK cells. *Gene Ther.* 2008, 15, 473–483. [CrossRef]

98. Hira, S.K.; Mondal, I.; Bhattacharya, D.; Manna, P.P. Downregulation of endogenous STAT3 augments tumoricidal activity of interleukin 15 activated dendritic cell against lymphoma and leukemia via TRAIL. *Exp. Cell Res.* 2014, 327, 192–208. [CrossRef]

99. You, R.I.; Chang, Y.C.; Chen, P.M.; Wang, W.S.; Hsu, T.L.; Yang, C.Y.; Lee, C.T.; Hsieh, S.L. Apoptosis of dendritic cells induced by decoy receptor 3 (DcR3). *Blood* 2008, 111, 1480–1488. [CrossRef]

100. Blum, A.; Chaperot, L.; Molens, J.P.; Foissaud, V.; Plantaz, D.; Plumas, J. Mechanisms of TRAIL-induced apoptosis in leukemic plasmacytoid dendritic cells. *Exp. Hematol.* 2006, 34, 1655–1662. [CrossRef]

101. Hayakawa, Y.; Serepani, V.; Yagita, H.; Grandien, A.; Ljunggren, H.G.; Smyth, M.J.; Chambers, B.J. NK cell TRAIL eliminates immature dendritic cells in vivo and limits dendritic cell vaccination efficacy. *J. Immunol.* 2004, 172, 123–129. [CrossRef]

102. Ciesek, S.; Liermann, H.; Hadem, J.; Greten, T.; Tillmann, H.L.; Cornberg, M.; Aslan, N.; Manns, M.P.; Wedemeyer, H. Impaired TRAIL-dependent cytotoxicity of CD1c-positive dendritic cells in chronic hepatitis C virus infection. *J. Viral Hepat.* 2007, 15, 200–211. [CrossRef]

103. Tyrinova, T.V.; Lepina, O.Y.; Mishinov, S.V.; Tikhonova, M.A.; Shevela, E.Y.; Stupak, V.V.; Pendyurin, I.V.; Shilov, A.G.; Alyamkina, E.A.; Rubsova, N.V.; et al. Cytotoxic activity of ex-vivo generated IFNα-induced monocyte-derived dendritic cells in brain glioma patients. *Cell. Immunol.* 2013, 284, 146–153. [CrossRef] [PubMed]

104. Lepina, O.Y.; Tyrinova, T.V.; Tikhonova, M.A.; Ostanin, A.A.; Chernykh, E.R. Interferon alpha induces generation of semi-mature dendritic cells with high pro-inflammatory and cytotoxic potential. *Cytokine* 2015, 71, 1–7. [CrossRef] [PubMed]

105. Tel, J.; Smits, E.L.; Anguille, S.; Joshi, R.N.; Figdor, C.G.; de Vries, I.J.M. Human plasmacytoid dendritic cells are equipped with antigen-presenting and tumoricidal capacities. *Blood* 2012, 120, 3936–3944. [CrossRef] [PubMed]

106. Iyori, M.; Zhang, T.; Pantel, H.; Gagne, B.A.; Sentman, C.L. TRAIL/DR5 Plays a Critical Role in NK Cell-Mediated Negative Regulation of Dendritic Cell Cross-Priming of T Cells. *J. Immunol.* 2011, 187, 3087–3095. [CrossRef] [PubMed]

107. Förster, A.; Falcone, E.H.; Gibbs, B.F.; Preussner, L.M.; Fiebig, B.S.; Alunok, H.; Seeger, J.M.; Cerny-Reiterer, S.; Rabenhorst, A.; Papenfuss, K.; et al. Anti-Fas/CD95 and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) differentially regulate apoptosis in normal and neoplastic human basophils. *Leuk. Lymphoma* 2012, 54, 835–842. [CrossRef]
108. Florian, S.; Sonneck, K.; Czerny, M.; Hennersdorf, F.; Hauswirth, A.W.; Buhring, H.J.; Valent, P. Detection of novel leukocyte differentiation antigens on basophils and mast cells by HLDA8 antibodies. *Allergy* 2006, 61, 1054–1062. [CrossRef] [PubMed]

109. Berent-Maoz, B.; Filipovsky, A.M.; Daigle, I.; Simon, H.U.; Levi-Schaffer, F. Human Mast Cells Undergo TRAIL-Induced Apoptosis. *J. Immunol.* 2006, 176, 2272–2278. [CrossRef]

110. Berent-Maoz, B.; Salemi, S.; Mankuta, D.; Simon, H.U.; Levi-Schaffer, F. Original article: TRAIL mediated signaling in human mast cells: The influence of IgE-dependent activation. *Allergy* 2008, 63, 333–340. [CrossRef]

111. Vassina, E.; Leverkus, M.; Yousefi, S.; Braathen, L.R.; Simon, H.U.; Simon, D. Increased Expression and a Potential Anti-Inflammatory Role of TRAIL in Atopic Dermatitis. *J. Investig. Dermatol.* 2005, 125, 746–752. [CrossRef] [PubMed]

112. Jakiela, B.; Szczeklik, W.; Sokolowska, B.; Mastalerz, L.; Sanak, M.; Plutecka, H.; Szczeklik, A. Intrinsic pathway of apoptosis in peripheral blood eosinophils of Churg–Strauss syndrome. *Rheumatology* 2009, 48, 1202–1207. [CrossRef] [PubMed]

113. Robertson, N.M.; Zangrilli, J.G.; Steplewski, A.; Hastie, A.; Lindemeyer, R.G.; Planeta, M.A.; Smith, M.K.; Innocent, N.; Musani, A.; Pascual, R.; et al. Differential Expression of TRAIL and TRAIL Receptors in Allergic Asthmatics Following Segmental Antigen Challenge: Evidence for a Role of TRAIL in Eosinophil Survival. *J. Immunol.* 2002, 169, 5986–5996. [CrossRef] [PubMed]

114. Mitsuyama, H.; Matsuyama, W.; Watanabe, M.; Shiraibana, Y.; Higashimoto, I.; Wada, T.; Osame, M.; Arimura, K. Increased expression of TRAIL receptor 3 on eosinophils in Churg–Strauss syndrome. *Arthritis Rheum.* 2007, 56, 662–673. [CrossRef]

115. Noth, I.; Strek, M.E.; Leff, A.R. Churg-Strauss syndrome. *Lancet* 2003, 361, 587–594. [CrossRef]

116. Weckmann, M.; Collison, A.; Simpson, J.L.; Kopp, M.V.; Wark, P.A.B.; Smyth, M.J.; Yagita, H.; Matthaei, K.I.; Hansbro, N.; Whitehead, B.; et al. Critical link between TRAIL and CCL20 for the activation of TH2 cells and the expression of allergic airway disease. *Nat. Med.* 2007, 13, 1308–1315. [CrossRef]

117. Collison, A.; Hatchwell, L.; Verrills, N.; Wark, P.A.B.; de Siqueira, A.P.; Tooze, M.; Carpenter, H.; Don, A.S.; Morris, J.C.; Zimmermann, N.; et al. The E3 ubiquitin ligase midline 1 promotes allergen and rhinovirus-induced asthma by inhibiting protein phosphatase 2A activity. *Nat. Med.* 2013, 19, 232–237. [CrossRef] [PubMed]

118. Mishra, A.; Hogan, S.P.; Brandt, E.B.; Rothenberg, M.E. IL-5 Promotes Eosinophil Trafficking to the Esophagus. *J. Immunol.* 2002, 168, 2464–2469. [CrossRef]

119. Flood-Page, P.; Menzies-Gow, A.; Phipps, S.; Ying, S.; Wangoo, A.; Ludwig, M.S.; Barnes, N.; Robinson, D.; Kay, A.B. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J. Clin. Invest.* 2003, 112, 1029–1036. [CrossRef]

120. Girkin, J.L.; Hatchwell, L.M.; Collison, A.M.; Starkey, M.R.; Hansbro, P.M.; Yagita, H.; Foster, P.S.; Mattes, J. TRAIL signaling is proinflammatory and proviral in a murine model of rhinovirus 1B infection. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 2017, 312, L89–L99. [CrossRef]

121. Collison, A.M.; Sokulsky, L.A.; Sherrill, J.D.; Nightingale, S.; Hatchwell, L.; Talley, N.J.; Walker, M.M.; Rothenberg, M.E.; Mattes, J. TNF-related apoptosis-inducing ligand (TRAIL) regulates midline-1, thymic stromal lymphopoietin, inflammation, and remodeling in experimental eosinophilic esophagitis. *J. Allergy Clin. Immunol.* 2015, 136, 971–982. [CrossRef] [PubMed]

122. Tsato, V.; Garrovo, C.; Biffi, S.; Petreza, F.; Voltan, R.; Casciano, F.; Menoni, G.; Agnoletto, C.; Zauli, G.; Secchiero, P. Intranasal Administration of Recombinant TRAIL Down-Regulates CXCL-1/KC in an Ovalbumin-Induced Airway Inflammation Murine Model. *PLoS ONE* 2014, 9, e115387. [CrossRef] [PubMed]

123. Faustino, L.; Fonseca, D.M.; Florsheim, E.B.; Resende, R.R.; Lepique, A.P.; Faquim-Mauro, E.; Gomes, E.; Silva, J.S.; Yagita, H.; Russo, M. Tumor necrosis factor-related apoptosis-inducing ligand mediates the resolution of allergic airway inflammation induced by chronic allergen inhalation. *Mucosal Immunol.* 2014, 7, 1199–1208. [CrossRef] [PubMed]

124. Collison, A.; Li, J.; Pereira de Siqueira, A.; Zhang, J.; Toop, H.D.; Morris, J.C.; Foster, P.S.; Mattes, J. Tumor Necrosis Factor–Related Apoptosis-Inducing Ligand Regulates Hallmark Features of Airways Remodeling in Allergic Airways Disease. *Am. J. Respir. Cell Mol. Biol.* 2014, 51, 86–93. [CrossRef]

125. Marvel, D.; Gabrilovich, D.I. Myeloid-derived suppressor cells in the tumor microenvironment: Expect the unexpected. *J. Clin. Investig.* 2015, 125, 3356–3364. [CrossRef] [PubMed]
126. Hartwig, T.; Montinaro, A.; von Karstedt, S.; Sevko, A.; Surinova, S.; Chakravarthy, A.; Taraborrelli, L.; Draber, P.; Lafont, E.; Vargas, F.A.; et al. The TRAIL-Induced Cancer Secretome Promotes a Tumor-Supportive Immune Microenvironment via CCR2. *Mol. Cell* **2017**, *65*, 730–742. [CrossRef]

127. Condamine, T.; Kumar, V.; Ramachandran, I.R.; Yoon, J.I.; Celis, E.; Finnberg, N.; El-Deiry, W.S.; Winograd, R.; Vanderheide, R.H.; English, N.R.; et al. ER stress regulates myeloid-derived suppressor cell fate through TRAIL-R–mediated apoptosis. *J. Clin. Investig.* **2014**, *124*, 2626–2639. [CrossRef]

128. Kajitani, K.; Tanaka, Y.; Arihiro, K.; Kataoka, T.; Ohdan, H. Mechanistic analysis of the antitumor efficacy of human natural killer cells against breast cancer cells. *Breast Cancer Res. Treat.* **2012**, *134*, 139–155. [CrossRef]

129. Berg, M.; Lundqvist, A.; McCoy, P., Jr.; Samsel, L.; Fan, Y.; Tawab, A.; Childs, R. Clinical-grade ex vivo-expanded human natural killer cells up-regulate activating receptors and death receptor ligands and have enhanced cytolytic activity against tumor cells. *Cytotherapy* **2009**, *11*, 341–355. [CrossRef]

130. Kashii, Y.; Giorda, R.; Herberman, R.B.; Whiteside, T.L.; Vujanovic, N.L. Constitutive expression and role of the TNF family ligands in apoptotic killing of tumor cells by human NK cells. *J. Immunol.* **1999**, *163*, 5358–5366.

131. Stegmann, K.A.; Björkström, N.K.; Veber, H.; Ciesek, S.; Riese, P.; Wiegand, J.; Hadem, J.; Suneetha, P.V.; Jaroszewicz, J.; Wang, C.; et al. Interferon-α–Induced TRAIL on Natural Killer Cells Is Associated With Control of Hepatitis C Virus Infection. *Gastroenterology* **2010**, *138*, 1885–1897. [CrossRef] [PubMed]

132. Allan, D.S.J.; Cerdeira, A.S.; Ranjan, A.; Kirkham, C.L.; Aguilar, O.A.; Tanaka, M.; Childs, R.W.; Dunbar, C.E.; Strominger, J.L.; Kopcow, H.D.; et al. Transcriptome analysis reveals similarities between human blood CD3−CD56bright cells and mouse CD127+ innate lymphoid cells. *Sci. Rep.* **2017**, *7*, 4480. [CrossRef] [PubMed]

133. Stegmann, K.A.; Robertson, F.; Hansi, N.; Gill, U.; Fallant, C.; Christophides, T.; Pallett, L.J.; Peppa, D.; Dunn, C.; Fusai, G.; et al. CXCR6 marks a novel subset of T-bet-lo Eomes-hi natural killer cells residing in human liver. *Sci. Rep.* **2016**, *6*, 26157. [CrossRef] [PubMed]

134. Hwang, S.; Han, J.; Baek, J.S.; Tak, E.; Song, G.W.; Lee, S.G.; Jung, D.H.; Park, G.C.; Ahn, C.S.; Kim, N. Cytotoxicity of Human Hepatic Intrasinusoidal CD56bright Natural Killer Cells against Hepatocellular Carcinoma Cells. *Int. J. Mol. Sci.* **2019**, *20*, 1564. [CrossRef] [PubMed]

135. Ishiyama, K.; Ohdan, H.; Ohira, M.; Mitsuta, H.; Arihiro, K.; Asahara, T. Difference in cytotoxicity against hepatocellular carcinoma between liver and periphery natural killer cells in humans. *Hepatology* **2006**, *43*, 362–372. [CrossRef] [PubMed]

136. Takeda, K.; Hayakawa, Y.; Smyth, M.J.; Kayagaki, N.; Yamaguchi, N.; Kakuta, S.; Iwakura, Y.; Yagita, H.; Okumura, K. Involvement of tumor necrosis factor-related apoptosis-inducing ligand in surveillance of tumor metastasis by liver natural killer cells. *Nat. Med.* **2001**, *7*, 94–100. [CrossRef]

137. Smyth, M.J.; Cretney, E.; Takeda, K.; Wiltrout, R.H.; Sedger, L.M.; Kayagaki, N.; Yagita, H.; Okumura, K. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) contributes to interferon gamma-dependent natural killer cell protection from tumor metastasis. *J. Exp. Med.* **2001**, *193*, 661–670. [CrossRef]

138. Ochi, M.; Ohdan, H.; Mitsuta, H.; Onoe, T.; Tokita, D.; Hara, H.; Ishiyama, K.; Zhou, W.; Tanaka, Y.; Asahara, T. Liver NK cells expressing TRAIL are toxic against self hepatocytes in mice. *Hepatology* **2004**, *39*, 1321–1331. [CrossRef]

139. Jiao, Y.; Huntington, N.D.; Belz, G.T.; Seillet, C. Type 1 Innate Lymphoid Cell Biology: Lessons Learnt from Natural Killer Cells. *Front. Immunol.* **2016**, *7*, 293. [CrossRef]

140. Robinette, M.L.; Colonna, M. Immune modules shaped by innate lymphoid cells and T cells. *J. Allergy Clin. Immunol.* **2016**, *138*, 1243–1251. [CrossRef]

141. Colonna, M. Innate Lymphoid Cells: Diversity, Plasticity, and Unique Functions in Immunity. *Immunity* **2018**, *48*, 1104–1117. [CrossRef] [PubMed]

142. Zhang, L.H.; Shin, J.H.; Haggadone, M.D.; Sunwoo, J.B. The aryl hydrocarbon receptor is required for the maintenance of liver-resident natural killer cells. *J. Exp. Med.* **2016**, *213*, 2249–2257. [CrossRef] [PubMed]

143. Dang, V.T.A.; Tanabe, K.; Tanaka, Y.; Tokumoto, N.; Misumi, T.; Saeki, Y.; Fujikuni, N.; Ohdan, H. Fasting Enhances TRAIL-Mediated Liver Natural Killer Cell Activity via HSP70 Upregulation. *PLoS ONE* **2014**, *9*, e110748. [CrossRef]

144. Peng, H.; Jiang, X.; Chen, Y.; Sojka, D.K.; Wei, H.; Gao, X.; Sun, R.; Yokoyama, W.M.; Tian, Z. Liver-resident NK cells confer adaptive immunity in skin-contact inflammation. *J. Clin. Investig.* **2013**, *123*, 1444–1456. [CrossRef] [PubMed]
145. Robinette, M.L.; Fuchs, A.; Cortez, V.S.; Lee, J.S.; Wang, Y.; Durum, S.K.; Gilfillan, S.; Colonna, M.; Consortium, I.G. Transcriptional programs define molecular characteristics of innate lymphoid cell classes and subsets. *Nat. Immunol.* 2015, 16, 306–317. [CrossRef] [PubMed]

146. Cortez, V.S.; Fuchs, A.; Cella, M.; Gilfillan, S.; Colonna, M. Cutting Edge: Salivary Gland NK Cells Develop Independently of Nfil3 in Steady-State. *J. Immunol.* 2014, 192, 4487–4491. [CrossRef] [PubMed]

147. Cortez, V.S.; Cervantes-Barragan, L.; Robinette, M.L.; Bando, J.K.; Wang, Y.; Geiger, T.L.; Gilfillan, S.; Fuchs, A.; Vivier, E.; Sun, J.C.; et al. Transforming Growth Factor-b Signaling Guides the Differentiation of Innate Lymphoid Cells in Salivary Glands. *Immunity* 2016, 44, 1127–1139. [CrossRef]

148. Cortez, V.S.; Fuchs, A.; Marçais, A.; Kueh, A.J.; Friede, M.E.; Liao, Y.; Willis, S.N.; Luong, K.; Faure, F.; Mercier, F.E.; et al. A point mutation in the Ncr1 signal peptide impairs the development of innate lymphoid cell subsets. *Oncoimmunology* 2018, 7, e1475875. [CrossRef] [PubMed]

149. Pallmer, K.; Barnstorf, I.; Baumann, N.S.; Borsa, M.; Jonjic, S.; Oxenius, A. NK cells negatively regulate CD8 T cells via natural cytotoxicity receptor (NCR) 1 during LCMV infection. *PloS Biol* 2018, 16, e2004867. [CrossRef] [PubMed]

150. Turchinovich, G.; Ganter, S.; Bärenwaldt, A.; Finke, D. NKp46 Calibrates Tumoricidal Potential of Type 1 Innate Lymphocytes by Regulating TRAIL Expression. *J. Immunol.* 2018, 200, 3762–3768. [CrossRef] [PubMed]

151. Sheppard, S.; Schuster, I.S.; Andoniou, C.E.; Cocita, C.; Adejumo, T.; Kung, S.K.P.; Sun, J.C.; Daussy, C.; Faure, F.; Mayol, K.; Viel, S.; Gasteiger, G.; Charrier, E.; Bienvenu, J.; Henry, T.; Debien, E.; Cortez, V.S.; Cervantes-Barragan, L.; Robinette, M.L.; Bando, J.K.; Wang, Y.; Geiger, T.L.; Gilfillan, S.; Colonna, M. Cutting Edge: Salivary Gland NK Cells Develop Independently of Nfil3 in Steady-State. *J. Immunol.* 2014, 192, 4487–4491. [CrossRef] [PubMed]

152. Wang, Y.; Dong, W.; Zhang, Y.; Caligiuri, M.A.; Yu, J. Dependence of innate lymphoid cell 1 development on T-bet and Eomes instruct the development of two distinct natural killer cell lineages in the liver and in the bone marrow. *J. Exp. Med.* 2014, 211, 563–577. [CrossRef]

153. Constantinides, M.G.; Gudjonson, H.; McDonald, B.D.; Ishizuka, I.E.; Verhoef, P.A.; Dinner, A.R.; Bendelac, A. PLZF expression maps the early stages of ILC1 lineage development. *Proc. Natl. Acad. Sci. USA* 2015, 112, 5123–5128. [CrossRef]

154. Almeida, F.F.; Tognarelli, S.; Marçais, A.; Kueh, A.J.; Friede, M.E.; Liao, Y.; Willis, S.N.; Luong, K.; Faure, F.; Mercier, F.E.; et al. A point mutation in the Ncr1 signal peptide impairs the development of innate lymphoid cell subsets. *Oncoimmunology* 2018, 7, e1475875. [CrossRef] [PubMed]

155. Gao, Y.; Souza-Fonseca-Guimaraes, F.; Bald, T.; Ng, S.S.; Young, A.; Ngioi, S.F.; Rautela, J.; Straube, J.; Waddell, N.; Blake, S.J.; et al. Tumor immunoevasion by the conversion of NK cells to a less cytotoxic ILC1-like phenotype. *PLoS Pathog.* 2019, 15, e1007725. [CrossRef] [PubMed]

156. Gao, Y.; Souza-Fonseca-Guimaraes, F.; Bald, T.; Ng, S.S.; Young, A.; Ngioi, S.F.; Rautela, J.; Straube, J.; Waddell, N.; Blake, S.J.; et al. Tumor immunoevasion by the conversion of effector NK cells into type 1 innate lymphoid cells. *Nat. Immunol.* 2017, 18, 1004–1015. [CrossRef]

157. Cuff, A.O.; Sillito, F.; Dertschnig, S.; Hall, A.; Luong, T.; Chakraverty, R.; Male, V. The obese liver environment mediates conversion of NK cells to a less cytotoxic ILC1-like phenotype. *Front. Immunol.* 2019, 10, 2180. [CrossRef]

158. Vivier, E.; Artis, D.; Colonna, M.; Diefenbach, A.; Di Santo, J.P.; Eberl, G.; Koyasu, S.; Locksley, R.M.; McKenzie, A.N.J.; Mebius, R.E.; et al. Innate Lymphoid Cells: 10 Years On. *Cell* 2018, 174, 1054–1066. [CrossRef] [PubMed]

159. Zamai, L.; Ahmad, M.; Bennett, I.M.; Azzoni, L.; Alnemri, E.S.; Perussia, B. Natural killer (NK) cell-mediated cytotoxicity: Differential use of TRAIL and Fas ligand by immature and mature primary human NK cells. *J. Exp. Med.* 1998, 188, 2375–2380. [CrossRef] [PubMed]

160. Mirandola, P.; Ponti, C.; Gobbi, G.; Sponzilli, I.; Vaccarezza, M.; Cocco, L.; Zauli, G.; Secchiero, P.; Manzoli, F.A.; Vitale, M. Activated human NK and CD8 T cells express both TNF-related apoptosis-inducing ligand (TRAIL) and TRAIL receptors but are resistant to TRAIL-mediated cytotoxicity. *Blood* 2004, 104, 2418–2424. [CrossRef]

161. Kayagaki, N.; Yamaguchi, N.; Nakayama, M.; Takeda, K.; Akiba, H.; Tsutsui, H.; Okamura, H.; Nakanoishi, K.; Okumura, K.; Yagita, H. Expression and function of TNF-related apoptosis-inducing ligand on murine activated NK cells. *J. Immunol.* 1999, 163, 1906–1913. [PubMed]

162. Zhang, C.; Zhang, J.; Niu, J.; Zhang, J.; Tian, Z. Interleukin-15 improves cytotoxicity of natural killer cells via up-regulating NKG2D and cytotoxic effector molecule expression as well as STAT1 and ERK1/2 phosphorylation. *Cytokine* 2008, 42, 128–136. [CrossRef] [PubMed]
163. Lelaidier, M.; Diaz-Rodriguez, Y.; Cordeau, M.; Cordeiro, P.; Haddad, E.; Herblot, S.; Duval, M. TRAIL-mediated killing of acute lymphoblastic leukemia by plasmacytoid dendritic cell-activated natural killer cells. *Oncotarget* **2015**, *6*, 29440–29455. [CrossRef] [PubMed]

164. Ahlenstiel, G.; Titerence, R.H.; Koh, C.; Edlich, B.; Feld, J.J.; Rotman, Y.; Ghany, M.G.; Hoofnagle, J.H.; Liang, T.J.; Heller, T.; et al. Natural Killer Cells Are Polarized Toward Cytotoxicity in Chronic Hepatitis C in an Interferon-Alpha–Dependent Manner. *Gastroenterology* **2010**, *138*, 325–335. [CrossRef] [PubMed]

165. Glässner, A.; Eisenhardt, M.; Krämer, B.; Körner, C.; Coenen, M.; Sauerbruch, T.; Spengler, U.; Nattermann, J. NK cells from HCV-infected patients effectively induce apoptosis of activated primary human hepatic stellate cells in a TRAIL-, FasL- and NKGD2-dependent manner. *Lab. Investig.* **2012**, *92*, 967–977. [CrossRef]

166. Song, D.Z.; Liang, Y.; Xiao, Q.; Yin, J.; Gong, J.L.; Lai, Z.P.; Zhang, Z.F.; Gao, L.X.; Fan, X.H. TRAIL is Involved in the Tumoricidal Activity of Mouse Natural Killer Cells Stimulated by Newcastle Disease Virus in Vitro. *Ana. Rec.* **2013**, *296*, 1552–1560. [CrossRef]

167. Tu, Z.; Hamalainen-Laanay, H.K.; Crispe, I.N.; Orloff, M.S. Synergy between TLR3 and IL-18 promotes IFN-γ dependent TRAIL expression in human liver NK cells. *Cell. Immunol.* **2011**, *271*, 286–291. [CrossRef]

168. Song, D.Z.; Liang, Y.; Xiao, Q.; Yin, J.; Gong, J.L.; Lai, Z.P.; Zhang, Z.F.; Gao, L.X.; Fan, X.H. TRAIL is Involved in the Tumoricidal Activity of Mouse Natural Killer Cells Stimulated by Newcastle Disease Virus in Vitro. *Ana. Rec.* **2013**, *296*, 1552–1560. [CrossRef]

169. Radaeva, S.; Sun, R.; Jaruga, B.; Nguyen, V.T.; Tian, Z.; Gao, B. Natural Killer Cells Ameliorate Liver Fibrosis by Killing Activated Stellate Cells in NKG2D-Dependent and Tumor Necrosis Factor–Related Apoptosis-Inducing Ligand–Dependent Manners. *Gastroenterology* **2006**, *130*, 435–452. [CrossRef]

170. Dunn, C.; Brunetto, M.; Reynolds, G.; Christophides, T.; Kennedy, P.T.; Lampertico, P.; Das, A.; Lopes, A.R.; Borrow, P.; Williams, K.; et al. Cytokines induced during chronic hepatitis B virus infection promote a pathway for NK cell–mediated liver damage. *J. Exp. Med.* **2007**, *204*, 667–680. [CrossRef] [PubMed]

171. Micco, L.; Peppa, D.; Loggi, E.; Schurich, A.; Jefferson, L.; Cursaro, C.; Panno, A.M.; Bernardi, M.; Brander, C.; Bihl, F.; et al. Differential boosting of innate and adaptive antiviral responses during pegylated-interferon-alpha therapy of chronic hepatitis B. *J. Hepatol.* **2013**, *58*, 225–233. [CrossRef] [PubMed]

172. Ahlenstiel, G.; Edlich, B.; Hogdal, L.J.; Rotman, Y.; Noureddin, M.; Feld, J.J.; Holz, L.E.; Titerence, R.H.; Liang, T.J.; Rehermann, B. Early changes in natural killer cell function indicate virologic response to interferon therapy for hepatitis C. *Gastroenterology* **2011**, *141*, 1211–1239. [CrossRef]

173. Takeda, K.; Cretney, E.; Hayakawa, Y.; Ota, T.; Akiba, H.; Ogasawara, K.; Yagita, H.; Kinoshita, K.; Okumura, K.; Smyth, M.J. TRAIL identifies immature natural killer cells in newborn mice and adult mouse liver. *Blood* **2005**, *105*, 2082–2089. [CrossRef]

174. Dunn, C.; Brunetto, M.; Reynolds, G.; Christophides, T.; Kennedy, P.T.; Lampertico, P.; Das, A.; Lopes, A.R.; Borrow, P.; Williams, K.; et al. Cytokines induced during chronic hepatitis B virus infection promote a pathway for NK cell–mediated liver damage. *J. Exp. Med.* **2007**, *204*, 667–680. [CrossRef] [PubMed]

175. Yoshiohka, T.; Tatsumi, T.; Miyagi, T.; Mukai, K.; Nishio, K.; Nishio, A.; Yokoyama, Y.; Suda, T.; Kegasawa, T.; Shigekawa, M.; et al. Frequency and role of NKp46 and NKG2A in hepatitis B virus infection. *PLoS ONE* **2016**, *11*, e0164401. [CrossRef] [PubMed]

176. Yoshioka, T.; Tatsumi, T.; Miyagi, T.; Mukai, K.; Nishio, K.; Nishio, A.; Yokoyama, Y.; Suda, T.; Kegasawa, T.; Shigekawa, M.; et al. Frequency and role of NKp46 and NKG2A in hepatitis B virus infection. *PLoS ONE* **2017**, *12*, e0174103. [CrossRef]

177. Peppa, D.; Gill, U.S.; Reynolds, G.; Eason, N.J.W.; Pallett, L.J.; Schurich, A.; Micco, L.; Nebbia, G.; Singh, H.D.; Adams, D.H.; et al. Up-regulation of a death receptor renders antiviral T cells susceptible to NK cell–mediated deletion. *J. Exp. Med.* **2013**, *210*, 99–114. [CrossRef] [PubMed]

178. Schuster, I.S.; Wikström, M.E.; Brizard, G.; Coudert, J.D.; Estcourt, M.J.; Manzur, M.; O’Reilly, L.A.; Smyth, M.J.; Trapani, J.A.; Hill, G.R.; et al. TRAIL+ NK Cells Control CD4+ T Cell Responses during Chronic Viral Infection to Limit Autoimmunity. *Immunity* **2014**, *41*, 646–656. [CrossRef]

179. Paul, S.; Lal, G. The Molecular Mechanism of Natural Killer Cells Function and Its Importance in Cancer Immunotherapy. *Front. Immunol.* **2017**, *8*, 347. [CrossRef]

180. Prager, I.; Watzl, C. Mechanisms of natural killer cell-mediated cellular cytotoxicity. *J. Leukoc. Biol.* **2019**, *105*, 1319–1329. [CrossRef]

181. Poli, A.; Michel, T.; Patil, N.; Zimmer, J. Revisiting the Functional Impact of NK Cells. *Trends Immunol.* **2018**, *39*, 460–472. [CrossRef] [PubMed]
182. Schuster, I.S.; Coudert, J.D.; Andoniou, C.E.; Degli-Esposti, M.A. “Natural Regulators”: NK Cells as Modulators of T Cell Immunity. Front. Immunol. 2016, 7, 230. [CrossRef] [PubMed]
183. Nielsen, N.; Ødum, N.; Urso, B.; Lanier, L.L.; Spee, P. Cytotoxicity of CD56bright NK Cells towards Autologous Activated CD4+ T Cells Is Mediated through NKG2D, LFA-1 and TRAIL and Dampered via CD94/NKG2A. PLoS ONE 2012, 7, e31959. [CrossRef] [PubMed]
184. Wendling, U.; Walczak, H.; Dörö, J.; Jaboci, C.; Weller, M.; Krammer, P.H.; Zipp, F. Expression of TRAIL receptors in human autoreactive and foreign antigen-specific T cells. Cell Death Differ. 2000, 7, 637–644. [CrossRef] [PubMed]
185. Rus, V.; Zernetkina, V.; Pulfiae, R.; Cudrici, C.; Mathai, S.; Via, C.S. Increased expression and release of functional tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) by T cells from lupus patients with active disease. Clin. Immunol. 2005, 117, 48–56. [CrossRef] [PubMed]
186. Dorothee, G.; Vergnon, I.; Menez, J.; Echchakir, H.; Grunenwald, D.; Kubin, M.; Chouaib, S.; Mami-Chouaib, F. Modulators of T Cell Immunity. Front. Immunol. 2016, 7, 1469 26 of 34.
Cancers 2019, 11, 1469

200. Feau, S.; Garcia, Z.; Arens, R.; Yagita, H.; Borst, J.; Schoenberger, S.P. The CD4+ T-cell help signal is transmitted from APC to CD8+ T-cells via CD27-CD70 interactions. *Nat. Commun.* 2012, 3, 948. [CrossRef] [PubMed]

201. Wolkers, M.C.; Bensinger, S.J.; Green, D.R.; Schoenberger, S.P.; Janssen, E.M. Interleukin-2 rescues helpless effectors CD8+ T cells by diminishing the susceptibility to TRAIL mediated death. *Immunol. Lett.* 2011, 139, 25–32. [CrossRef] [PubMed]

202. Oh, S.; Perera, L.P.; Terabe, M.; Ni, L.; Waldmann, T.A.; Berzofsky, J.A. IL-15 as a mediator of CD4+ help for CD8+ T cell longevity and avoidance of TRAIL-mediated apoptosis. *Proc. Natl. Acad. Sci. USA* 2008, 105, 5201–5206. [CrossRef] [PubMed]

203. Sun, J.C.; Williams, M.A.; Bevan, M.J. CD4+ T cells are required for the maintenance, not programming, of memory CD8+ T cells after acute infection. *Nat. Immunol.* 2004, 5, 927–933. [CrossRef] [PubMed]

204. Wolkers, M.C.; Gerlach, C.; Arens, R.; Janssen, E.M.; Fitzgerald, P.; Schumacher, T.N.; Medema, J.P.; Green, D.R.; Schoenberger, S.P. Nab2 regulates secondary CD8+ T-cell responses through control of TRAIL expression. *Blood* 2012, 119, 798–804. [CrossRef] [PubMed]

205. Gurung, P.; Kucaba, T.A.; Schoenberger, S.P.; Ferguson, T.A.; Griffith, T.S. TRAIL-expressing CD8+ T cells mediate tolerance following soluble peptide-induced peripheral T cell deletion. *J. Leukoc. Biol.* 2010, 88, 1217–1225. [CrossRef] [PubMed]

206. Griffith, T.S.; Kazama, H.; VanOosten, R.L.; Earle, J.K.; Herndon, J.M.; Green, D.R.; Ferguson, T.A. Apoptotic Cells Induce Tolerance by Generating Helpless CD8+ T Cells That Produce TRAIL. *J. Immunol.* 2007, 178, 2679–2687. [CrossRef]

207. Kuerten, S.; Asaad, R.J.; Schoenberger, S.P.; Angelov, D.N.; Lehmann, P.V.; Tary-Lehmann, M. The TRAIL of Helpless CD8+ T Cells in HIV Infection. *AIDS Res. Hum. Retrovir.* 2008, 24, 1175–1183. [CrossRef] [PubMed]

208. Wang, S.H.; Cao, Z.; Wolf, J.M.; Van Antwerp, M.; Baker, J.; James, R. Death Ligand Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Inhibits Experimental Autoimmune Thyroiditis. *Endocrinology* 2005, 146, 4721–4726. [CrossRef]

209. Chou, A.H.; Tsai, H.F.; Lin, L.H.; Hsieh, S.L.; Hsu, P.L.; Hsu, P.N. Enhanced Proliferation and Increased IFN-γ Expression from APC to CD8+ T cells by diminishing the susceptibility to TRAIL mediated death. *Immunol. Cell Biol.* 2008, 86, 351–357. [CrossRef] [PubMed]

210. Bosque, A.; Pardo, J.; Martinez-Lorenzo, M.J.; Lasierra, P.; Larrad, L.; Marzo, I.; Naval, J.; Anel, A. Human CD8+ T cell blasts are more sensitive than CD4+ T cell blasts to regulation by APO2L/TRAIL. *Eur. J. Immunol.* 2005, 35, 1812–1821. [CrossRef]

211. Song, K.; Chen, Y.; Göke, R.; Wilmen, A.; Seidel, C.; Göke, A.; Hilliard, B.; Chen, Y. Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (Trail) Is an Inhibitor of Autoimmune Inflammation and Cell Cycle Progression. *J. Exp. Med.* 2000, 191, 1095–1104. [CrossRef] [PubMed]

212. Chyuan, I.T.; Tsai, H.F.; Liao, H.J.; Wu, C.S.; Hsu, P.N. An apoptosis-independent role of TRAIL in suppressing joint inflammation and inhibiting T-cell activation in inflammatory arthritis. *Cell. Mol. Immunol.* 2017, 15, 846. [CrossRef] [PubMed]

213. Chyuan, I.T.; Tsai, H.F.; Wu, C.S.; Sung, C.C.; Hsu, P.N. TRAIL-Mediated Suppression of T Cell Receptor Signaling Inhibits T Cell Activation and Inflammation in Experimental Autoimmune Encephalomyelitis. *Front. Immunol.* 2018, 9, 15. [CrossRef] [PubMed]

214. Chyuan, I.T.; Tsai, H.F.; Wu, C.S.; Hsu, P.N. TRAIL suppresses gut inflammation and inhibits colitogenic T-cell activation in experimental colitis via an apoptosis-independent pathway. *Mucosal Immunol.* 2019, 12, 980–989. [CrossRef] [PubMed]

215. Cretney, E.; McQualter, J.L.; Kayagaki, N.; Yagita, H.; Bernard, C.C.; Grewal, I.S.; Ashkenazi, A.; Smyth, M.J. TNF-related apoptosis-inducing ligand (TRAIL)/Apo2L suppresses experimental autoimmune encephalomyelitis in mice. *Immunol. Cell Biol.* 2005, 83, 511–519. [CrossRef] [PubMed]

216. Wang, S.H.; Chen, G.H.; Fan, Y.; Van Antwerp, M.; Baker, J.; James, R. Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Inhibits Experimental Autoimmune Thyroiditis by the Expansion of CD4+CD25+Regulatory T Cells. *Endocrinology* 2009, 150, 2000–2007. [CrossRef]

217. Hirata, S.; Matsuyoshi, H.; Fukushima, D.; Kurisaki, A.; Uemura, Y.; Nishimura, Y.; Senju, S. Involvement of Regulatory T Cells in the Experimental Autoimmune Encephalomyelitis-Preventive Effect of Dendritic Cells Expressing Myelin Oligodendrocyte Glycoprotein plus TRAIL. *J. Immunol.* 2007, 178, 918–925. [CrossRef] [PubMed]
218. Nieda, M.; Nicol, A.; Koezuka, Y.; Kikuchi, A.; Lapteva, N.; Tanaka, Y.; Tokunaga, K.; Suzuki, K.; Kayagaki, N.;
Yagita, H.; et al. TRAIL expression by activated human CD4(+)/V alpha 24NK T cells induces in vitro and
in vivo apoptosis of human acute myeloid leukemia cells. *Blood* **2001**, *97*, 2067–2074. [CrossRef]

219. Nishihori, Y.; Kato, K.; Tanaka, M.; Okamoto, T.; Hagiwara, S.; Araki, N.; Kogawa, K.; Kuribayashi, K.;
Nakamura, K.; Niitsu, Y. Interleukin-2 gene transfer potentiates the alpha-galactosylceramide-stimulated
antitumor effect by the induction of TRAIL in NK and NK cells in mouse models of subcutaneous and
metastatic carcinoma. *Cancer Biol. Ther.* **2009**, *8*, 1763–1770. [CrossRef]

220. Huang, J.R.; Tsai, Y.C.; Chang, Y.J.; Wu, J.C.; Hung, J.T.; Lin, K.H.; Wong, C.H.; Yu, A.L. Alpha. alpha-Galactosylceramide
but not phenyl-glycolipids induced NK cell anergy and IL-33-mediated myeloid-derived suppressor cell
accumulation via upregulation of egr2/3. *J. Immunol.* **2014**, *192*, 1972–1981. [CrossRef]

221. Wolf, B.J.; Choi, J.E.; Exley, M.A. Novel Approaches to Exploiting Invariant NKT Cells in Cancer
Immunotherapy. *Front. Immunol.* **2018**, *9*, 975. [CrossRef] [PubMed]

222. Kronenberg, M. Toward an understanding of NKT cell biology: Progress and paradoxes. *Annu. Rev. Immunol.*
**2005**, *23*, 877–900. [CrossRef] [PubMed]

223. Metelitsa, L.S.; Weinberg, K.I.; Emanuel, P.D.; Seeger, R.C. Expression of CD1d by myelomonocytic leukemias
provides a target for cytotoxic NKT cells. *Leukemia* **2003**, *17*, 1068–1077. [CrossRef]

224. Cretney, E.; Takeda, K.; Yagita, H.; et al. CD1d expression by activated human CD4(+) and CD8(+) T cells induces in vitro
antitumor activity through mechanisms distinct from T cells and natural killer cells. *Immunology* **2000**, *99*, 229–234.
[CrossRef]

225. Kawano, T.; Cui, J.; Koezuka, Y.; Toura, I.; Kaneko, Y.; Sato, H.; Harada, M.; Koseki, H.;
Nakayama, T.; et al. Natural killer-like nonspecific tumor cell lysis mediated by specific ligand-activated
Valpha14 NKT cells. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 5690–5693. [CrossRef] [PubMed]

226. Teng, M.W.L.; Westwood, J.A.; Darcy, P.K.; Sharkey, J.; Tsuji, M.; Franck, R.W.; Porcelli, S.A.; Besra, G.S.;
Takeda, K.; Yagita, H.; et al. Combined Natural Killer T-Cell Based Immunotherapy Eradicates Established
Tumors in Mice. *J. Immunol.* **2002**, *168*, 1356–1361. [CrossRef]

227. Dieli, F.; Vermijlen, D.; Fulfaro, F.; Caccamo, N.; Meraviglia, S.; Cicero, G.; Roberts, A.; Buccheri, S.;
D’Asaro, M.; Gebbia, N.; et al. Targeting Human γδ T Cells with Zoledronate and Interleukin-2 for
Immunotherapy of Hormone-Refractory Prostate Cancer. *Cancer Res.* **2007**, *67*, 7495–7504. [CrossRef]

228. D’Asaro, M.; La Mendola, C.; Di Liberto, D.; Orlando, V.; Todaro, M.; Spina, M.; Guggino, G.; Meraviglia, S.;
Caccamo, N.; Messina, A.; et al. Vgamma9 Vdelta2 T lymphocytes efficiently recognize and kill
zoledronate-sensitized, imatinib-sensitive, and imatinib-resistant chronic myelogenous leukemia cells.
*J. Immunol.* **2010**, *184*, 3260–3268. [CrossRef] [PubMed]

229. Dokouhaki, P.; Han, M.; Joe, B.; Li, M.; Johnston, M.R.; Tsao, M.S.; Zhang, L. Adoptive immunotherapy of
cancer using ex vivo expanded human gammadelta T cells: A new approach. *Cancer Lett.* **2010**, *297*, 126–136.
[CrossRef] [PubMed]

230. Todaro, M.; D’Asaro, M.; Caccamo, N.; Iovino, F.; Francipane, M.G.; Meraviglia, S.; Orlando, V.; La Mendola, C.;
Gulotta, G.; Salerno, A.; et al. Efficient killing of human colon cancer stem cells by gammadelta T lymphocytes.
*J. Immunol.* **2009**, *182*, 7287–7296. [CrossRef] [PubMed]

231. Meraviglia, S.; Eberl, M.; Vermijlen, D.; Todaro, M.; Buccheri, S.; Cicero, G.; La Mendola, C.; Guggino, G.;
D’Asaro, M.; Orlando, V.; et al. In vivo manipulation of Vgamma9 Vdelta2 T cells with zoledronate and
low-dose interleukin-2 for immunotherapy of advanced breast cancer patients. *Clin. Exp. Immunol.* **2010**, *161*, 290–297. [CrossRef] [PubMed]
Cancers 2019, 11, 1469

235. Dokouhaki, P.; Schuh, N.W.; Joe, B.; Allen, C.A.D.; Der, S.D.; Tsao, M.S.; Zhang, L. NKG2D regulates production of soluble TRAIL by ex vivo expanded human γδ T cells. *Eur. J. Immunol.* 2013, 43, 3175–3182. [CrossRef] [PubMed]

236. Todaro, M.; Orlando, V.; Cicero, G.; Caccamo, N.; Meraviglia, N.; Stassi, G.; Dieli, F. Chemotherapy Sensitizes Colon Cancer Initiating Cells to Vγ9Vδ2 T Cell-Mediated Cytotoxicity. *PLoS ONE* 2013, 8, e65145. [CrossRef]

237. Caccamo, N.; La Mendola, C.; Orlando, V.; Meraviglia, S.; Todaro, M.; Stassi, G.; Sireci, G.; Fournie, J.J.; Dieli, F. Differentiation, phenotype, and function of interleukin-17-producing human Vγ9Vδ2 T cells. *Blood* 2011, 118, 129–138. [CrossRef] [PubMed]

238. Secchiero, P.; Tribelli, M.; Barbarotto, E.; Celeghini, C.; Michelutti, A.; Masolini, P.; Fanin, R.; Zauli, G. Aberrant expression of TRAIL in B chronic lymphocytic leukemia (B-CLL) cells. *J. Cell. Physiol.* 2005, 205, 246–252. [CrossRef]

239. Staniek, J.; Lorenzetti, R.; Heller, B.; Janowska, I.; Schneider, P.; Unger, S.; Warnatz, K.; Seidl, M.; Venhoff, N.; Thiel, J.; et al. TRAIL-R1 and TRAIL-R2 Mediate TRAIL-Dependent Apoptosis in Activated Primary Human B Lymphocytes. *Front. Immunol.* 2019, 10, 951. [CrossRef]

240. Guerreiro-Cacais, A.O.; Levitskaya, J.; Levitsky, V. B cell receptor triggering sensitizes human B cells to TRAIL-induced apoptosis. *J. Leukoc. Biol.* 2010, 88, 937–945. [CrossRef]

241. Crowder, R.N.; Zhao, H.; Chatham, W.W.; Zhou, T.; Carter, R.H. B lymphocytes are resistant to death receptor 5-induced apoptosis. *Clin. Immunol.* 2011, 139, 21–31. [CrossRef] [PubMed]

242. Smulski, C.R.; Decossas, M.; Chekkat, N.; Beyrath, J.; Willen, L.; Guichard, G.; Lorenzetti, R.; Rizzi, M.; Eibl, H.; Schneider, P.; et al. Hetero-oligomerization between the TNF receptor superfamily members CD40, Fas and TRAILR2 modulate CD40 signalling. *Nat. Publ. Group* 2017, 8, e2601. [CrossRef] [PubMed]

243. Ursini-Siegel, J.; Zhang, W.; Altmeyer, A.; Hatada, E.N.; Do, R.K.G.; Yagita, H.; Chen-Kiang, S. TRAIL/Apo-2 Ligand Induces Primary Plasma Cell Apoptosis. *J. Immunol.* 2002, 169, 5505–5513. [CrossRef] [PubMed]

244. Travert, M.; Ame-Thomas, P.; Pangualt, C.; Morizot, A.; Micheau, O.; Semana, G.; Lamy, T.; Fest, T.; Tarte, K.; Guillaudeau, T. CD40 Ligand Protects from TRAIL-Induced Apoptosis in Follicular Lymphomas through NF-xB Activation and Up-Regulation of c-FLIP and Bcl-xL. *J. Immunol.* 2008, 181, 1001–1011. [CrossRef] [PubMed]

245. Grieben, P.; Beskorwayne, T.; Van den Broeke, A.; Ferrari, G. CD40 signaling induces B cell responsiveness to multiple members of the gamma chain-common cytokine family. *Int. Immunol.* 1999, 11, 1139–1147. [CrossRef]

246. van Grevenynghe, J.; Cubas, R.A.; Noto, A.; DaFonseca, S.; He, Z.; Peretz, Y.; Filali-Mouhim, A.; Dupuy, F.P.; Procopio, F.A.; Chomont, N.; et al. Membrane-bound Fas/CDC95 Ligand to Its Soluble Form Is Associated with Downregulation of Its Proapoptotic Activity and Loss of Liver Toxicity. *J. Exp. Med.* 2000, 191, 1205–1213. [CrossRef]

247. Kayagaki, N.; Yagita, H. Suppression of antibody production by TNF-related apoptosis-inducing ligand (TRAIL). *Cell. Immunol.* 2002, 219, 82–91. [CrossRef]

248. Schneider, P.; Holler, N.; Bodmer, J.L.; Hahne, M.; Frei, K.; Fontana, A.; Tschopp, J. Conversion of Membrane-bound Fas(CD95) Ligand to Its Soluble Form Is Associated with Downregulation of Its Proapoptotic Activity and Loss of Liver Toxicity. *J. Exp. Med.* 1998, 187, 1205–1213. [CrossRef]

249. Wajant, H.; Moosmayer, D.; Wiest, T.; Bartke, T.; Gerlach, E.; Schönherr, U.; Peters, N.; Scheurich, P.; Pfizenmaier, K. Differential activation of TRAIL-R1 and -2 by soluble and membrane TRAIL allows selective surface antigen-directed activation of TRAIL-R2 by a soluble TRAIL derivative. *Oncogene* 2001, 20, 4101–4106. [CrossRef]

250. Clancy, L.; Mruk, K.; Archer, K.; Woelfel, M.; Mongkolsapaya, J.; Screamton, G.; Lenardo, M.J.; Chan, F.K.M. Preligand assembly domain-mediated ligand-independent association between TRAIL receptors 4 (TR4) and TR2 regulates TRAIL-induced apoptosis. *Proc. Natl. Acad. Sci. USA* 2005, 102, 18099–18104. [CrossRef]

251. Truneh, A.; Sharma, S.; Silverman, C.; Khandekar, S.; Reddy, M.P.; Deen, K.C.; Mclaughlin, M.M.; Srinivasula, S.M.; Livì, G.P.; Marshall, L.A.; et al. Temperature-sensitive Differential Affinity of TRAIL for Its Receptors. *J. Biol. Chem.* 2000, 275, 23319–23325. [CrossRef] [PubMed]

252. Martinez-Lorenzo, M.J.; Anel, A.; Gamen, S.; Monle n, I.; Lasieria, P.; Larrad, L.; Pineiro, A.; Alava, M.A.; Naval, J. Activated human T cells release bioactive Fas ligand and APO2 ligand in microvesicles. *J. Immunol.* 1999, 163, 1274–1281. [PubMed]
253. Monleon, I.; Martinez-Lorenzo, M.J.; Monteagudo, L.; Lasierra, P.; Taules, M.; Iturralde, M.; Pineiro, A.; Larrad, L.; Alava, M.A.; Naval, J.; et al. Differential Secretion of Fas Ligand- or APO2 Ligand/TNF-Related Apoptosis-Inducing Ligand-Carrying Microvesicles During Activation-Induced Death of Human T Cells. J. Immunol. 2001, 167, 6736–6744. [CrossRef] [PubMed]

254. Bosque, A.; Dietz, L.; Gallego-Lleyda, A.; Sanclemente, M.; Iturralde, M.; Naval, J.; Alava, M.A.; Martinez-Lostao, L.; Thierse, H.J.; Anel, A. Comparative proteomics of exosomes secreted by tumoral Jurkat T cells and normal human T cell blasts unravels a potential tumorigenic role for valosin-containing protein. Oncotarget 2016, 7, 29287–29305. [CrossRef] [PubMed]

255. Munich, S.; Sobo-Vujanovic, A.; Buchser, W.J.; Beer-Stolz, D.; Vujanovic, N.L. Dendritic cell exosomes directly kill tumor cells and activate natural killer cells via TNF superfamily ligands. Oncoimmunology 2014, 1, 1074–1083. [CrossRef]

256. Huber, V.; Fais, S.; Iero, M.; Lugini, L.; Canese, P.; Squarcina, P.; Zaccheddu, A.; Colone, M.; Arancia, G.; Gentile, M.; et al. Human Colorectal Cancer Cells Induce T-Cell Death Through Release of Proapoptotic Microvesicles: Role in Immune Escape. Gastroenterology 2005, 128, 1796–1804. [CrossRef]

257. Martinez-Lorenzo, M.J.; Anel, A.; Alava, M.A.; Piñeiro, A.; Naval, J.; Lasierra, P.; Larrad, L. The human melanoma cell line MelJuSo secretes bioactive Fasl and APO2L/TRAIL on the surface of microvesicles. Possible contribution to tumor counterattack. Exp. Cell Res. 2004, 295, 315–329. [CrossRef]

258. Lo Cicero, A.; Schiera, G.; Proia, P.; Saladino, P.; Savettiieri, G.; Di Liegro, C.M.; Di Liegro, I. Oligodendroglioma cells shed microvesicles which contain TRAIL as well as molecular chaperones and induce cell death in astrocytes. Int. J. Oncol. 2011, 39, 1353–1357. [CrossRef]

259. Wan, C.; Fu, J.; Wang, Y.; Miao, S.; Song, W.; Wang, L. Exosome-related multi-pass transmembrane protein TSAP6 is a target of rhomboid protease RHBD1-induced proteolysis. PLoS ONE 2012, 7, e37452. [CrossRef]

260. Martinez-Lorenzo, M.J.; Anel, A.; Saez-Gutierrez, B.; Rojo-Canas, M.; Bosque, A.; Alava, M.A.; Piñeiro, A.; Lasierra, P.; Asin-Urgria, J.; Larrad, L. Rheumatoid synovial fluid T cells are sensitive to APO2L/TRAIL. Clin. Immunol. 2007, 122, 28–40. [CrossRef] [PubMed]

261. Thayanithy, V.; O’Hare, P.; Wong, P.; Zhao, X.; Steer, C.J.; Subramanian, S.; Lou, E. A transwell assay that excludes exosomes for assessment of tunneling nanotube-mediated intercellular communication. Cell Commun. Signal. 2017, 15, 46. [CrossRef] [PubMed]

262. Robbins, P.D.; Morelli, A.E. Regulation of immune responses by extracellular vesicles. Nat. Publ. Group 2014, 14, 195–208. [CrossRef] [PubMed]

263. Anel, A.; Gallego-Lleyda, A.; de Miguel, D.; Naval, J.; Martinez-Lostao, L. Role of Exosomes in the Regulation of T-cell Mediated Immune Responses and in Autoimmune Disease. Cells 2019, 8, 154. [CrossRef] [PubMed]

264. Bosque, A.; Pardo, J.; Martinez-Lorenzo, M.J.; Iturralde, M.; Marzo, I.; Piñeiro, A.; Alava, M.A.; Naval, J.; Anel, A. Down-regulation of normal human T cell blast activation: Roles of APO2L/TRAIL, FasL, and c-FLIP, Bim, or Bcl-x isoform expression. J. Leukoc. Biol. 2005, 77, 568–578. [CrossRef]

265. Grootjans, J.; Kaser, A.; Kaufman, R.J.; Blumberg, R.S. The unfolded protein response in immunity and inflammation. Nat. Publ. Group 2016, 16, 469–484. [CrossRef]

266. Kemp, K.; Poe, C. Stressed: The Unfolded Protein Response in T Cell Development, Activation, and Function. Int. J. Mol. Sci. 2019, 20, 1792. [CrossRef]

267. Janssens, S.; Pulendran, B.; Lambrecht, B.N. Emerging functions of the unfolded protein response in immunity. Nat. Publ. Group 2014, 15, 910–919. [CrossRef]

268. Smith, J.A. Regulation of Cytokine Production by the Unfolded Protein Response; Implications for Infection and Autoimmunity. Front. Immunol. 2018, 9, 6. [CrossRef]

269. Jiang, Y.; Chen, X.; Fan, M.; Li, H.; Zhu, W.; Chen, X.; Cao, C.; Xu, R.; Wang, Y.; Ma, Y. TRAIL facilitates cytokine expression and macrophage migration during hypoxia/reoxygenation via ER stress-dependent NF-κB pathway. Mol. Immunol. 2017, 82, 123–136. [CrossRef] [PubMed]
Cancers 2019, 11, 1469

272. Chattergoon, M.A.; Muthumani, K.; Tamura, Y.; Ramanathan, M.; Shames, J.P.; Saulino, V.; Robinson, T.M.; Montaner, L.J.; Weiner, D.B. DR5 activation of caspase-8 induces DC maturation and immune enhancement in vivo. *Mol. Ther.* 2008, 16, 419–426. [CrossRef] [PubMed]

273. Brincks, E.L.; Katawa, A.; Kucaba, T.A.; Griffith, T.S.; Legge, K.L. CD8 T Cells Utilize TRAIL to Control Influenza Virus Infection. *J. Immunol.* 2008, 181, 4918–4925. [CrossRef] [PubMed]

274. Lamhamedi-Cherradi, S.E.; Zheng, S.J.; Maguschak, K.A.; Peschon, J.; Chen, Y.H. Defective thymocyte apoptosis and accelerated autoimmune diseases in TRAIL−/− mice. *Nat. Publ. Group* 2003, 4, 255–260. [CrossRef] [PubMed]

275. Lamhamedi-Cherradi, S.E.; Zheng, S.; Tisch, R.M.; Chen, Y.H. Critical role for tumor necrosis factor-related apoptosis-inducing ligand in immune surveillance against tumor development. *Cancer Res.* 2003, 63, 161–169. [CrossRef] [PubMed]

276. Liu, Z.; Xu, X.; Hsu, H.C.; Tousson, A.; Yang, P.A.; Wu, Q.; Liu, C.; Yu, S.; Zhang, H.G.; Mountz, J.D. CII-DC-AdTRAIL cell gene therapy inhibits infiltration of CII-reactive T cells and CII-induced arthritis. *J. Clin. Investig.* 2003, 112, 1332–1341. [CrossRef] [PubMed]

277. Jin, C.H.; Chae, S.Y.; Kim, T.H.; Yang, H.K.; Lee, E.Y.; Song, Y.W.; Jo, D.G.; Lee, K.C. E

278. Mi, Q.S.; Ly, D.; Lamhamedi-Cherradi, S.E.; Salojin, K.V.; Zhou, L.; Grattan, M.; Meagher, C.; Zucker, P.; Chen, Y.H.; Nagle, J.; et al. Blockade of tumor necrosis factor-related apoptosis-inducing ligand exacerbates type 1 diabetes in NOD mice. *Diabetes* 2003, 52, 1667–1975. [CrossRef] [PubMed]

279. Hirata, S.; Senju, S.; Matsuyoshi, H.; Fukuma, D.; Uemura, Y.; Nishimura, Y. Prevention of experimental autoimmune encephalomyelitis by transfer of embryonic stem cell-derived dendritic cells expressing myelin oligodendrocyte glycoprotein peptide along with TRAIL or programmed death-1 ligand. *J. Immunol.* 2005, 174, 1888–1997. [CrossRef]

280. Aktas, O.; Smorodchenko, A.; Brocke, S.; Infante-Duarte, C.; Tophoff, U.S.; Vogt, J.; Prozorovski, T.; Meier, S.; Osmanova, V.; Pohl, E.; et al. Neuronal Damage in Autoimmune Neurominflammation Mediated by the Death Ligand TRAIL. *Neuron* 2005, 46, 421–432. [CrossRef] [PubMed]

281. Hilliard, B.; Wilmen, A.; Seidel, C.; Liu, T.S.T.; Goke, R.; Chen, Y. Roles of TNF-Related Apoptosis-Inducing Ligand in Experimental Autoimmune Encephalomyelitis. *J. Immunol.* 2001, 166, 1314–1319. [CrossRef] [PubMed]

282. Takeda, K.; Smyth, M.J.; Cretney, E.; Hayakawa, Y.; Yamaguchi, N.; Yagita, H.; Okumura, K. Involvement of tumor necrosis factor-related apoptosis-inducing ligand in immune surveillance against tumor development. *J. Exp. Med.* 2001, 194, 2274–2278. [CrossRef] [PubMed]

283. Thomas, W.D.; Hersey, P. TNF-related apoptosis-inducing ligand (TRAIL) induces apoptosis in Fas ligand-resistant melanoma cells and mediates CD4 T cell killing of target cells. *J. Immunol.* 1998, 161, 2195–2200. [PubMed]

284. van der Most, R.G.; Currie, A.J.; Cleaver, A.L.; Salmons, J.; Nowak, A.K.; Mahendran, S.; Larraza, I.; Prosser, A.; Robinson, B.W.S.; Smyth, M.J.; et al. Cyclophosphamide Chemotherapy Sensitizes Tumor Cells to TRAIL-Dependent CD8 T Cell-Mediated Immune Attack Resulting in Suppression of Tumor Growth. *PloS ONE* 2009, 4, e6982. [CrossRef] [PubMed]

285. Wang, R.; Zhang, L.; Zhang, X.; Moreno, J.; Luo, X.; Tondravi, M.; Shi, Y. Differential Regulation of the Expression of CD95 Ligand, Receptor Activator of Nuclear Factor- B Ligand (RANKL), TNF-Related Apoptosis-Inducing Ligand (TRAIL), and TNF- During T Cell Activation. *J. Immunol.* 2001, 166, 194–200. [CrossRef] [PubMed]

286. Zerafa, N.; Westwood, J.A.; Cretney, E.; Mitchell, S.; Waring, P.; Iezzi, M.; Smyth, M.J. Cutting Edge: TRAIL Deficiency Accelerates Hematological Malignancies. *J. Immunol.* 2005, 175, 5586–5590. [CrossRef]

287. Seki, N.; Hayakawa, Y.; Brooks, A.D.; Wine, J.; Wiltrout, R.H.; Yagita, H.; Tanner, J.E.; Smyth, M.J.; Sayers, T.J. Defective thymocyte apoptosis and accelerated autoimmune diseases in TRAIL−/− mice. *Cancer Res.* 2003, 63, 207–213. [CrossRef] [PubMed]

288. Takeda, K.; Smyth, M.J.; Cretney, E.; Hayakawa, Y.; Kayagaki, N.; Yagita, H.; Okumura, K. Critical role for tumor necrosis factor-related apoptosis-inducing ligand in immune surveillance against tumor development. *J. Exp. Med.* 2002, 195, 161–169. [CrossRef] [PubMed]
Cancers 2019, 11, 1469

301. Micheau, O. Regulation of TNF-Related Apoptosis-Inducing Ligand Signaling by Glycosylation. J. Exp. Med. 2000, 191, 661–668. [CrossRef]

302. Smyth, M.J.; Crowe, N.Y.; Godfrey, D.I. Differential tumor surveillance by natural killer (NK) and NKT cells. J. Exp. Med. 2002, 196, 119–127. [CrossRef]

303. Crowe, N.Y.; Smyth, M.J.; Godfrey, D.I. A Critical Role for Natural Killer T Cells in Immunosurveillance of Methylcholanthrene-induced Sarcomas. J. Exp. Med. 2002, 196, 119–127. [CrossRef]

304. Smyth, M.J.; Crowe, N.Y.; Godfrey, D.I. NK cells and NKT cells collaborate in host protection from methylcholanthrene-induced fibrosarcoma. Int. Immunol. 2001, 13, 459–463. [CrossRef] [PubMed]

305. Spencer, S.L.; Gaudet, S.; Albeck, J.G.; Burke, J.M.; Sorger, P.K. Non-genetic origins of cell-to-cell variability in TRAIL-induced apoptosis. Nature 2009, 459, 428–432. [CrossRef] [PubMed]

306. Tian, F.; Lu, J.J.; Wang, L.; Li, L.; Yang, J.; Li, Y.; Liu, Y.Q.; Shen, G.X.; Tu, Y.T.; Tao, J. Expression of c-FLIP in malignant melanoma, and its relationship with the clinicopathological features of the disease. Clin. Exp. Dermatol. 2011, 37, 259–265. [CrossRef]

307. Watanabe, F.; et al. Nuclear Death Receptor TRAIL-R2 Inhibits Maturation of Let-7 and Promotes Autophagic Removal of Death Receptor 5: Evidence from an In Vitro Model. Cancers 2019, 11, 1469. [CrossRef] [PubMed]

308. Wang, W.; Li, J.; Wang, L.; Li, L.; Yang, J.; Li, Y.; Liu, Y.Q.; Shen, G.X.; Tu, Y.T.; Tao, J. Expression of c-FLIP in malignant melanoma, and its relationship with the clinicopathological features of the disease. Clin. Exp. Dermatol. 2011, 37, 259–265. [CrossRef]

309. Zhang, B.; Quax, W.J. Death receptor 5 is activated by fucosylation in colon cancer cells. FEBS J. 2018, 286, 555–571. [CrossRef] [PubMed]

310. Micheau, O. Regulation of TNF-Related Apoptosis-Inducing Ligand Signaling by Glycosylation. Inter. J. Mol. Sci. 2018, 19, 715. [CrossRef] [PubMed]

311. Dufour, F.; Rattier, T.; Shirley, S.; Picarda, G.; Constantinescu, A.A.; Morle, A.; Zakaria, A.B.; Marcion, G.; Causse, S.; Szegedi, E.; et al. N-glycosylation of mouse TRAIL-R and human TRAIL-R1 enhances TRAIL-induced death. Cell Death Differ. 2017, 24, 500–510. [CrossRef] [PubMed]

312. Wang, W.; Qi, X.; Wu, M. Effect of DR4 promoter methylation on the TRAIL-induced apoptosis in lung squamous carcinoma cell. Oncol. Rep. 2015, 34, 2115–2125. [CrossRef] [PubMed]

313. Kriegl, L.; Jung, A.; Engel, J.; Jackstadt, R.; Gerbes, A.L.; Gallmeier, E.; Reiche, J.A.; Hermeking, H.; Rizzani, A.; Bruns, C.J.; et al. Expression, Cellular Distribution, and Prognostic Relevance of TRAIL Receptors in Hepatocellular Carcinoma. Clin. Cancer Res. 2010, 16, 5529–5538. [CrossRef]

314. Twomey, J.; Zhang, B. Circulating Tumor Cells Develop Resistance to TRAIL-Induced Apoptosis Through Autophagic Removal of Death Receptor 5: Evidence from an In Vitro Model. Cancers 2019, 11, 94. [CrossRef]

315. Haselmann, V.; Kurz, A.; Bertsch, U.; Hübner, S.; Müller, M.O.; Fritsch, J.; Häsler, R.; Pickl, A.; Fritsche, H.; Annenwanter, F.; et al. Nuclear Death Receptor TRAIL-R2 Inhibits Maturation of Let-7 and Promotes Proliferation of Pancreatic and Other Tumor Cells. Gastroenterology 2014, 146, 278–290. [CrossRef]

316. Ganten, T.M.; Sykora, J.; Koschny, R.; Batke, E.; Aulmann, S.; Mansmann, U.; Stremmel, W.; Sinn, H.P.; Walczak, H. Prognostic significance of tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor expression in patients with breast cancer. J. Mol. Med. 2009, 87, 995–1007. [CrossRef]

317. Koksal, I.T.; Sanlioglu, A.D.; Karacay, B.; Griffith, T.S.; Sanlioglu, S. Tumor necrosis factor-related apoptosis inducing ligand-R4 decoy receptor expression is correlated with high Gleason scores, prostate-specific antigen recurrence, and decreased survival in patients with prostate carcinoma. Urol. Oncol. Semin. Orig. Investig. 2008, 26, 158–165. [CrossRef]

318. Riccioni, R.; Pasquini, L.; Mariani, G.; Saulle, E.; Rossini, A.; Diverio, D.; Pelosi, E.; Vitale, A.; Chierichini, A.; Cedrone, M.; et al. TRAIL decoy receptors mediate resistance of acute myeloid leukemia cells to TRAIL. Haematologica 2005, 90, 612–624.
310. Chamuleau, M.E.D.; Ossenkoppele, G.J.; van Rhenen, A.; van Dreunen, L.; Jirka, S.M.G.; Zevenbergen, A.; Schuurhuis, G.J.; van de Loosdrecht, A.A. High TRAIL-R3 expression on leukemic blasts is associated with poor outcome and induces apoptosis-resistance which can be overcome by targeting TRAIL-R2. *Leuk. Res.* **2011**, *35*, 741–749. [CrossRef]

311. Macher-Goeppinger, S.; Aulmann, S.; Tagscherer, K.E.; Wagener, N.; Haferkamp, A.; Penzel, R.; Brauchhoff, A.; Hohenfellner, M.; Sykora, J.; Walczak, H.; et al. Prognostic Value of Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) and TRAIL Receptors in Renal Cell Cancer. *Clin. Cancer Res.* **2009**, *15*, 650–659. [CrossRef] [PubMed]

312. Imaoka, Y.; Ohira, M.; Yano, T.; Nakano, R.; Tanimine, N.; Shimizu, S.; Kuroda, S.; Tahara, H.; Kobayashi, T.; Ohdan, H. Polymorphisms in TRAIL predict long-term survival and extrahepatic recurrence following initial hepatectomy for hepatocellular carcinoma. *J. Hepat. Biliary Pancreat. Sci.* **2018**, *25*, 370–376. [CrossRef] [PubMed]

313. Ehrhardt, H.; Fulda, S.; Schmid, I.; Hiscott, J.; Debatin, K.M.; Jeremias, I. TRAIL induced survival and proliferation in cancer cells resistant towards TRAIL-induced apoptosis mediated by NF-κB. *Oncogene* **2003**, *22*, 3842–3852. [CrossRef] [PubMed]

314. Ishimura, N.; Isomoto, H.; Bronk, S.F.; Gores, G.J. Trail induces cell migration and invasion in apoptosis-resistant cholangiocarcinoma cells. *Am. J. Physiol. Gastroint. Liver Physiol.* **2006**, *290*, G129–G136. [CrossRef] [PubMed]

315. von Karstedt, S.; Conti, A.; Nobis, M.; Montinaro, A.; Hartwig, T.; Lemke, J.; Legler, K.; Annweanter, F.; Campbell, A.D.; Taraborrelli, L.; et al. Cancer Cell-Autonomous TRAIL-R Signaling Promotes KRAS-Driven Cancer Progression, Invasion, and Metastasis. *Cancer Cell* **2015**, *27*, 561–573. [CrossRef] [PubMed]

316. Trauzold, A.; Siegmund, D.; Schniewind, B.; Sipos, B.; Egberts, J.; Zorenkov, D.; Emme, D.; Röder, C.; Kalthoff, H.; Wajant, H. TRAIL promotes metastasis of human pancreatic ductal adenocarcinoma. *Oncogene* **2006**, *25*, 7434–7439. [CrossRef] [PubMed]

317. Dufour, F.; Rattier, T.; Constantinescu, A.A.; Zischler, L.; Morlé, A.; Ben Mabrouk, H.; Humblin, E.; Jacquemin, G.; Szegezdi, E.; Delacote, F.; et al. TRAIL receptor gene editing unveils TRAIL-R1 as a master player of apoptosis induced by TRAIL and ER stress. *Oncotarget* **2017**, *8*, 9974–9985. [CrossRef] [PubMed]

318. Tang, W.; Wang, W.; Zhang, Y.; Liu, S.; Liu, Y.; Zheng, D. TRAIL receptor mediates inflammatory cytokine release in an NF-κB-dependent manner. *Cell Res.* **2009**, *19*, 758–767. [CrossRef] [PubMed]

319. Varfolomeev, E.; Maecker, H.; Sharp, D.; Lawrence, D.; Renz, M.; Vucic, D.; Ashkenazi, A. Molecular determinants of kinase pathway activation by Apo2 ligand/tumor necrosis factor-related apoptosis-inducing ligand. *J. Biol. Chem.* **2005**, *280*, 40599–40608. [CrossRef] [PubMed]

320. Henry, C.M.; Martin, S.J. Caspase-8 Acts in a Non-enzymatic Role as a Sca...
328. O’Leary, L.; van der Sloot, A.M.; Reis, C.R.; Deegan, S.; Ryan, A.E.; Dhami, S.P.S.; Murillo, L.S.; Cool, R.H.; Correa de Sampaio, P.; Thompson, K.; et al. Decoy receptors block TRAIL sensitivity at a supracellular level: The role of stromal cells in controlling tumour TRAIL sensitivity. *Oncogene* 2016, 35, 1261–1270. [CrossRef]

329. Song, M.; Cubillos-Ruiz, J.R. Endoplasmic Reticulum Stress Responses in Intratumoral Immune Cells: Implications for Cancer Immunotherapy. *Trends Immunol.* 2019, 40, 128–141. [CrossRef]

330. Wilson, N.S.; Yang, A.; Yang, B.; Couto, S.; Stern, H.; Gogineni, A.; Pitti, R.; Marsters, S.; Weimer, R.M.; Singh, M.; et al. Proapoptotic activation of death receptor 5 on tumor endothelial cells disrupts the vasculature and reduces tumor growth. *Cancer Cell* 2012, 22, 80–90. [CrossRef]