Review

TRAIL-Non-Apoptotic Signalling

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Review

TRAIL-Non-Apoptotic Signalling

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Abstract: TNF-related apoptosis-inducing ligand (TRAIL or Apo2 or TNFSF10) belongs to the TNF superfamily. When bound to its agonistic receptors, TRAIL can induce apoptosis in tumour cells, while sparing healthy cells. This tumour selectivity prompted, over the last three decades, many studies aiming at evaluating the anti-tumoral potential of TRAIL or its derivatives. Although most of these attempts have failed, so far, novel formulations are still being evaluated. Yet, emerging evidence indicates that TRAIL can also trigger, on the other hand, a non-canonical signal transduction pathway that is likely to be detrimental for its use in oncology. Likewise, increasing studies suggest that TRAIL can induce, through Death receptor 5 (DR5) in some circumstances, tumour cell motility, potentially leading to and contributing to tumour metastasis. While the pro-apoptotic signal transduction machinery of TRAIL is well known from a mechanistic point of view, that of the non-canonical pathway is less understood. We are reviewing here the current state of knowledge of TRAIL non-canonical signalling.

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1. Introduction

TNF-Related Apoptosis Ligand (TRAIL) is known as a type II transmembrane protein belonging to the TNF ligands superfamily (TNFSF) and reported for the first time as a cytokine coded by a gene TNFSF10 in 3q26 position on human chromosome 3 [1,2]. TRAIL can bind to six receptors. Two agonist receptors have been reported to induce the canonical pro-apoptotic signal transduction, upon binding to TRAIL, namely DR4 (TRAIL-R1 encoded by TNFRSF10A gene) [3] and DR5 (two splice variants of TRAIL-R2 encoded by TNFRSF10B gene)[4–8]. The TRAIL agonist receptors, DR4 and DR5, are able to trigger apoptosis because they harbour a death domain (DD) in their c-terminal part (Figure 1), which is also found in TNF-R1 and Fas [9–14], and which is necessary and sufficient to engage the pro-apoptotic machinery [9,10].

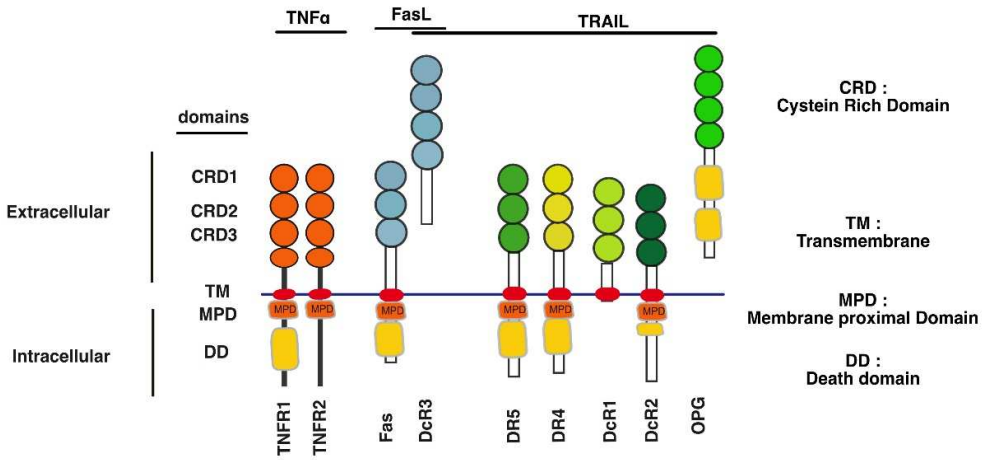

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Figure 1. Schematic representation of TNFRSF sub-family receptors binding to TNFα, FasL and TRAIL. Receptors are depicted with their three main functional domains. The extracellular domain of these receptors is composed of Cystein Rich Domains (CRD), Orange for TNFR1/2; blue for Fas and DcR3 and a panel of greens for DR4, DR5, DcR1, DcR2 and OPG. Their TM (Transmembrane Domain) is represented in red, whereas their Intracellular domains, with the exception of DcR3 and OPG which are secreted, is represented either by a bar (solid or not). Some of these receptors harbour in addition a Death Domain (DD), represented as a yellow box. Note that the DD of DcR2 is truncated. The solid bar underneath each ligand encompasses the receptors with which a physical interaction has been demonstrated experimentally.

In addition to these two agonists, TRAIL can also bind to four other receptors (Figure 2), but the latter are unable to induce apoptosis due either to the absence of a functional death domain (DD), in their intracellular c-terminal portion, or because these receptors are secreted to the extracellular compartment [15]. DcR1, DcR2 and OPG [16–20] solely interact with TRAIL, while DcR3, which has more recently been found to interact both with TRAIL [21], was originally found to interact with Fas ligand [18]. Both DcR1 (TRAIL-R3 encoded by TNFRSF10C) [22,23] and DcR2 [24] (TRAIL-R4 encoded by TNFRSF10D) are expressed at the cell surface. Albeit DcR1 lacks an intracellular domain, it is expressed on the cell surface, thanks to a GPI-anchor. DcR2, on the other hand is a transmembrane protein, but its truncated DD precludes the recruitment of the pro-apoptotic machinery and thus makes DcR2 unable to trigger apoptosis [16,25–28]. The two other antagonist receptors, OPG (osteoprotegerin) [29] and DcR3 [21] are secreted as soluble receptors in the extracellular compartment, and are thus unable to transduce cell death, including OPG which harbours two DD (Figure 2). All four antagonist receptors are capable of competing with TRAIL to inhibit apoptosis-induced by either DR4 or DR5 [16,17,30] (Figures 1 and 2).

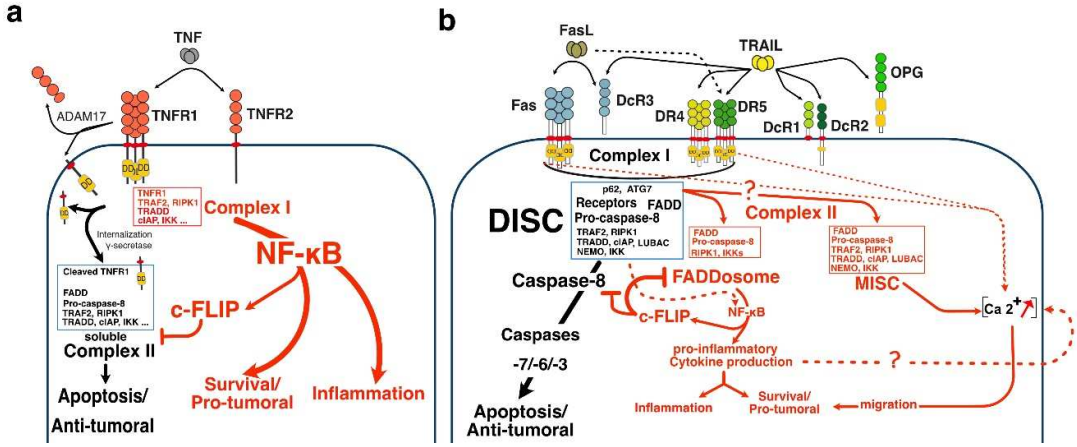

Figure 2. Comparison of the signalling pathways triggered by TNFR1, Fas and TRAIL agonist receptors. a) TNFR1 signalling complexes upon TNFα stimulation are depicted in this panel (see also the text). TNFR1 engages first of all the formation of complex I, a survival membrane platform which leads to the activation of the NF-κB pathway, leading, in most cases to cell survival and inflammation. Regardless of the outcome, complex I is processed during activation to give rise to a secondary soluble complex (complex II), that recruits pro-apoptotic components such as the adaptor protein FADD and the caspase-8 to induce apoptosis. Cell death is usually never happening, unless activation of the NF-kB pathway fails, because the latter induce the transcriptional regulation of cellular FLIP (c-FLIP), the main inhibitor of caspase-8. b) Engagement of Fas, DR4 or DR5, contrary to TNFR1 enable direct recruitment of FADD and caspase-8 at the membrane complex I, and are thus more prone in triggering apoptosis than TNFR1. Non-apoptotic signal transduction, however, is thought to proceed from a secondary complex coined complex II, which has been described as the FADDosome or the MISC (Migration signalling complex). The latter leads to the activation of the NF-κB pathway to induce survival, pro-inflammatory and pro-tumoral effects (see text for more details). Proteins indicates in the rectangles have been described to be recruited in the distinct complexes depicted in this figure.

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Like other members of the TNF superfamily, increasing evidence indicate that TRAIL can also, besides inducing cell death, display pleiotropic signalling activities ranging from cell differentiation [31–34], tumour progression, invasion to metastasis [35–41]. Although TNFRSF share both structural characteristics and signalling activation partners [42], and despite the fact that a large number of these receptors also share the ability to trigger similar signalling pathways, the modus operandi is not similar, involving distinct sequence of events, depending both on the considered receptor and ligand [43].

Likewise, and albeit much less efficiently than TNFR1, both TRAIL and Fas-ligand agonist receptors are able to trigger NF-kB signalling, leading in some cases to increased tumour growth and inflammation [44–58] (Figure 2). Moreover, increasing evidence indicate that soluble FasL or TRAIL may confer tumour cell resistance to apoptosis, contributing to pro-tumoral signalling or even inducing tumour cell growth [57,59–61]. For instance, seminal findings from Seamus Martin's laboratory demonstrated that caspase-8, regardless of its proteolytic activity, serves as a scaffold for the formation of a FADD containing soluble complex recruiting RIPK1 and is necessary for NF-κB activation and pro-inflammatory proteins secretion, upon TRAIL stimulation [52,62,63]. The formation of this complex has been found to be directly controlled by the caspase-8 inhibitor c-FLIP [52] (Figure 2b).

Alternatively, although much less represented in the literature, other studies suggest that non-conventional ligand-to-receptor interactions may also exist, explaining how these agonist receptors may transduce non-apoptotic signalling pathways, such as the recently described soluble FasL/DR5 interaction, whose role during auto-antibody-induced arthritis has been associated with exacerbated inflammation *in-vivo* through regulation of NF-κB -mediated production of CX3XL1 [64].

While it is still unclear how these complexes are formed, these less studied, non-apoptotic signalling capabilities are likely to contribute to a large variety of human diseases. It is thus of utmost importance to study them, since only a better understanding of their mechanistic will allows us to develop novel therapeutic drugs to be tested in the clinic, to cure or at least alleviate patients suffering from autoimmune, inflammatory and cancer diseases.

We aim with this comprehensive review at discussing and at delineating the current understanding of the molecular events governing cell fate decision after TRAIL stimulation, with a special emphasis for non-apoptotic signal transduction.

2. The TRAIL System:

2.1. TRAIL-Induced Cell Death:

TRAIL was described for the first time as a pro-apoptotic ligand that induces apoptosis [1,2]. TRAIL is expressed as a cell surface protein, mostly by activated immune cells such as T and B cells [65], neutrophils [66–68], dendritic cells [69], monocytes and macrophages [70–74], natural killer and NKT cells (NK) [75–85]. TRAIL plays a crucial role both during viral clearance [86–98] and tumour immune surveillance [99–104]. Mechanistically, during innate immunity, NK cells and CTLs (cytotoxic T cells) promote apoptosis of target cells, either by releasing soluble factors such as the cytolytic granules [68,105–107], which contain perforin and granzymes, or by engaging membrane-bound death ligands like FasL or TRAIL [84,105,108–113].

Unlike FasL or TNFα [114,115], TRAIL induces apoptosis in tumour cells, selectively [116] and exhibits little to no cytotoxicity against normal human cells or mice cells [117–123]. Given that DR4 and DR5 are usually upregulated on cancer cells [124–132], and that TRAIL induces apoptosis in a p53-independent manner [133,134], contrary to most chemotherapeutic drugs [135], overcoming p53 escape [23], it has soon attracted major attention in oncology [136–139].

TRAIL binding to its two agonist receptors, DR4 and DR5, lead to the formation of homo or hetero multimeric complex on the cell surface, which in turn enable the recruitment of the adaptor protein FADD (Fas Associated via Death Domain) and the initiator pro-caspases-8 and/or -10, leading to the formation of the Death-Inducing Signalling Complex or DISC [48,140–143], in which the initiator caspase-8, like in the Fas DISC, is activated by mere proximity-induced dimerization [144–

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146]. Once activated this initiator caspase, self cleaves itself enabling it not only its free itself from the DISC, but also to reach and cleave substrates localized in the cytosol, such as the executioner caspases-3, -6 and -7 [147], which ultimately will concur in the execution of apoptosis, culminating in DNA fragmentation and the formation of apoptotic bodies [148].

Commitment to apoptosis upon TRAIL stimulation may further be regulated either by genetically regulated events, see below, or by cellular heterogeneity and stochasticity. Likewise, it has been demonstrated that random assembly of the receptors upon ligand stimulation [149], as well as intracellular or membrane-bound proteins stochastic distribution during cell division [150], may contribute to cell fate decision.

In the late 90's two type of cells, found to rely or not on the activation of mitochondria, were described to transduce differentially apoptosis upon Fas ligand and TRAIL stimulation [151,152]. In type I cells, sufficient caspase-8 is activated to undergo apoptosis [153], regardless of mitochondria [154,155]. The intrinsic pathway is, however, required in type II cells, to fully transduce apoptosis upon TRAIL or FasL stimulation. Likewise, contrary to type I cells, mere loss of Bax expression [156] or overexpression of Bcl-2 anti-apoptotic members [153,157,158], is sufficient to abrogate the execution of apoptosis. Activation of the mitochondrial pathway by TRAIL receptors is mediated, in these cells, by a caspase-8-dependent cleavage of Bid [152,159], a BH3-only Bcl-2 family member, whose cleavage allows truncated Bid (tBid) insertion into mitochondrial membranes where it induces the translocation and oligomerization of Bax and Bak [160–162], inducing the release of cytochrome-c (Cyt-c). Once released from the outer membranes of mitochondria, cytochrome c forms, together with the initiator caspase-9 and APAF-1 (Apoptotic peptidase activating factor-1), the apoptosome complex [163–165], which allows the activation of the caspase-9 by mere dimerization [166] and which culminates in the activation of the executioner caspases (Figure 3).

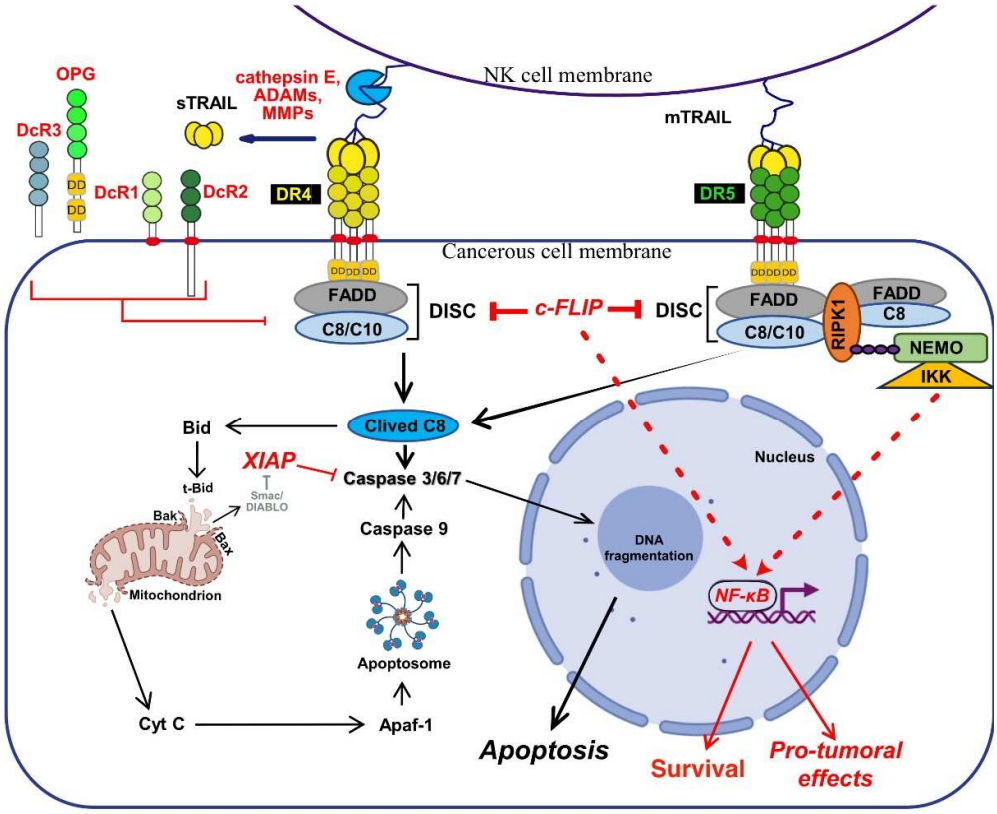

Figure 3. Schematic representation of TRAIL canonical signalling pro-apoptotic pathway. Membrane-bound TRAIL, expressed by cytolytic immune cells such as NK cells induces apoptosis in cancer cells. TRAIL binding to DR4 and/or DR5 agonist receptors, induce their aggregation and the recruitment of FADD and caspase-8/10 forming the DISC (Death-Inducing Signalling Complex), or

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complex I, which ultimately will lead to the activation of the effector caspases 3/6/7, whose activation by enzymatic cleavage is either triggered directly by the active caspase-8 or indirectly through caspase-8-mediated Bid cleavage, allowing Bax translocation to mitochondria and the release of cytochrome c, whose binding with Apaf-1, amplifies apoptosis-induced by TRAIL receptors (extrinsic pathway), through the formation of a soluble pro-apoptotic complex coined apoptosome, that allows activation of the initiator caspase-9, that in turn will amplify the signal by cleaving and activating the effector caspases 3/6/7. The main inhibitors of this signalling pathway are represented in red, including the antagonist receptors (DcR1/2/3 and OPG) which compete for TRAIL binding or c-FLIP and XIAP the main caspase-8 and effector caspases inhibitor inhibitors, respectively. In addition, a schematic representation of the non-canonical signalling associated with complex I is shown, mainly describing potential activation of NF-κB which besides protecting the cells from TRAIL-induced apoptosis is involved in promoting TRAIL's pro-tumoral activity. Main TRAIL-induced apoptosis inhibitors are shown in red.

Besides apoptosis, cell death induced by TRAIL may proceed through necrosis, in specific cell types or under certain conditions. Likewise, and similar to TNFα and FasL, TRAIL has been found, by a seminal work by the late Pr Jurg Tschopp [167], to induce necroptosis in the human jurkat T cell line, in a RIPK1-dependant manner, in the presence of a pan-caspase inhibitor or in the absence of FADD [167]. It was next found that at acidic extracellular pH (pHe), a condition that can be encountered in the tumour microenvironment (TME), TRAIL induced cell death proceeds through necroptosis. Likewise, mere acidification of the extracellular pH, *in vitro*, switches TRAIL-induced cell death from apoptosis to necroptosis [168], in a RIPK1-dependent manner [169]. The first inhibitor of this programmed inflammatory cell death, the necrostatine [170], was later found to inhibit RIPK1 [171]. RIPK1 is an integrator of cellular stimulation with protein kinase activity and scaffolding functions. RIPK1 is composed of a N-terminal kinase domain, an intermediary domain (ID), a C-terminal homology interaction motif (RHIM), and a DD. Owing to homotypic interactions, RIPK1 can be recruited to DD-containing receptors through its DD, and provided that it is not cleaved by the caspase-8 within the DISC [172,173], RIPK1 can recruit RIPK3 through the RHIM [174,175] and phosphorylate RIPK3 [176–179], forming the ripoptosome [180], which then phosphorylates and activates the pseudo kinase mixed lineage kinase domain-like protein (MLKL) [181,182]. Activation of MLKL leads to its oligomerization, translocation to the plasma membrane, forming large pores which engage ion channels to mediates ion influx, cell swelling, and plasma membrane rupture followed by the uncontrollable release of intracellular material [181,183–185] (Figure 4). Changes of pH naturally occur in the vicinity of tumour cells [186] as well as during ischemia [187]. The latter are, thus, likely to regulate TRAIL-induced cell death efficacy and modalities [188] and ultimately to affect immune antitumoral responses [189,190].

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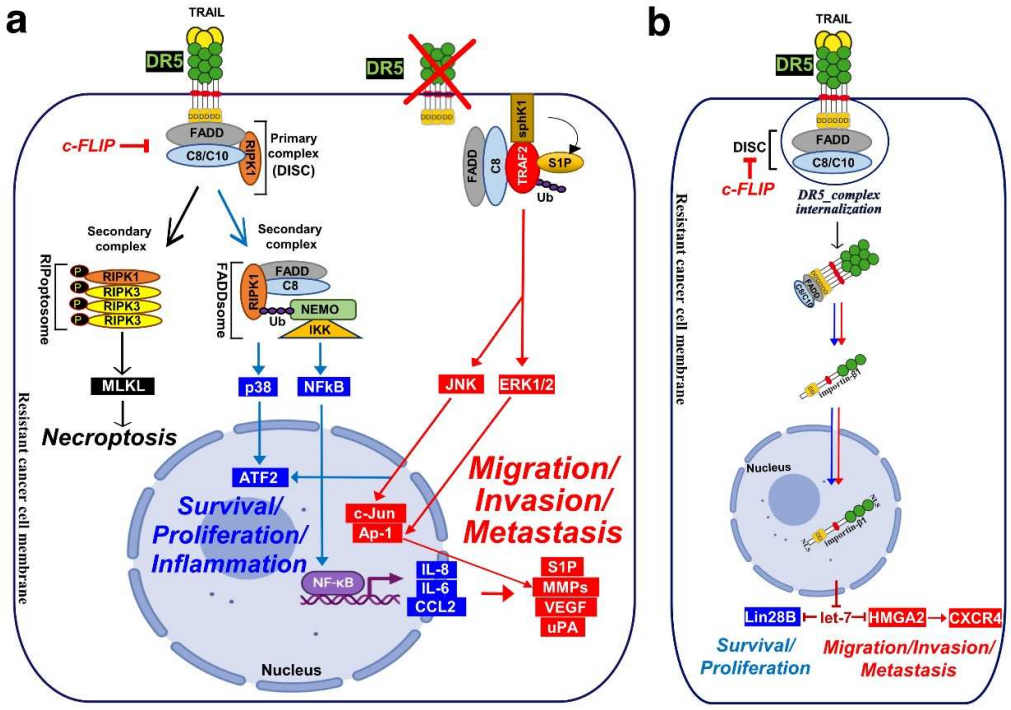

Figure 4. Schematic representation of DR5 non-apoptotic signalling pathways. Illustration of **a**) DR5-mediated RIPoptosome and FADDosome secondary complexes and b) nuclear translocation of DR5 in the nucleus, potentially mediating cell migration. See text for explanation.

Last but not least, TRAIL agonist receptors have been found to induce cell death, in a ligand-independent manner, during unresolved unfolded-protein stress-induced response [191–195]. DR5 was found to serve as a receptor for misfolded proteins, explaining, at least in part, how apoptosis is transduced through this receptor during ER stress, in the absence of TRAIL [196]. Albeit it remains to be determined whether DR4 binds or not unfolded proteins, and despite the fact that most studies have focused on DR5, this second agonist TRAIL receptor has also been found to contribute to apoptosis during ER stress [63,193,194]. Moreover, although caspase-8 is involved during DR4- and DR5-mediated ER-stress-induced cell death [192], it has also been found, associated within an atypical platform devoid of DR4 and DR5, to be required for ER-induced apoptosis in an osteosarcoma cell line [197]. Yet, it has also been reported that TRAIL agonist receptors or caspase-8 are negligeable in some cases, such as in B-cell malignant cells or the colorectal cancer cell line HCT116 [198,199].

2.2. Comparison of the Proximal Regulatory Mechanisms Governing TRAIL-Induced Cell Death with Other TNFRSF Members

TNFα was the first ligand of the TNFSF superfamily tested for its anti-tumoral activity [200,201], followed by Fas-ligand [115,202]. While Fas-ligand [14,203,204] and to a much lesser extend TNFα, due to the requirement of protein synthesis or transcription inhibitors [205–207], are efficient in killing a variety of tumour cells, these ligands cause significant damage to normal tissues that result in life-threatening toxicities [116]. Despite the fact that TRAIL, TNFα and Fas share common pro-apoptotic partners and modalities, solely TRAIL displays tumour selective pro-apoptotic activity, sparing normal tissues or cells [116,123], including when administered to small animals or humans [122]. Administration of Fas or TNFα in rodents, on the other hand, is lethal [115,208–210]. Moreover, TNF is involved in sepsis-mediated organ failure due to cellular toxicity [200,211,212].

Unlike TNF-R1 [213], engagement of apoptosis induced by DR4, DR5 or Fas is primarily initiated directly from the plasma membrane, through the formation of a complex coined Death-inducing

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signalling complex (DISC) [140,141,143] after TRAIL or Fas ligand binding to their respective cognate agonist receptors (Figure 2). TNFR1 membrane-bound complex, on the other hands, triggers a NF-kB-dependant survival pathway on the first instance, without recruiting FADD nor the caspase-8, due essentially to the recruitment of the kinase RIPK1 [214–216] and the adaptor protein TRADD [217,218]. The group of David Goeddel in the late 90's provided the first molecular demonstration that divergent signalling complexes could lead to distinct and antagonist signalling pathways [217]. Albeit FADD and caspase-8 have long been known to be required for TNF-induced apoptosis [219,220], the molecular comprehension of their temporal and spatial contribution was unveiled, almost a decade later, by the discovery that a secondary complex was required to initiate apoptosis. Complex II is a soluble scaffold multimeric protein complex which arises from complex I [213]. It contains, amongst others, the adaptor protein FADD, the cysteine protease caspase-8, as well as the post-translationally modified forms of RIPK1 and TRADD, whose modification is primarily initiated in complex I [213]. Transition from complex I to complex II, albeit still not fully understood, was later on found to involve two proteolytic steps, starting first with the shedding of TNFR1 extracellular domain by TACE (TNF-Alpha Converting Enzyme), also known as ADAM17 [221], and leading to the internalization of complex I through a clathrin-dependent mechanism, followed by an additional cleavage within TNFR1 transmembrane domain, by the γ-secretase, allowing the release of its intracellular domain, which contains bound TRADD, TRAF2 and RIPK1 amongst others proteins [221]. The release of complex I to the cytosol, in turn, subsequently allows the recruitment of FADD and caspase-8, forming the pro-apoptotic TNFR1-complex II (Figure 2).

Regardless of the *modus operandi* required for engaging cell death by these receptors, the latter have been found to form dimers or trimers, due to spontaneous self-association of their N-terminal extracellular domain, called pre-ligand assembly domain (PLAD) [222,223], which is generally present in the first cysteine-rich domain of some TNFSFRs (Figure 1). By favouring ligand-independent receptor multimerizations, the PLAD was both find to limit apoptosis induced by TRAIL due to the homodimerization of DR5 [224], or to the formation of heteromeric complexes DR4, DR5, DcR1 or DcR2 [16,30,225]. These self-association motifs have recently been demonstrated to be targetable. Interestingly it was found that, mere administration of a TNFR1 PLAD-Fc recombinant protein improves skin lesions in MRL/lpr [226], arthritis [227], as well as experimental autoimmune encephalomyelitis or diabetes [228], in experimental animal models.

Organization and arrangement of TNFRSF in homo- and heteromeric complexes into higher-order complexes has profound effect on their signalling capabilities [42,229,230] and is often required for efficient apoptosis triggering, as demonstrated with DR5 [231–233]. Likewise, it has been proposed that DR4, DR5 and Fas form, first of all, upon cognate ligand binding, trimer complexes whose multimerization or crosslinking with neighbouring trimers occurs via the dimerization between receptor interfaces, either located opposite the ligand-binding interfaces, resulting in a hexameric honeycomb-like structure [234]. A dimerization motif found in the transmembrane helix domain of the receptors is also suspected to play an important role for the assembly of the DISC, its stability and potency [231,234,235]. Moreover, as suggested for Fas, DISC stability may also be regulated at the level of the cytoplasmic domain of some agonist receptors by the adaptor protein FADD [236–238].

Furthermore, in line with the fact that most TNFSF receptors harbour putative glycosylation sites, it has been demonstrated that O- and N-glycosylations, post-translational modifications, also regulate TNFRSFs pro-apoptotic signalling transduction [239,240]. Likewise, based on the observation that TRAIL sensitivity in cancer cells was associated with high glycosylation profiles, the seminal work of Avi Ashenazi's laboratory, provided the first molecular demonstration that DR5-mediated TRAIL-induced cell death could be regulated by the O-glycosylation [241]. While it remains to be determined whether O-glycosylation affects other receptors of the family [242], receptors such Fas, TNFR1 or DR4 were found, on the other hand, to be N-glycosylated [243–247]. This post-translational modification of DR4 or Fas increases cancer cell lines sensitivity to TRAIL- or FasL-induced cell death, respectively [243,245]. Similar gain of function associated with the fly tumour necrosis factor (TNF) receptor homolog glycosylation were demonstrated [248]. It shall be noted,

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however, N-glycosylation, on the other hand, was found to prevent TRAIL-induced cell death in normal mouse fibroblastic cells [244], suggesting that the increase in signal transduction induced by TNFRSFR mediated by their O- or N-glycosylation, maybe restricted to cancer cells. Regardless, it has been demonstrated that the gain of function associated with the O- or N-glycosylation of these agonist receptors, with the exception of one study [248], is not related to a change in ligand binding to its cognate receptor, but rather a stabilization of the membrane-bound primary complex, likely mediated by an increase in receptor aggregation, that ultimately leads to a better signalling activity, which in the case of Fas or TRAIL is associated with an increase in caspase-8 activation [241,243,245,249–251]. Consistent with this, glycan modifications or glycan-binding proteins were found to enhance or impair apoptosis induced both by TNFR1, FasL and TRAIL [242,250,252–262]. These post-translational modifications shall be distinguished from the O-GlcNAcylations or O-GlcNAc, as contrary to the O- or N-glycosylation, O-GlcNAc takes place within the cytosol, and shall thus affect the C-terminal cytosolic domains of TNFRSFs. Likewise, there have also been reports demonstrating that GlcNAcylation of both DR4 or DR5 C-termini, could be required for, or enhance, DISC formation and receptor clustering [249,263,264]. On the other hand, O-GlcNAc of death-domain containing proteins, has also been demonstrated to protect cells, infected by pathogens, from apoptosis induced by TNFRSF-death-containing receptors [265–267], and to protect erythrocytes from necroptosis by targeting RIPK1 [268]. Another intracellular post-translational modification may also affect death-domain containing receptor localization, aggregation and function. Likewise, it has been found that palmitoylation of DR4, Fas and TNFR1, but not DR5, enhances apoptosis induced by TRAIL [269] and Fas ligand [270–272] and is required for TNFR1 signal transduction [273].

3. Physiological and physiopathological functions of TRAIL:

TRAIL exhibits pleiotropic physiological functions which are regulated by its cognate receptors due to their ability to trigger or not cell death. TRAIL and its receptors play an important role in maintaining tissue homeostasis [274–278]. Through transducing cell death, TRAIL and its agonist receptors are most notoriously known for their ability to kill cancerous cells and cells infected by viruses [91]. Yet, a tremendous amount of work also suggests that TRAIL and its receptors are also likely to play a role in several human diseases including, but not limited to, obesity and diabetes [279], associated with inflammation [32,63,280], neurological disorders [281] or cardiac diseases [282].

3.1. In Immune System:

In the immune system, TRAIL helps maintain lymphocyte homeostasis. Likewise, while activated CD8+ cells were described to be more sensitive than CD4+ T cells to TRAIL-induced cell death [283], CD8+ T cells can protect themselves from apoptosis induced by TRAIL by up-regulating both the antagonist receptors and c-FLIP [77,284]. Variation of TRAIL sensitivity, in CD8+ T cell blast, is both time- and stimuli-dependent, explaining TRAIL's ability to actively contribute to CD8+ T cell AICD and to generate memory-like CD8+ T-cells [285–291]. Interestingly, using experimental animal models, TRAIL was found to inhibit autoimmune lymphoproliferative syndrome as well as spontaneous idiopathic thrombocytopenia purpura, due to its active contribution during activation induced cell-death (AICD) [290,292].

Besides its role in adaptative immunity, TRAIL plays an important role during in innate immunity [293], such as in anti-tumour immune surveillance [80,99,101,293,294]. TRAIL is often instrumental for the cytotoxic activity of immune cells. It is upregulated and contributes to the cytolytic activity of T cells, neutrophiles or monocytes stimulated by type I interferons [71,72,284], or after stimulation with IL-2 plus phytohemagglutinin [65], contributing to their anti-tumoral activity. TRAIL expression can also be induced in plasmacytoid dendritic cells by microbial or viral products such as LPS or Toll receptor agonists, contributing to their cytotoxic activity [295]. TRAIL is also thought to contribute to ocular [296] and placental immune privilege [297].

A recent study analysing the immune repertoire, in TRAIL-deficient mice, found organ-distribution differences of several types of immune cells, such as dendritic cells, in these animals as compared to parental mice [298]. Keeping in mind that CD8+ T cells were recently found to contribute

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to tissue remodelling [299] and that TRAIL can be expressed by a large number of immune cells, as mentioned above, including CD8+ cells, these studies collectively suggest that TRAIL may play a wider role in the immune system than expected. Indeed, growing evidence suggests that TRAIL non-apoptotic functions may also play a role in shaping and orchestrating the immune response to pathogens or cancer cells. TRAIL has for example recently been demonstrated to inhibit IL-15-induced cytotoxic granule granzyme B production in NK cells during viral infection, limiting viral clearance [91]. By regulating inflammation, in the absence of apoptosis, TRAIL can also contribute to the dysregulation of the immune system. Likewise, using TRAIL-R-deficient mice, it was found that TRAIL, by inhibiting T cell activation, supresses gut inflammation [300] or arthritis [301,302], in an apoptosis-independent manner [303]. Injection of TRAIL itself was also found to be beneficial in experimental animal models to inhibit autoimmune thyroiditis [304] or arthritis [305]. Suppression of auto-immunity by TRAIL, can proceed both through caspase-dependent and independent manner, as it was shown that TRAIL can on the one hand inhibit Th1 cells proliferation and on the other promote that of regulatory T cells, as demonstrated in TRAIL- [306] and TRAIL-R- deficient mice [301]. TRAIL deficient mice also unveiled the critical role of TRAIL in supressing experimental autoimmune encephalomyelitis [307]. In a remarkable way, TRAIL functions in autoimmune diseases by transducing both canonical and non-canonical signalling pathways, holding promises in autoimmune therapy [308,309]. Yet in other instances, TRAIL has also been found to trigger inflammation and/or to amplify other autoimmune diseases such as lupus erythematosus [310] and lupus nephritis [311].

Finally, TRAIL may also play a role in allergy, given that oesinophils and granulocytes express TRAIL receptors, but are insensitive to TRAIL-induced cell death [312,313], TRAIL is abundantly expressed in the airway epithelium, in response to allergen provocation, in the initial step [313–315].

3.2. In Diseases:

TRAIL is associated with diseases beyond of the immune system. Likewise, TRAIL may play a physiological role in endothelial cell function [316], since it has been found to exhibit a pro-angiogenic activity [317,318] and to stimulate the proliferation of vascular smooth muscle cells [319]. In another study, TRAIL, on the contrary, was shown to inhibit angiogenesis-mediated by VEGF, through both a caspase-8-dependent and -independent manner [320]. *In vivo*, however, it was found, using *Trail-/-* mice, that TRAIL is able to promote angiogenesis and neovascularization after ischemia [321]. In the same line, an increasing number of studies also indicate that TRAIL could be involved during cell differentiation. Likewise, TRAIL induces the differentiation of intestinal cells [31], osteoblasts [322,323], skeletal muscle or myoblast cells [34,324] or keratinocytes [325], but appears to inhibit adipocyte differentiation [326].

TRAIL has also been described in lung and heart diseases. TRAIL induces survival, proliferation, and migration of human vascular smooth muscle cells (VSMC) in Pulmonary arterial hypertension (PAH) [327–329]. Its high expression levels in the serum of PAH patients correlates with the severity of the disease [329]. Through non-canonical signalling TRAIL promotes VSMC and fibroblasts proliferation and migration through ERK1/2 MAPK and the Serine/Threonine Kinase Akt activation, without affecting p38 MAPK or c-Jun N-terminal kinases (JNK) activation [330]. TRAIL stimulates proliferation of VSMC after Insulin-like growth factor-1 receptor (IGR1) regulation through NF-κB activation [319]. In addition to VSMC, TRAIL promotes survival and proliferation of primary human vascular endothelial cells, as well after Akt and ERK activation without affecting NF-κB pathway [331]. Activation of NF-κB in vascular smooth muscle cells by TRAIL has also been described to require the cleavage of protein kinase C-delta (PKC-δ) by caspases [332].

TRAIL and its three receptors, DR4, DR5 and DcR1, are highly expressed in human heart [127], and while cardiomyocytes express DR5, they are resistant to apoptosis, yet after TRAIL stimulation DR5 transduces the activation of the ERK1/2 pathway, in these cells, in a MMP-EGFR-dependent manner, as described by Panner et al. [333]. It has been proposed that TRAIL, by inducing the production of MMPs trigger the cleavage of the Epithelial Growth Factor Receptor ligand (HB-EGF)

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in the cell membrane to induce EGFR signalling, which promotes cardiomyocyte proliferation and ERK 1/2 signalling [333].

TRAIL pro-apoptotic or non-apoptotic signalling is also suspected to contribute at some extent to Alzheimer's disease [334–338], and non-alcoholic fatty liver disease [339–342]. Like cancer cells [52,63,343], the molecular mechanisms driving TRAIL-induced non-apoptotic signalling, including cell motility in normal cells remain poorly understood.

4. Signalling Machinery Associated with TRAIL Non-Canonical Transduction:

TRAIL, as reported in a growing number of studies, triggers the differentiation, proliferation or survival of normal cells, such as macrophages [32,322], intestinal mucosal cells [31], Skeletal myoblasts [324], keratinocytes, osteoclasts [323,344], vascular smooth muscle cells [34,330,331,345] or mouse fibroblasts [346].

In cancer cells, on the other hand, if apoptosis is not efficiently triggered, TRAIL can be detrimental to patients given that this cytokine also exhibits pro-tumoral properties, associated with TRAIL's ability to induce inflammation, tumour cell motility and invasion, ultimately leading to metastasis [35,38,39,43,193,347–350]. Likewise, TRAIL was found to promote the proliferation in human glioma cells through ERK1/2 phosphorylation and the stabilization of the long form of c-FLIP(L) [351], in cholangiocarcinoma cells via NF-kB [40]. Migration and invasion were also promoted by TRAIL in NSCLC the A549 cell line in a RIPK1-dependent manner through phosphorylation of Src and STAT3 [39], in pancreatic ductal adenocarcinoma [38], in colorectal cancer cells, resistant [349] or not [193] to TRAIL-induced cell death, and in the triple negative breast cancer cell line MDA-MB-231 (TNBCs) [193]. In oesophageal squamous cell carcinomas (Figure 5), TRAIL induced epithelial-mesenchymal transition (EMT) and metastasis through ERK1/2 and stat3-dependent upregulation of PD-L1 [352]. PD-L1 regulation through ERK phosphorylation induced by TRAIL was also reported in TNBCs [294]. Using a TNBC xenograft model, TRAIL was also demonstrated to promote skeletal metastasis [350]. Consistent with these findings, deletion of murine TRAIL-R, in a non-small-cell lung cancer (NSCLC) and pancreatic ductal adenocarcinoma (PDAC) using a KRAS-driven experimental model, was found to drastically impair metastasis, and this effect was associated with a loss of cell migration, proliferation, and invasion [35].

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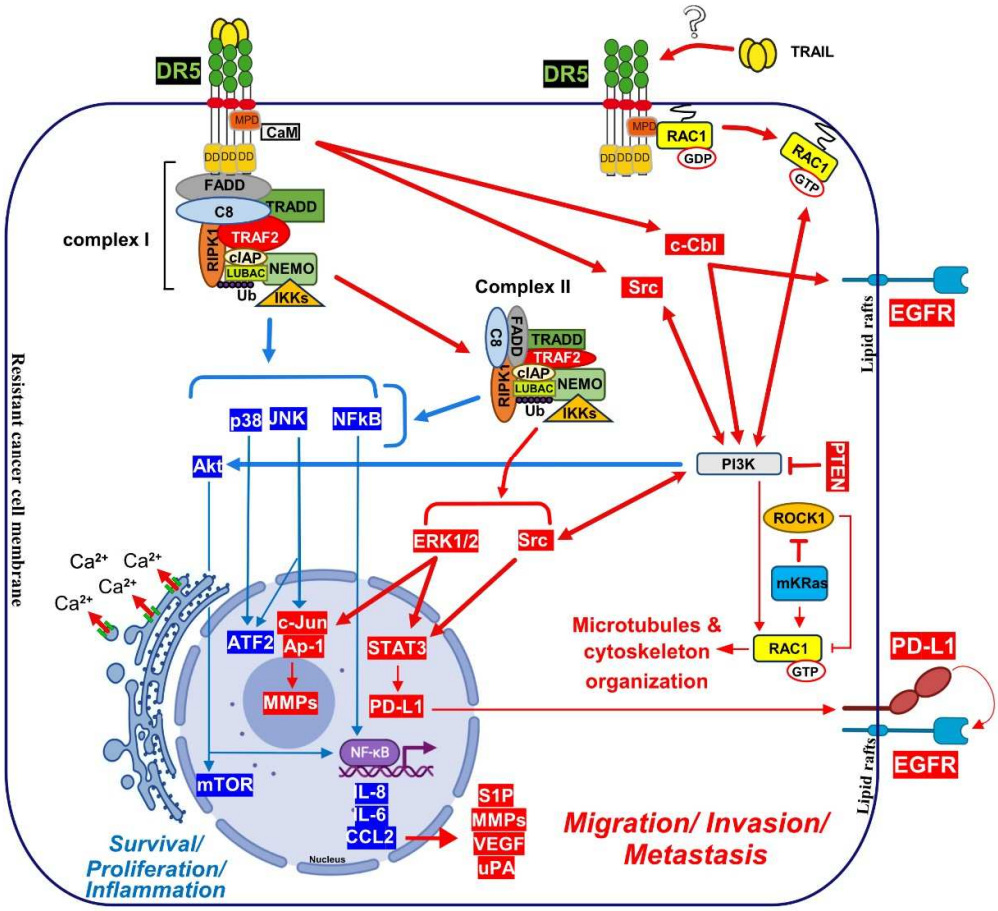

Figure 5. TRAIL-induced non-canonical pro-tumoral signalling via DR5 secondary complex formation. TRAIL agonist receptors, especially DR5, depending on cancer type and stage, can promote tumour growth and metastasis either through complex I or through a soluble secondary complex. Complex II arises from complex I and contains amongst other FADD, caspase-8, RIPK1, TRAF2, TRADD, cIAP, LUBAC, NEMO and IKKs. While complex I. is associated with survival and proliferation through p38, JNK and NF-kB activation, complex II appears in addition able to activate ERK1/2 pathway and Src leading to metastasis in vivo (See text for explanations). DR5 can directly activate signalling proteins involved in metastasis, thanks to its membrane-proximal domain (MPD), represented in orange, which directly recruits a Ca $[2]^{+}$ binding protein, the CaM whose recruitment, in the presence of calcium, induce the activation of the proto-oncogene Src and the ubiquitin ligase c-Cbl, leading to PI3K, JUN, STAT3 and Rac1 activation. Activation of Rac1 promotes microtubules and cytoskeleton organization to activate cell migration. Rac1 was also found, as illustrated here to be activated by direct recruitment to DR5 MPD, in a ligand independent manner. See text for additional details. Colours: writing highlights and arrows illustrate TRAIL-induced proliferation and inflammation (in blue), or TRAIL-induced metastasis (in red).

Mechanistically, TRAIL was shown to induce NF-κB activation [48,353,354] and by analogy with TNFR1 signalling [213], albeit in a distinct manner, it was next found that TRAIL could lead to the formation of two main distinct molecular complexes, explaining, at least in part, how TRAIL receptors can transduce cell death or pro-inflammatory pathways [39,43]. The primary pro-apoptotic complex, known as TRAIL DISC, is mostly composed of the TRAIL receptors, FADD, caspase-8 or -10 and the inhibitor c-FLIP, and is localized at the level of cellular membranes [16,140,143,355,356]. RIPK1 is also present in this complex [52,357] as well as TRADD [48,353,358,359], albeit there might be some differences in TRADD binding to TRAIL receptors, given that TRADD seems to be preferentially recruited to DR4 [48,353,357]. In addition to these adaptor proteins and kinases,

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originally found to compose TRAIL membrane-Bound complex, kinases such as IKKα, IKKβ and IKKγ, recruited to complex I, explaining how NF-κB may be induced by TRAIL [360]. Native recruitment of ubiquitin ligases can also happen in the TRAIL DISC as demonstrated with the presence of the linear ubiquitin chain assembly complex LUBAC (Figure 2), whose components SHARPIN and HOIP limits TRAIL-induced cell death as well as NF-κB activation [360–362], due to RIPK1 and FADD linear ubiquitination [360]. Moreover, other proteins such as c-IAPs, A20 and TRAF-2 are also recruited in complex I [360].

The secondary non-apoptotic complex, on the other hand, is found in the cytosol, albeit it arises from complex I [361] (Figure 3). Complex II contains not only FADD and caspase-8, but also RIPK1, TNF receptor-associated factor 2 (TRAF2), TRADD, as well as a large number of apoptosis inhibitors, NF-κB regulators, including IKK and NEMO [43], not to mention LUBAC [360] (Figure 4). It must be stressed here that RIPK1 can not only be directly recruited to TRAIL receptors, as evidenced in native complex I [360,363,364], because it contains a death-domain [365], but that the latter is required for TRAIL-induced NF-κB activation [366]. Of interest, similar to Fas DISC [173], membrane-proximal localization of RIPK1 allows its cleavage by the initiator caspase-8 within its intermediary domain, abolishing TRAIL-induced NF-kB activation [363,364].

Given that RIPK1 is recruited to the TRAIL DISC and present in the cytosolic complex II, it is easy to understand how TRAIL triggers the NF-κB pathway. Yet, as demonstrated by Azijli and co-workers, more than 10 years ago, in the TRAIL-resistant cancer cell line A549, TRAIL also induces besides NF-κB, the phosphorylation of a large number of substrates associated with activation of the P38, ERK1/2, JNK1, Src, AKT, Raf1 and ROCK [367]. While the implication of TRADD for TRAIL signalling is less investigated, TRADD was found to afford protection against TRAIL-induced apoptosis [358,368,369], but more interestingly TRADD could play an important role in the secondary complex to induces IL-8 secretion in NSCLC, under TRAIL treatment [370]. Furthermore, TRADD and RIPK1 redundantly mediate pro inflammatory signalling in response to TRAIL in human ovarian HeLa metastatic cell line [357]. Despite the fact that several experimental evidence link for example ERK1/2 activation in glioma cells with c-FLIP [351] or JNK activation with RIPK1 [366], it remains unclear how upstream kinases are integrated and activated in the molecular platforms triggered by TRAIL, whether it be complex I or complex II.

Evidence accumulates demonstrating that TRAIL can be detrimental in oncology due to its ability to promote cell migration and metastasis, but it still remains unknown, however, whether both TRAIL agonist receptor trigger similar non canonical signalling activity. Contrary to rodents [8], primates express two TRAIL agonist receptors [1,4,6], and therefore findings obtained from genetically modified mice may not always transpose to primates. For instance, with the exception of one study [371], migration and metastasis promoting TRAIL's activity seem to be mostly associated with DR5 [35,39,193,350]. While it remains unclear whether this peculiarity is due to DR5 splice variants or not [372], DR5 is found to be overexpressed in several cancer types and this overexpression is often associated with tumour aggressiveness and poor patient prognosis [373]. For example, DR5-positive staining is associated with increased risk of patient death in non-small cell lung cancer [126], breast [374] and renal cancer [375].

Activation of this non-canonical signalling pathway by DR5, which promotes tumour growth and metastasis through MAPK, PI3K/AKT or NF-κB signalling, is likely to be only visible in TRAIL-resistant cancer cells [39,349], including cell expressing TRAIL decoy receptors [27,376]. Alternatively, transition of the receptors once engaged with the ligand to membrane lipid rafts, may as demonstrated for TNF [377], contribute to induction of the pro-migratory signal. It has been suggested for example, that lipid rafts may provide an adequate membrane platform for aggregation for DR4/DR5 to transduce apoptosis [378]. Localization to lipid raft may be differentially occurring depending on the receptor and its potential palmitoylation status. Likewise, DR4 can be palmitoylated, translocating to lipid raft, where it was proposed to form and activate the pro-apoptotic complex I [269]. In B-cell hematologic malignant cells, DR4 was even proposed to be constitutively localized within lipid rafts [379]. Albeit DR5 was not found to be palmitoylated, it has also been described in lipid raft and described to recruit and activate the caspase-8 in these subcellular

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compartments [378,380–383]. However, while there is no doubt that TRAIL complex I may transit to lipid rafts, native TRAIL DISC formation in these lipid rich structures have never been demonstrated. On the contrary, it was found that TRAIL DISC-mediated activation of the initiator caspase-8, which is required for initiating apoptosis, rather occurs in non-lipid rich membranes [16,384]. Nonetheless, it cannot be excluded that transient translocation to lipid raft may account for TRAIL pro-tumoral properties.

4.1. Lessons from Fas/CD95 induced non-canonical signalling (secondary complex):

Non-canonical pro-motile and pro-metastatic signalling was also documented for Fas, a receptor of the TNF superfamily which like DR4 and DR5 is able to engage apoptosis from the membrane in a FADD- and caspase-8 dependent manner [385]. Fas ligand (FasL) was found to redistribute its agonist receptor Fas dynamically into lipid rafts, contributing to the elimination of activated T cells [386]. Lipid rafts were, thus, soon considered as possible check point controls for FasL-induced Fas signalling cellular outcome [387,388]. Like TRAIL, but to a much lesser extent than TNFα, FasL is also able to transduce NF-κB, regardless of its ability to trigger apoptosis [53,389]. NF-κB activation by FasL was associated with resistance to apoptosis in cancer cells [44], but also appeared to be associated, in addition, to cell motility and invasiveness [57]. It was also demonstrated that naturally cleaved FasL could induce cell migration [390–392]. Fas was found to induce proinflammatory cytokines in human monocytes [54,393]. In dendritic cells, Fas stimulation induce IL1β and IL-12 production and cell maturation [394].

Mechanistically, it remains unclear how Fas induce cytokine production or how it activates its pro-metastatic signalling pathway. FasL-induced cell motility and invasion has been associated with TRAF2 [395], PDGFR-β-mediated PLC-γ1 activation and PIP2 hydrolysis [396], activation of the kinase c-Yes and AKT and changes in cytosolic calcium [390], Rac1 [397], or through phosphorylation of Rock1 and involvement of the Na^+/H^+ exchanger NHE1 [392].

TRAF2 is recruited within the TRAIL DISC [360,398]. By allowing recruitment of ubiquitin ligases within the primary complex TRAF2 is able to limit caspase-8 activation [360,398,399]. TRAIL-induced JNK activation was found in cancer cell lines to require RIP and TRAF2 [400], suggesting that many of the non-canonical signalling pathways may be readily engaged from complex I. Alternatively, it has recently been proposed that NF-κB-mediated initiation of inflammation upon TRAIL stimulation may be induced, at least in part, through TRAF-2-mediated recruitment of cIAP1/2 and LUBAC into complex I, leading to the formation of a secondary complex coined ''FADDosome'' in which RIPK1 undergoes linear ubiquitination, allowing assembly of the NF-kB machinery and NF-κB-dependent regulation of inflammatory cytokines and chemokines [62] (Figure 5).

Linear ubiquitination and stabilization of the NF-κB signalling by LUBAC was first uncovered in TNFR1 complex I and found to rely on TRADD, whose absence precludes both TRAF2 and LUBAC recruitment to TNFR1 [401], consistent with the need of TRADD to induce NF-κB activation by TNFR1[218] and to allow TRAF2 recruitment to TNFR1 [217]. Within the Fas DISC, the caspase-8 inhibitor c-FLIP was also found in the early days as a protein that could integrate at TRAF2, to induce both NF-κB and ERK signalling [402,403]. Keeping in mind that TRADD could be essential too, for TRAIL-mediated non-apoptotic signalling, including induction of NF-κB [357,369], it is worth mentioning that TRADD is found both associated with TRAIL receptors membrane complex I [353,360] and soluble complex II [43]. An alternative molecular circuitry may explain the biological activity of TRAF2 in driving TRAIL pro-tumoral effects. Likewise, it was described that NF-kB activation by TNFR1 requires sphingosine-1-phosphate (S1P). S1P interacted with TRAF2 as a co-factor to catalyze RIPK1 poly-ubiquitination and NF-κB activation [404]. Given that S1P may be critically linked to metastasis [405,406], it may be worth considering, in addition, the interesting work demonstrating that deletion of DR5 induce cell motility and promotes cell invasion in a TRAF2 and S1P-dependent manner, through activation of the JNK/AP-1 pathway in lung cancer cells [371,407] (Figure 4).

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Direct recruitment of kinases associated with non-apoptotic Fas signal transduction as also been found, including Rac1 activation after binding to Fas membrane proximal domain (MPD), located in the intracellular part of the receptor, during neurite growth [397]. Albeit not characterized molecularly, TRAIL-induced cell motility was also associated with Rac1 activation in monocytes [408] and HeLa cells [409]. Interestingly, though, while Rac1 appears dispensable for the regulation of inflammatory proteins after TRAIL stimulation [410], Rac1 was required for DR5-mediated cancer cell motility and metastasis [35], and similar to Fas, the MPD of DR5 was also required to trigger this effect. (Figure 5). Rac1 was found to be directly recruited to DR5 [35], and consistent with mutated KRAS's ability to inhibit ROCK1 [411], ROCK1 inhibitors allowed Rac1 recruitment to DR5 and transduction of a signalling pathway leading to invasion in non-mutated KRAS cells [35]. It is thus likely that direct recruitment of RAC1 into the TRAIL DISC may, due to its ability to promote filopodia and lamellipodia formation, lead to microtubules and cytoskeleton organization [412], accounting for the cell migration induced by DR5 [35] (Figure 5).

4.1. Calcium Signalling Inducing Cell Motility and Metastasis:

Calcium signalling induced by ligands of the TNF family has initially been addressed with TNF [413] and FasL [414]. Increased cytosolic Ca2+ was found to occur almost immediately after stimulation, within the first 50 seconds. High calcium levels have been recorded after stimulation by FasL following activation of phospholipase C γ1 (PLCγ1), inositol 1,4,5-trisphosphate (IP3) generation, IP3 receptor (IP3R) calcium ionic channels stimulation and a late secondary Cytochrome-c-triggered activation of endoplasmic reticulum (ER)-resident calcium channels [415]. The role of Ca2+ in cancer cell proliferation, migration, and invasion has been well established [416]. Likewise, Ca2+ signalling is a potential key regulator for breast cancer bone metastasis and prostate cancer cells proliferation, angiogenesis, EMT, migration, and bone colonization [417]. Interestingly, both TRAIL- and FasL-induced pro-metastatic pathways are associated with an early increase in intracellular Ca2+ and tyrosine kinase signalling [193,418,419]. The use of isogenic stable cancer cells deficient for either DR4 or DR5 [193], demonstrated that TRAIL-induced pro-metastatic signalling was solely triggered by DR5 and correlated with a rapid Ca2+ flux [193,420,421]. Furthermore, early increased cytosolic Ca2+ was shown to be activated upon TRAIL exposure in both Jurkat and NB4 leukemia cells, protecting the latter from apoptosis [421]. It was found in these cells that recruitment of both p62 and ATG7 to complex I was required for calcium influx induced by TRAIL [421].

Like TRAIL, FasL also induces an increase of cytosolic Ca2+, associated with cell-motility and metastasis [390,418,422–424]. Intracellular increase in Ca2+ is generally induced by PLCγ1 and IP3R activation, due to ER Ca2+ release [425], but may also be triggered, as demonstrated in leukemia cells, after ORAI1 activation and CRAC channels opening [421]. Autophagy Related 7 (ATG7) [426] and Sequestosome 1 (p62/SQSTM1) [427], are two autophagic proteins related to ORAI1 and CRAC channels, whose recruitment to DR5 induce the release of Ca2+ from the ER [421]. Keeping in mind that DR5 is also involved during apoptosis induced during the ER stress and that this process is associated with Ca2+ release [191,196], while DR5, but not DR4, is able to induce a change in calcium flux after TRAIL stimulation, these findings suggest that calcium regulation is probably important for the triggering of TRAIL-mediated non-apoptotic signalling. Indeed, FasL also can induce high intracellular levels of Ca2+ ions to promote, depending on the context and cancer cell type, apoptosis or non-canonical signalling [415]. How Fas or DR5 trigger these changes in intracellular calcium remain unknown. However, in two studies performed using breast cancer models DR5 was proposed to directly interact with a protein which has a calcium dependent activity, the calmodulin (CaM) [428,429] (Figure 5 and 6). CaM is a small Ca2+ binding protein that interacts with a large group of intracellular proteins and which participates in signalling pathways that regulate proliferation and motility [430,431]. In PDAC cells, CaM was also found to be recruited in the DR5 DISC together with c-FLIP and the proto-oncogene Src, contributing to cell resistance [432]. In NSCLC cells, CaM inhibition or Ca2+ deprivation inhibited the recruitment of Src and was associated with an increase in c-FLIP short degradation, sensitizing cells to DR5 agonist-induced apoptosis [433]. Src could play a role during TRAIL-induces non-canonical signalling [39], given that Src was described, in addition,

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to phosphorylate and, thus, to inhibit caspase-8 enzymatic activity [434]. Furthermore, CaM may allow recruitment and activation of the Src [435]. Interestingly, CaM has also been found to be recruited within the Fas DISC [424,436,437], and associated with the regulation of Src pro-tumoral activity [424,435]. Last, caspase-8, alone, was found to bind to the Focal Adhesion Kinase (FAK) and Calpain-2 Ca2+ dependent protease (CPN2), displaying, thus, pro-metastatic function properties in glioblastoma cell lines [438], (Figure 6).

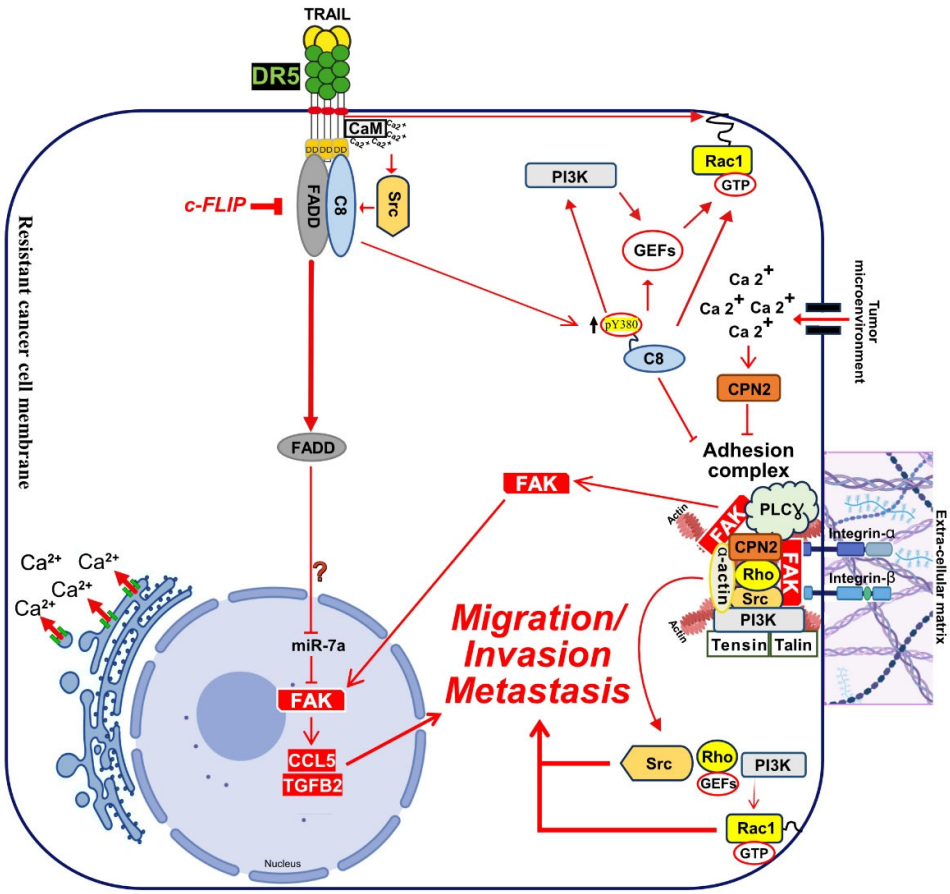

Figure 6. TRAIL non-canonical signalling pathway associated with caspase-8 non-enzymatic functions. Caspase-8 is a pro-apoptotic protein that, in the presence of c-FLIP, can activate TRAIL non-canonical signalling in an enzymatic-independent manner. If an increase in Ca [2]$^{+}$ ions from the ER is initiated at some point of the stimulation, the CaM can be recruited to DR5 MPD. Activated CaM, by inducing Src activation induces next the phosphorylation of the caspase-8, see text for details, enabling PI3K activation and subsequent activation of Rac1, leading to cell migration and invasion. Caspase-8 phosphorylation can also inhibit adhesion complex through complex elements FAC and CPN2 interaction. This interaction inhibits cell adhesion and allow complex elements activation. Then, cell migration and invasion can be induced by activating FAK and additional adhesion complex elements like PLCy, FAK, Rho, PI3K, and Src. Curiously, FADD seems to have the ability to trigger FAK-inhibited miR7a expression through unknown mechanisms. This is linked to the expression of pro-metastatic cytokines TGFβ and CCL5. Colours: writing highlights and arrows illustrate TRAIL-induced proliferation and inflammation (in blue), or TRAIL-induced metastasis (in red).

4.2. Nuclear DR5 Regulates Both Proliferation and Metastasis:

In other studies, regulation of TRAIL's pro-tumoral signalling has been suggested to be due to the subcellular compartmentalization of DR5 in the nucleus [439,440]. It is not clear how DR5 goes to the nucleus, but it has been proposed that DR5 may undergo proteolytic cleavage or internalization

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upon ligand binding, allowing its translocation into the nucleus [441–443]. Interestingly, mostly DR5 but not DR4 is found in nuclear compartment in late cancer stage of NSCLC [440], pancreatic [444], and breast cancer [445]. DR5 harbours two nuclear localization signals (NLS) sequences which promote importin-β1 binding and nuclear translocation of the complex, limiting thus TRAIL-induced cell death sensitivity [442]. In the nucleus importin-β1/DR5 was found to regulates the micro-RNA let-7 maturation and to promote tumour cell proliferation [444].

Mature let-7 is known to control cell proliferation by inhibiting its targets, such as, the High mobility group AT-Hook protein-2 (HMGA2) and the Lin-28 homolog-B (Lin28B) protein expression. Upregulation of HMGA2 and Lin28B enhance cell proliferation and malignant progression [446–449] (Figure 4). HMGA2 and Lin28B are two proteins overexpressed in embryonic tissues and downregulated in differentiated tissues because of low expression of let-7. Let-7 overexpression prevent cell transformation in epithelial cells [450]. Furthermore, knockdown of DR5 using shRNA results in increased levels of mature let-7, consequently in reduced abundance of let-7 targets, which induce cell proliferation in pancreatic cancer cells [444]. Interestingly, knockdown of DR5 in metastatic breast cancer cells decrease bone homing and early colonization to the bone marrow and induce E-cadherin overexpression which contraries EMT in xenograft mice model [350]. Impaired cell migration was linked to decreased CXCR4 expression [350] and increased E-cadherin expression [451]. CXCR4 selectively binds the CXC chemokine stromal cell-derived factor-1 (SDF-1), also known as CXCL12, and plays a crucial role in several biological processes, including in cancer biology, where it was associated with tumour dissemination and metastasis [452]. CXCR4 is a marker of breast cancer cells poor prognosis. High CXCR4 expression is significantly correlated with lymph node status, distant metastasis, and poor survival [453]. Interestingly, nuclear DR5 regulates CXCR4 expression through inhibiting let-7 maturation [41,350], leading, as a consequence, to the expression of HMGA2 and CXCR4, and bone metastases formation of breast primary tumours [350,444,454] (Figure 4). All these findings suggest that nuclear DR5 may also play an important function in tumour aggressiveness. Yet, whether translocation of DR5 to the nucleus is fast enough to explain and concur to calcium-mediated pro-motile and metastatic signalling after TRAIL treatment, remains to be determined?

4.3. Caspase-8 contribution in TRAIL non-canonical signalling:

Caspase-8 and FADD are required for TRAIL to induce apoptosis and are both recruited to TRAIL DISC upon TRAIL treatment [140,141], but recent evidence suggest that they may also contribute to TRAIL non-canonical signalling. Likewise, caspase-8 has been reported to be recruited to a FADDosome complex, whose formation after TRAIL stimulation is associated with cell proliferation and/or migration [62]. Interestingly, mutations of caspase-8 in head and neck squamous cell carcinomas represent almost 9% of the cases, and three out of the four mutations examined in Li's study conferred caspase-8 with pro-motile and pro-invasive properties [455]. Moreover, phosphorylation of caspase-8 on tyrosine 380 by the Src kinase, which inhibits its aspartate protease activity and, thus, protect cells from TRAIL-induced cell death [434], was associated the likelihood of a regulation of caspase-8 functions, switching its pro-apoptotic activity to cell migration by SH2 kinases [456,457]. Caspase-8 Y380 residue was described to be essential for caspase-8 relocalization to lamella of migrating cells [458]. Src-induced phosphorylation of caspase-8 on Y380 was also found to drive the assembly of a soluble complex, containing IKKα, IKKβ and p65, that tiggers NF-kB activation in glioblastoma cells, leading to inflammation and angiogenesis [459].

Caspase-8 has been described to interact with p85α, subunit of PI3K to activate Rac1 through lipid products generation (PIP2 and PIP3) that activate guanine nucleotides-exchange factors (GEFs), [460] which are necessary to Rac1 activation [461]. In Neuroblastoma cell lines caspase-8 pro-migratory signalling capability was associated with its ability to interact with the focal adhesion kinase (FAK) and calpain 2 (CPN2) [462], two components of the focal adhesion complex (FAC) [438] (Figure 6). FAC is a signalling complex anchored by cell actin cytoskeleton, membrane integrins and extracellular matrix (ECM). This complex is known to contain many cytosolic proteases, phosphatases, and kinases, including the FAK, a key effector of metastasis [463]. Cytoplasmic

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phosphorylated FAK induce cell migration and invasion, cytoskeleton organization and EMT through FAC protein elements activation, like PI3K, Src and Rho [464]. Caspase-8 interacts with components of the FAC in a tyrosine-kinase dependent manner, promoting both cell migration and metastasis [456,464,465]. Of interest, it was also found that FADD, by inhibiting miR7a expression, is associated with an increase in FAK and spontaneous invasion and metastasis of the melanoma cell line B16 [466]. The increase in FAK overexpression, induced by a FADD-mediated downregulation of miR7a, leading to the expression of CCL5 and TGFβ expression, two cytokines involved in triggering metastasis [466,467] (Figure 6). Last, but not least, caspase-8 pro-motile and metastatic signalling has also been associated with its ability to promote Rab5-mediated internalization and recycling of β1 integrins [468,469].

Consistent with the findings described above and the work of Henry et al. [62], indicating that both FADD and caspase-8 may account for TRAIL non-apoptotic signalling, is the demonstration, in rheumatoid arthritis fibroblast-like synoviocytes, that caspase-8 is responsible for the cellular migration of these synoviocytes stimulated with PDGF, regardless of its enzymatic activity [470].

4.4. TRAIL Induce Cancer Metastasis after uPA and c-cbl Regulation:

TRAIL was found to enhance inflammation and promote invasion of PDAC cells in vitro and metastasis in vivo by inducing the up-regulation of the urokinase-type plasminogen activator (uPA), IL-8 and CCL2 [38]. uPA is an agonist of the urokinase-type plasminogen activator receptor (uPAR) which can induce metastasis [471]. It has been found to be involved in triggering FasL-induced invasiveness [57]. uPA converts plasminogen to plasmin then activates MMPs under matrix extracellular degradation [472]. Activated uPAR can also, on the other hand, interact with other transmembrane receptors, including integrins and growth factor receptors [473–475]. These interactions trigger activation of the ERK1/2, FAK, Src and PI3K/Akt signalling pathways [476,477].

Besides regulating metastasis, uPAR was found to inhibit TRAIL-induced apoptosis, in glioma cells by regulating the expression of DR4 and DR5 [478], in colon cancer by the intrinsic mitochondrial pathway [477] or in TNBC through the regulation of miR-17 and miR-20, two miRNAs that were shown to impair DR4 expression [479]. Using a RAS-derived stepwise tumorigenesis models to recapitulate TRAIL selectivity, Pavet et al. demonstrated that PLAU mRNA levels, encoding uPA, increase with transformation, preventing TRAIL-induced apoptosis [480]. Depletion of uPA restored TRAIL sensitivity, through inhibiting ERK1/2 activation and DcR2 recruitment to the TRAIL DISC [480]. Mechanistically, how uPA/uPAR regulate TRAIL signalling and more specifically cell motility and metastasis is still unknow. Yet given that uPA is known to promote, not only cancer cell survival or proliferation, but also migration from primary tissues to distant organs [481], it remains an interesting potential TRAIL receptor complex partner to study.

In addition to uPA, the ubiquitin ligase Cbl proto-oncogene (c-Cbl) has also attracted attention as a potential TRAIL receptor partner for the triggering of TRAIL pro-metastatic signalling. This ubiquitin ligase was found to regulate both DR5 and DR4 expression levels [482–484].

c-Cbl was found to interact with the caspase-8 inhibitor c-FLIP and to induce its proteasomal degradation, sensitizing macrophages, infected by mycobacteria, to TNF-induced cell death [485]. A number of studies point to c-Cbl as a potential regulator of TRAIL non-canonical signalling pathways [486–488]. Likewise, after TRAIL stimulation, c-CBL appears to be involved in a complex involving Src and PI3K, which induces the phosphorylation of AKT [486]. CBL-b and c-CBL were found to interact with DR5, linking DR5 with TRAF2 and inducing ubiquitination of caspase-8 in TRAIL resistant gastric cancer cells [398]. CIN85 is an important c-Cbl binding protein which plays an essential role in cell survival (Dikic, 2002), such as for example in prostate adenocarcinoma cells, in which CIN85 was found to enhance the phosphorylation and activation of MAPKs during TRAIL treatment, leading to their survival [488].

Interestingly, and albeit only cell death was analysed in Xu and al.'s study, it was also found in these cells that deletion of CBL-b, restored TRAIL sensitivity, but also had an impact towards TRAIL receptor subcellular localization [487,489]. Besides TRAIL agonist receptors, it was found that

activated c-Cbl induce EGFR redistribution into lipid rafts, facilitating its activation (L. Xu et al., 2012), which might ultimately promote metastasis in gastric cancer cells (Figure 5).

5. Conclusion and Perspectives:

TRAIL has emerged as a promising anticancer agent, however, resistance to TRAIL is a major problem, not only because targeted tumours will likely survive to the treatment, but most of all because TRAIL may trigger, in resistant cells, a non-conventional signalling pathway that may ultimately lead to tumour spreading and metastasis.

While signalling pathways triggering cell death are well understood, non-canonical signalling pathways driving cell motility and leading to metastasis are still unclear. As discussed in this review, a number of molecular complexes have been described, explaining how TRAIL receptors may drive cell survival, proliferation, inflammation, and metastatic signal transduction. Yet it is still unclear whether NF-κB or MAP Kinase signal transduction requires a secondary complex or not, given that main kinases or adaptor proteins, including RIPK1, TRADD or TRAF2 can readily interact with complex I. Comprehension of both the temporality and the subcellular localization and composition of these complexes is still missing to provide a comprehensive view of the molecular circuitry which dictate pro-apoptotic or non-apoptotic signalling pathways triggered by TRAIL receptors.

Regardless, a better understanding of the molecular events involved during TRAIL-induced pro-metastatic signalling or non-apoptotic signalling pathways shall be beneficial for both cancer therapies and auto-immune diseases, as this will likely open interesting opportunities to prevent autoimmune diseases associated or not with inflammation or to inhibit or cure metastasis formation in patients.

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