Death Receptors and Their Ligands in Inflammatory Disease and Cancer

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On binding to their cognate ligands, death receptors can initiate a cascade of events that can result in two distinct outcomes: gene expression and cell death. The study of three different death receptor–ligand systems, the tumor necrosis factor (TNF)–TNF receptor 1 (TNFR1), the CD95L–CD95, and the TNF-related apoptosis-inducing ligand (TRAIL)–TRAIL-R1/2 system, has drawn the attention of generations of scientists over the past 50 years. This scientific journey, as often happens in science, has been anything but a straight line to success and discoveries in this field were often made by serendipity, catching the scientists by surprise. However, as Louis Pasteur pointed out, luck prefers the prepared mind. It is therefore not surprising that the most impactful discovery of the field to date, the fact that TNF inhibition serves as an effective treatment for several inflammatory and autoimmune diseases, has been like this. Luckily, the scientists who made this discovery were prepared and, most importantly, determined to harness their discovery for therapeutic benefit. Today's research on these death receptor–ligand systems has led to the discovery of a causal link between cell death induced by a variety of these systems and inflammation. In this review, we explain why we predict that therapeutic exploitation of this discovery may profoundly impact the future treatment of inflammatory disease and cancer.

SIGNALING BY DEATH RECEPTORS AND THEIR LIGANDS

Before we discuss the role of death receptor (DR)–ligand systems in inflammation-associated diseases and cancer, we will give an update on the current understanding of ligand-stimulated signaling by these receptors. DRs are a class of cell surface–expressed type I transmembrane receptors that form part of the tumor necrosis factor (TNF) receptor superfamily (TNFRSF) (Walczak 2013). The defining characteristic of a DR is the presence of the so-called death domain (DD) within the cytoplasmic portion. This class of receptors includes TNF receptor 1 (TNFR1) (Loetscher et al. 1990; Schall

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et al. 1990), CD95 (Fas/APO-1) (Oehm et al. 1992; Itoh and Nagata 1993), TNF-related apoptosis-inducing ligand (TRAIL)-R1 (DR4) (Pan et al. 1997b), TRAIL-R2 (DR5, APO-2/TRICK/DR5/KILLER) (Pan et al. 1997a; Screaton et al. 1997a; Sheridan et al. 1997; Walczak et al. 1997; Wu et al. 1997), and DR3 (TRAMP) (Chinnaiyan et al. 1996). On cross-linking by their respective cognate ligands, DRs have the capacity to induce the death of the cell on which they are expressed. However, despite the concept implicit in their name, cell death is by no means the only possible functional signaling outcome of DR stimulation and, at least for some of them, it is also not the default outcome (Fig. 1).

TNF binds to TNFR1 and TNFR2. However, only TNFR1 contains a DD and therefore forms part of the DR subfamily (Medler and Wajant 2019; Wajant and Siegmund 2019). The TNFR1 signaling pathway is the best studied of all DR signaling pathways and we will begin by providing an in-depth explanation of this pathway (Fig. 1). TNF binding to TNFR1 triggers receptor trimerization and the formation of the TNFR1 signaling complex (TNFR1-SC; also referred to as TNF–RSC or complex I of TNFR1 signaling) (Micheau and Tschopp 2003; Annibaldi and Meier 2018). TNFR1-SC formation is initiated by DD-dependent recruitment of TRADD and RIPK1 to the receptor (Kelliher et al. 1998). Subsequent binding of the adaptor TRAF2 to TRADD, in turn, mediates recruitment of the E3 ligases cIAP1 and cIAP2 (Rothe et al. 1995; Hsu et al. 1996; Micheau and Tschopp 2003; Ermolaeva et al. 2008). These two cIAPs place ubiquitin chains of various topologies (i.e., K11, K48, and K63 linkages) on RIPK1 and other components of the TNFR1-SC (Dynek et al. 2010; Annibaldi et al. 2018). These ubiquitin chains serve as scaffolds to recruit the linear ubiquitin chain assembly complex (LUBAC) (Haas et al. 2009). LUBAC is a tripartite E3 ligase complex that consists of the central catalytic component HOIP (also called RNF31), HOIL-1 (also called RBCK1), and SHARPIN (also called SIPL1) (Gerlach et al. 2011; Ikeda et al. 2011). LUBAC conjugates linear ubiquitin chains (also referred to as Met1 or M1 chains) to several TNFR1-SC components, including RIPK1, NEMO, TRADD, and TNFR1 itself (Gerlach et al. 2011; Draber et al. 2015). To date, LUBAC is the only E3 ligase known to generate linear ubiquitin chains de novo (Haas et al. 2009; Gerlach et al. 2011). This activity is crucial in the context of various signaling pathways, including in TNFR1 signaling (Zinngrebe et al. 2014; Peltzer et al. 2016). The ubiquitin chains generated by cIAP1/2 and LUBAC recruit different kinase-containing subcomplexes: the TAK1/TAB2/TAB3 (Ori et al. 2013), NEMO/IKKα/IKKβ (Rahighi et al. 2009), NEMO/TANK/TBK1/IKKε, and NEMO/NAP1/TBK1 complexes (Lafont et al. 2018). Although the TAK1 and IKKα/β complexes are necessary for gene activation via MAPKs and NF-κB, the different NEMO-containing kinase complexes are required to phosphorylate RIPK1 in TNFR1-SC at distinct sites, and this inhibits TNF-induced cell death (Dondelinger et al. 2015, 2019; Jaco et al. 2017; Lafont et al. 2018). TNF-induced gene expression leads to the production of cytokines and prosurvival proteins, which are required to mount an innate immune response.

TNF signaling is tightly regulated by a series of checkpoints that are dependent on ubiquitination, phosphorylation, gene expression, and protein cleavage events (Ting and Bertrand 2016; Annibaldi and Meier 2018). Circumstances that compromise these checkpoints often result in the formation of a secondary, cytoplasmic complex, referred to as complex II (Micheau and Tschopp 2003). The core components of complex II are RIPK1, FADD, caspase-8, cFLIP and, if expressed in the cell, RIPK3 (Wang et al. 2008; Zhang et al. 2009; Feoktistova et al. 2011; Tenev et al. 2011). The signals that induce cell death by apoptosis and necroptosis emanate from this complex. Apoptosis is initiated by RIPK1/FADD-mediated activation of caspase-8, which in turn activates the executioner caspase-3 and caspase-7. Necroptosis is mediated by the RIPK1/RIPK3/MLKL axis on genetic deletion or pharmacological inhibition of caspase-8. It requires the kinase activities of both RIPK1 and RIPK3 (Pasparakis and Vandenabeele 2015; Peltzer and Walczak 2019). Both ubiquitination and phosphorylation of RIPK1 are required to

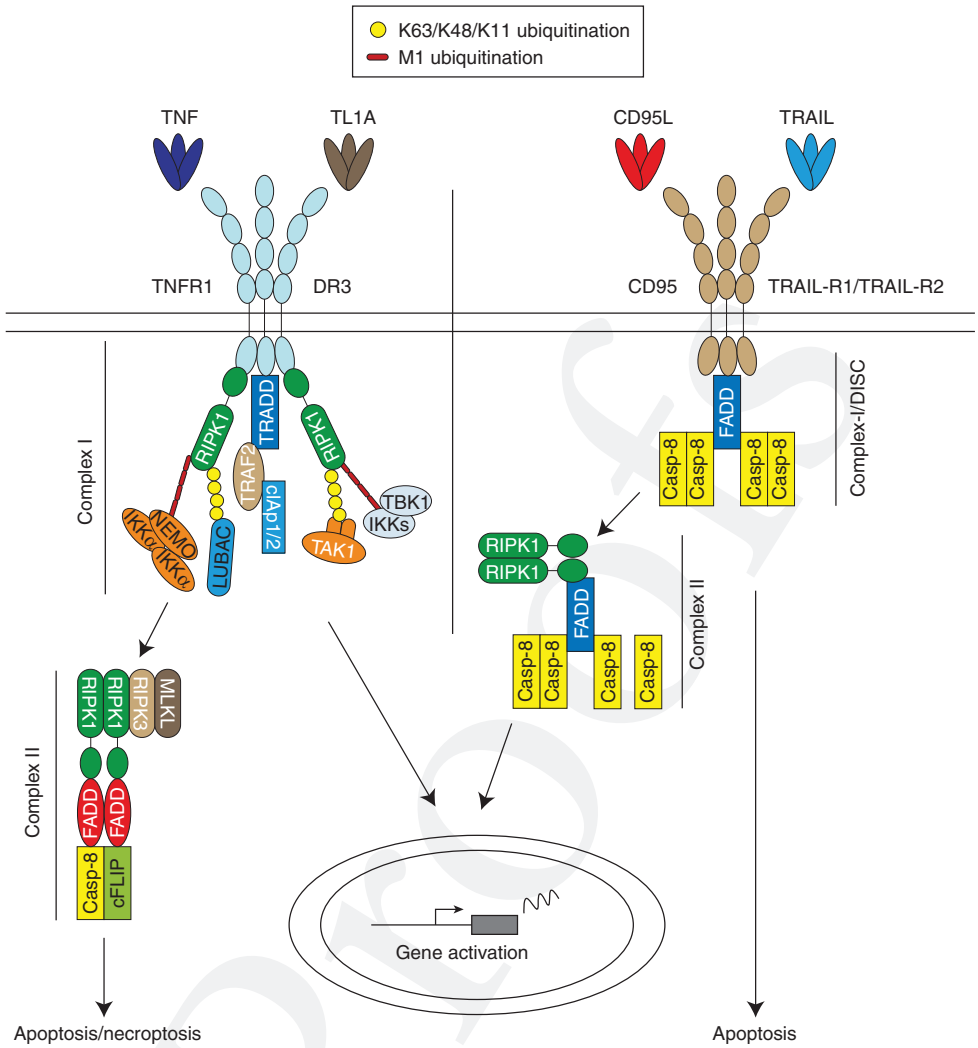

Figure 1. Tumor necrosis factor (TNF) receptor 1 (TNFR1)/DR3 and CD95/TNF-related apoptosis-inducing ligand (TRAIL)-R1/2 signaling pathways. Binding of TNF and TL1A to TNR-R1 and DR3, respectively, and CD95L and TRAIL to CD95 and TRAIL-R1/2, respectively, induces formation of a membrane-bound complex referred to as complex I or death-inducing signaling complex (DISC) in the case of CD95 and TRAIL-R1/2. TNFR1- and DR3-mediated complex I triggers gene expression via NF-κB and MAPKs, whereas the DISC has the potential to induce cell death by apoptosis or necroptosis. These two primary complexes dissociate from the respective receptors and incorporate additional proteins to form a secondary cytosolic complex called complex II. In the case of TNFR1 and TL1A, this complex induces caspase-8-mediated apoptosis or RIPK3/MLKL-mediated necroptosis. CD95 and TRAIL-R1/2 complex II triggers gene activation via NF-κB and MAPKs.

prevent it from leaving TNFR1-SC and nucleating a death-promoting complex II.

Until a few years ago, the prevailing concept was that abnormally high TNF-induced gene expression was the (only) cause of TNF-induced inflammation. TNF-induced cell death was regarded as less relevant, perhaps even irrelevant, to the chronic inflammatory and autoimmune disorders known to be driven by TNF. However, this view has dramatically changed in recent years as explained in the next section of this review.

DR3 and its ligand TL1A appear to signal in essentially the same way as TNF and TNFR1 (Fig. 1). Expression of TL1A and DR3 is mainly restricted to immune cells (Marsters et al. 1996; Screaton et al. 1997b). This system has been reviewed thoroughly elsewhere (Richard et al. 2015), but suffice to state that little is known regarding the relative contribution of TL1A-mediated gene activation versus TL1A-induced cell death to inflammation. This topic likely represents an interesting field for future study of TL1A and DR3.

The TRAIL and CD95L (FasL/APO-1L) signaling pathways share many components with the TNF pathways. Both ligands trigger the formation of membrane-bound and cytoplasmic complexes, but their roles are reversed in comparison to TNFR1 complexes (Walczak 2013). Although TNFR1-SC mediates gene activation and TNFR1 complex II triggers cell death, TRAIL and CD95L assemble a primary death-inducing signaling complex (DISC). Secondly, cytoplasmic complexes activate gene expression. TRAIL binding to TRAIL-R1 and/or TRAIL-R2 (or CD95L binding to CD95) oligomerizes the receptor and the intracellular DDs adopt a conformation that enables FADD recruitment (Chinnaiyan et al. 1995; Shirley et al. 2011). It has been shown that receptor hexamerization is the optimal assembly for cell death induction by these two death ligands, which explains why hexameric receptor agonists are potent inducers of cell death by TRAIL-R1/2 and CD95 (Holler et al. 2003; Valley et al. 2012). FADD in turn recruits caspase-8 and caspase-10 via death effector domain (DED) interactions. Caspase-8 undergoes ubiquitination by cullin-3, increasing its clustering and activation (Jin et al. 2009). Besides inducing cell death, TRAIL and CD95L can also activate NF-κB and MAPKs through a secondary complex, complex II, whose core components are RIPK1, NEMO, TRAF2, caspase-8, and FADD (von Karstedt et al. 2017). Recently, it was shown that the TRAIL DISC can also elicit gene activation through NF-κB (Hartwig et al. 2017; Henry and Martin 2017) using LUBAC (Lafont et al. 2017). Interestingly, whereas RIPK1 is only important for TNF-induced gene activation in some instances (Wong et al. 2010), RIPK1 is required for TRAIL-induced gene expression (Hartwig et al. 2017; Henry and Martin 2017).

DEATH RECEPTORS AND THEIR LIGANDS IN INFLAMMATORY DISEASES

TNF in Chronic Inflammation and Autoimmunity

TNF is a potent inflammatory cytokine that coordinates immune responses following tissue damage or pathogen infection. Initially, however, TNF was thought to induce necrosis in tumor cells, a concept that obviously inspired the naming of this cytokine. Although the purified activity then referred to as TNF did induce tumor necrosis, most strikingly in certain sarcomas (Carswell et al. 1975), this proved the exception rather than rule after TNF was cloned. Most cell types exposed to TNF induce the expression of a plethora of proinflammatory cytokines and chemokines, rather than dying (Beutler 1999). It is therefore not surprising that the study of TNF-induced cell death became the wallflower of cell death research for many years. The pathway appeared obscure at a time when the field was focused on deciphering the canonical apoptosis program. A few scientists kept studying this form of cell death, inspired by the fact that it could clearly be triggered, and thus occurred in a programmed manner (Vanden Berghe et al. 2004; Vandenabeele et al. 2006).

The concept of TNF being a potent proinflammatory factor became entrenched in the scientific community in the late 1980s and early 1990s, which is when scientists were trying to understand how inhibition of cytokines could be used in the treatment of inflammatory diseases. According to one school of thought, therapeutic intervention in such multifactorial diseases would be impossible because of redundancy among the cytokines instigating inflammation. However, the optimists' view was that an apical cytokine triggered the inflammatory cascade involving a plethora of cytokines. The first indication that TNF might be that apical cytokine, and consequently a worthy therapeutic target, came from cultures of dissociated

rheumatoid synovial membranes obtained from rheumatoid arthritis (RA) patients. In this study, blocking TNF prevented the production of many inflammatory cytokines, including interleukin (IL)-1, IL-6, and IL-8, which had also been considered candidate apical cytokines (Brennan et al. 1989). Further support for this concept came from studies showing that TNF and TNFR1 are up-regulated in inflamed tissues of RA patients (Chu et al. 1991; Deleuran et al. 1992). The ultimate proof for this groundbreaking discovery came when TNF inhibitors afforded therapeutic benefit to patients suffering from RA (Elliott et al. 1993; Moreland et al. 1999; Weinblatt et al. 1999; Bathon et al. 2000; Lovell et al. 2000). Shortly after the approval of the first TNF inhibitor (enbrel/etanercept) in 1997, other biotherapeutic inhibitors of TNF were approved for the treatment of various chronic inflammatory and autoimmune diseases. Besides RA and other arthritides, the most prominent indications were psoriasis, and the two most prevalent forms of inflammatory bowel disease (IBD) in Crohn's disease (CD) and ulcerative colitis (UC) (Monaco et al. 2015). The therapeutic success of TNF inhibition has been tremendous, indeed unprecedented in the treatment of chronic inflammatory and autoimmune diseases (Brenner et al. 2015; Kalliolias and Ivashkiv 2016). Since their introduction in 1997, TNF blockers have helped millions of patients live a life in which their disease is controlled, albeit not cured.

Death Ligands beyond TNF in Inflammation and Autoimmunity

Unfortunately, anti-TNF therapy does not help all patients suffering from one of the aforementioned disorders. In about half the patients suffering from RA, long-lasting benefits can be achieved through the inhibition of TNF, whereas the other half of RA patients do not benefit from this treatment. The same is true for ~35% of patients with psoriasis and between 20% and 40% of patients suffering from the different forms of IBD (Cho and Feldman 2015; Lopetuso et al. 2017). TNF inhibition also provided no therapeutic benefit in patients with the autoimmune disorders multiple sclerosis (MS) and amyotropic lateral sclerosis (ALS), despite a clear up-regulation of the TNF system in these disorders (Lenercept Multiple Sclerosis Study Group 1999). One interpretation of these failures is that TNF is not the apical regulator of inflammation in nonresponding patients, and inflammation is instead instigated by different means.

This view was challenged by the realization that TNF can mediate inflammation not only by activating gene expression, but also by inducing aberrant cell death (Fig. 2). For example, mutation of the *Sharpin* gene in mice causes chronic proliferative dermatitis (cpdm) (Seymour et al. 2007). In cells of these mice, TNF-induced gene activation is attenuated, whereas the induction of cell death is increased (Gerlach et al. 2011). At the time, this result provided a conundrum: how did the mouse develop an inflammatory disease if proinflammatory gene expression in response to TNF was compromised? One could argue that an inflammatory mediator other than TNF drove inflammation. However, gene activation by other inflammatory mediators, including CD40L, was also compromised in *Sharpin*-deficient cells (Gerlach et al. 2011). Given that TNF-induced cell death was aberrantly increased, we reasoned that genetic ablation of *Tnf* could address two questions: (1) does aberrant cell death cause the inflammatory syndrome in *cpdm* mice, and (2) is TNF the intrinsic *agent provocateur* of this cell death? Indeed, genetic deletion of *Tnf*, even heterozygous deletion of *Tnf*, prevented both cell death in the skin and inflammatory disease in *cpdm* mice. Therefore, we concluded that TNF-induced cell death caused inflammation in these mice (Gerlach et al. 2011). This discovery was genetically confirmed when it was shown that codeletion of *Casp8* and *Mlkl*, or *Fadd* and *Ripk3*, also prevented cell death in the skin and inflammatory disease in *cpdm* mice (Kumari et al. 2014; Rickard et al. 2014; Peltzer et al. 2018). Other genetic mouse models of inflammatory disease have also been shown to be driven by excessive cell death (Welz et al. 2011; Dannappel et al. 2014; Kumari et al. 2014; Vlantis et al. 2016). Important-

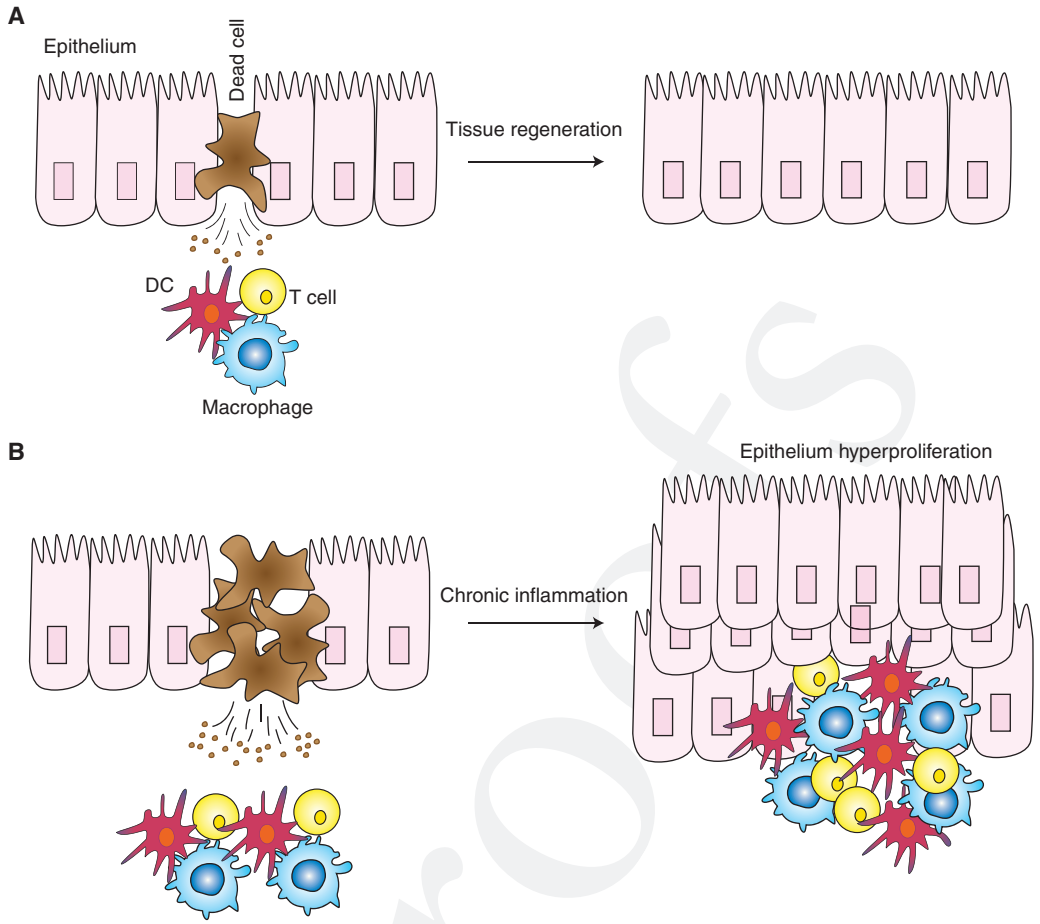

Figure 2. Aberrant cell death in chronic inflammation. (*A*) Cell death is important for the repair and regeneration programs of different types of tissues, such as the epithelium of the skin and the intestine. Dying cells release factors that trigger the activation of an inflammatory program, whose ultimate purpose is to restore tissue integrity. (*B*) Deregulated cell death determines the persistence of tissue repair programs, which in turn leads to chronic inflammation, epithelial cell hyperproliferation, and, ultimately, to an autoinflammatory or autoimmune disorder. (DC) Dendritic cell.

ly, several of these genetic alterations have also been found in humans, although these alterations appear to be rare. These individuals often suffer from a combination of autoinflammation and immunodeficiency (Fusco et al. 2008; Cuchet-Lourenco et al. 2018; Oda et al. 2019).

A further advance in the understanding of the etiology of inflammatory diseases came when it was shown that pharmacologic or genetic inhibition of RIPK1 prevented dermatitis in *cpdm* mice (Berger et al. 2014). Thus, by blocking the kinase activity of RIPK1, TNF-induced cell death and skin inflammation was prevented. These findings raised the possibility that inhibition of RIPK1 might suffice to block aberrant TNF-induced cell death and consequent inflammation. If this were the case, then TNF blockade could potentially be replaced by inhibition of RIPK1. Additional preclinical studies showed that inhibition of RIPK1 could also ameliorate TNF-induced septic shock, anticollagen antibody-induced arthritis, and inflammation and tissue injury caused by A20 deficiency, but it provided no benefit in other models, such as

chemically induced pancreatitis (Newton et al. 2016; Patel et al. 2020).

Given that several biotherapeutic inhibitors of TNF figure in the list of the world's top 10 best-selling drugs, it is not surprising that this concept garnered the attention of the biotech and pharmaceutical industries. Many companies are currently bringing RIPK1 kinase inhibitors into clinic testing. However, the first phase II clinical trials, which were performed in RA, psoriasis, and IBD patients, did not appear to reveal a benefit and the inhibitor has recently "moved back to research" (see gsk.com/media/5745/q3-2019-results-slides.pdf). Could it be that the notion of inflammatory disease being caused by aberrant TNF-induced RIPK1-kinase-dependent cell death is just too simple? Recent evidence suggests this might indeed be the case. For example, lethal dermatitis induced by keratinocyte-specific genetic deletion of *Hoip* or *Hoil-1* ($Hoip^{E\text{-}KO}$ or $Hoil\text{-}1^{E\text{-}KO}$) is considerably delayed by codeletion of *Tnfr1*, whereas inhibition of RIPK1 only delays lethal dermatitis by a few days (Taraborrelli et al. 2018). Intriguingly, however, when $Hoip^{E\text{-}KO};Tnfr1^{-/-}$ or $Hoil\text{-}1^{E\text{-}KO};Tnfr1^{-/-}$ mice are given an RIPK1 kinase inhibitor, lethal dermatitis is prevented (Taraborrelli et al. 2018). Thus, at least in this genetic model, TNFR1 ablation and RIPK1 kinase inhibition are synergistic at inhibiting cell death and consequent inflammation. Nevertheless, this discovery suggests that combining a TNF inhibitor and an RIPK1-specific inhibitor might benefit certain autoimmune or autoinflammatory disease patients. For patients with rare germline mutations impacting LUBAC components, this combination may represent an alternative treatment strategy if their current therapies do not work or if they develop resistance to them. An outstanding question, however, is what drives RIPK1-dependent cell death and disease when the TNF/TNFR1 system is absent.

The idea that TNF superfamily (TNFSF) cytokines beyond TNF itself could act individually or in a concerted manner to promote inflammation has been proposed, albeit with cell-death-independent mechanisms and disease etiologies in mind (Croft and Siegel 2017). At present, several TNFSF proteins are under evaluation in preclinical and clinical studies as potential targets in various rheumatic and chronic inflammatory diseases. Especially noteworthy in the context of this review are TRAIL and CD95L. The primary signaling output of these two TNFSF members is cell death, which is in contrast to that of TNF and TL1A (Fig. 1). Nevertheless, as described earlier, both the TRAIL–TRAIL-R1/R2 and CD95L–CD95 systems can induce gene activation (Hartwig et al. 2017; Henry and Martin 2017). The CD95L–CD95 system drives activation-induced T-cell death, which is instrumental in immune homeostasis (Alderson et al. 1995; Brunner et al. 1995; Dhein et al. 1995; Ju et al. 1995). Indeed, mutations in *CD95* cause the accumulation of aberrant T cells, which ultimately results in autoimmunity (Watanabe-Fukunaga et al. 1992). The TRAIL–TRAIL-R system has mainly been characterized for its ability to selectively kill cancerous, but not essential normal cells. In addition to being expressed in cancer cells, TRAIL-R1 and TRAIL-R2 are also expressed on different subpopulations of T cells, whose apoptosis they can promote (Roberts et al. 2003; Zhang et al. 2003). Hence, the immunological "day job" of the CD95 and TRAIL systems appears to be the proper termination of an immune response and the prevention of autoimmunity. Indeed, the killing function of CD95 and TRAIL-R1/R2 in activated or autoreactive T cells has led to the idea that autoreactive T cells might be eliminated in the context of autoimmunity using CD95L, TRAIL, or other DR agonists. The severe hepatotoxicity of CD95 agonists (Ogasawara et al. 1993) excludes their use, but TRAIL and other agonists of the TRAIL DRs may yet be an option, although this awaits therapeutic validation in patients.

Given that caspase-8-dependent cell death causes lethal inflammation in $Hoip^{E\text{-}KO}$ and $Hoil\text{-}1^{E\text{-}KO}$ mice, as well as in $Hoil\text{-}1^{E\text{-}KO};Tnfr1^{-/-}$ and $Hoip^{-KO};Tnfr1^{-/-}$ mice, the role of other DRs in inflammation must be considered (Taraborrelli et al. 2018). Indeed, cells deficient for HOIL-1 or HOIP are more sensitive to killing by TNF, TRAIL, or CD95L. Although neither constitutive deletion of *Trail-r* nor ker-

atinocyte-specific deletion of the DD of CD95 ameliorated dermatitis in *Hoil-1*$^{E\text{-}KO}$*;Tnfr1* mice, eliminating both CD95 and TRAIL-R signaling significantly ameliorated dermatitis (Taraborrelli et al. 2018). Hence, cell death driven by CD95L and TRAIL also contributes to inflammation. The therapeutic potential this discovery may unleash is tremendous because it suggests that the prevention of disease-causing inflammation may require the simultaneous neutralization of cell death induction by multiple DR–ligand systems. Thus, for patients with a cell death-dependent disease etiology, blocking TNF may not be sufficient to achieve a lasting therapeutic benefit, whereas blocking TNF and these additional death ligands or their cell death–inducing signaling pathways, may well afford such benefit.

In summary, during the past decade we learned that (1) TNF-driven inflammatory and autoimmune disorders can also stem from TNF-induced cell death and not only from TNF-induced gene activation; (2) failure of TNF inhibitors to provide therapeutic benefit in all patients with inflammation-associated disease does not necessarily mean that TNF is not a valuable target in nonresponders; it might simply mean that blocking TNF is not sufficient and other death ligands—or their downstream effectors—have to be blocked in addition; and (3) these other death ligands can be TRAIL and CD95L, and the downstream effector essential for mediating cell death by them and not TNF could be the kinase activity of RIPK1. This last point leaves us with an intriguing biochemical question because, if anything, TNF-induced cell death would have been expected to require RIPK1 activity but not cell death induced by TRAIL and CD95L. This unexpected result leaves us with the realization that there is more plasticity between cell death pathways triggered by the different DRs than previously thought. Extending this concept, two recent studies showed that when the proteolytic activity of caspase-8 is genetically ablated and necroptosis is inhibited, the system is rewired to activate yet a third modality of programmed cell death, caspase-1-dependent pyroptosis (Fritsch et al. 2019; Newton et al. 2019). This discovery exposes a previously unappreciated plasticity between the three major programmed cell death pathways. This rewiring likely represents an evolutionary necessity to survive the challenge of infection. The other, pathological side of the coin is something we are only beginning to unearth. It may have a major impact on our understanding of neuroinflammatory and neurodegenerative diseases (Ising et al. 2019), possibly guiding how we treat these diseases effectively in the future.

In conclusion, combining a TNF inhibitor with an RIPK1 kinase inhibitor or with inhibitors of CD95L, TRAIL, and/or other death ligands, might extend the reach of TNF-inhibitory therapies to patients who currently do not benefit from them. For example, patients with a disorder in which TNF inhibitors provide therapeutic benefit in many, but not all patients, such as RA, IBD (CD and UC), or psoriasis. However, equally, or perhaps even more, excitingly, this concept could extend to chronic inflammatory, autoimmune, and neuroinflammatory disorders in which TNF inhibition so far failed. Only future clinical trials testing the therapeutic concepts summarized here will reveal whether the insights gained from studying mouse models are also relevant to human patients.

DEATH RECEPTORS AND THEIR LIGANDS IN CANCER

The TNF System in Cancer

TNF owes its name to the fact that it was identified as the agent responsible for the tumor-necrotizing activity of "Coley's toxins." Discovered and used at the end of the 19th century by William Coley in New York (Coley 1893), Coley's toxins consisted of a mixture of bacterial lysate products. It induced regressions of certain tumors, especially sarcomas (Nauts et al. 1946). However, enthusiasm for the identification of a soluble factor that could revolutionize cancer treatment did not persist in an era when the discoveries of chemo- and radiotherapy dominated cancer research and therapy. Nevertheless, scientists kept chasing this ominous activity

and TNF was cloned with the advent of modern biochemical and genetic techniques (Gray et al. 1984; Pennica et al. 1984; Marmenout et al. 1985). The promise held by TNF for cancer treatment proved short-lived because systemic treatment with TNF caused a lethal inflammatory shock syndrome with massive cytokine induction (Tracey et al. 1988). For a long time, this was thought to be the result of increased TNF-induced gene expression rather than cell death (Balkwill 2009). Intriguingly, however, the cytokine storm responsible for TNF-induced shock was recently shown to indeed be a consequence of TNF-induced cell death (Newton et al. 2016). Today, TNF is exploited to treat cancer locally by isolated limb perfusion (ILP). In ILP, TNF is used in combination with chemotherapy (melphalan) for the treatment of locally advanced extremity soft tissue sarcoma (STS) (Neuwirth et al. 2017). In this case, the toxicity linked to systemic administration of TNF is circumvented by local treatment. At present, it is not entirely clear why some types of cancer, especially sarcomas, are susceptible to TNF, whereas the vast majority of cancers are not. TNF killing of tumor endothelial cells is likely involved in the observed tumor necrosis (Robaye et al. 1991).

Further discouraging the use of TNF as a cancer drug, a study published in 1999 showed that *Tnf*$^{-/-}$ mice challenged with the skin carcinogen DMBA and the tumor promoter TPA developed fewer tumors than wild-type mice (Moore et al. 1999). TNF also promotes the growth of syngeneic and carcinogen-induced tumors of the skin, pancreas, colon, and ovary (Suganuma et al. 1999; Kulbe et al. 2007; Zins et al. 2007; Egberts et al. 2008). These findings, together with evidence indicating that TNF is produced by both malignant cells and cells in the tumor microenvironment, suggest that TNF is a crucial, if not the central, regulator of cancer-related inflammation (Mantovani et al. 2008; Balkwill and Mantovani 2012). Mechanistically, we now know that cancer cells promote a proinflammatory microenvironment that supports tumor cell survival and proliferation, angiogenesis, and metastasis, although dampening adaptive antitumor immune responses. The ability of cancer cells to promote such an inflammatory microenvironment is often mediated by the production of TNF. Collectively, these discoveries led to a paradigm shift with TNF being regarded as an endogenous tumor-promoting agent. Consequently, inhibition of TNF started to be considered in cancer therapy.

Our knowledge of the role of TNF in inflammation-related disorders might give us clues on how to best harness the biology of TNF in cancer therapy. As explained in the previous section, TNF-dependent autoimmune and inflammatory disease can be caused by aberrant TNF-induced cell death. Given the abundance of TNF in the microenvironment of many different cancers, the question arises as to whether we can rewire TNF signaling from its prosurvival and proliferative function into a cell death–inducing function. In other words, can we harness endogenous TNF in the microenvironment and use it to kill cancer cells? Several reports indicate this might indeed be possible. In these studies, some of the checkpoints that prevent TNF-induced cell death were manipulated for TNF to trigger cell death. For example, SMAC mimetics, which degrade cIAP1/2 and promote TNFR1 complex II formation, rendered cancer cells susceptible to TNF-induced cell death (Beug et al. 2014, 2017; Lalaoui et al. 2016). Pan-caspase inhibitors, like zVAD or emricasan, can also convert the TNF-induced signal in cancer cells into a necroptosis-inducing one (Brumatti et al. 2016). Intriguingly, cell death induced by TNF, especially necroptosis, appears to be highly immunogenic, facilitating tumor immunity. A recent study reported that lowering the threshold of TNF cytotoxicity increases the efficacy of cancer immunotherapy (Vredevoogd et al. 2019). Thus, if we could manipulate TNF signaling in cancer cells to trigger an immunogenic cell death, we might kill a fraction of the cells directly and evoke an antitumor immune response to target the escapees.

In summary, more than a century of biomedical research on TNF has been highly stimulating from a scientific perspective. Realization of the extraordinary potential of TNF inhibition in the treatment of autoimmune and chronic inflammatory diseases represents a striking advance of modern medicine. Future opportuni-

ties related to its role in cancer-related inflammation await further preclinical research followed by clinical validation. Efforts focused on harnessing endogenous TNF in the tumor microenvironment and rendering it capable of killing cancer cells in a manner that stimulates antitumor immunity represents a fascinating new challenge. Clearly, TNF's exciting journey in tumor biology and immunology is far from over.

The CD95 and TRAIL Systems in Cancer

Coincident with hope fading for TNF as a viable cancer therapeutic, two antibodies, anti-APO-1 and anti-Fas, drew attention owing to their ability to directly kill cancer cells (Trauth et al. 1989; Yonehara et al. 1989). Their targets, Fas and APO-1, were found to belong to the TNFRSF (Itoh et al. 1991; Oehm et al. 1992). Disappointingly, however, both antibody and ligand-derived CD95 agonists were highly toxic, causing massive hepatocyte death and fulminant hepatitis (Ogasawara et al. 1993).

Subsequently, the CD95L–CD95 system was shown to stimulate cancer cell proliferation, migration, and invasion (Owen-Schaub et al. 1993; Barnhart et al. 2004; Chen et al. 2010), including in glioblastoma (Kleber et al. 2008). Subsequent clinical testing of CD95-Fc (APG101/asunercept), a CD95L antagonist, showed that glioblastoma patients treated with this inhibitor plus radiotherapy benefited when compared with radiotherapy alone (Wick et al. 2014). Thus, based on our current understanding of the cancer biology of the CD95L–CD95 system, its inhibition rather than activation appears to provide benefit for cancer patients.

Soon after it was realized that CD95 agonists, like TNF, would not be a "magic bullet" for killing cancer cells, a new member of the TNFSF was identified. It most resembled CD95L, which was also known as FasL or APO-1L. Given that it could induce apoptosis similar to FasL, this new TNFSF member was named TRAIL or Apo2L (Wiley et al. 1995; Pitti et al. 1996). Importantly, TRAIL selectively killed cancer cells, without killing any essential normal cells, a unique combination of characteristics, which holds true both in vitro and in vivo (Walczak et al. 1997). This finding provided the scientific basis for developing TRAIL-receptor agonists (TRAs) as novel cancer therapeutics. However, TRAIL-R1- and TRAIL-R2-specific antibodies as well as a first recombinant form of TRAIL showed very limited anticancer activity in patients in clinical trials. As recently thoroughly reviewed elsewhere (von Karstedt et al. 2017), various strategies are currently underway to overcome the two issues which, together, are likely responsible for the failure of these first-generation TRAs, that is, (1) poor agonistic activity, and (2) resistance of most primary cancers to TRAIL-induced apoptosis.

Additionally, however, it recently emerged that the TRAIL–TRAIL-R system can be "hijacked" by certain cancers. Rather than killing cancer cells, recombinant TRAIL was found to act in a tumor-supportive manner (Trauzold et al. 2006), particularly in KRAS-mutated cancers (Hoogwater et al. 2010). It was then realized that endogenous TRAIL can be recruited by KRAS-mutated cancers to act in this manner. The mechanism whereby this is achieved is two-pronged: (1) by enhancing tumor cell proliferation, invasion, and metastasis in a TRAIL-R2 DD- and FADD-independent manner (von Karstedt et al. 2015), and (2) by creating a TRAIL-R2 DD- and FADD-dependent cytokine-rich micromilieu in which monocytes are polarized to become myeloid-derived suppressor cells (MDSCs) or alternatively activated (M2) macrophages (Fig. 3; Hartwig et al. 2017). Interestingly, the latter mechanism not only supports tumor growth, it also acts via immunosuppression. Therefore, TRAIL may represent a previously unrecognized immune checkpoint whose inhibition may unleash tumor immunity. It is interesting to note that TRAIL, albeit mostly in non-cancer-related contexts, has been shown to inhibit T helper type 1 (Th1) cells (Ikeda et al. 2010), promote regulatory T cells (Pillai et al. 2011), and suppress T-cell activation and proliferation by interfering with proximal T-cell receptor (TCR) signaling (Lehnert et al. 2014). It can also kill immature dendritic cells (Leverkus et al. 2000). Thus, TRAIL inhibition may act via tumor-cell-centered suppressive as well as immunity-enabling antitumor effects.

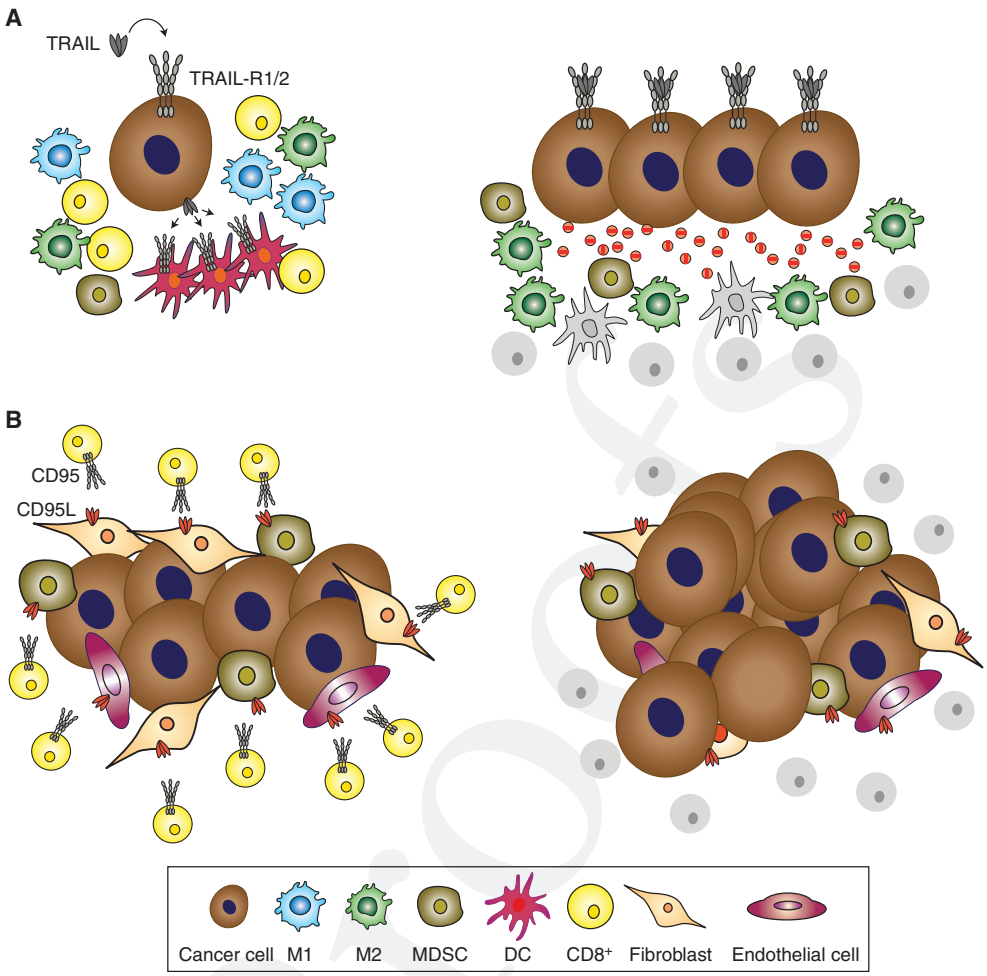

Figure 3. Mechanisms of death receptor (DR)-mediated immunosuppression in cancer. (*A*) The TNF-related apoptosis-inducing ligand (TRAIL)/TRAIL-R1/2 system contributes to immunosuppression via distinct mechanisms. The activation of TRAIL-R1/2 expressed by cancer cells induces the secretion of cytokines that polarize monocytes into myeloid-derived suppressor cells (MDSCs) and alternatively activated (M2) macrophages. These cell types in turn create an immunosuppressive tumor microenvironment that prevents $CD8^+$ T-cell-mediated antitumor immune responses. In addition, TRAIL expressed by cancer cells or noncancer cells in the tumor microenvironment can directly kill TRAIL-R1/2-expressing immune cells, which are required for mounting an adaptive immune response, such as dendritic cells (DCs) or T cells, and thereby interfere with adaptive antitumor immunity. (*B*) Cancer cells have the potential to induce the expression of CD95L on different cell types of the tumor microenvironment, such as endothelial cells, MDSCs, and fibroblasts. By cross-linking CD95 on the surface of T cells, CD95L induces their demise by apoptosis, thereby facilitating tumor cell evasion from an adaptive immune attack.

Intriguingly, CD95L, arguably the best T-cell killer encoded by our genome and the physiological mediator of activation-induced T-cell death (Alderson et al. 1995; Brunner et al. 1995; Dhein et al. 1995; Ju et al. 1995), can also be expressed by various cells in the tumor microenvironment, including endothelial cells (Motz et al. 2014), MDSCs (Zhu et al. 2017), and cancer-associated fibroblasts (Lakins et al. 2018). Thus, CD95L inhibition may also act by a combination of tumor-cell-centered suppressive and immunity-enabling antitumor effects (Fig. 3).

In summary, both TRAIL and CD95L may represent the ultimate form of immune checkpoint. Rather than suppressing tumor immunity in the subtle manner of CTLA4 and PD-1/PD-L1, they can remove question cells simply by killing them. Whether or not these different means are co-opted by a given cancer, or represent alternative ways by which particular cancers circumvent immune recognition, will determine whether TRAIL and/or CD95L inhibitors can serve as immune checkpoint blockers in their own right or whether they may (only) act in synergy with CTLA4- and/or PD-1/L1-targeting therapeutics. It will be exciting to answer these imminent questions in cancer immunotherapy.

CONCLUDING REMARKS

From today's perspective, it may appear surprising that, following the tremendous success of inhibitors of the first death ligand, TNF, the entire pharmaceutical world did not follow their usual strategy, which is to move to the next family member and develop an inhibitor for that one. Although this appears the obvious strategy with the hindsight we have today, the fact that for the past 30 years the concept prevailed that TNF blockers worked because they blocked TNF-induced gene expression and not TNF-induced cell death, blurred the picture. However, now that it has been realized that in many cases it is indeed the inhibition of TNF-induced cell death that affords therapeutic benefit, the blurring is gone. Consequently, there is no excuse for the pharmaceutical industry not to tackle TNF's closest relatives, that is, the other death ligands, with the aim to provide therapies for patients with autoimmune or chronic inflammatory diseases, perhaps also neuroinflammatory and neurodegenerative diseases, who do not benefit from the inhibition of TNF(-induced cell death), or at least the inhibition of TNF alone. Given the newly appreciated role of DRs and their ligands in cancer-related inflammation, tumor promotion, and tumor immune suppression and evasion, the therapeutic principle of death ligand inhibition may also extend to cancer therapy.

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Queries

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Q1 Please confirm that "imminent" is meant.

Q2 Reference entry for "Kelliher et al. 1998" was updated to match details for this article record; please confirm accuracy of updated entry.