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Title: CD95 (Fas) and CD95L (FasL)-mediated non-canonical signaling pathways.

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Abstract

Although the interaction of CD95L (also known as FasL) with its so-called death receptor CD95 (Fas) induces an apoptotic signal responsible for the elimination of infected and cancer cells and maintenance of tissue homeostasis, this receptor can also implement non apoptotic signaling pathways. This latter signaling is involved in metastatic dissemination in certain cancers and the severity of auto-immune disorders. The signaling complexity of this pair is increased by the fact that CD95 expression itself seems to contribute to oncogenesis via a CD95L-independent manner and, that both ligand and receptor might interact with other partners modulating their pathophysiological functions. Finally, CD95L itself can trigger cell signaling in immune cells rendering complex the interpretation of mouse models in which CD95 or CD95L are knocked out. Herein, we discuss these non-canonical responses and their biological functions.

1. Introduction

CD95 (also known as Fas or TNFRSF6) is a death receptor (DR) belonging to the tumor necrosis factor (TNF) receptor family. In humans, its gene is located on chromosome 10, and the corresponding 335 amino acid long protein is expressed at the plasma membrane in most cells of the human body. Additionally to the 16 first amino acids consisting in the signal peptide [1], (**Fig.1A**) 3 cysteine rich domains (CRDs) form the extracellular region (**Fig.1B**). The amino-terminal and membrane-distal CRD1 encompasses a region between amino acids 17 to 82 designated as pre-ligand assembly domain" (PLAD) [2]. This region is necessary for receptor auto-association in a ligand-independent manner (**Fig.1B**). The following domains, CRD2 and CRD3, interact with CD95L [3]. Interestingly, CD95 is cleaved by MMP7 between Asp36 and Leu37 within the PLAD [4, 5] (**Fig.1A-B**), releasing a fragment involved in receptor aggregation [4]. In addition to the PLAD, the transmembrane domain of CD95 contributes to its self-association and the right conformation of the receptor at the plasma membrane as demonstrated by NMR using isolated transmembrane peptides in lipid micelles [6].

CD95 does not possess any enzymatic activity but it can trigger many dynamic multi-protein complexes through different intracellular domains including a calcium-inducing domain (CID), which interacts with ezrin [7] or phospholipase C γ 1 [8-10], a death domain (DD) [11], which binds the adaptor protein Fas-associated protein with death domain (FADD), and a C-terminal region (15 last amino acid residues), which is able to interact with the phosphatase FAP-1 [12], Dlg1 [13] or the ubiquitin ligase KPC2/KPC1 pair [14] (**Fig.1B**). Overall, these domains engender dynamic and complex signaling pathways responsible for biological functions going from apoptosis to cell survival by way of differentiation and cell migration. For instance, recruitment of FADD by CD95-DD promotes the activation of caspase-8 [15, 16] and the induction of the apoptotic program, while CD95-CID interacts with phospholipase C γ 1 to implement a Ca²⁺ signals promoting cell migration [7, 17-19] (**Fig.1B**).

CD95 interacts with its cognate ligand CD95L (FasL, CD178, TNFSF6) [20], which can also bind DcR3, a decoy receptor described to compete with CD95 for CD95L binding [21]. CD95L

is a type II transmembrane protein (m-CD95L) harboring a long intracellular domain, and an extracellular domain including a stalk region connecting the transmembrane (TM) domain to the TNF homology domain (THD) [22] (**Fig.2A-B**). The THD is responsible for the ligand homotrimerization and the binding to CD95 [23]. Although CD95L expression at the surface of activated T-cells and natural killer (NK) cells serves to kill infected and transformed cells and allows the immune contraction [24, 25], the biological roles of this ligand expressed by non-immune cells in damaged tissues including endothelial cells [8-10, 26-28] remain to be elucidated. The membrane-bound CD95L (m-CD95L) can be cleaved within its stalk region (a.a. 103-136 [29]) by several metalloproteases (MMPs) such as MMP7 [30] and a disintegrin and metalloprotease domain-containing protein (ADAM)-10 [31, 32] to release a soluble ligand (sCD95L) (**Fig.2B**). sCD95L fails to trigger cell death [8, 33, 34] but enhances inflammation in lupus patients [9, 10, 35] and promotes metastasis in several cancer types [36-40]. sCD95L can trigger different pro-survival or inflammatory signaling pathways including NF- κ B, PI3K or Ras that have been discussed previously [22, 41, 42].

Herein we discuss the “non-canonical” signaling pathways associated to CD95 and CD95L including the CD95-mediated and CD95L-independent mechanisms, the signals induced upon binding to non-classical ligands or receptors, and the CD95L-induced reverse signaling pathway.

2. Non-canonical CD95 signals

2.1. Non-canonical ligands of CD95

Recent data suggest that CD95 can not only bind to CD95L, but also to osteoprotegerin (OPG) [43] (**Fig.3A**). OPG (TNFRSF11B) belongs to the tumor necrosis factor (TNF) receptor family and this soluble receptor inhibits osteoclastogenesis by interacting with receptor activator of nuclear factor- κ B ligand (RANKL, TNFSF11) [44] and apoptosis by interacting with tumor-necrosis-factor related apoptosis inducing ligand (TRAIL, TNFSF10), another TNF family member [45]. The concentration of OPG is increased in serum of patients affected by

idiopathic pulmonary arterial hypertension (PAH) [46], in whom it stimulates proliferation and migration of pulmonary artery smooth muscle cells (PASMCs) by interacting with CD95 [43]. Like sCD95L [8], the concentration of OPG is increased in sera of lupus patients [47]. In addition, OPG exerts different pro-oncogenic features according to its ligands since it can prevent the elimination of breast cancer cells by trapping TRAIL [48], and promote angiogenesis and metastasis dissemination through a molecular mechanism that remains to be identified [49]. In triple negative breast cancers (TNBC), CD95 engagement promotes the metastatic dissemination of these cells [40], raising the question whether the combination of OPG and sCD95L in TNBC women might contribute to the metastatic process. Two questions remain to be addressed: how two members of the TNF-R (i.e., CD95 and OPG) superfamily can interact and what is the impact on downstream signaling ?

2.2. CD95 hetero-dimers

CD95 self-associates in a ligand-independent manner and this aggregation is crucial for the induction of apoptosis in cells exposed to CD95L [2, 50]. Because the PLAD is also present in several TNFR family members including TNFR1 [51], CD40 and DR4 [51], Smulski and colleagues wondered whether hetero-complexes could be formed with these receptors [52] (**Fig.3A**). They observed in B cells, that CD40 and CD95 interact together in a ligand-independent manner and this interaction occurs through their respective CRD1. Although DR5 (TRAIL-R2) does not bind CD95, it prevents the CD95/CD40 interaction, suggesting that both DR5 and CD95 can bind a similar region within CD40 (**Fig.3A**). Interestingly, the presence of CD95 or DR5 in the CD40 hetero-complex impinges on the CD40L-induced NF- κ B response in the BJAB B-cell lymphoma cell line. However, the study does not tell us whether and how these hetero-complexes can in turn affect the ligand-mediated signaling pathways in cells exposed to CD95L or TRAIL.

2.3. CD95-mediated and CD95L-independent signaling pathways

2.3.1. CD95 aggregation and lipid rafts

The plasma membrane is a heterogeneous and asymmetrical lipid bilayer containing some lipid-specific-ordered domains designated as lipid or membrane rafts [53]. These domains are described to be more packed than the surrounding bilayer and they can aggregate to form larger platforms under certain stimuli, leading to the accumulation of specific receptors and the implementation of cell signaling [54].

Some chemotherapeutic treatments exhibit a CD95-dependent apoptotic signal in cancer cells through a CD95L-independent mechanism. For instance, the topoisomerase I inhibitor camptothecin promotes the expression of CD95 and CD95L in colon cancer cells and trigger an apoptotic signal independently of the CD95L expression [55]. A potential explanation for this activation is the redistribution of CD95 into lipid rafts, inducing its oligomerization and aggregation and the downstream activation of the apoptotic program [54] (**Fig.3A**). A basal caspase-8 activation might serve to initiate the process of CD95 aggregation and redistribution into the lipid rafts [56, 57]. Palmitoylation of the receptor on the cysteine at position 199 (human) could also contribute to redistribute CD95 within lipid rafts [58] and promote the induction of the apoptotic signal [59]. The redistribution of CD95 into lipid rafts in T-cells stimulated with PMA and anti-CD3 monoclonal antibody (mAb) occurs independently of CD95L [59]. The antitumor ether phospholipid edelfosine (1-O-octadecyl-2-O-methyl-rac-glycero-3-phosphocholine) aggregates CD95 into lipid rafts leading to the induction of apoptosis in lymphocytes [60]. Interestingly, the CD95-mediated apoptotic signal observed in PMA/a-CD3-stimulated T-cells and edelfosine-treated lymphocytes occurs through a CD95L-independent mechanism [59, 61, 62] and how these stimuli engender such CD95 aggregation remains to be elucidated. It seems plausible that different ligand-dependent and -independent signals converge in CD95 translocation to lipid rafts though palmitoylation of Cys199.

2.3.2. CD95L-independent CD95 signalling

Although CD95L-expressing T-cells and NK cells eliminate tumor cells with high CD95 membrane levels, they spare those cells with lower expression of CD95 at their plasma

membrane [63]. Unexpectedly, CD95 expression remains elevated in TNBC cells [64]. We observed that the elimination of CD95 in these cancer cells activates a NF- κ B-driven pro-inflammatory response [14], which might promote a NK-mediated anti-tumor response [65]. These observations could explain why TNBC cells are selected to keep a certain expression level of CD95.

The intracellular C-terminal region of CD95 directly binds to KIP1 ubiquitination-promoting complex (KPC)-2 (UBAC1), which in turn recruits the ubiquitin ligase KPC1, responsible for the partial degradation of p105 into p50 [66]. The accumulation of p50 into TNBC cells favors the formation of homodimers, which bind NF- κ B promoters but fail to induce transcription because they do not possess the transactivation domain present in the Rel proteins including RelA (p65), RelB, and c-Rel. Beyond its role in TNBCs, KPC2/KPC1 complex also inhibits the growth of glioblastoma [66] suggesting that the presence of CD95 could also promote oncogenesis in this brain tumor. Interestingly, the elimination of CD95 in human glioma-initiating cells (GIC), a stem cell-like glioblastoma cell, reduces tumor growth *in vitro* in a CD95L-independent fashion [67, 68] but does not affect the tumor progression in a xenograft mouse model (*i.e.*, immune-deficient mice). Because in our hands, CD95 loss in TNBC cells mainly impairs tumor growth in immunocompetent mouse models (*i.e.*, syngeneic graft of 4T1 cells in BalB/c mice [65]) *via* the activation of a NK-mediated antitumor response, we envision that such biological responses could be phenocopied with glioblastoma and thereby, the loss of CD95 in GICs might prevent tumor growth when grafted in a syngeneic and immunocompetent environment. Notably, ligand-independent signaling transduction has also been shown in other TNFR family members such as DR5 [69] and TACI [70].

3. Non-canonical CD95L signals

3.1. Non-canonical partners of CD95L

Beyond its cognate receptor CD95, CD95L can also bind the decoy receptor DcR3 [21, 71] (**Fig.3B**). The soluble DcR3 is up-regulated in certain cancers and not only inhibits the CD95-mediated apoptotic signal but also the immune landscape in the tumor suggesting that the CD95/CD95L-mediated signaling pathways can affect the trafficking of immune cells in different types of cancer [72].

TRAIL interacts with DR4 [73] and DR5 [74, 75] but does not bind DcR3 [72]. Surprisingly, the metalloprotease-cleaved CD95L (sCD95L) seems to interact with DR5 with rather high affinity ($K_D = 1.23 \times 10^{-12}$ M) [76] (**Fig.3B**). This interaction promotes inflammation in a mouse model of autoantibody-induced arthritis where the inflammatory effect of CD95L/DR5 interaction is not related to the induction of apoptosis but relies on the activation of the NF- κ B signaling pathway [76]. Of note, although sCD95L [77] and sTRAIL [78] exhibit a homotrimer structure, only sCD95L induced the secretion of CX3CL1 by fibroblast-like synovial cells (FLSCs) in a DR5-dependent fashion. These findings suggest that not only DR5 aggregation, but also the modulation of its conformation, which might vary between sCD95L and sTRAIL interaction, could be involved in the implementation of the NF- κ B signal in FLSCs.

3.2. CD95L reverse signaling.

CD95L is a transmembrane protein, which encompasses an 81 amino acid long cytoplasmic tail with multiple recruitment motifs. This intracellular domain is the longer one among the 19 members of TNF superfamily [79]. The intracellular region of CD95L harbors a casein kinase 1 (CK1) binding motif (-SXXS-) [80] involved in β -catenin/Lymphoid Enhancer-binding Factor-1 (LEF-1)/T cell factor-1 (TCF-1) activation [81] (**Fig.2B**), two proline-rich domains serving as a binding site for class I Src homology 3 (SH3)-containing proteins including p85 α , Fyn, Lck and, class II SH3-binding site interacting with the SH3 domains of the adaptor molecules Grb2, Gads, and Grap (**Fig.2A-B**) and nine Gads-interacting motifs (PXXP). CD95L also contains a WW domain-binding motif (XPPPXXPX) that might interact with Dystrophin, FBP11, and FE65 (**Fig.2A**) [79]. The presence of these domains in the intracellular region of CD95L suggests

that the binding of CD95 to CD95L is able to induce PI3K, NF- κ B and calcium (Ca²⁺) responses in the CD95L-expressing cells [79].

Like CD95, CD95L can also undergo palmitoylation at Cys82 promoting its localization within lipid rafts and enhancing its oligomeric level [82] (**Fig.3B**). The cleavage of CD95L also seems to mainly occur within lipid rafts [82]. In addition, CD95L palmitoylation is not only critical for the redistribution of CD95L within lipid rafts, but also for the efficiency of CD95L/CD95 interaction and the implementation of the subsequent apoptotic signal [82].

The cleavage of the extracellular region of CD95L is a two-step process, which relies on a disintegrin and metalloprotease-10 (ADAM-10)-dependent mechanism releasing sCD95L and the intracellular processing by signal peptide peptidase-like 2a (SPPL2a) engendering the release of the intracellular region of CD95L into the cytoplasm. This latter fragment translocates into the nucleus where it promotes gene transcription by interacting with the transcription factor lymphoid-enhancer binding factor-1 (LEF-1) [83]. Accordingly, the accumulation of soluble CD95L observed in different cancers and chronic inflammatory disorders [42] could reflect the activation of the reverse signaling. The role of this reverse signaling on the immune response remains to be further investigated since *in vivo*, this signal seems to down-regulate GC formation and B-cell differentiation [83], whereas the reverse signaling in T-cells is ambivalent and while it enhances the activation/proliferation of CD8+ cells, it dampens the proliferation of activated CD4+ T-cells [84].

Conclusion

For three decades, CD95 and its cognate ligand CD95L have been mainly (only) considered as a death receptor and ligand, respectively, but recent and accumulating evidence point out that this pair can induce different non-apoptotic signals responsible for the immune homeostasis. In addition, this couple can signal in an independent manner from each other,

and this review emphasizes on these non-canonical functions. We envision that the non-canonical CD95/CD95L signaling pathways might reflect the phenotypic differences observed in pathologies in which CD95 or CD95L is mutated or deleted [85]. This review focuses on the non-canonical signaling pathways induced by CD95 and CD95L proteins, but recent data from Peter's laboratory showed that CD95L mRNAs can also engender an atypical and delayed (more than a day) cell death program exhibiting features of apoptosis, autophagy, cell cycle arrest, senescence and mitotic catastrophe through the implementation of a mechanism designated death induced by survival gene elimination (DISE) [86, 87]. RNA-induced silencing complex (RISC) generates DISE *via* the production of toxic short RNA (sRNA)s down-regulating a set of pivotal genes for cell proliferation/survival [88]. This non-canonical CD95L-mediated cell death program does not require CD95 expression [88]. Because activated T cells and NK cells over-express CD95L to eliminate infected or transformed cells, DISE might collaborate with the classical paracrine and apoptotic signal induced by CD95/CD95L interaction [89] to stop the immune response and eliminate immune cells through activation-induced cell death (AICD).

CD40 is essential for germinal center formation and production of plasma cells through the activation of the NF- κ B signaling pathway [90]. Because CD95/CD40 heterodimer implements a weaker NF- κ B response than the CD40 homodimer in B-cells [52], we cannot rule out that the mutations or loss of CD95, which are associated with an autoimmune disorder designated autoimmune lymphoproliferative syndrome (ALPS) type 0, Ia or Im [24, 25, 91], not only protect immune cells from the CD95-mediated apoptotic signal, but might also release a CD95-mediated break on the CD40-driven B-cell differentiation/maturation. Similarly, we cannot rule out that the autoimmune phenotype observed in ALPS type IB patients, who exhibit mutation in CD95L, is not only associated with the failure to form homotrimer or to bind CD95 [92] but also in a difference in the implementation of the reverse signaling.

The reverse signaling pathways raise the question of whether its response can vary according to the CD95L partners, meaning CD95, DcR3 or DR5

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Figures:

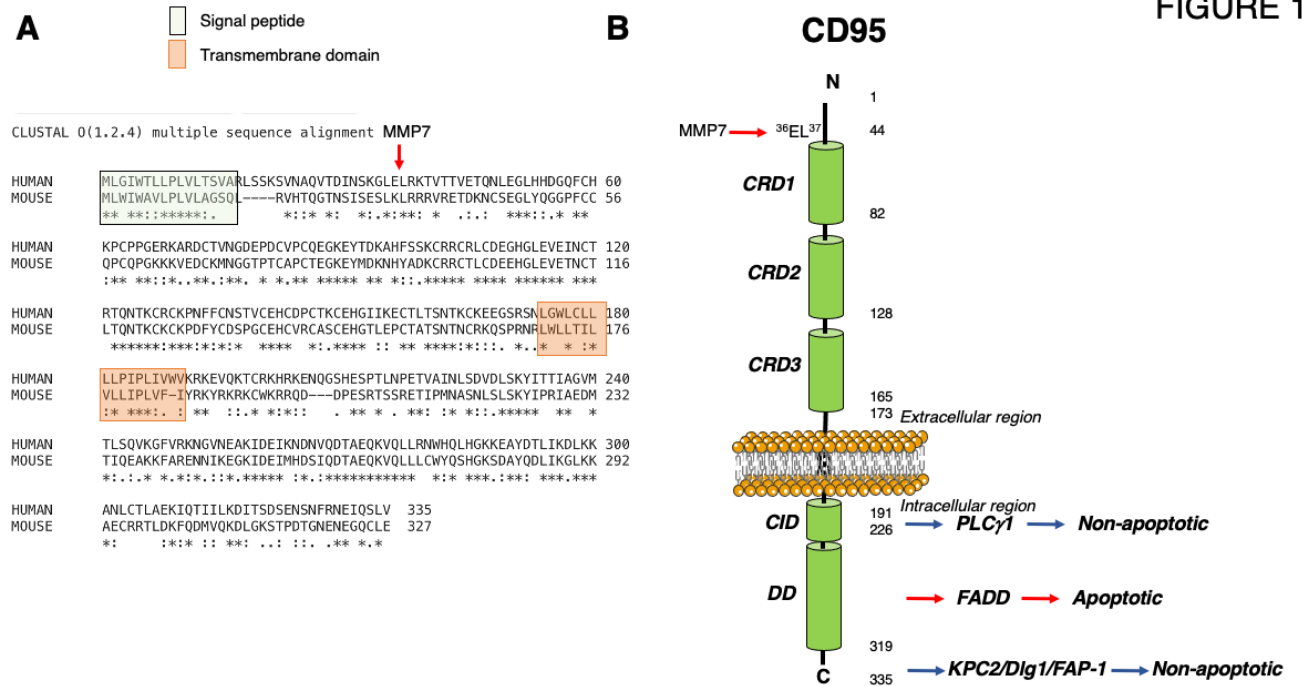


Figure 1. The receptor CD95

- A. Alignment of human and mouse CD95 protein sequences using clustal software. Signal peptide, transmembrane domain and the MMP7-driven cleavage site are depicted.
- B. Schematic representation of CD95 protein at the plasma membrane. The intracellular domains, their direct binding partners and the downstream signaling pathway triggered are depicted.

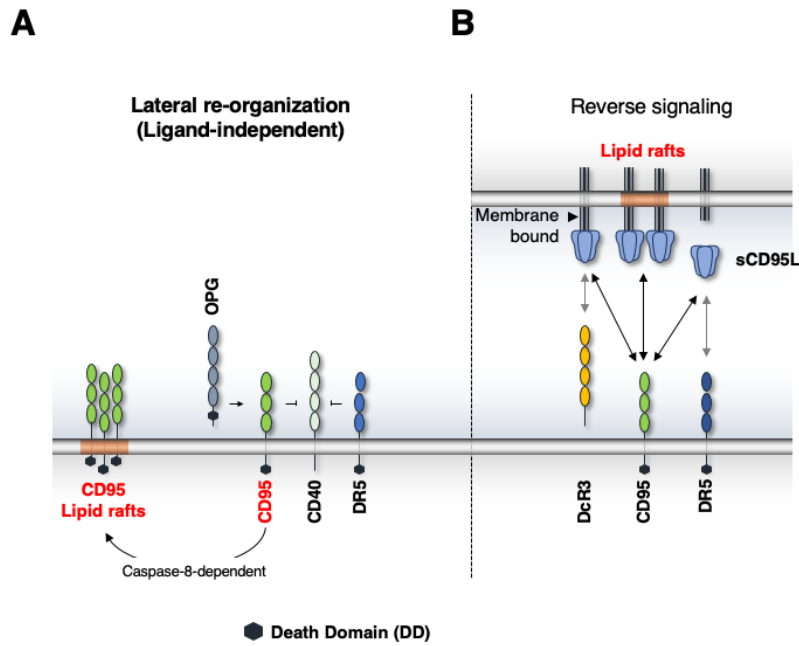


Figure 3. Non-canonical CD95 and CD95L signals

- A. The CD95 distribution within lipid rafts and/or its interaction with CD40 modulate different signaling pathways in a CD95L-independent manner.
- B. CD95L aggregation can stimulate CD95 and induce different signaling pathways in the CD95L-expressing cell.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:
Legembre has patent #WO2015158810 issued to inserm transfert. Legembre has patent #WO2017149012 pending to inserm transfert. Legembre has patent #WO2018130679 issued to inserm transfert. no other conflict of interest