Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Review

TRAIL mediated signaling as a double-edged sword in pancreatic cancer: Analysis of brighter and darker sides of the pathway

Ammad Ahmad Farooqi[1*], Rabbia Zahid[2], Areesha Maryam[3], Humaira Naureen[4], Rukset Attar[5], Uteuliyev Yerzhan Sabitaliyevich[6], Konysbayeva Kenzhekul Konysbayevna[7]

[1] Institute of Biomedical and Genetic Engineering (IBGE), Islamabad, Pakistan
[2] Institute of Chemistry, University of Punjab, Lahore, Pakistan
[3] Forman Christian College University, Lahore, Pakistan
[4] Riphah Institute of Pharmaceutical Sciences, Riphah International University, Islamabad, Pakistan.
[5] Department of Obstetrics and Gynecology, Yeditepe University, Turkey
[6] Department of Health Policy and Health Care Development, Kazakh Medical University of Continuing Education, Almaty 050004, Kazakhstan
[7] Ministry of Health of the Republic of Kazakhstan. Zhibek zholy 5, Almaty, Kazakhstan

*Correspondence to: farooqiammadahmad@gmail.com

Received May 15, 2020; **Accepted** May 28, 2020; **Published** June 5, 2020

Doi: http://dx.doi.org/10.14715/cmb/2020.66.3.35

Abstract: Genetic, genomic and proteomic studies have refined our concepts related to underlying mechanisms of pancreatic cancer. Increasingly sophisticated knowledge has started to shed light on the fact that pancreatic cancer harbored multiple epigenetic and genetic alterations and revealed complicated and dense tumor microenvironments. Our rapidly evolving knowledge about pancreatic cancer has helped us in identification of myriad of underlying mechanisms which play instrumental role in disease onset, drug resistance and epithelial to mesenchymal transition (EMT). Additionally, loss of apoptosis is the cornerstone of cancer biology and researchers have devoted considerable attention to the versatile regulators involved in loss and restoration of apoptosis. Discovery of TNF/TNFR, FasL/Fas and TRAIL/TRAIL-R opened new horizons for detailed analysis of intracellular mechanisms regulated by these pro-apoptotic molecules. Decades of cutting-edge research helped in translation of TRAIL-based therapeutics into clinically effective therapeutics. In this review, we will focus specifically on groundbreaking achievements which have leveraged our concepts related to TRAIL-mediated signaling to yet another level. We will also discuss how basic and clinical scientists are making efforts to overcome the stumbling blocks associated with efficacy of TRAIL-based therapeutics against TRAIL-resistant pancreatic cancers. We partition this multi-component review into overview of the conceptual breakthroughs in regulation of TRAIL-mediated signaling in pancreatic cancers, push and pull between pro- and anti-apoptotic proteins to regulate TRAIL-mediated apoptosis and how researchers have identified different natural and synthetic molecules to restore apoptosis in TRAIL-resistant pancreatic cancer. We have also summarized how long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) regulated TRAIL-mediated apoptosis in pancreatic cancer. More importantly we will also set spotlight on the darker side of TRAIL/TRAIL-R pathway in pancreatic cancer. Circumstantial evidence highlighted cancer promoting role of TRAIL/TRAIL-R in pancreatic cancer. These diametrically opposed context-dependent roles of TRAIL-pathway are intriguing and need comprehensive research to address outstanding questions.

Key words: TRAIL; Apoptosis; Signaling; Transduction cascades.

Introduction

Pancreatic cancer is a multifaceted disease and based on sophisticated data obtained from high-throughput technologies, therapeutically challenging nature of cancer is becoming more understandable (1,2). Pancreatic cancer is a multistep process which is orchestrated by highly complicated web of cell signaling pathways (3,4,5). Intra- and inter tumor heterogeneity, clonal expansion and rapid development of resistance against mainstream therapeutics are some of the major challenges which have to be overcome to improve clinical outcome and minimize off-target effects. More importantly, loss of apoptosis is a central mechanism which promotes cancer development and consequent progression because of loss of spatio-temporal control of signal transduction cascades (6). There has always been a quest to search for the molecules which can effectively induce apoptosis in resistant cancers. There has been a continuous and rapid development in unraveling of the versatile regulators of apoptosis and strategies to restore apoptotic cell death in cancer cells. One of the most noteworthy and groundbreaking discovery of scientists was identification of TRAIL (TNF-related apoptosis-inducing ligand) as an anticancer molecule (7). TRAIL discovery meaningfully opened new avenues for investigation of TRAIL-mediated pathway in cancer cells (8). Overwhelmingly increasing high-quality research has unveiled repertoire of pro and anti-apoptotic proteins which play contributory role in regulation of TRAIL-driven signaling. Discovery of TRAIL attracted considerable attention of molecular and clinical oncologists and mechanistic insights revealed that TRAIL transduced the signals intracellularly through death recep-

tors (9; 10). However, contemporary researchers also reported TRAIL resistance in different cancers. These findings impelled scientists to re-investigate the TRAIL pathway in TRAIL-resistant cancers. Experimentally verified findings clearly suggested that downregulation of death receptors, overexpression of decoy receptors, impairment of DISC (Death inducible signaling complex) formation, and imbalance of pro- and anti-apoptotic proteins severely abrogated TRAIL-induced apoptosis (11-16). Conceptually, TRAIL biology can be compartmentalized into different sections. Mechanistic findings related to TRAIL-mediated pathway, regulation of TRAIL-induced signaling by pro-and anti-apoptotic proteins, use of different synthetic and natural products to restore apoptosis in TRAIL-resistant cancers, design and development of TRAIL-based therapeutics.

Substantial fraction of knowledge has been added into conceptual framework of TRAIL-mediated signaling. In this review we will comprehensively summarize high-impact research findings which have paved the way for efficient translation of preclinical studies into various phases of clinical trials.

In the following section, we will set spotlight on extrinsic and intrinsic pathways and how these pathways play mandatory role in apoptosis.

Extrinsic and Intrinsic pathways as Gateways of Death

TRAIL transmitted the signals intracellularly through death receptors. Death receptors are structurally and characteristically unique and contain highly specialized domains. Death receptors are members of tumor necrosis factor receptor superfamily and possess a cytoplasmic death domain (DD). DRs transduce signals through well co-ordinated molecular complexes, which are nucleated by the DD-containing adaptor protein FADD to induce apoptosis. However, this signalosome is incomplete without pro-caspase-8. Pro-caspase-8 and FADD assemble and interact through specialized domains with death receptor to trigger activation of caspase-8 (shown in figure 1) (17). Functionally active caspase-8 induced activation of another essential downstream effector caspase. c-FLIP (cellular FLICE-inhibitory protein) has been shown to interfere with DISC formation (18).

Structural studies have shown that mitochondrially located proteins have an essential role to play in functionalizing intrinsic pathway. SMAC/DIABLO is a mitochondrially located protein and shuttles out to the cytoplasm alongwith cytochrome c during apoptosis and promotes cytochrome c-dependent activation of caspase by neutralization of IAPs (inhibitor of apoptotic proteins) (19). N terminus of SMAC/DIABLO is essential for interaction with the baculovirus IAP repeat (BIR3) of XIAP and to enhance cytochrome c-induced activation of caspase (19). In the upcoming section, we will provide an overview of the molecules which negatively regulate TRAIL-mediated apoptotic cell death.

Regulation of TRAIL Pathway

TRAIL-mediated apoptosis is necessary to induce regression of tumors in tumor bearing mice. However, there are direct pieces of evidence which underline oncogenic role of different proteins. Overexpression of different proteins resulted in abrogation of apoptosis in pancreatic cancer cells. Therefore, in this section, we will exclusively discuss how different oncogenic proteins impaired TRAIL-mediated apoptosis.

HuR or ELAVL1 (ELAV-like RNA-binding protein-1) played central role in inhibition of TRAIL-mediated apoptosis (20). It has been shown that TRAIL treatment induced cytoplasmic accumulation of HuR and consequential binding of HuR to 3′-UTR of DR4 in pancreatic cancer cells. Multiple AU-rich elements containing HuR motifs are present within 3′-UTR of DR4. (shown in figure 1). HuR induced translational repression of DR4. However, MS-444 (HuR inhibitor) enhanced TRAIL-induced apoptosis by enhancing the protein levels of DR4 (20).

O-GlcNAcylation is a post-translational modification and has a critical role in different molecular activities (21). O-GlcNActransferase (OGT), an enzyme catalyzed the addition of O-GlcNAc to different target proteins. Importantly, O-GlcNAcylation of DR5 did not allow TRAIL-induced DR5 oligomerization. TRA-8, an anti-DR5 monoclonal antibody markedly reduced growth of the tumors in mice xenografted with OGT-silenced S2VP10 pancreatic cancer cells (21).

HIF (Hypoxia-inducible factor) are involved in transcriptional regulation of myriad of genes (22). HIF-2α transcriptionally upregulated survivin expression in PANC-1 cells (shown in figure 1). Importantly, enforced expression of survivin in HIF-2α-silenced PANC-1 cells enhanced TRAIL resistance. YM155, a survivin inhibitor markedly reduced tumor growth in mice xenografted with PANC-1 cells (22).

Gemcitabine and TRAIL combinatorially reduced phosphorylation of mTOR at 2448th serine residue in PANC-1 cells (23). Additionally, there was TRAIL-induced caspase-dependent cleavage of RAPTOR and RICTOR in PANC-1 cells (shown in figure 1). Inactivation of mTOR resulted in considerable reduction in the phosphorylation of 4E-BP1 at 65th serine residue (23).

Non-coding RNA Regulation of TRAIL-mediated Signaling

Non-coding RNAs have revolutionized the field of molecular oncology and we have witnessed exponential growth in high-quality research related to regulation of signaling pathways by non-coding RNAs in different cancers (24-32).

Discovery of non-coding RNAs has added another layer of complexity to already convoluted network of TRAIL-mediated signaling. It seems exciting to note that there is an increase in the number of publications related to regulation of TRAIL-mediated signaling by non-coding RNAs. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have been shown to modulate pro- and anti-apoptotic proteins to mediate apoptosis in cancer cells. In the upcoming section we will emphasize on current concepts about regulation of TRAIL-driven pathway associated genes by miRNAs and lncRNAs. Initially, we will give examples of miRNA regulation of different components of TRAIL pathway in different cancers, gradually we will narrow down our focus to TRAIL pathway regulation in pan-

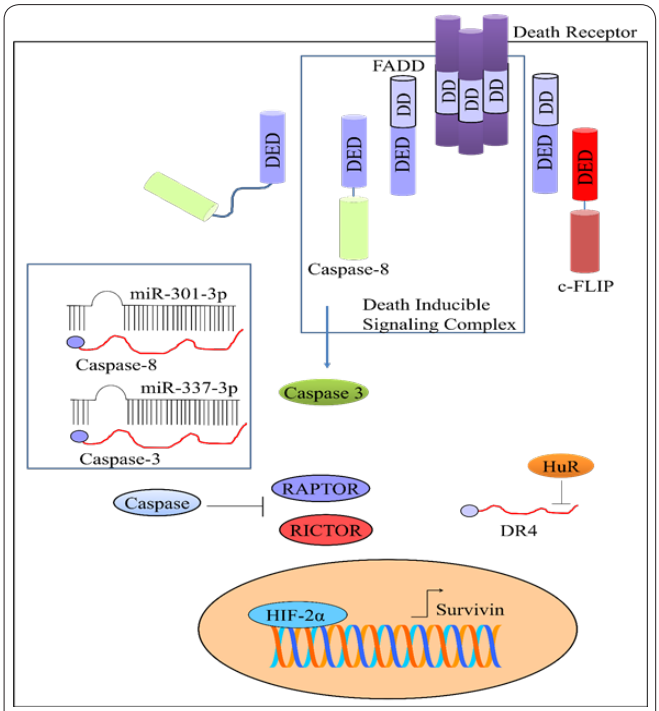

Figure 1. TRAIL-mediated signaling. FADD and pro-caspase-8 formed a complex at death receptor. This complex, death inducible signaling complex (DISC) is necessary to activate caspase-8 and trigger downstream signaling. c-FLIP may interfere with DISC formation. Caspase has been shown to proteolytically process RAPTOR and RICTOR to induce apoptosis. Different oncogenic proteins impaired TRAIL-mediated apoptosis. HuR translationally repressed DR4. Whereas, HIF-2α transcriptionally upregulated survivin gene in cancer cells. Non-coding RNA mediated regulation of different components of TRAIL pathway is very complicated. Different oncogenic miRNAs have been shown to directly target caspase-8 and caspase-3.

creatic cancer.

It has recently been shown that enforced expression of miR-125b re-sensitized glioma cells to TRAIL-mediated apoptosis by activation of intrinsic pathway and consequent activation of caspase-9 and -3 (33).

WP1130 is a partially selective inhibitor of deubiquitinases that interferes with deubiquitinating activities of USP9X (Ubiquitin-Specific Protease 9, X-linked) (34). USP9X knockdown induced an increase in the expression of miR-708 and simultaneously reduced wild type c-FLIP 3′-UTR luciferase activity. USP9X inhibition by WP1130 stimulated the expression of miR-708 (34). Collectively these findings suggested that USP9X inhibition potentiated miR-708 mediated targeting of c-FLIP and sensitized cancer cells to TRAIL mediated apoptosis.

Certain hints had emerged which suggested that TGFβ1 reduced plasma membrane-associated levels of TRAIL-R1 but TRAIL-R2 remained unchanged. TGFβ1 induced downregulation of TRAIL-R1 mainly through SMAD4. TGFβ1 did not downregulate TRAIL-R1 in SMAD4-silenced PANC-1 cells (35). Interestingly, TRAIL-R1 stimulated the expression of miR-370. Accordingly, miR-370 was found to be downregulated in TRAIL-R1 depleted pancreatic cancer cells. miR-370-3p negatively regulated TGFβRII in PDAC cells (36). These findings clearly suggested that TRAIL-triggered miR-370 negatively regulated TGFβRII in PDAC cells. Further experimental work is necessary to unfold how TRAIL-R1 regulated miR-370 expression in PDAC cells.

Luteolin is a bioactive molecule having high pharmacological properties. Caspase-8 activated by extrinsic pathway is frequently targeted by miRNAs (37). miR-301-3p negatively regulated caspase-8 in pancreatic cancer cells (shown in figure 1). Luteolin markedly reduced miR-301-3p and promoted the expression of caspase-8 (37).

miRNA-132-3p, miRNA-212-3p and miRNA-17-5p downregulated caspase-7 partly via degradation of mRNA in PANC-1 cells (38). miR-337-3p directly targeted caspase-3 and consequentially, miR-337-3p overexpressing PANC-1 cells were found to be resistant to different TRAIL concentrations (38).

Central role of NF45, NF90, hnRNPA1 and p68 is the regulation of miRNA processing via association with the microprocessor constituents Drosha and DGCR8 (diGeorge syndrome critical region gene 8) (39). Results revealed that Drosha and DGCR8 physically interacted with TRAIL-R2. Processing of pri-let-7 by Drosha was strongly enhanced in TRAIL-R2 knockdown PANC-1 cells. HMGA2 and Lin28B have been linked to tumor progression. let-7 directly targeted HMGA2 and Lin28B and reduced tumor progression. TRAIL-R2 overexpression stimulated expression of HMGA2 and Lin28B and increased proliferation of PANC-1 cells. TRAIL-R2 knockdown inhibited orthotopic tumor growth in SCID (severe combined immunodeficiency) mice (39).

HOTAIR overexpression in TRAIL-sensitive cells severely impaired TRAIL-mediated apoptosis, whereas inhibition of HOTAIR sensitized TRAIL-resistant PANC-1 cells to TRAIL-induced apoptotic cell death (40). HOTAIR overexpression in sensitive BxPC3 and MiaPaCa-2 cells induced transcriptional downregulation of DR5. Detailed mechanistic insights revealed that HOTAIR interacted with PRC2 (polycomb repressive complex- 2) containing EZH2 (enhancer of zeste homolog-2). Binding of the multi-protein complex to the promoter regions of target genes resulted in transcriptional repression. HOTAIR transcriptionally inactivated DR5 via increased H3K27me3 (histone H3 trimethylation) (40). (shown in figure 2).

LOC389641 knockdown attenuated the migratory and invasive potential of SW1990 and AsPC-1 cells (41). LOC389641 enhanced tumor invasion by negative

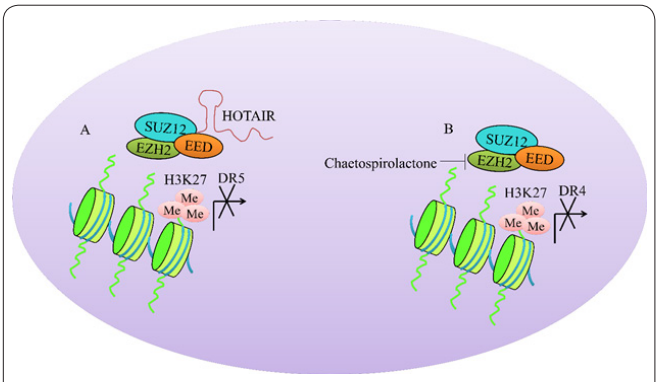

Figure 2. Epigenetic regulation of TRAIL/TRAIL-R pathway. (A) HOTAIR epigenetically inactivated DR5. (B) Chaetospirolactone stimulated DR4 expression by inhibition of EZH2.

regulation of E-cadherin in PDAC cells. Tumor growth was significantly reduced in mice subcutaneously injected with SW1990 cells. Intriguingly, LOC389641 knockdown decreased the levels of DR4. It is still unclear how LOC389641 regulates DR4 but BLAST analysis provides clues that the region of 378 bp from the 5′ end of LOC389641 is reverse and complementary to the promoter of DR4 (41). Future studies must converge on the identification of mechanistic link between DR4 and LOC389641. Did LOC389641 play fundamental role in maintenance of higher levels of DR4 and critically potentiate DR4-related metastasis?

Regulation of TRAIL pathway by Pharmacologically active Molecules

Restoration of apoptosis in TRAIL-resistant pancreatic cancers has remained the main goal in molecular oncology. Researchers have scientifically analyzed broad-range of natural and synthetic molecules which can selectively induce apoptosis in cancer cells while sparing normal cells.

Vitamin E δ-tocotrienol, a vitamin E compound significantly improved TRAIL-mediated apoptosis by potentiating the degradation of c-FLIP in MiaPaCa-2 and BxPC-3. Vitamin E δ-tocotrienol induced regression of the tumors in mice subcutaneously injected with MiaPaCa-2 cells (42).

Triptolide, a diterpenoid triepoxide effectively reduced DcR3 (decoy receptor-3) levels and enhanced apoptosis in pancreatic cancer cells (43).

Chaetospirolactone isolated from an endophytic fungus *Chaetomium sp*. NF00754 restored apoptotic cell death in TRAIL-resistant pancreatic cancer cells (44). EZH2 catalyzed H3K27me3 and transcriptionally repressed target genes. Chaetospirolactone significantly reduced H3K27me3 levels and stimulated DR4 expression (shown in figure 2). Chaetospirolactone and TRAIL combinatorially induced regression of tumors in mice inoculated with AsPC-1 cells (44).

Quercetin effectively enhanced TRAIL-induced apoptosis via proteasomal degradation of c-FLIP (45).

Chloroquine reduced c-$FLIP_S$ levels in MiaPaCa-2 cells and c-$FLIP_L$ in PANC-1 cells. Series of experiments revealed that PANC-1 pancreatic cancer cells were found to be more resistant as compared to MiaPaCa-2 cells (46). Accordingly, PANC-1-bearing mice were administered with high doses of chloroquine and TRAIL as compared to MiaPaCa-2- bearing mice (46).

7-Benzylidenenaltrexone maleate promoted the ubiquitin/proteasome-mediated degradation of XIAP protein. 7-Benzylidenenaltrexone maleate and TRAIL suppressed growth of tumor in mice xenografted with AsPC-1 (47).

Darker Side: Non-apoptotic Signaling

TRAIL-induced signaling cascade has been comprehensively explored and resultantly, entry of TRAIL-based therapeutics in various phases of clinical trials in encouraging. However, parallel studies have also revealed non-apoptotic role of TRAIL pathway in different cancers. Accordingly, underlying mechanisms of pancreatic cancer also indicate that TRAIL-mediated non-apoptotic signaling play fundamental role in onset and progression of pancreatic cancer.

Different studies had shown that TRAIL-expressing regulatory CD8 cells played instrumental role in enhancing immunosuppressive effects of TRAIL which potentiated cancer progression (48). In preclinical mouse models, regulatory T cells accumulated in the tumor tissues where they severely interfered with antitumor immunological response. The ratio of regulatory CD4 cells was significantly lower in tumors of $TRAIL^{-/-}$ mice but TRAIL treatment stimulated ratio of regulatory CD4 cells within tumors (48).

KRAS mutations is relatively higher in PDAC which also overexpresses TRAIL receptors (49). TRAIL-R-mediated signaling contextually played a role in the initiation of pancreatic cancer. Deletion of TRAIL-receptor in KRAS-driven PDAC delayed growth of the primary tumors, prolonged survival and inhibited metastasis. GTP-bound Rac1 formed a complex with TRAIL-R2 and TRAIL. TRAIL/TRAIL-R2 promoted a Rac1/PI3K-driven transduction cascade and potentiated proliferative and migratory potential of KRAS-mutated cells (49).

TRAIL strongly enhanced distant metastases of pancreatic tumors in vivo (50). Orthotopic transplantation of human PDAC cells to the pancreata of SCID mice induced an increase in metastatic spread. Importantly, there was a fourfold increase in the number of liver metastases and sixfold increase in the volume upon TRAIL treatment (50).

The NF-κB transcriptional factor family consists of different subunits, NF-κB1, NF-κB2, RelA, RelB and c-Rel. TRAIL induced upregulation of CX3CL1 in resistant PDAC in a RelA dependent manner (51). Chemokine CX3CL1 acted as chemoattractant for monocytes, macrophages, dendritic cells, T-cells and natural killer cells that expressed its receptor CX3CR1. Paracrine-signaling pathway played central role in potentiation of pro-tumorigenic action of CX3CL1 in pancreatic cancer cells. PBMC (Peripheral blood mononuclear cells)-mediated resistance towards TRAIL was noted to be regulated partially by RelA-CX3CL1 paracrine pathway (51).

Better knowledge of the TRAIL-R2 mediated metastatic spread can be gained comprehensively through cell lines in which TRAIL-R2 expression was stably reduced. TRAIL-R2 knockdown in PancTu-I cells resulted in marked reduction of macroscopic liver metastases (52). However, higher numbers of small metastatic lesions were noted because of liver inflammation after resection of primary tumors *in vivo* (52).

Concluding remarks

TRAIL has emerged as a highly acclaimed anticancer agent and entry of TRAIL-based therapeutics in various phases of clinical trials advocate its potential as a premium molecule for cancer therapy. It is becoming progressively more understandable that TRAIL mediated signaling can be effectively restored in resistant cancers as evidenced by significant regression in tumors in xenografted mice. Interdisciplinary research has helped us in improving the bioavailability of TRAIL using different technological approaches. Multipronged

approach consisting of inhibitors of anti-apoptotic proteins, mimics of pro-apoptotic proteins and TRAIL-based therapeutics have also shown encouraging results. More importantly, involvement of myriad of cell signaling pathways in regulation of TRAIL-mediated apoptosis has added another layer of intricacy to already complicated nature of TRAIL/TRAIL-R signaling pathway.

Downregulation of death receptors was considered to be central cause of development of resistance against TRAIL based therapeutics. Researchers tackled this challenge at two frontiers. Firstly, by identification of mechanisms which triggered downregulation of death receptors and secondly, by searching for options to stimulate expression of death receptors on surface of pancreatic cancer cells. Results revealed that epigenetic modifications, internalization and degradation of death receptors are major causes of downregulation of death receptors. Different natural products have been shown to restore apoptosis in TRAIL-resistant cancers mainly through upregulation of death receptors, inhibition of anti-apoptotic proteins and activation of pro-apoptotic proteins. Transcriptional regulation of death receptors is also a very exciting area that is currently under extensive research. Different cell signaling pathways have been shown to transcriptionally regulate expression of death receptors. Therefore, therapeutic targeting of downstream effectors of oncogenic pathways will be helpful in improving the clinical outcome. Different long non-coding RNAs have been shown to transcriptionally repress death receptors. Therefore, there is a need to search for the molecules which can effectively target oncogenic lncRNAs and epigenetic modifying machinery to potential the expression of pro-apoptotic components of TRAIL pathway in pancreatic cancer.

Likewise, non-coding RNA mediated regulation of TRAIL pathway is also attracting considerable interest. It will be intriguing to see how mimics of tumor suppressor miRNAs and inhibitors of oncogenic miRNAs improve TRAIL-mediated apoptosis in pancreatic cancer.

Lastly, activation of TRAIL-mediated non-apoptotic pathway is a rapidly growing concern which may be challenging in future. It is still unclear how TRAIL mediated pathway is re-wired from apoptotic to non-apoptotic signaling. How TRAIL-treatment potentiates metastatic spread of cancer cells is an outstanding question and needs detailed research. Mechanistically, components of non-apoptotic machinery are characteristically and functionally unique from apoptotic machinery. Therefore, there is a need to take a step back and re-interpret the ways to therapeutically target pancreatic cancer.

References

1. Ho WJ, Jaffee EM, Zheng L. The tumour microenvironment in pancreatic cancer - clinical challenges and opportunities. Nat Rev Clin Oncol. 2020 May 12. doi: 10.1038/s41571-020-0363-5.
2. Stan SD, Singh SV, Brand RE. Chemoprevention strategies for pancreatic cancer. Nat Rev Gastroenterol Hepatol. 2010;7(6):347-56. doi: 10.1038/nrgastro.2010.61.
3. Costello E, Greenhalf W, Neoptolemos JP. New biomarkers and targets in pancreatic cancer and their application to treatment. Nat Rev Gastroenterol Hepatol. 2012;9(8):435-44.
4. Neoptolemos JP, Kleeff J, Michl P, Costello E, Greenhalf W, Palmer DH. Therapeutic developments in pancreatic cancer: current and future perspectives. Nat Rev Gastroenterol Hepatol. 2018;15(6):333-348.
5. Makohon-Moore A, Iacobuzio-Donahue CA. Pancreatic cancer biology and genetics from an evolutionary perspective. Nat Rev Cancer. 2016 Sep;16(9):553-65. doi: 10.1038/nrc.2016.66.
6. Carneiro BA, El-Deiry WS. Targeting apoptosis in cancer therapy. Nat Rev Clin Oncol. 2020. doi: 10.1038/s41571-020-0341-y.
7. Gura T. How TRAIL kills cancer cells, but not normal cells. Science. 1997;277(5327):768.

Snell V, Clodi K, Zhao S, Goodwin R, Thomas EK, Morris SW, Kadin ME, Cabanillas F, Andreeff M, Younes A. Activity of TNF-related apoptosis-inducing ligand (TRAIL) in haematological malignancies. Br J Haematol. 1997;99(3):618-24.

Pan G, Ni J, Wei YF, Yu G, Gentz R, Dixit VM. An antagonist decoy receptor and a death domain-containing receptor for TRAIL. Science. 1997 Aug 8;277(5327):815-8.

MacFarlane M, Ahmad M, Srinivasula SM, Fernandes-Alnemri T, Cohen GM, Alnemri ES. Identification and molecular cloning of two novel receptors for the cytotoxic ligand TRAIL. J Biol Chem. 1997 Oct 10;272(41):25417-20.

Ashkenazi A. Targeting death and decoy receptors of the tumour-necrosis factor superfamily. Nat Rev Cancer. 2002;2(6):420-30. doi: 10.1038/nrc821.

Mahalingam D, Szegezdi E, Keane M, de Jong S, Samali A. TRAIL receptor signalling and modulation: Are we on the right TRAIL? Cancer Treat Rev. 2009;35(3):280-8. doi: 10.1016/j.ctrv.2008.11.006.

Takeda K, Stagg J, Yagita H, Okumura K, Smyth MJ. Targeting death-inducing receptors in cancer therapy. Oncogene. 2007;26(25):3745-57. doi: 10.1038/sj.onc.1210374.

Fulda S. Targeting extrinsic apoptosis in cancer: Challenges and opportunities. Semin Cell Dev Biol. 2015;39:20-5. doi: 10.1016/j.semcdb.2015.01.006.

Johnstone RW, Frew AJ, Smyth MJ. The TRAIL apoptotic pathway in cancer onset, progression and therapy. Nat Rev Cancer. 2008;8(10):782-98. doi: 10.1038/nrc2465.

von Karstedt S, Montinaro A, Walczak H. Exploring the TRAILs less travelled: TRAIL in cancer biology and therapy. Nat Rev Cancer. 2017 May 24;17(6):352-366. doi: 10.1038/nrc.2017.28.

Kischkel FC, Lawrence DA, Chuntharapai A, Schow P, Kim KJ, Ashkenazi A. Apo2L/TRAIL-dependent recruitment of endogenous FADD and caspase-8 to death receptors 4 and 5. Immunity. 2000;12(6):611-20.

Thome M, Schneider P, Hofmann K, Fickenscher H, Meinl E, Neipel F, Mattmann C, Burns K, Bodmer JL, Schröter M, Scaffidi C, Krammer PH, Peter ME, Tschopp J. Viral FLICE-inhibitory proteins (FLIPs) prevent apoptosis induced by death receptors. Nature. 1997 ;386(6624):517-21.

Srinivasula SM, Datta P, Fan XJ, Fernandes-Alnemri T, Huang Z, Alnemri ES. Molecular determinants of the caspase-promoting activity of Smac/DIABLO and its role in the death receptor pathway. J Biol Chem. 2000;275(46):36152-7.

Romeo C, Weber MC, Zarei M, DeCicco D, Chand SN, Lobo AD, Winter JM, Sawicki JA, Sachs JN, Meisner-Kober N, Yeo CJ, Vadigepalli R, Tykocinski ML, Brody JR. HuR Contributes to TRAIL Resistance by Restricting Death Receptor 4 Expression in Pancreatic Cancer Cells. Mol Cancer Res. 2016 Jul;14(7):599-611. doi: 10.1158/1541-7786.MCR-15-0448.

Yang SZ, Xu F, Yuan K, Sun Y, Zhou T, Zhao X, McDonald JM, Chen Y. Regulation of pancreatic cancer TRAIL resistance by protein O-GlcNAcylation. Lab Invest. 2020 May;100(5):777-785. doi: 10.1038/s41374-019-0365-z.

Harashima N, Takenaga K, Akimoto M, Harada M. HIF-2α dictates the susceptibility of pancreatic cancer cells to TRAIL by regulating

survivin expression. Oncotarget. 2017;8(26):42887-42900.
Elia A, Henry-Grant R, Adiseshiah C, Marboeuf C, Buckley RJ, Clemens MJ, Mudan S, Pyronnet S. Implication of 4E-BP1 protein dephosphorylation and accumulation in pancreatic cancer cell death induced by combined gemcitabine and TRAIL. Cell Death Dis. 2017;8(12):3204.
Nair L, Chung H, Basu U. Regulation of long non-coding RNAs and genome dynamics by the RNA surveillance machinery. Nat Rev Mol Cell Biol. 2020;21(3):123-136.
Uszczynska-Ratajczak B, Lagarde J, Frankish A, Guigó R, Johnson R. Towards a complete map of the human long non-coding RNA transcriptome. Nat Rev Genet. 2018;19(9):535-548.
Chan E, Prado DE, Weidhaas JB. Cancer microRNAs: from subtype profiling to predictors of response to therapy. Trends Mol Med. 2011;17(5):235-43.
Zhang Y, Yang P, Wang XF. Microenvironmental regulation of cancer metastasis by miRNAs. Trends Cell Biol. 2014;24(3):153-60.
Ling H, Fabbri M, Calin GA. MicroRNAs and other non-coding RNAs as targets for anticancer drug development. Nat Rev Drug Discov. 2013;12(11):847-65.
Anastasiadou E, Jacob LS, Slack FJ. Non-coding RNA networks in cancer. Nat Rev Cancer. 2018 Jan;18(1):5-18.
Treiber T, Treiber N, Meister G. Regulation of microRNA biogenesis and its crosstalk with other cellular pathways. Nat Rev Mol Cell Biol. 2019;20(1):5-20.
Ameres SL, Zamore PD. Diversifying microRNA sequence and function. Nat Rev Mol Cell Biol. 2013;14(8):475-88.
Di Leva G, Croce CM. Roles of small RNAs in tumor formation. Trends Mol Med. 2010;16(6):257-67.
Ma W, Cui Y, Liu M, Tan Z, Jiang Y. Downregulation of miR-125b promotes resistance of glioma cells to TRAIL through overexpression of Tafazzin which is a mitochondrial protein. Aging (Albany NY). 2019 May 5;11(9):2670-2680. doi: 10.18632/aging.101939.
Kim S, Woo SM, Min KJ, Seo SU, Lee TJ, Kubatka P, Kim DE, Kwon TK. WP1130 Enhances TRAIL-Induced Apoptosis through USP9X-Dependent miR-708-Mediated Downregulation of c-FLIP. Cancers (Basel). 2019 Mar 11;11(3). pii: E344. doi: 10.3390/cancers11030344.
Radke DI, Ungefroren H, Helm O, et al. Negative control of TRAIL-R1 signaling by transforming growth factor β1 in pancreatic tumor cells involves Smad-dependent down regulation of TRAIL-R1. Cell Signal. 2016;28(11):1652-1662.
Radke DI, Ling Q, Häsler R, Alp G, Ungefroren H, Trauzold A. Downregulation of TRAIL-Receptor 1 Increases TGFβ Type II Receptor Expression and TGFβ Signalling Via MicroRNA-370-3p in Pancreatic Cancer Cells. Cancers (Basel). 2018;10(11):399.
Moeng S, Son SW, Seo HA, Lee JS, Kim CK, Kuh HJ, Park JK. Luteolin-regulated MicroRNA-301-3p Targets Caspase-8 and Modulates TRAIL Sensitivity in PANC-1 Cells. Anticancer Res. 2020 Feb;40(2):723-731.
Park JK, Doseff AI, Schmittgen TD. MicroRNAs Targeting Caspase-3 and -7 in PANC-1 Cells. Int J Mol Sci. 2018 Apr 16;19(4):1206. doi: 10.3390/ijms19041206.
Haselmann V, Kurz A, Bertsch U, Hübner S, Olempska-Müller M, Fritsch J, Häsler R, Pickl A, Fritsche H, Annewanter F, Engler C, Fleig B, Bernt A, Röder C, Schmidt H, Gelhaus C, Hauser C, Egberts JH, Heneweer C, Rohde AM, Böger C, Knippschild U, Röcken C, Adam D, Walczak H, Schütze S, Janssen O, Wulczyn FG, Wajant H, Kalthoff H, Trauzold A. Nuclear death receptor TRAIL-R2 inhibits maturation of let-7 and promotes proliferation of pancreatic and other tumor cells. Gastroenterology. 2014;146(1):278-90. doi: 10.1053/j.gastro.2013.10.009.
Yang SZ, Xu F, Zhou T, Zhao X, McDonald JM, Chen Y. The long non-coding RNA HOTAIR enhances pancreatic cancer resistance to TNF-related apoptosis-inducing ligand. J Biol Chem. 2017 Jun 23;292(25):10390-10397. doi: 10.1074/jbc.M117.786830.
Zheng S, Chen H, Wang Y, Gao W, Fu Z, Zhou Q, Jiang Y, Lin Q, Tan L, Ye H, Zhao X, Luo Y, Li G, Ye L, Liu Y, Li W, Li Z, Chen R. Long non-coding RNA LOC389641 promotes progression of pancreatic ductal adenocarcinoma and increases cell invasion by regulating E-cadherin in a TNFRSF10A-related manner. Cancer Lett. 2016 Feb 28;371(2):354-65. doi: 10.1016/j.canlet.2015.12.010.
Francois RA, Zhang A, Husain K, Wang C, Hutchinson S, Kongnyuy M, Batra SK, Coppola D, Sebti SM, Malafa MP. Vitamin E δ-tocotrienol sensitizes human pancreatic cancer cells to TRAIL-induced apoptosis through proteasome-mediated down-regulation of c-FLIPs. Cancer Cell Int. 2019 Jul 22;19:189. doi: 10.1186/s12935-019-0876-0.
Wang W, Li X, Sun W, Zhang L, Zhang M, Hong B, Lv G. Triptolide triggers the apoptosis of pancreatic cancer cells via the downregulation of Decoy receptor 3 expression. J Cancer Res Clin Oncol. 2012 Sep;138(9):1597-605.
Hu W, Jia X, Gao Y, Zhang Q. Chaetospirolactone reverses the apoptotic resistance towards TRAIL in pancreatic cancer. Biochem Biophys Res Commun. 2018 Jan 1;495(1):621-628. doi: 10.1016/j.bbrc.2017.10.144.
Kim JH, Kim MJ, Choi KC, Son J. Quercetin sensitizes pancreatic cancer cells to TRAIL-induced apoptosis through JNK-mediated cFLIP turnover. Int J Biochem Cell Biol. 2016 Sep;78:327-334. doi: 10.1016/j.biocel.2016.07.033.
Monma H, Iida Y, Moritani T, Okimoto T, Tanino R, Tajima Y, Harada M. Chloroquine augments TRAIL-induced apoptosis and induces G2/M phase arrest in human pancreatic cancer cells. PLoS One. 2018;13(3):e0193990.
Kim SY, Park S, Yoo S, Rho JK, Jun ES, Chang S, Kim KK, Kim SC, Kim I. Downregulation of X-linked inhibitor of apoptosis protein by '7-Benzylidenenaltrexone maleate' sensitizes pancreatic cancer cells to TRAIL-induced apoptosis. Oncotarget. 2017;8(37):61057-61071.
Beyer K, Normann L, Sendler M, et al. TRAIL Promotes Tumor Growth in a Syngeneic Murine Orthotopic Pancreatic Cancer Model and Affects the Host Immune Response. Pancreas. 2016;45(3):401-408.
von Karstedt S, Conti A, Nobis M, Montinaro A, Hartwig T, Lemke J, Legler K, Annewanter F, Campbell AD, Taraborrelli L, Grosse-Wilde A, Coy JF, El-Bahrawy MA, Bergmann F, Koschny R, Werner J, Ganten TM, Schweiger T, Hoetzenecker K, Kenessey I, Hegedüs B, Bergmann M, Hauser C, Egberts JH, Becker T, Röcken C, Kalthoff H, Trauzold A, Anderson KI, Sansom OJ, Walczak H. Cancer cell-autonomous TRAIL-R signaling promotes KRAS-driven cancer progression, invasion, and metastasis. Cancer Cell. 2015;27(4):561-73. doi: 10.1016/j.ccell.2015.02.014.
Trauzold A, Siegmund D, Schniewind B, Sipos B, Egberts J, Zorenkov D, Emme D, Röder C, Kalthoff H, Wajant H. TRAIL promotes metastasis of human pancreatic ductal adenocarcinoma. Oncogene. 2006;25(56):7434-9.
Geismann C, Erhart W, Grohmann F, Schreiber S, Schneider G, Schäfer H, Arlt A. TRAIL/NF-κB/CX3CL1 Mediated Onco-Immuno Crosstalk Leading to TRAIL Resistance of Pancreatic Cancer Cell Lines. Int J Mol Sci. 2018 Jun 4;19(6):1661. doi: 10.3390/ijms19061661.
Miarka L, Hauser C, Helm O, Holdhof D, Beckinger S, Egberts JH, Gundlach JP, Lenk L, Rahn S, Mikulits W, Trauzold A, Sebens S. The Hepatic Microenvironment and TRAIL-R2 Impact Outgrowth of Liver Metastases in Pancreatic Cancer after Surgical Resection. Cancers (Basel). 2019 ;11(6):745. doi: 10.3390/cancers11060745.