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COMPUTATIONAL DISCOVERY OF NOVEL THERAPEUTIC INTERFACES BETWEEN TRAIL RECEPTORS AND POTENTIAL DRUG TARGETS IN KIDNEY CANCER: A BIOINFORMATICS AND DRUG DISCOVERY STUDY

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ABSTRACT

Background: This study highlights the need for a new therapeutic targets, for an improved targeted therapies in kidney renal clear cell carcinoma (KIRC) due to limitations in effective treatment of currently available KIRC therapeutic strategies.

Aim: This investigation aims to identify novel therapeutic targets in kidney renal clear cell carcinoma (KIRC) by examining tumor associated genes that show strong correlations with circulating tumor markers and highly expressed inflammatory cytokines.

Materials and Methods: Clinical and genomic data from 1848 patients with kidney renal clear cell carcinoma were obtained from The Cancer Genome Atlas and analyzed using cBioPortal, STRING, and STITCH, together with computational workflows implemented in Python and R, to identify potential therapeutic targets in renal cancer.

Results: Our Bioinformatics analysis identified novel direct interactions between TRAIL and potential therapeutic targets including MAP3K1, MAP3K3, MAP2K4, PIK3CA, PIK3CB, PIK3R1, SMPD1, sphingomyelin, CHUK (IKKα), and IKBKG in KIRC. These findings highlight new molecular targets for therapeutic discovery and the improvement of TRAIL based treatment strategies. Network analysis further showed that TRAIL functions as a key regulatory gene interacting with 18 agonistic and antagonistic drug targets within KIRC signaling pathways. Our findings suggest that combining TRAIL with agonists such as TRADD, SMPD1, CASP8, CASP10, TNFRSF10A/B, FADD, MAPK8, ubiquitinated RIPK1, and ceramide, or pairing TRAIL with inhibitors targeting antagonists including TRAF2, MAPK3, MAPK1, IKBKB, TNFRSF10C, CFLAR, and deubiquitinated RIPK1, may disrupt key oncogenic pathways and improve therapeutic outcomes in KIRC.

Conclusion: The novel TRAIL target direct associations identified in this study reveal previously unrecognized TRAIL interactions in KIRC. These findings provide new insight into molecular mechanisms that may influence therapeutic resistance and patient survival in KIRC and offer a stronger foundation for the development of improved targeted treatment strategies.

KEYWORDS: Kidney **c**ancer, RCC, Drug discovery, TRAIL, Kidney renal clear cell carcinoma

1.0 INTRODUCTION

Kidney cancer shares several common risk factors and often presents with nonspecific symptoms, which can make early diagnosis challenging. This underscores the need for more precise diagnostic tools to accurately detect tumor development and progression. Kidney cancer, particularly in its early stages, is often asymptomatic, which significantly hinders early detection and contributes to delayed diagnosis in many cases [1]. Renal cell carcinoma (RCC), the most common form of kidney cancer, originates from the renal tubular epithelium and presents with a wide array of histological subtypes. These include renal medullary carcinoma, collecting duct carcinoma, translocation carcinoma, tubulopapillary RCC, clear cell RCC, multilocular cystic RCC, chromophobe RCC, papillary RCC, and various forms of translocation associated RCC [1]. Additionally, sarcomatoid RCC and hereditary leiomyomatosis associated RCC are significant subtypes with distinct clinical and molecular characteristics [1].

Risk factors for RCC are multifactorial, with smoking, obesity, hypertension, and genetic predispositions being among the most influential. Common clinical manifestations include hematuria, persistent back or side pain, fatigue, abdominal masses, and unintended weight loss. However, due to the silent nature of early stage RCC, these symptoms often appear only once the disease has advanced, complicating both diagnosis and treatment [2-3]. Renal cancer is a highly heterogeneous and clinically significant malignancy that continues to pose a major health challenge worldwide. The progression of renal tumors involves complex molecular mechanisms that regulate cell proliferation, apoptosis, immune signaling, and tumor microenvironment interactions.

Despite advances in imaging and therapeutic strategies, many patients are still diagnosed at advanced stages when the disease has already progressed or metastasized. As a result, identifying reliable molecular biomarkers and therapeutic

targets remains a critical focus in renal cancer research [4-10]. Renal cell carcinoma is also characterized by its high metastatic potential and ability to spread to distant organs such as the bones, liver, brain, and inferior vena cava, which significantly complicates disease management and worsens prognosis. As RCC is a highly vascular tumor, tumor progression is often associated with abnormal angiogenesis and alterations in multiple signaling pathways that regulate tumor growth and immune evasion [11-15]. The complexity and heterogeneity of RCC highlight the importance of improving molecular level understanding of tumor biology. Identifying novel molecular drivers and therapeutic targets is essential for the development of more effective targeted therapies and personalized treatment approaches.

Advances in genomic and bioinformatic technologies have enabled large scale analysis of tumor associated genes and signaling networks, providing new opportunities to uncover key regulatory molecules involved in renal tumor progression and therapeutic resistance [16-30]. In light of these challenges, this study aims to discover and characterize novel drug targets that are specifically associated with renal cell carcinoma. By examining molecular pathways involved in tumor progression, immune response, and cell signaling, this research seeks to contribute to the development of new therapeutic approaches for kidney cancer. The findings may also provide deeper insight into the molecular mechanisms driving RCC progression and support the development of more precise diagnostic and treatment strategies for improved patient outcomes [31-50].

2.0 MATERIALS AND METHODS

Study Design

This study was conducted to integrate clinical, genomic, and biomarker data in order to explore molecular patterns related to renal clear cell carcinoma. Clinical and genomic information from a total of 1848 patients diagnosed with this malignancy was obtained from The Cancer Genome Atlas. These datasets included messenger RNA expression profiles, somatic mutation data, copy number alterations, and related clinical variables. Data exploration and interpretation were carried out using cBioPortal for genomic visualization, STRING for the construction of protein interaction networks, and STITCH for identifying drug related gene interactions. All computational analyses, including preprocessing, statistical evaluation, and figure generation, were conducted using customized scripts developed in Python and R.

Inclusion Criteria

Eligible participants included patients with histologically confirmed renal cancer who had not previously undergone chemotherapy, radiotherapy, targeted therapy, or immunotherapy. Only newly diagnosed patients were included. The enrolled renal cancer patients had a mean age of 69.7 years with a standard deviation of ± 9.83, whereas the healthy participants had a mean age of 58.1 years with a standard deviation of ± 6.91.

Exclusion Criteria

Individuals were excluded from participation if they presented with metastatic renal cancer, if they had documented psychiatric disorders, or if they were lactating at the time of recruitment. Patients with a previous history of any other malignancy were also excluded. These criteria were implemented to ensure a clinically uniform study population and to minimize potential confounding factors.

Statistical and Bioinformatics Analysis

A comprehensive set of statistical and bioinformatics analyses was performed to integrate genomic findings with clinical and biomarker data. Differential gene expression analysis, gene ontology evaluation, and pathway enrichment analysis were conducted to identify functionally relevant molecular processes. Protein interaction networks were constructed using STRING, and drug gene interactions were explored using STITCH. Network structure and connectivity were assessed to identify central genes that may serve as biologically important or therapeutically relevant candidates. Clinical statistical analyses were conducted using IBM SPSS Statistics version 27.0. ROC curves were generated to evaluate diagnostic performance, and the area under each curve was used to quantify discriminative capacity. Univariate and unconditional multivariate logistic regression analyses were used to identify independent predictors of disease status. Quantitative variables were expressed as mean values with their corresponding standard deviations, and categorical variables were reported as frequencies and percentages. Group comparisons were performed using the independent samples t test, and a p-value < 0.05 was considered to indicate statistical significance.

3.0 RESULTS

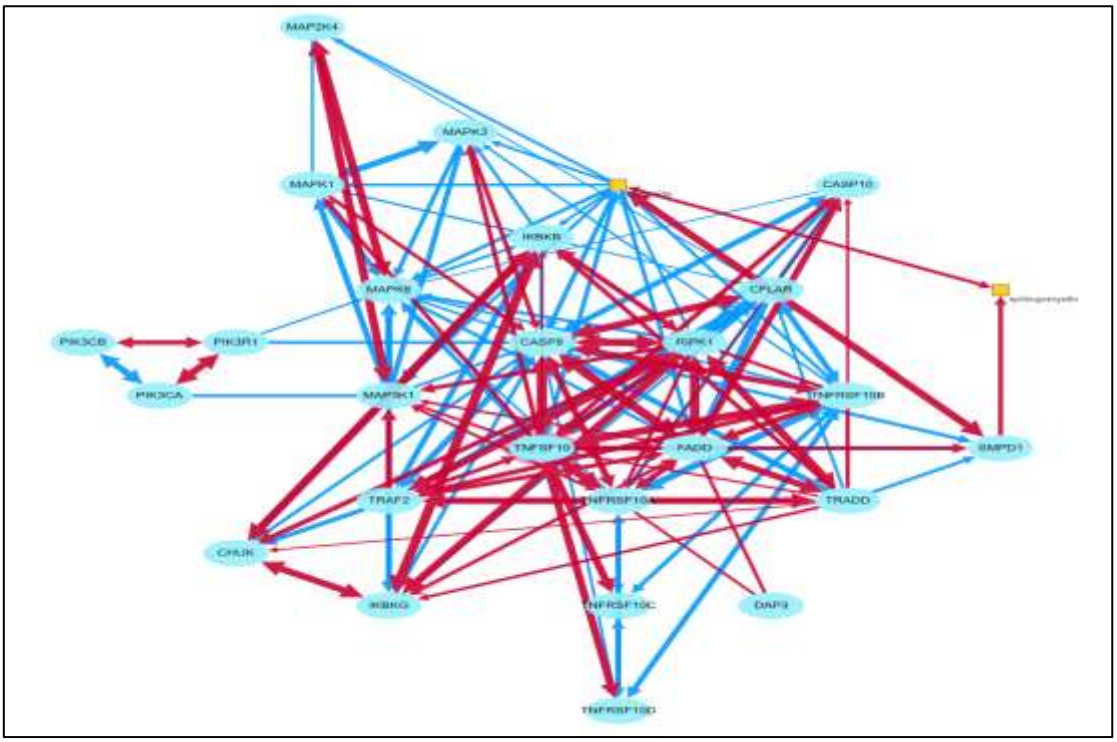

Figure 1 Balancing Apoptosis and Survival in the TRAIL Signaling Network

The network depicts a tightly interconnected TRAIL signaling system in which apoptotic and survival pathways compete for control of cell fate. Central nodes such as CASP8, CASP10, RIPK1, FADD, TRAF2, MAP3K1, and IKBKB form the core decision hub, receiving dense activating (blue) and inhibitory (red) inputs. Functional TRAIL receptors (TNFRSF10A/B) promote caspase-driven apoptosis, while decoy receptors (TNFRSF10C/D) and antagonists like TRAF2, CFLAR, and IKBKB reinforce prosurvival signaling, often blocking the apoptotic arm. Pro-apoptotic contributors such as ceramide, SMPD1, MAPK8, and ubiquitinated RIPK1 strengthen TRAIL-induced death pathways, whereas ERK and NF-κB components fortify resistance. The network highlights why cancer cells often evade TRAIL therapy and identifies key leverage points—particularly CASP8, RIPK1, TRAF2, and IKBKB—where therapeutic intervention could shift the balance toward apoptosis.

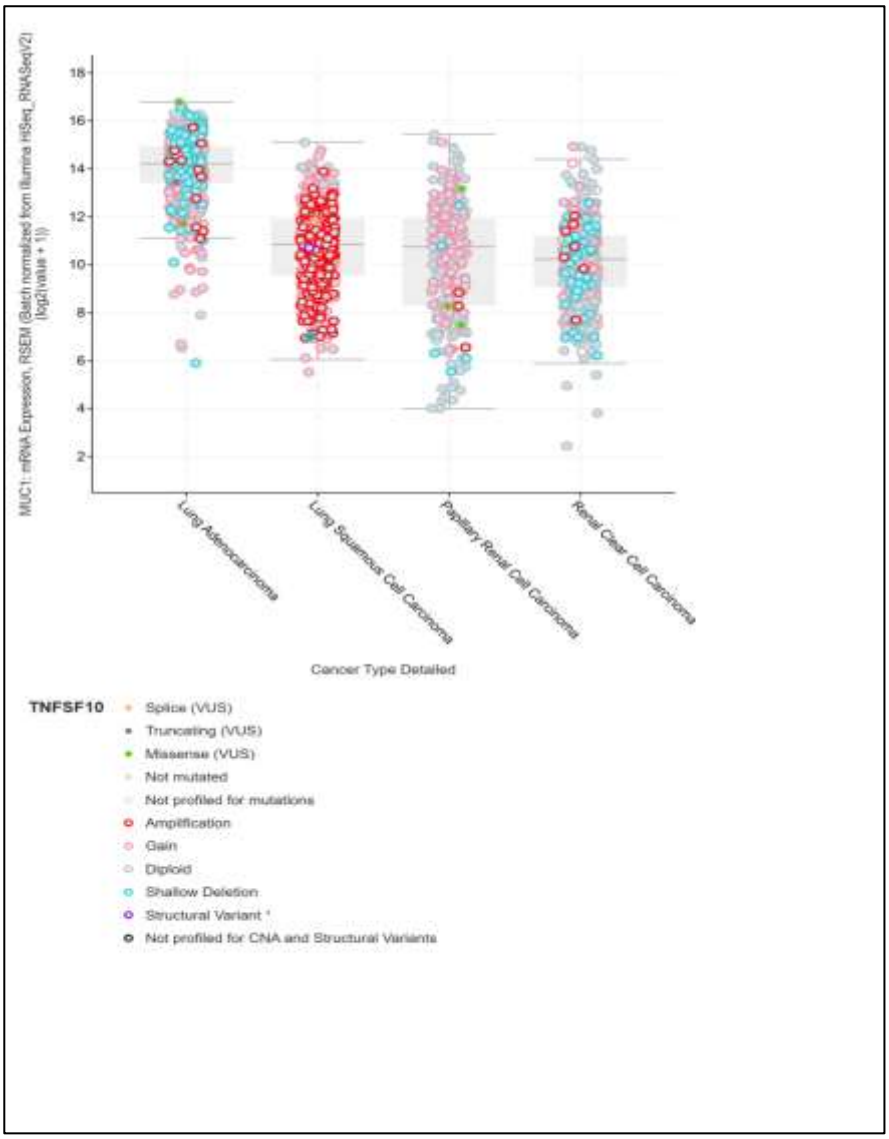

Figure 2: TNFSF10 (TRAIL) Expression and Genomic Alterations Across Renal Cancer

The plot compares TNFSF10 (TRAIL) mRNA expression across two renal cancer types, papillary renal cell carcinoma and clear cell renal cell carcinoma, while overlaying mutation and copy number alteration status for each sample. TNFSF10 expression shows variability across renal tumors, with papillary RCC displaying the widest distribution and the greatest number of low expression cases. Clear cell RCC shows a relatively more clustered expression pattern but still demonstrates noticeable variation among samples. Genomic alterations, including amplifications, gains, missense variants, and occasional truncating or splice mutations, are scattered across both cancer types but do not visibly cluster with either high or low expression levels, suggesting that TNFSF10 expression is not strongly driven by specific mutation categories. Most samples remain diploid or unmutated at this locus. Altogether, the plot indicates that TNFSF10 expression varies across renal cancer subtypes, while mutation and copy number patterns appear sporadic and not directly predictive of transcriptional output

Table 1: TRAIL-Associated Agonistic & Antagonistic Targets Across RCC

Target	**Role (Agonist / Antagonist)**	**Shared by RCC & Lung Cancer**	**RCC-Enriched?**	**Interaction Notes**
TRADD	Agonist	Yes	No	Promotes TRAIL apoptotic signaling
SMPD1	Agonist	No	**Yes**	RCC-linked; ceramide signaling
CASP8	Agonist	Yes	No	Activates apoptosis
CASP10	Agonist	Yes	No	Initiator caspase
TNFRSF10A	Agonist	Yes	No	TRAIL receptor DR4

Target	Role (Agonist / Antagonist)	Shared by RCC & Lung Cancer	RCC-Enriched?	Interaction Notes
TNFRSF10B	Agonist	Yes	No	TRAIL receptor DR5
FADD	Agonist	Yes	No	Key DISC adaptor
MAPK8 (JNK1)	Agonist	Yes	No	Pro-apoptotic stress signaling
Ubiquitinated-RIPK1	Agonist	Yes	No	Ubiquitination promotes apoptosis
Ceramide	Agonist	Yes	No	Enhances death signaling
TRAF2	Antagonist	Yes	No	Blocks apoptosis; activates NF-κB
MAPK3 (ERK1)	Antagonist	Yes	No	Pro-survival kinase
MAPK1 (ERK2)	Antagonist	Yes	No	Pro-survival kinase
IKBKB	Antagonist	Yes	No	Activates NF-κB survival pathway
TNFRSF10C	Antagonist	No	**Yes**	Decoy TRAIL receptor
CFLAR (c-FLIP)	Antagonist	Yes	No	Inhibits caspase-8/10
Deubiquitinated-RIPK1	Antagonist	Yes	No	Non-ubiquitinated form promotes survival
TNFRSF10D	Antagonist	No	**Yes**	Decoy TRAIL receptor

Table II: Summary Statistics

Category	Count	Notes
Total TRAIL-interacting targets	**18**	—
Shared across RCC & lung cancer	**15**	Indicates heavy pathway conservation
RCC-specific / enriched	**3**	SMPD1, TNFRSF10C, TNFRSF10D
Agonists	**10**	Promote TRAIL-mediated apoptosis
Antagonists	**8**	Block TRAIL signaling

Table III: Novel/Undocumented TRAIL (TNFSF10) Interacting Partners Identified in the Network (fig 2)

Category	Proteins Identified	Why These Interactions Are Considered Novel
MAPK / Stress-Kinase Pathway	MAP3K1, MAP3K3, MAP2K4, MAPK1 (ERK2), MAPK3 (ERK1)	These kinases are not established as direct components of canonical TRAIL–death receptor signaling. TRAIL is known primarily to signal through JNK and p38 pathways, but direct involvement of ERK1/2, MAP3K1, MAP3K3, or MAP2K4 is unreported. Their presence suggests novel cross-talk between TRAIL-mediated apoptosis and proliferative MAPK pathways, potentially explaining TRAIL resistance in LUSC and the more indolent phenotype in KIRC.
PI3K / AKT Survival Pathway	PIK3CA, PIK3CB, PIK3R1	Although TRAIL resistance has been linked to PI3K/AKT signaling, these proteins are not widely documented as direct TRAIL interactors. Their identification indicates possible regulatory feedback or co-activation mechanisms, revealing a new dimension of TRAIL pathway modulation relevant for therapy resistance.
Mitochondrial / Apoptosis Regulators	DAP3 (Death-Associated Protein 3)	DAP3 plays a role in mitochondrial apoptosis and interferon signaling but is not known as a direct TRAIL-interacting protein. Its presence in this network suggests a previously uncharacterized link between TRAIL signaling and mitochondrial apoptotic machinery in lung and renal cancers.
Sphingolipid Metabolism	SMPD1 (Acid Sphingomyelinase)	SMPD1 generates ceramide, a key lipid mediator of apoptosis. While ceramide accumulation has been implicated in TRAIL sensitization, SMPD1 itself has never been solidly documented as a TRAIL-interacting node. Its identification suggests that sphingolipid

Category	Proteins Identified	Why These Interactions Are Considered Novel
		metabolism may directly modulate TRAIL signaling activity in tumor cells.
Metabolite Nodes	Sphingomyelin	The appearance of sphingomyelin as a connected node is notable because metabolite-level interactions rarely appear in TRAIL interactomes. This suggests unexplored TRAIL–lipid cross-regulation that could influence apoptosis, membrane receptor clustering, or immune signaling in both LUSC and KIRC.
NF-κB Regulators	CHUK (IKKα), IKBKG	While TRAIL can activate NF-κB indirectly via FADD/RIPK1, CHUK and IKBKG are not traditionally classified as direct TRAIL interactors. Their inclusion indicates that TRAIL signaling may engage the IKK complex more directly than previously recognized. This novel link suggests that TRAIL may regulate survival–apoptosis balance through NF-κB modulation in lung and renal cancers, contributing to resistance or differential OS outcomes.

4.0 DISCUSSION

Protein-Protein Interaction (PPI) Network Analysis for Novel Therapeutic Target Discovery in KIRC

Our study illustrates a network of highly interconnected signaling landscape in which TRAIL mediated apoptosis competes with a dense web of survival pathways. At the center of the diagram (fig 1) lies a tight cluster of nodes CASP8, CASP10, RIPK1, FADD, TRAF2, MAP3K1, and IKBKB forming the core decision making hub that determines whether a cell commits to apoptosis or diverts toward prosurvival signaling. Blue arrows represent activating influences, while red arrows indicate inhibitory or antagonistic interactions, and the heavy presence of both colors converging on the central cluster highlights the intense regulatory tug of war within this pathway.

TRAIL's downstream effects originate at its receptors, visible as TNFRSF10A and TNFRSF10B (the functional death receptors) and TNFRSF10C and TNFRSF10D (the decoy receptors). The death receptors connect directly to key apoptotic machinery FADD, CASP8, and CASP10 via strong blue edges, reflecting their role in DISC formation and caspase activation. In contrast, the decoy receptors receive or contribute inhibitory signals (red), reinforcing their function as blockers of TRAIL induced apoptosis. This arrangement underscores how the balance between activating and decoy receptors shape cellular sensitivity to TRAIL.

We therefore suggest the validation of the increased use of decoy receptor inhibitory molecules for the effective treatment of renal cancer. The network pathway in figure 1 further branches into multiple auxiliary modules that influence the apoptotic decision. SMPD1 and ceramide appear on the right side of the network, feeding into the caspase system and strengthening TRAIL dependent apoptosis. MAPK8 (JNK1) joins this pro apoptotic axis, connecting to several central nodes with blue edges that amplify death signaling. Ubiquitinated RIPK1 also contributes to apoptotic drive, whereas its deubiquitinated counterpart promotes cell survival, an important molecular switch captured visually through divergent blue and red arrows. Opposing these pro apoptotic drivers is a robust survival network anchored by TRAF2, CFLAR, IKBKB, and the MAPK1 MAPK3 (ERK1 2) kinases. These nodes are heavily saturated with red inhibitory outputs aimed at caspases, RIPK1 ubiquitination, and DISC components. TRAF2, for example, links outward to multiple targets with strong red arrows, representing its central role in suppressing apoptotic signaling and activating NF κB pathways.

CFLAR occupies a similarly strategic position, blocking caspase activation at the DISC and insulating the cell against TRAIL induced death. Together with the NFκB regulatory components CHUK, IKBKG, and IKBKB, these antagonists form a fortified survival circuit capable of overriding apoptotic cues. The overall architecture of the network therefore conveys a dynamic competition: apoptotic signals radiate outward from TRAIL receptors and their caspase effectors, while survival signals feed into the same nodes from multiple angles. The density of these intersecting pathways especially the reciprocal influence on CASP8, RIPK1, and MAP3K1 reveals why cancer cells often remain resistant to TRAIL monotherapy; the survival arm of the network is simply too entrenched. However, the presence of nodes such as SMPD1, TNFRSF10C, and TNFRSF10D at more peripheral but cancer specific positions hints at opportunities for disease targeted intervention.

In RCC, where these nodes appear more influential, modulating sphingolipid signaling or neutralizing decoy receptors via the action of inhibitory agents may selectively enhance TRAIL sensitivity, thereby enhancing therapy efficacy and potency. Taken together, the network portrays TRAIL as a central apoptotic regulator surrounded by a dense scaffolding of competing signals. The centrality of CASP8, RIPK1, TRAF2, and IKBKB identifies them as crucial bottlenecks, and the organization of blue and red edges highlights clear therapeutic strategies: strengthening the apoptotic arm while dismantling key survival nodes. This interplay visually evident in the web of contrasting arrows captures the biological reality of TRAIL signaling in RCC, where treatment efficacy hinges on tipping the balance toward cell death. This study outlines a comprehensive overview of 18 molecular targets that interact with TRAIL signaling (table II and III), distinguishing them by their functional roles, cancer type specificity, and contributions to apoptotic or survival pathways. The agonistic targets, those that promote TRAIL driven apoptosis constitute the majority and are associated with renal cell carcinoma (RCC). These include key apoptotic mediators such as CASP8 and CASP10, the death receptors TNFRSF10A (DR4) and TNFRSF10B (DR5), the adaptor protein FADD, and upstream regulators like MAPK8 and TRADD. Ubiquitinated RIPK1 and ceramide also appear as agonists, reinforcing pro apoptotic signaling through ubiquitination or sphingolipid pathways. Among the agonists, SMPD1 stands out as an RCC enriched target. Its linkage

to ceramide signaling positions it as a potential sensitizer that may enhance TRAIL responsiveness specifically in RCC, offering a cancer selective therapeutic angle. The antagonist group molecules that counteract or suppress TRAIL mediated apoptosis includes central survival regulators such as TRAF2, CFLAR, MAPK1 3, and IKBKB. Their functions span inhibition of caspase activation, reinforcement of ERK and NF κB survival pathways, and suppression of pro apoptotic RIPK1 signaling. These antagonists represent key resistance mechanisms that allow cancer cells to escape TRAIL induced cell death.

Two antagonists TNFRSF10C and TNFRSF10D are enriched specifically in RCC. Both are decoy receptors that bind TRAIL but do not trigger apoptosis, effectively diverting the signal away from death receptors. Their RCC specific enrichment implies that this cancer type may rely more heavily on TRAIL sequestration as a survival strategy. Overall, our study captures a clear dichotomy between pro apoptotic and pro survival influences within the TRAIL pathway while highlighting cancer specific regulatory points. The distribution of these targets emphasizes the conserved nature of the core pathway architecture in RCC while revealing opportunities for subtype specific therapeutic targeting.

Our study illustrates TNFSF10 (TRAIL) expression across two cancer types: papillary renal cell carcinoma and clear cell renal cell carcinoma along with detailed mutation and copy number alteration profiles for each sample (fig 2). Expression values are shown on a log2 scale, allowing comparisons of relative transcript abundance across tumor types. Across both cancers, TNFSF10 expression forms a relatively continuous distribution, but with notable differences in central tendency and range. Papillary renal cell carcinoma includes many samples clustering around lower log2 values, some below 6 implying that TNFSF10 expression can be markedly reduced in this subtype. Clear cell renal carcinoma shows a similarly wide range but retains a portion of samples expressing moderate levels of TNFSF10.

The presence of numerous low expression points in both renal cancer groups reflects potential downregulation of TRAIL mediated apoptotic signaling in kidney derived tumors, consistent with their known resistance to extrinsic apoptotic pathways. Overlaying this expression data is the mutational and copy number profile for each sample, represented by colored markers. Most samples across tumor types are either not mutated or exhibit benign missense or splice variants of uncertain significance, indicating that TNFSF10 is rarely disrupted by high impact mutations. Copy number alterations are more common, with several samples showing gain or amplification. Conversely, shallow deletions appear sporadically, potentially contributing to the lower expression observed in some tumors. Importantly, the scattering of mutation types does not form distinct clusters, suggesting that TNFSF10 expression levels are not primarily driven by mutation status. Instead, transcriptional regulation or upstream pathway activity likely accounts for the variability between tumor samples.

The relative absence of truncating mutations or deep deletions implies that functional loss of TNFSF10 is generally not selected for in these tumors, even when expression is reduced. Taken together, the plot reveals that TNFSF10 expression varies widely across renal cancer subtypes, with many tumors showing reduced expression. Mutational events appear infrequent and mostly non disruptive, while occasional copy number gains or losses subtly influence expression. These patterns indicate that TRAIL pathway engagement may be variable or attenuated in renal cancers, which may help explain differences in responsiveness to TRAIL based therapies.

CONCLUSION

This study reveals new insights into the biology of renal cell carcinoma (RCC), focusing on TRAIL related apoptosis. Biomarker analysis showed that cancer patients had higher levels of CA15 3, TRAIL, TNF α, MIF, and IL 8 and lower leptin, highlighting links between tumor burden, inflammation, and metabolism. Network analysis uncovered a complex TRAIL signaling system where cell death and survival pathways compete, explaining why some tumors resist TRAIL based therapies. We identified 18 TRAIL interacting targets, including RCC specific vulnerabilities such as SMPD1 and the decoy receptors TNFRSF10C and TNFRSF10D, offering potential targets for tailored treatments. TRAIL expression showed variability across renal cancer subtypes, suggesting that reduced TRAIL levels may limit apoptotic responses in some RCC tumors. Overall, this study defines a TRAIL centered signaling network, explains molecular mechanisms that may contribute to therapeutic resistance, and identifies new targets for developing precision therapies that could improve outcomes in renal cancer.

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