SETDB1 as a Novel Determinant of PARP1 Inhibitor Sensitivity in Pancreatic Ductal Adenocarcinoma

Aarush Shah[1]

[1] Issaquah High School, Issaquah, WA, USA

ABSTRACT:

PARP inhibitors (like Olaparib) kills cancer cells by blocking single-strand DNA repair and are most conducive for BRCA-mutant patients which represents 10% of Pancreatic Ductal Adenocarcinoma (PDAC). However, it showed no overall survival benefits despite improving progression-free survival while it does not work on the remaining 90% of PDAC patients without BRCA mutations. We hypothesized that SETDB1 acts as a master epigenetic regulator that confers resistance to PARP1 inhibitors by elevating the apoptotic threshold. To test this we performed a multi-cohort transcriptomic analysis utilizing 332 PDAC patient tumors across TCGA and QCMG screening them for genes that were co-expressed with PARP1. Among those, 19 genes were identified through co-expression filtering, with SETDB1 selected based on correlation strength (R=0.75), hazard ratio (HR=1.54). Pathway analysis was done via GSEA and DAVID and revealed that PARP1-high PDAC was significantly enriched in pathways related to chromatin remodeling, DNA damage repair, and Ubl conjugation. SETDB1 knockdown across multiple PDAC cell lines (PANC-1, SU8686, CAPAN-1) enhanced Olaparib sensitivity, suppressing proliferation and increasing apoptosis compared to either treatment alone ($p<0.0001$). While Olaparib alone showed no significant effect on wildtype PANC-1 cells, SETDB1 expression correlated positively with Olaparib IC50 values across PDAC cell lines, supporting its role as a predictive biomarker for PARPi sensitivity. The findings suggest SETDB1 plays a key role in allowing cancer cells to survive Olaparib treatment, and hence using SETDB1 as a determinant alongside PARP1 drugs (like Olaparib) can be a viable strategy to improve outcomes across both BRCA-mutant and non-BRCA mutant PDAC patients.

INTRODUCTION

PDAC is infamously known as a “silent killer” because of the difficulty in early-stage detection. The structure itself reveals the tumor’s origin, arising from the exocrine component of the pancreas, specifically the epithelial cells in the pancreatic ducts. These ducts are the main route for transporting digestive enzymes to the small intestine. Changes in gene expression and mutations lead to their accumulation in the pancreas, resulting in an aggressive infiltrative malignancy.

In contrast to other types of cancer that have identifiable screening modalities, ductal lineage pancreatic cancer is typically asymptomatic until the tumor obstructs the bile duct or innervates the local area. At this stage, when patients experience jaundice due to bile duct obstruction, abdominal pain, or weight loss, the cancer would have already metastasized or progressed to an irreparable local disease, explaining the poor 5-year survival rate estimated to be approximately 11%. Owing to the anatomical position of the pancreas, which is seated behind large vascular structures in the abdominal cavity, surgical approaches to cancer are impaired, allowing the cancer to grow silently behind the thick fibrotic wall.

The therapeutic approach focuses almost exclusively on patients with germline BRCA1/2 mutations(gBRCAm). PARP inhibitors trap PARP1 on damaged DNA, creating cytotoxic lesions that BRCA1/2-deficient cells cannot resolve through homologous recombination repair (HRR), thereby inducing selective cell death via synthetic lethality (Masi et al., 2025). BRCA mutations are present in 10 percent of the entire PDAC population, consisting of defects in the HR pathway, creating a “hole” in the cell’s DNA repair machinery, making it a viable option for PARPi via the principle of synthetic lethality.

By prioritizing germline inheritance as the primary criterion, the clinical community neglects a major patient population without BRCA mutations including those with somatic alterations or epigenetic silencing. Furthermore, this focus fails to address the dominant genomic drivers, such as KRAS, TP53, CDKN2A, and SMAD4, which are involved in survival in the remaining 90% of cases and contribute to a state of chronic genomic instability that should, theoretically, be exploitable by PARP inhibition.

Despite the mechanistic promise of PARP trapping, real-world data from the POLO trial revealed a significant "survival gap" where radiographic stability failed to translate into overall

survival (OS) benefits (Golan et al., 2019; Kindler et al., 2022)). The current literature identifies several resistance patterns, including shieldin complex-mediated fork stabilization, compensatory DNA repair activation, and restoration of HR function. Furthermore, while PARPi can activate the cGAS-STING pathway to trigger innate immunity via cytosolic DNA sensing (Wang et al., 2022), many tumors remain "cold" and non-immunogenic. These observations suggest that mutation-centric or DNA repair-focused models are insufficient to explain the broad recalcitrance of PDAC to genotoxic stress (Oluwalana, 2025).

The interim analysis of POLO Overall Survival showed results similar to those of placebo, as it is expensive and toxic. “Future therapeutic strategies should prioritize enhancing clinical response by combining PARP inhibitors with synergistic agents,” (Sonbol & Bekaii-Saab, 2019). Clinical analysis confirms that the interim OS was nearly identical between the two groups (18.9 vs 18.1 months), revealing a "profound resistance barrier" (Golan et al., 2019), though progression-free survival showed improvement (7.4 vs 3.8 months; HR 0.53, P=0.004).

Transcriptomic studies have identified SETDB1 as a driver of aggressive malignancies. Traditionally known as a repressor, it catalyzes the trimethylation of H3K9 marks associated with transcriptional downregulation. SETDB1 has been identified as a specific global modulator of the cancer transcriptome. Federico et al. (2020) demonstrated aberrant SETDB1 amplification and overexpression in melanoma zebrafish models and clinical samples, with SETDB1 directly contributing to metastasis formation. In aggressive models such as malignant melanoma, SETDB1 has been shown to silence tumor suppressor pathways and remodel the transcriptome to favor cell cycle progression and stress survival (Lazaro-Camp et al., 2021; Ogawa et al., 2020). The dual functionality of SETDB1 enables cells to maintain their proliferative capacity while silencing pro-apoptotic responses to genotoxic stress. Furthermore, the development of EC-8042, a novel mithralog and DNA-binding agent, has provided a pharmaceutical tool to downregulate SETDB1, demonstrating efficacy in reversing SETDB1-mediated oncogenic phenotypes (Federico et al., 2020). Unlike traditional repair factors, SETDB1 acts as an architect of a repressive transcriptional landscape. Targeting SETDB1 along with PARP1 can be crucial in breaking the resistance patterns that currently limit the efficacy of PARP inhibition. However, the specific role of SETDB1 in modulating PARP1 inhibitor sensitivity in PDAC, mainly in BRCA wildtyle cases remains poorly understood. This investigation addresses a critical question: Does SETDB1 expression dictate the therapeutic efficacy of PARP inhibitors in non-BRCA mutant PDAC populations?

We hypothesized that SETDB1 acts as a master epigenetic regulator that raises the apoptotic threshold, allowing PDAC cells to functionally bypass the synthetic lethality of PARP1 inhibition. To test this prediction, we integrated multi-cohort transcriptomic analysis with targeted in vitro validation and siRNA-mediated knockdown. In this study, we provide the first evidence that SETDB1 is a critical determinant of resistance in pancreatic cancer, demonstrating that its co-expression with PARP1 correlates with poor clinical outcomes and that its inhibition restores sensitivity to Olaparib.

RESULTS*:*

Among both the TCGA and QCMG PDAC datasets, PARP1-high tumors showed significant upregulation of genes involved in cell cycle regulation, DNA replication, oxidative metabolism, and DNA repair compared with PARP1-low tumors (FDR < 0.1).

GSEA against the MSigDB Hallmark gene sets revealed significant enrichment of MYC_TARGETS_V1 (NES=2.69, FDR q<0.001), E2F_TARGETS (NES=2.53, FDR q<0.001), G2M_CHECKPOINT, OXIDATIVE_PHOSPHORYLATION, and DNA_REPAIR in PARP1-high tumors across both cohorts.

In the Volcano plots, genes that later formed the 19-gene intersection, such as SETDB1 and PSMB4, were among the significantly upregulated transcripts in PARP1 High tumors. This supports the concept that the genes are embedded within the coordinated PARP1- linked responses mechanism rather than outliers. Differential expression analysis showed sets of genes significantly upregulated in PARP1 high tumors compared to PARP1 low tumors within each cohort after multiple testing. Intersecting the two cohorts upregulated gene lists revealed a conserved 19-gene signature that was shared in both datasets, including PARP1, SETDB1, ILF2, and additional nucleoplasm and proteostasis-related factors. Functional annotation of this 19 gene signature demonstrated over-represented pathways linked to nucleoplasm organization, ubiquitin-like conjugation, proteasome function, chromatin remodeling, and DNA repair. The combination of these processes implies that the PARP1-high PDAC cell line co-selects a small transcriptional module that integrates epigenetic suppression, protein quality control, and repair capability, which corresponds to the concept of an ‘escape network’ for surviving genotoxic conditions.

This narrowed the vast genome to core 19 genes possible involved in the resistance mechanism, within which SETDB1 was identified as an epigenetic regulator and prominent oncogene. SETDB1 is a nuclear protein and a histone methyl transferase potentially involved in transcriptional regulation and DNA damage response SETDB1 is co-expressed with PARP1 and is associated with poor outcomes and Olaparib resistance. These findings align with published data demonstrating SETDB1’s critical role in suppressing apoptosis in PDAC, where SETDB1 deletion in mouse models prevented tumor formation through increased p53-mediated cell death (Ogawa et al., 2020). In PDAC patient datasets, SETDB1 expression was positively correlated with PARP1 levels, indicating that tumors with high PARP1 activity tend to upregulate

chromatin modifiers. Using the IC50 values with SETDB1, a strong positive correlation was observed, indicating that higher SETDB1 expression matched increased drug resistance, as more Olaparib is needed to inhibit cell proliferation in pancreatic cancer cell lines. SETDB1 expression is positively correlated with Olaparib IC50 values, as shown in genomics-based drug-sensitivity datasets, and cell lines with higher SETDB1 require higher drug concentrations to achieve growth inhibition. This supports a link between SETDB1 activity and reduced PARPi sensitivity, positioning SETDB1 as both a marker and functional effector of Olaparib resistance in pancreatic cancer cells. To test whether SETDB1 directly affects PARPi response, PANC-1 cells with high baseline PARP1 expression and PARylation were selected for siRNA-mediated SETDB1 knockdown. Under control conditions with intact SETDB1, Olaparib treatment reduced proliferation but induced only modest increases in apoptosis (Sytox green positive cells, indicative of apoptosis), consistent with the predominant loss of cell proliferation. When SETDB1 was knocked down and cells were treated with 20 μM Olaparib, the proportion of apoptotic cells increased at the specified doses and time points, indicating enhanced drug sensitivity and cytotoxicity. These findings support a model in which SETDB1 enables cells to tolerate PARP1 driven replication stress by maintaining a resistant state in which disrupting SETDB1 restores apoptotic reliance and converts PARPi damage to cell death, fulfilling synthetic lethality

DISCUSSION

The PDAC mutational landscape is driven by KRAS gain-of-function and TP53 loss-of-function. This creates a cellular environment of intense replication stress. Despite this, cells remain relatively insensitive to PARP1 inhibition as seen in the POLO clinical trial. The mechanism behind this is under active research. However, potential mechanisms include chromatin- mediated elevation of the apoptotic threshold (Ogawa et al., 2020), preventing genotoxic damage from triggering cell death despite ongoing genomic instability. We hypothesize that a specific “Escape network” serves as a primary barrier to synthetic lethality in PDAC. Identifying upregulated genes in PARP1-high PDAC can lead to identification of potential co-inhibitors as viable therapeutic targets.

While SETDB1 was the focused target for this study, the 19 gene signature, including PSMB4, ILF2 and others all point to coordinated resistance rather than individual epigenetic alone. PSMB5 upregulation degrades accumulated PARylated proteins, while nuclear transport factors repair stalled forks. These factors suggest SETDB1 creates the repressive setting while other factors effectors handle proteotoxic and repair burdens. Testing combination therapies targeting

multiple nodes of this escape network will be critical, as inhibiting a single resistance mechanism is unlikely to be sufficient given the redundancy of stress-tolerance pathways. However, SETDB1 is a nuclear histone methyltransferase. A similar type of protein (SET1A, Hitpredict 175825) was identified to interact with PAPR1. Therefore, we focused on SETDB1 for in-vitro validation studies.

TCGA findings show SETDB1 and PARP1 dual expression independent of BRCA ½ status, and CCLE correlations hold across multiple PDAC lines against HRD signature. In BRCA wild-type tumors (90% of PDAC) where intact HR limits PARPi efficacy, SETDB1 inhibition could induce a BRCAness-like phenotype by damaging repair pathways and restoring apoptosis mechanism. BRCA-mutant cases such as POLO, where HR reversion drives resistance, SETDB1 therapies bypass reversion by directly activating death signaling, leading to longer progression-free survival beyond 7 months.

While the cross-cohort approach provides a robust discovery, single-cell RNA seq of PARPi-treated PDAC would reveal whether SETDB1 marks resistance or is dynamically induced under therapeutic pressures. In the future, genome-wide CRISPR screens in Olaparib-adapted PDAC models could rank all 19 genes by identifying dominant effectors like direct p53 repressors or other protection factors of SETDB1.Emerging evidence suggests that SETDB1-mediated epigenetic silencing contributes to PARPi resistance across multiple PDAC genotypes. By targeting SETDB1 in combination with PARP inhibition, this dual approach could restore synthetic lethality across both BRCA-mutant and BRCA-wildtype PDAC. In KRAS-mutant tumors — which constitute the majority of PDAC — co-targeting PARP and SETDB1 could convert a cytostatic PARPi response into genuine synthetic lethality by dismantling the chromatin-based apoptotic suppression that currently limits efficacy. The epigenetic silencing mediated by SETDB1 has been demonstrated in other malignancies to suppress cell death pathways through H3K9me3 deposition at pro-apoptotic gene promoters (Cao et al., 2020), suggesting a conserved mechanism of therapeutic resistance across cancer types.

The results of this study support our initial hypothesis that SETDB1 acts as a functional determinant of PARP1 inhibitor sensitivity. Through this inquiry, it was learned that the resistance observed in BRCA-wildtype PDAC is not merely a lack of targetable mutations, but is actively driven by SETDB1’s regulation of the apoptotic threshold. By studying these results, we discovered a previously uncharacterized link where SETDB1 co-expression effectively 'shields' cancer cells from the synthetic lethality typically induced by Olaparib. This confirms that

SETDB1 is not just a correlation found in data, but a biological driver of treatment failure. The POLO trial demonstrated improved progression-free survival (7.4 vs 3.8 months) but failed to show overall survival benefit (18.9 vs 18.1 months) in gBRCAm PDAC (Golan et al., 2019). This dissociation between radiographic response and survival benefit suggests that mechanisms beyond restoration of DNA repair contribute to resistance. Our finding that SETDB1 knockdown restores Olaparib sensitivity by lowering the apoptotic threshold provides a mechanistic rationale for combining SETDB1 inhibitors with PARP inhibition to achieve synthetic lethality across the broader PDAC population, including the 90% lacking BRCA mutations.

Unlike resistance mechanisms involving HR pathway restoration or metabolic reprogramming (Stoof et al., 2025), SETDB1-mediated resistance operates through transcriptional silencing. This epigenetic approach may be particularly relevant in KRAS-mutant, TP53-mutant PDAC, where chronic replication stress persists but apoptotic responses are suppressed. The availability of SETDB1 inhibitors such as EC-8042 (Federico et al., 2020) provides an immediate translational opportunity to test whether disrupting this chromatin-based resistance mechanism can restore PARPi efficacy in previously resistant populations. Ultimately, this research demonstrates that overcoming PARPi resistance requires a dual-target approach, moving beyond current clinical standards to address the epigenetic barriers identified in this study.

MATERIALS AND METHODS

2.1 Data Mining using cBioPortal

Patient transcriptomic datasets on clinical data were retrieved from the Cancer Genome Atlas (TCGA) and Queensland Centre for Medical Genomics (QCMG) from cBIOportal. The initial dataset included 19000 genes from TCGA and 16,500 genes from the QCMG cohort. Gene expression values normalized by RSEM (RNA-Seq by Expectation-Maximization) were used for all analyses. These data were grouped into PARP1 high-expression, low-high-expression, and low-expression groups. We selected the filter for PARP expression greater than or equal to 1or less than one, respectively. Subsequently, we conducted a comparative analysis between the PARP1 high and low groups to determine differentially expressed genes.

2.2 Venn diagram Analysis to identify common target genes

To isolate universal drivers of cancer resistance, we applied a cross-cohort method across two independent patient datasets. We first identified (FDR < 0.1) significantly upregulated genes in the PARP1 high group in both datasets. A Venn Diagram analysis was performed using Interactive Venn to identify the intersection of shared upregulated genes among both patient cohorts.

2.3 Pathway Analysis and Functional Clustering

We conducted Gene Set Enrichment Analysis (GSEA) and Database for Annotation, Visualization, and Integrated Discovery (DAVID) bioinformatic Gene Ontology (GO) analysis of the TCGA and QCMG cohorts. GSEA was used for a more sensitive functional class scoring analysis of the entire list of genes ranked by expression change. DAVID performs overrepresentation analysis on a specific list of genes with highly changed genes. DAVID was access at https://davidbioinformatics.nih.gov/

GSEA was performed using the GSEA app (v4.4.0) to analyze the shift in gene expression signatures driven by PARP1, patients were stratified into High and Low PARP1 expression groups using upper and lower quartile thresholds. Pre-ranked gene lists were generated by calculating the fold-change between these groups, representing a "High vs. Low PARP1" differential expression signature. This list was tested against the MSigDB Hallmark Gene Sets using 1,000 permutations to calculate the Normalized Enrichment Score (NES) and False Discovery Rate (FDR).

DAVID: Gene subsets were processed through functional annotation clustering to identify linked biological processes related to H3K9 methylation and the negative regulation of apoptosis. The nominal p-values were adjusted via the Benjamini-Hochberg procedure, as provided by the software.

2.4 Correlation analysis

Pearson's correlation analysis was performed between SETDB1 expression levels and Olaparib IC50 values retrieved from the Cancer Cell Line Encyclopedia (CCLE). Based on this silico trend, cell lines were selected for laboratory preparation to represent the “High setdb1/Resistance” sets.

2.5 Cell Culture

Human pancreatic cancer cell lines PANC-1, SU8686, and CAPAN-1 were maintained in T75 and T25 flasks in a humidified incubator with 5% CO2. Both cell lines were grown in Dulbecco's Modified Eagle Medium Nutrient Mixture F-12 Ham (1:1) (1X) (DMEM/F12 containing 10% FBS and 1% penicillin-streptomycin).

2.6 siRNA Transfection.

SETDB1 knockdown was achieved by reverse transfection of PANC-1 cells with siRNA targeting SETDB1 (siSETDB1) or a non-targeting scrambled control (siScr) using Lipofectamine RNAiMAX (Thermo Fisher Scientific) according to the manufacturer's protocol. Cells were seeded at 5,000 cells per well in 96-well plates simultaneously with the transfection complex. Knockdown efficiency was confirmed by western blot at 48 hours post-transfection prior to drug treatment.

2.7 Cell proliferation assay

A total of 5000 cells were seeded in each well of a 96-well plate. Cells were treated with the indicated inhibitors in triplicate while simultaneously adding 5uM Sytox green. Cell death/Sytox positive, green) cells were counted using the automated Cytation 1 system. *Cells were treated with Olaparib (Selleck hem, S1060) at the indicated doses.*

2.8 Cell lysate preparation

Cells were cleaned with 1 mL of PBS for 2 minutes, lysed, and then added RIPA buffer with DNase and Protease inhibitor cocktail, totaling 300µL per well Lysates were incubated on ice for 10 minutes, followed by 5 minutes at room temperature.

2.9 Western Blotting

The cells were trypsinized and lysed. Protein concentrations were determined using the Pierce BCA Protein assay kit and measured using the GloMax® Discover (Promega Instrument, Madison, WI) at 562 nm. Proteins were separated using sodium dodecyl Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). Samples were loaded in a precast 10-well plate, using 1X Tris-Glycine-SDS running buffer, and transferred to a nitrocellulose membrane. In each well, the concentration of loading samples was ~ 25 µg, and the gel was run for 1 hour at 100V. Western blotting transfer process from the gel to the nitrocellulose membrane using a

Bio-Rad Mini Trans-Blot® at 4°C for 1 hour, at 150V and 300mA. After transfer process, membrane is the cut to desired size and blocked in 1X TBSTween (TBST) containing 5% BSA buffer and membranes were incubated at 4°C overnight on a low-speed shaker with the following primary antibodies: anti-Poly (ADP-ribose) [PAR] #9542 monoclonal antibody (anti-PAR) at a 1:1000 dilution (Cell Signaling Technology,, GAPDH ((0411): sc-47724), PARP antibody (#9542) and (77G2) Rabbit mAB (1:500 dilution) (Cell Signaling, #9967). Remove and add the following secondary antibodies in a 1:5000 dilution: Anti-Rabbit and Anti-Mouse, with 1X TBST on the orbital shaker for 45 min at room temperature. Then wash with 1X TBST twice for 10 minutes each. The membrane was analyzed using an LI-COR imaging machine. Proteins were visualized.

Ethical declarations:

The study utilized publicly available cancer data set from the TCGA cohort via cBioPortal, which provides deidentified data. Therefore, separate IRBs were not utilized. All in-vitro experiments were conducted at Biosafety Level 1 (BSL-1) and followed standard environmental health and safety guidelines for the proper disposal of any research-related materials.

ACKNOWLEDGMENTS

Special thanks to Dr. Suhui Yang for her administrative support and advice throughout the project. The author also acknowledges the Division of Cancer Research and Training at CDU for the facilities used for *in vitro* validation and cell culture experiments.

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FIGURES AND TABLES

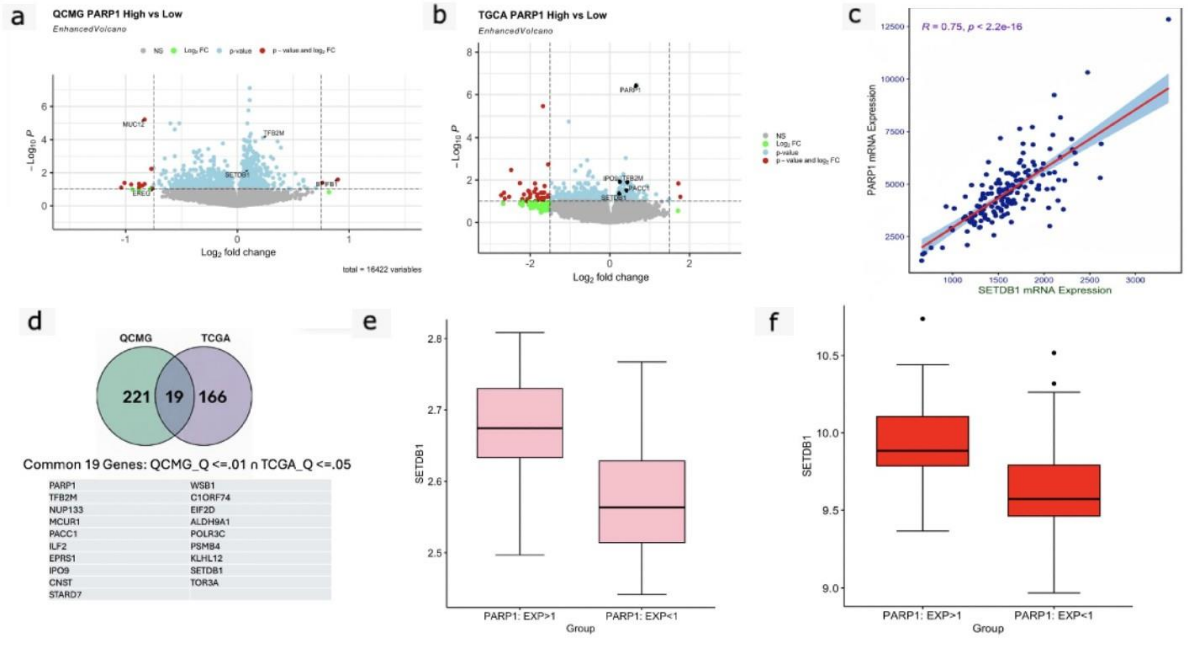


Figure 1. Identification of a conserved 19-gene “escape” signature in PDAC. Panels (a) and (b) show volcano plots of the upregulated genes in the QCMG and TCGA cohorts,

respectively. Panel (c) shows a strong correlation between PARP1 and SETDB1 (R=0.75). Panel (d) shows the intersection of 19 genes common to both datasets, including SETDB1. Panels (e) and (f) confirm SETDB1 is significantly higher in PARP1-high tumors.

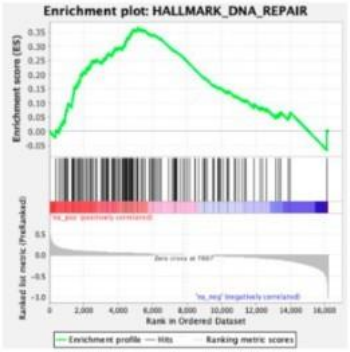
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NAME	SIZE	ES	NES	FDR q-val
HALLMARK_MYC_TARGETS_V1	200	0.51601017	2.450904	0
HALLMARK_OXIDATIVE_PHOSPHORYLATION	200	0.4643635	2.1849036	0
HALLMARK_ALLOGRAFT_REJECTION	199	0.42336252	1.9803206	0
HALLMARK_MYC_TARGETS_V2	58	0.4419108	1.6621479	0.0078863
HALLMARK_UNFOLDED_PROTEIN_RESPONSE	113	0.33887172	1.4421395	0.0395026
HALLMARK_DNA_REPAIR	150	0.31213403	1.4011837	0.04317686
HALLMARK_E2F_TARGETS	200	0.23325872	1.0598242	0.4281904
HALLMARK_REACTIVE_OXYGEN_SPECIES_PATHWAY	49	0.27922902	1.0347806	0.4425203
HALLMARK_SPERMATOGENESIS	131	0.21637964	0.9940273	0.5196206

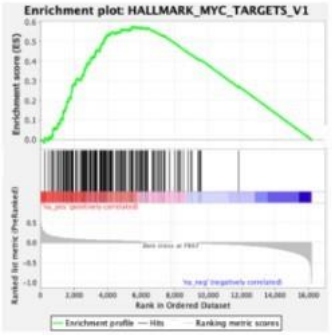
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NAME	SIZE	ES	NES	FDR Q-VAL
HALLMARK_MYC_TARGETS_V1	192	0.57735074	2.6920333	0
HALLMARK_E2F_TARGETS	198	0.5792187	2.5352132	0
HALLMARK_MYC_TARGETS_V2	55	0.66425234	2.4182541	0
HALLMARK_G2M_CHECKPOINT	197	0.5152239	2.3161461	0
HALLMARK_OXIDATIVE_PHOSPHORYLATION	196	0.4987612	2.210417	0
HALLMARK_MTORC1_SIGNALING	199	0.44173428	1.9941226	9.92E-04
HALLMARK_DNA_REPAIR	147	0.36558896	1.6263444	0.01468254
HALLMARK_CHOLESTEROL_HOMEOSTASIS	74	0.39231634	1.508774	0.03539186
HALLMARK_IL6_JAK_STAT3_SIGNALING	78	0.35536435	1.3735873	0.07164588

c



d



e



Figure 2. GSEA pathway enrichment results. Panels (a) and (b) present tables of the top Hallmark gene sets enriched in the TCGA and QCMG cohorts, ranked by Normalized Enrichment Score (NES) and False Discovery Rate (FDR). These tables list specific pathways, including MYC targets, DNA repair, and E2F targets, alongside their corresponding gene set sizes and statistical significance values. Panels (c), (d), and (e) show the individual GSEA enrichment plots for the DNA_REPAIR and MYC_TARGETS_V1 pathways. Each plot displays the running enrichment score (green line), the position of gene set members within the ranked list (black vertical bars), and the distribution of the ranking metric across the entire transcriptome (gray profile).

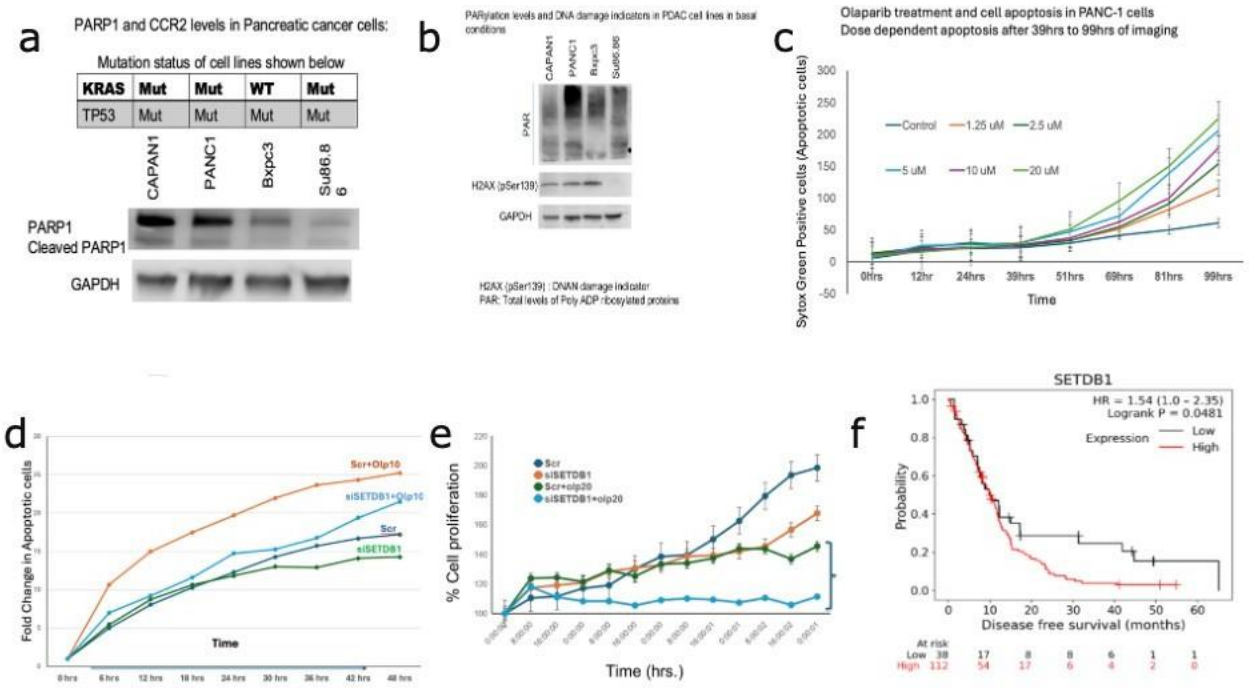


Figure 3. Laboratory validation and clinical survival analysis. (a) Western blot analysis displaying baseline protein levels of PARP1, Cleaved PARP1, and a GAPDH loading control across four pancreatic cancer cell lines (CAPAN1, PANC-1, Bxpc3, and Su86.86) alongside their KRAS and TP53 mutation status. (b) Immunoblotting results showing PARylation levels and H2AX (pSer139) DNA damage indicators in the same cell lines under basal conditions. (c) Line graph quantifying Sytox Green positive (apoptotic/stressed) cells over a 99-hour period following treatment with graded doses of Olaparib (1.25µM to 20µM) compared to a control. (d) Time-course analysis showing the fold change in apoptotic cells comparing Scrambled control (Scr), siSETDB1 knockdown, and combinations with Olaparib (Olp10). (e) Cell proliferation assay showing the percentage of cell growth over time for Scrambled control, siSETDB1, Olaparib alone (olp20), and the synergistic siSETDB1 + Olaparib combination. (f) Kaplan-Meier survival curve plotting the probability of disease-free survival in patients over 60 months, stratified by high (red) and low (black) SETDB1 expression, including a Hazard Ratio (HR) = 1.54, Logrank P = 0.0481.