Molecular correlates of DSCR1 expression in pancreatic cancer (PDAC)

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Introduction

- Down syndrome (DS), a genetic disorder caused by trisomy of chr 21, is associated with a considerably lower risk for solid tumors and other angiogenesis related diseases.
- *Down syndrome critical region gene 1* (*DSCR1*) belongs to a family of evolutionary conserved protein-coding genes located on chr 21 and is highly upregulated in DS patients. Its product, calcipressin-1, has been shown to reduce cancer risk by suppressing angiogenesis.
- High DSCR1 expression has been reported to decrease PDAC growth and metastasis in animal models.
- Here, we analyzed the molecular landscape and clinical outcomes associated with *DSCR1* gene expression in PDAC.

Methods

- A total of 8352 tumor samples tested at Caris Life Sciences (Phoenix, AZ) with whole-transcriptome sequencing (WTS, Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSEQ, WES) were analyzed.
- Top quartile transcripts per million (TPM) for *DSCR1* expression were considered high (Q4) while bottom quartile low (Q1).
- Cell infiltration (CI) in the tumor microenvironment (TME) was estimated by RNA deconvolution analysis using QuantiSEQ.
- Interferon-gamma and T-cell inflamed (TIS) signatures were also calculated from RNA data.
- X2 and Fisher-Exact tests were used, and statistical significance was determined as *P*-value adjusted for multiple comparisons ($q < 0.05$).
- Real world survival was obtained from insurance claims data (N = 4223) and Kaplan-Meier estimates were calculated.

Patient Demographic

DSCR1 Expression	Q1	Q4	P-value	q-value
Count (N)	2088	2088		
Median Age (range)	68 [13 - >89]	67 [26 - >89]	0.25	-
Male	53%	55%	0.29	-
Female	47%	45%	0.29	-

Results

Figure 1. *DSCR1* Expression According to Primary Tumor vs Metastases.

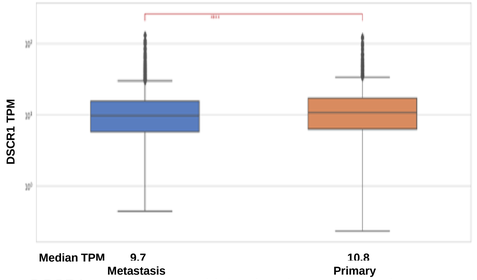
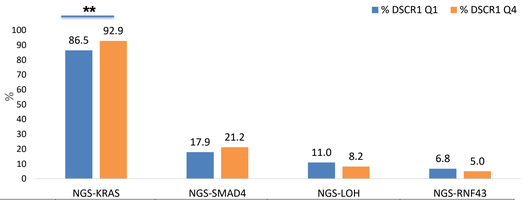


Figure 2. Association with Tumor Molecular Characteristics.



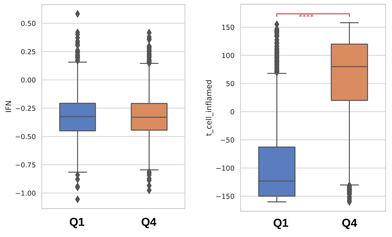
	NGS-KRAS	NGS-SMAD4	NGS-LOH	NGS-RNF43
p-value	**<0.0001**	**0.01**	**0.01**	**0.02**
q-value	**<0.0001**	0.44	0.44	0.61

- *DSCR1* expression was higher in primary tumors than metastases ($q < 0.05$).
- No significant differences were observed between high vs low DSCR1 PDAC in immune-related biomarkers (TMB, dMMR/MSI-H and PD-L1 protein), gene mutations and copy number alterations except for KRAS mutations which were more frequent in DSCR1 Q4 (93 vs 86%, Q4 vs Q1, q < 0.0001).

Figure 3. Association of *DSCR1* Expression with Pathway Enrichment, Immune-related Gene Expression, IFG and TIS Scores..

Pathway	ES	NES	P-value	FDR
HALLMARK_XENOBIOTIC_METABOLISM	-0.71	-1.27	0.034	0.14
HALLMARK_NOTCH_SIGNALING	-0.79	-1.26	0	0.15
HALLMARK_COAGULATION	-0.71	-1.26	0.034	0.15
HALLMARK_DNA_REPAIR	-0.79	-1.25	0	0.18
HALLMARK_INTERFERON_GAMMA_RESPONSE	-0.76	-1.21	0.037	0.18
HALLMARK_MYOGENESIS	-0.71	-1.27	0	0.19
HALLMARK_UV_RESPONSE_DN	-0.77	-1.22	0	0.19
HALLMARK_PROTEIN_SECRETION	-0.83	-1.24	0.032	0.20
HALLMARK_BILE_ACID_METABOLISM	-0.71	-1.20	0.037	0.21
HALLMARK_ADIPOGENESIS	-0.76	-1.23	0.033	0.22

- Gene set enrichment analysis showed that *DSCR1* high tumors were enriched in alterations of several pathways including NOTCH signaling, DNA repair, IFG response, myogenesis and adipogenesis (*P* < 0.05, false discovery rate < 0.25).
- *DSCR1* Q4 was associated with higher TIS score (50% inflamed vs 3.6%, $q < 0.05$) and positively associated with immune-related gene expression including *CTLA4*, *IDO1*, *CD80*, *PD-L1*, *LAG3*, *CD86*, *TIM3*, IFG, *PD-1*, and *PD-L2* (fold change: 2-4, $q < 0.0001$).



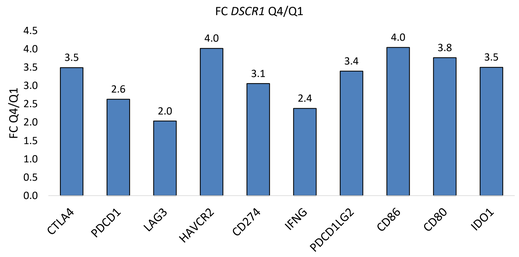
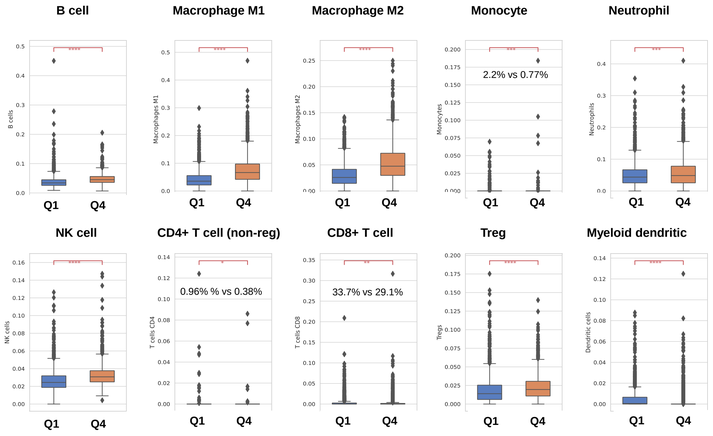
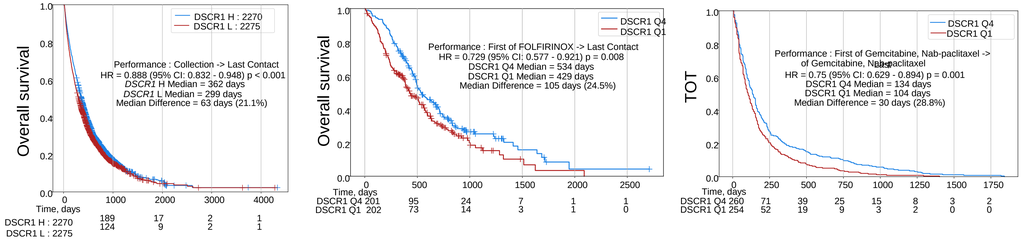


Figure 4. TME Cell Infiltration According to *DSCR1* Expression in pMMR/MSS Tumors.



- B cells, M1 and M2 macrophages, neutrophils, NK cells, and Tregs were more abundant in the TME of tumors with high *DSCR1,* whereas dendritic cells, CD4+ T cells and monocytes were lower ($q < 0.05$).

Figure 5. Association between Gene Expression and Patient Outcomes.



- Overall, *DSCR1* expression above median was associated with longer median OS (17 vs 11 months, HR 0.89 [0.83-0.95], $P < 0.0001$).
- When stratified by quartiles, *DSCR1* Q4 was associated with longer time on treatment [ToT] with gemcitabine/nab-paclitaxel (HR 0.75 [0.63-0.89], $P = 0.001$), and marginal benefit on ToT (HR 0.81 [0.65-1.0]) but longer survival in FOLFIRINOX treated patients (HR 0.73 [0.58-0.92], $P = 0.008$).

CONCLUSIONS

This is the first and most extensive profiling study to investigate DSCR1 expression in PDAC.
Our data show a strong association between tumor DSCR1 gene expression, several pathway alterations, immune-related gene expression, TME cell infiltration and patient survival.
These findings suggest DSCR1 as a candidate prognostic biomarker and as a potential treatment target in PDAC.