Characterization of the Cachexia Pathway in Pancreatic Ductal Adenocarcinoma

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Abstract ID: 699

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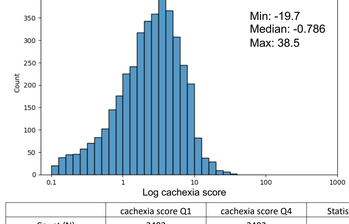
Introduction

- Cancer cachexia is characterized by progressive weight loss and skeletal muscle degradation, contributing to 33% of pancreatic ductal adenocarcinoma (PDAC) deaths.
- Novel therapeutics targets of myostatin in the myostatin-activin pathway have been shown to reverse cachexia.
- Here, we present a large clinical and molecular characterization of the myostatin-activin pathway in PDAC.

Methods

- 9,607 samples of PDAC tested at Caris Life Sciences (Phoenix, AZ) with WTS (Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSEQ, WES) were analyzed.
- Cachexia gene scores (GS) were calculated by averaging the positive z scores of activators and negative z scores of repressors in the myostatin-activin pathway.
- Activators were *ACVR1B*, *ACVR1C*, *ACVR2A*, *ACVR2B*, *SMAD2*, *SMAD3*, *SMAD4*, and *TGFBR1*, while repressors were *SMAD1*, *SMAD5*, *SMAD6*, *SMAD7*, *SMURF1*, and *SMURF2*.
- The top quartile (Q4) and bottom quartile (Q1) of GS were compared using chi-squared and Fisher-Exact tests.
- Gene expression was analyzed for T cell inflamed score as a predictor of immunotherapy response.
- Differences in overall survival (OS) were analyzed from insurance claims data and calculated from time of tissue collection using Kaplan-Meier estimates.
- Statistical significance was determined as a *P*-value adjusted for multiple comparisons (q<0.05).

Distribution and Demographic



Activators	Repressors
ACVR2B	SMAD6
ACVR2A	SMAD7
ACVR2A	SMURF1
ACVR1B	SMURF2
TGFBR1	SMAD1
ACVR1C	SMAD5
SMAD2	
SMAD3	
SMAD4	

	cachexia score Q1	cachexia score Q4	Statistic	p-value	q-value
Count (N)	2402	2402			
Median Age [range] (N)	68 [23 - 89] (2402)	67 [17 - 89] (2402)	Mann-Whitney U	0.698	0.698
Median TMB [range] (N)	3.0 [0.0 - 37.0] (2118)	3.0 [0.0 - 47.0] (2124)	Mann-Whitney U	0.245	0.310
Male	51.5% (1237/2402)	53.2% (1277/2402)	chi-square	0.2479	0.310
Female	48.5% (1165/2402)	46.8% (1125/2402)	chi-square	0.248	0.310

Results

Figure 1: Immune related markers.

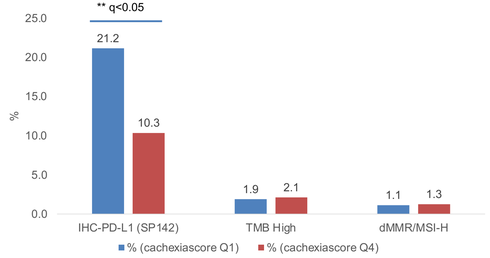
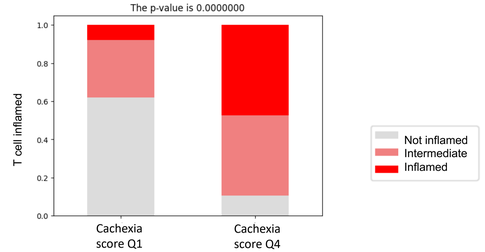
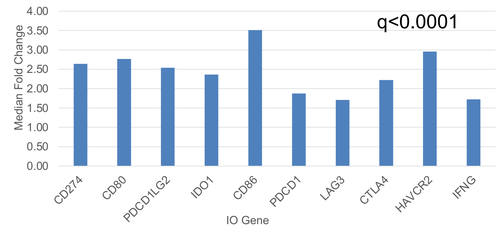


Figure 2: T-Cell Inflamed Score.



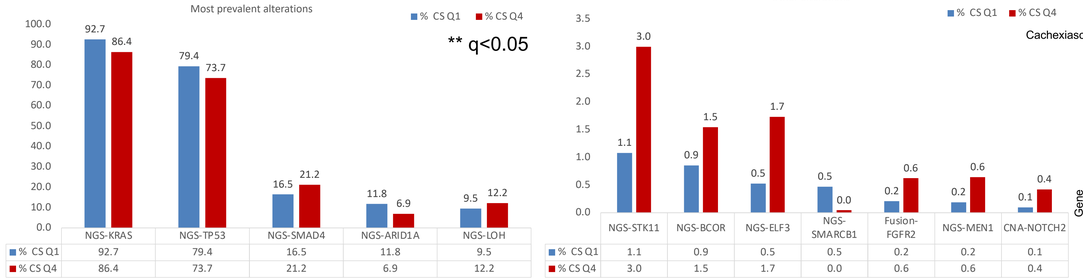
GS were higher in primary tumors compared to metastases (median: -0.71 vs -0.86, q<0.05). GS was associated with increased PD-L1 IHC expression (Q1 21.2% vs Q4 10.3%) [Figure 1] and T-Cell inflamed score[Figure 2] (all q<0.0001), but not TMB-high (1.9% vs 2.1%, q=1) or MSI-H status (1.1% vs 1.3%, q=1).

Figure 3: Immune-Related Gene Expression.



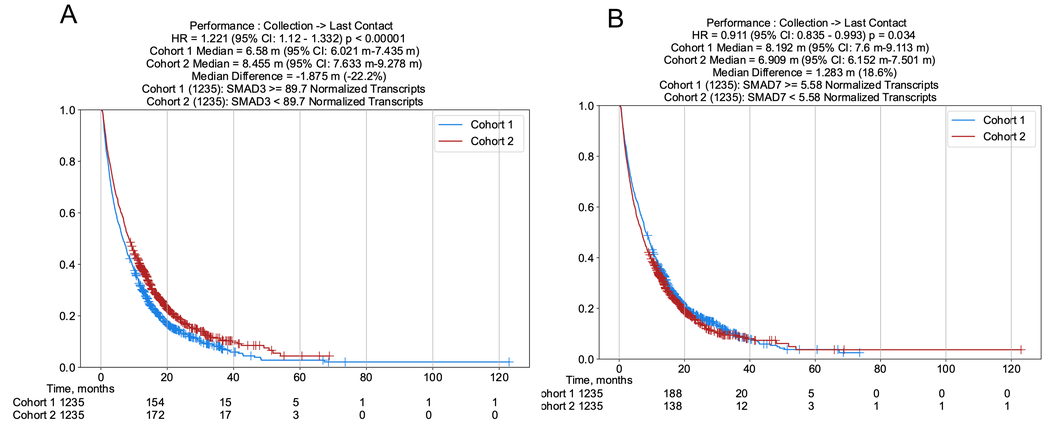
GS correlated with increased expression of immune related genes (*CD274*, *CD80*, *IDO1*, *CD86*, *PDCD1*, *LAG3*, *CTLA4*, *HAVCR2*, and *IFNG*, q<0.0001)[Figure 3] but TME immune cell infiltration did not vary.

Figure 4: Tumor Molecular Characteristics According to GS.



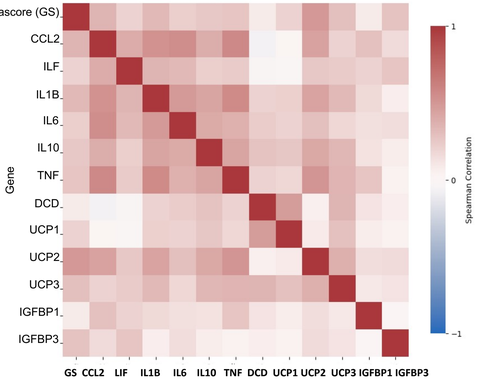
Mutation rates of *TP53* (Q1 79.4% vs Q4 73.7%), *ARID1A* (Q1 11.8% vs Q4 6.9%) and *KRAS* (Q1 92.7% vs Q4 86.4%) were associated with Q1-GS (all q<0.01), while *STK11 mutations* (1.1% vs 3.0%, q=0.001) were associated with Q4-GS. [Figure 4]

Figure 5: OS of Metastatic PDAC by Myostatin Activin Genes: A) *SMAD3* B) *SMAD7*.



Decreased OS was seen with higher tumor expression of myostatin activin pathway activators, *SMAD3* (6.6 vs 8.5 mo, HR=1.22, CI 1.12-1.33, *P*<0.0001), and lower expression of the repressor *SMAD7* (6.9 vs 8.2 mo, HR=0.91, CI 0.84-0.99, *P*=0.034). [Figure 5]

Figure 6: Correlation of GS with inflammatory or metabolic gene expression.



Inflammatory:	Lipid metabolism/lipolysis:	Insulin resistance:	Proteolysis:
monocyte chemoattractant protein 1 (CCL2/ MCP-1)	Uncoupling protein 1 (UCP1)	insulin growth factor binding protein 1 (IGFBP1)	Proteolysis-inducing factor (DCD/PIF)
Leukemia inhibitory factor (LIF)	Uncoupling protein 2 (UCP2)	insulin growth factor binding protein 3 (IGFBP3)	
Interleukin 1 Beta (IL1B)	Uncoupling protein 3 (UCP3)		
Interleukin 6 (IL6)			
Interleukin 8 (IL8)			
Interleukin 10 (IL-10)			
Tumor necrosis factor (TNF)			

Spearman correlation linked cachexia GS with the lipid metabolizing genes *UCP2* (rho=0.49) and *UCP3* (rho=0.30), as well as the inflammatory markers *CCL2/MCP-1*(rho=0.34) and *IL1B* (rho=0.33). [Figure 6]

CONCLUSIONS

This is the largest molecular and clinical characterization of the myostatin activin cachexia pathway in PDAC. Our data shows that increased activation of the myostatin activin pathway is associated with immune mediators, lipid metabolism, and inflammatory gene activation. Activators and repressors are significant predictors of survival in PDAC, suggesting possible novel therapeutic targets.