Molecular correlates of DSCR1 expression in pancreatic cancer (PDAC)

Francesca Battaglini*, Yasmine Baca*, Joanne Xiu†, Phil Walker‡, Shivani Soni§, Jae Ho Lo†, Jingyang Wang†, Sandra Algaze†, Priya Jayachandran†, Pooja Mittal*, Leslie Torres-Gonzalez†, Wu Zhang†, Richard M. Goldberg*, Benjamin A. Weinberg*, Emil Lou*, Anthony F. Shields*, John L. Marshall*, Sanjay Goel‡, Fariborz Nasertorabi‡, Heinz-Josef Lenz†

1 Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA. 2 Carsi Life Sciences, Phoenix, AZ. 3 West Virginia University Cancer Institute, Morgantown, WV. 4 Rush University Medical Center. 5 The University of Chicago, Chicago, IL. 6 University of California, San Francisco, CA. 7 University of California, Los Angeles, CA. 8 University of Southern California, Los Angeles, CA.

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 anogenitalis related diseases.
• Down syndrome critical region gene 1 (DSCR1) belongs to a family of evolutionarily conserved protein-coding genes located on chr 21 and is highly upregulated in DS patients.
• Its product, calpilipin-1, has been shown to reduce cancer risk by suppressing angiogenesis.
• High DSCR1 expression has been reported to decrease 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 Carsi Life Sciences (Phoenix, AZ) with whole-transcriptome sequencing (WTS, Illuma NovaSeq) and NextSeq DNA sequencing (NextSeq 500, San Diego, CA) were analyzed.
• Top quintile 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 (TIF) 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.

Results

• 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, MMR/MSI-H and PD-L1 protein), gene expression and copy number alterations except for KRAS mutations which were more frequent in DSCR1 Q4 (95 vs 86%, q < 0.001).

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

• 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 was associated with higher TIS score (60% inflamed vs 36%, q = 0.05) and positively associated with immune-related gene expression including CTLA-4, CD103, 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 MPM/MS tumors.

• B cells, Mf and M2 macrophages, neutrophils, NK, CD8, 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).

CONCLUSIONS

This is the first and most extensive profiling study to investigate DSCR1 expression in PDAC. Our data show a strong association between 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.