GDF15 Expression in Metastatic Colorectal Cancer (CRC)

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Background

- Cachexia affects many cancer patients.
- Growth differentiation factor-15 (GDF15) is a protein that regulates weight and the stress response of cells.
- The GDF15 gene encodes a ligand of TGF-beta that triggers cachexia and modulates the progression from tumorigenesis to metastasis.
- Inhibition of GDF15 with an antibody restored muscle mass and fat in animal models.
- Serum levels rise in proportion to the progression of colon cancer, predict outcome, and have been correlated with CEA.

The Multiple Roles of GDF-15 in CRC

Promotes cell migration and invasion in vitro
- In CRC promotes epithelial to mesenchymal transition via TGFB and Smad2/3
- Upregulates expression of N-cadherin, vimentin and Twist1. Downregulates E-cadherin
- Activates c-Fos by separating it from Lamin A/C, increasing transcriptional activity of c-Fos and regulating EMT gene expression

Promotes metastasis in vivo
- Activated PERK-eIF2α signaling promotes GDF15 transcription
- Hypoxia-induced GDF15 expression promotes the mitochondrial oxidation of fatty acids in colorectal cancer cells. Supression of GDF15 results in smaller xenograft tumors and impaired metastasis in animal models
- GDF15 is expressed much more in tumor tissues of CRC patients and displays positive correlations with CHOP and HIF1α in mRNA levels

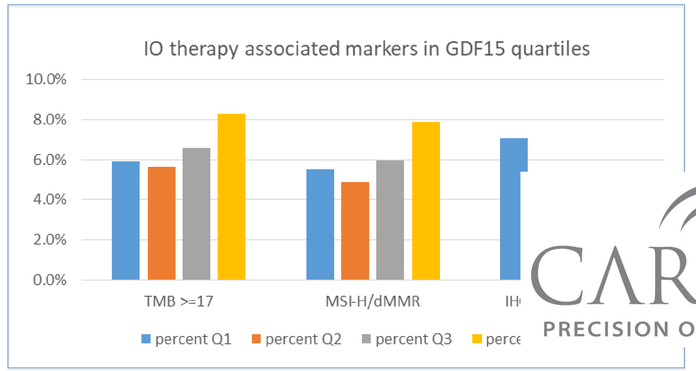
Increased GDF-15 levels in the serum correlate with disease progression and decreased survival
- A novel biomarker
- Comparable to CEA in CRC – more sensitive to detect hepatic metastasis

Methods

- We retrospectively reviewed 7607 CRC tumors profiled by Caris Life Sciences (Phoenix, AZ) from 2019 to 2020.
- Profiling included whole transcriptome sequencing (RNA-Seq by NovoSeq).
- Tumor mutational burden, mismatch repair status, and pathway genomic alterations were evaluated.
- QuantiSEQ was used to assess immune cell infiltration in the tumor microenvironment.

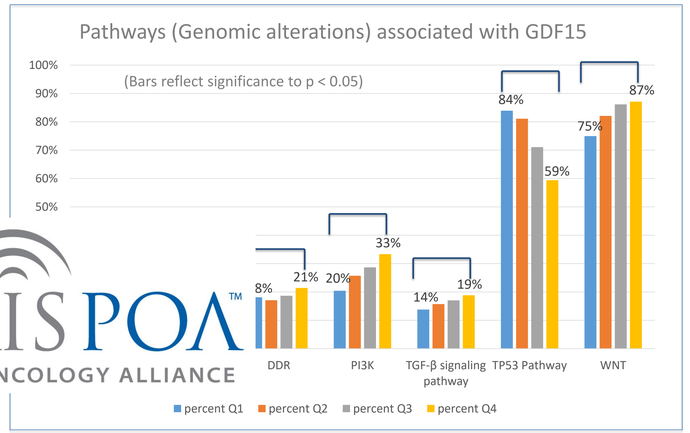
Results

- GDF15 expression ranged from 0 to 593 transcripts per million (TPM) with median of 30 (IQR=15.02). There was no association with age, sex, or primary tumor sidedness.
- MSI-H/dMMR tumors had higher GDF15 expression (median 37 vs 30, p=0.0004); TMB>=17 tumors was seen in 5.9% of bottom quartile (Q1) GDF15 expressors and 8.3% of top quartile (Q4).
- PDL1 IHC positivity was inversely correlated with GDF15 expression (7.1% in Q1 vs. 2.6% in Q4, p<0.0001).
- Genomic alterations associated with higher GDF15 expression (Q4 vs Q1) included genes on TGF-B (SMAD2/4), PI3K (PIK3CA, MTOR), chromatin remodeling (ARID1A, KMT2C), DDR (ATM) and Wnt pathway (APC); those inversely associated included MYC CNA and TP53. Q1 tumors had higher CNA of ERBB2 and FGFR1.
- Relative neutrophils and NK cells in the TME increased from Q1 to Q4 (p<0.001).
- There was a decrease in CD8+ T-cells and Treg cells from Q1 to Q4.

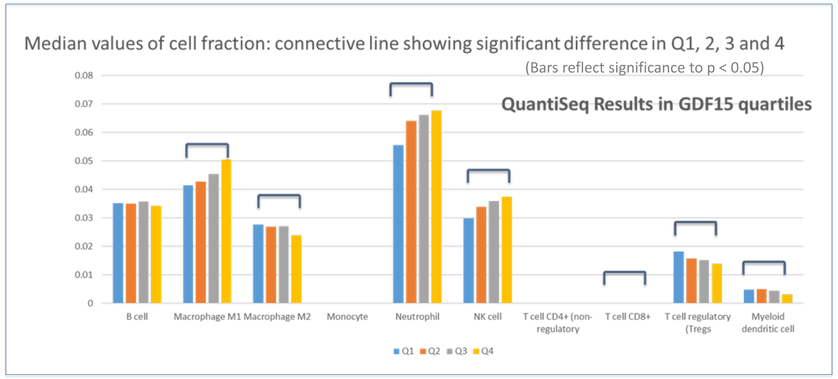


Strong positive association with MSI-H/dMMR and TMB>17.

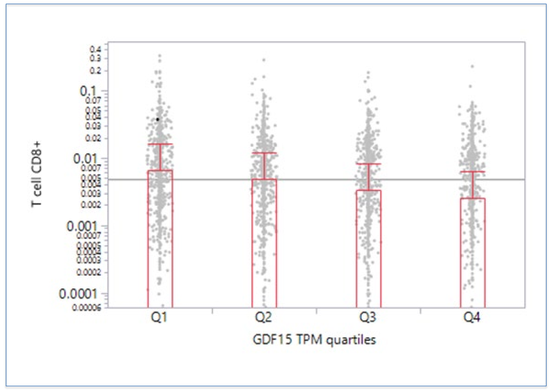
Strong negative association with PDL1.



Positive association with TGFbeta, Wnt→ immune suppression



Inverse association with T-cell infiltration



Significant difference in CD8+ T cells in GDF15 quartiles

Conclusions

- **GDF15 expression correlates with increased dMMR/MSI-H and TMB, but not with PDL1 expression.**
- **GDF15 is associated with chromatin remodeling which may warrant therapies targeting histone modification and epigenetics.**
- **GDF15 expression is associated with increase in NK cells but decrease in CD8+ T cells in the TME.**
- **The decrease in CD8+ T cells and PDL1 positivity with rising GDF15 suggests worse outcome and a lack of response to anti-PDL1 therapy.**
- **High GDF15 expressing tumors may benefit from immune treatment strategies.**
- **Understanding GDF15 regulation and expression in metastatic colon cancer may reveal which patients could benefit from developing anti-GDF15 targeted therapies against cancer progression.**

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