Claudin 18 (*CLDN18*) gene expression and related molecular profile in gastric cancer (GC)

Annika Lenz[1], Jia Zeng[2], Joanne Xiu[2], Sandra Algaze[1], Priya Jayachandran[1], Shivani Soni[1], Jae Ho Lo[1], Hiroyuki Arai[1], Wu Zhang[1], Pavel Brodskiy[2], Peter Hosein[7], Benjamin A. Weinberg[3], Emil Lou[4], Anthony F. Shields[5], Richard M. Goldberg[6], John L. Marshall[3], W. Michael Korn[2], Heinz-Josef Lenz[1], Francesca Battaglin[1], Evanthia Roussos-Torres[1]

1 Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA 2 Caris Life Sciences, Phoenix, AZ, USA 3 Ruesch Center for The Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA 4 Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, USA 5 Department of Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA 6 West Virginia University Cancer Institute, Morgantown, WV, USA7 University of Miami, Miami, FL, USA

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fbattagl@usc.edu

Introduction

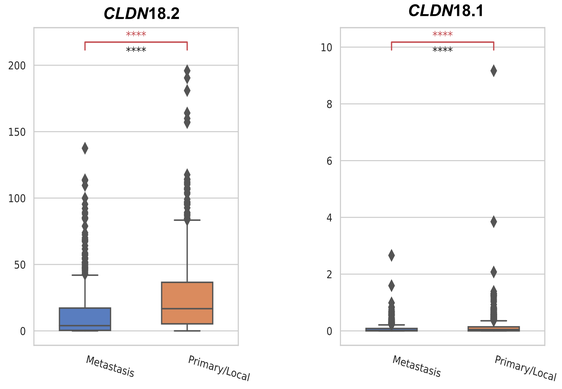
- Claudins are transmembrane proteins which maintain the tight junction between cells.
- The stomach specific isoform, CLDN18 isoform 2 (CLDN18.2), is emerging as a promising treatment target because of high expression in GC cells, including targeting via adoptive T-cell strategies for gastric cancer immunotherapy treatments
- Previous clinical trials using antibodies targeting *CLDN18.2* have demonstrated promising results with improved survival in *CLDN18.2*-expressing patients compared to those who only received chemotherapy.
- We characterized the molecular features associated with CLDN18 isoform 1 and 2 (*CLDN18.1/18.2*) gene expression in GC.
- We tested whether tumor expressing high levels of *CLDN18.1/18.2* display distinct molecular features, exhibit specific tumor immune biomarkers, and reveal trends with levels of immune cells in the tumor microenvironment (TME) in comparison to low expressing tumors.

Methods

- A total of 1967 CRC tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (Illumina Next Seq, 592 genes, or Illumina NovaSeq, WES) and RNA (Illumina NovaSeq, WTS) were analyzed.
- Top quartile transcripts per million (TPMs) for *CLDN18.1/18.2* expression were considered high (Q4) while bottom quartile low (Q1) expression.
- EBER (Epstein Barr Virus) was tested by CISH.
- Cell infiltration in the tumor microenvironment (TME) was estimated by quanTIseq.
- Gene expression profiles were analyzed for a transcriptional signature predictive of response to immunotherapy (T cell-inflamed signature, TIS).
- X^2, Fisher-exact, and Mann Whitney U tests were used and significance adjusted for multiple testing by Benjamini-Hochberg (q < .05).

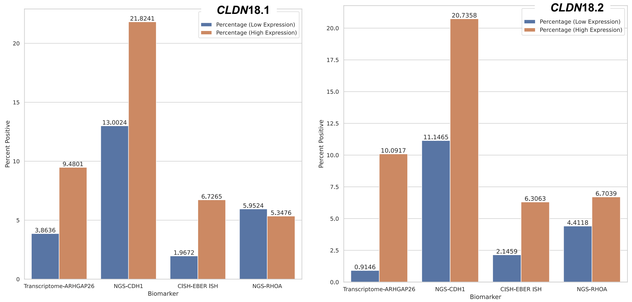
Results

Figure 1. *CLDN*18.1 and 18.2 Expression between Primary Tumors vs Metastatic Sites.



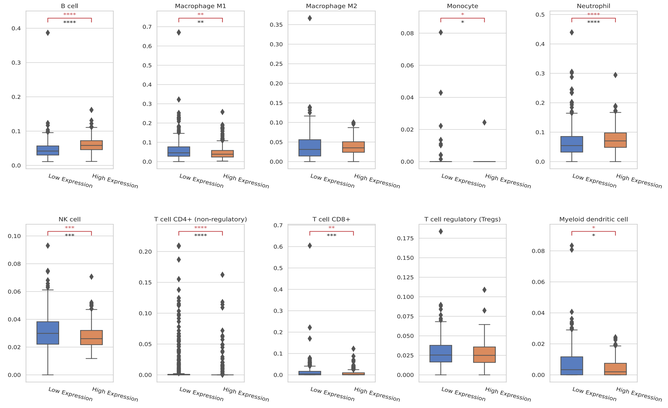
Primary tumors had significantly higher expression levels of both *CLDN18.1/18.2* (Fold Change *18.1*: 0.50; *18.2*: 0.65), compared to metastatic tumors ($p < .05$). *CLDN18.2* expression was detected in 97% of the samples and *CLDN18.1* in 63%.

Figure 2. Primary *CLDN*18.1 and 18.2 Low and High Expression in relation to Genomic Alteration Markers.



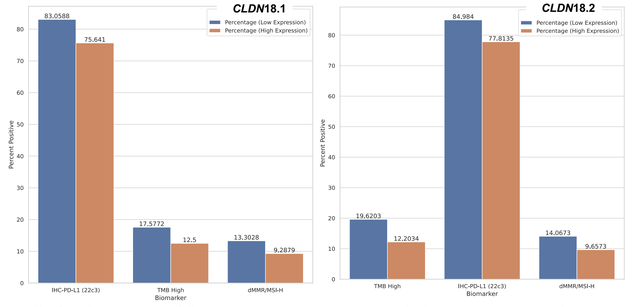
CLDN18.1 and 18.2 high expression group had trending association with *CDH1* mutation and EBER ($p < .05$, $q > .05$).

Figure 3. Primary CLDN18.2 Low and High Expression in relation to TME quanTIseq.



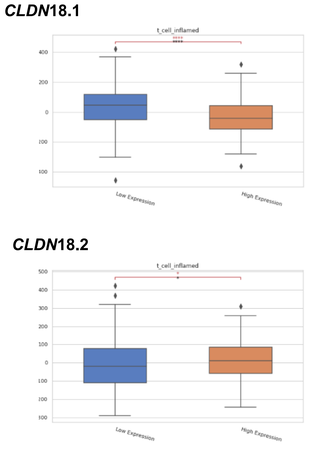
CLDN18.1/18.2 displayed an inverse relationship with M1 Macrophages, NK cells, CD4+ T cells, myeloid dendritic cells in the TME ($q < .05$). Higher *CLDN18* expression was associated with fewer immune cells and a colder TME, especially in isoform 2.

Figure 4. Primary *CLDN*18.1 and 18.2 Low and High Expression in relation to Immuno-Oncology Markers.



CLDN18.1 and *18.2* high expression demonstrated an inverse trending correlation with PD-L1 and TMB-H ($p < .05$; $q > .05$).

Figure 5. Association between *CLDN* Expression and TIS Score .



The TIS score was significantly higher in the *CLDN18.2* high expression group ($q < .05$), but lower in *CLDN18.1* high expression group ($q < .0001$), respectively.

Figure 6. ARHGAP26 Fusions in *CLDN*18.2

A. High Group

Gene1	Gene2	Exon1	Exon2	count
CLDN18	ARHGAP26	exon 4	exon 11	2
CLDN18	ARHGAP26	exon 5	exon 10	5
CLDN18	**ARHGAP26**	**exon 5**	**exon 12**	**19**
CLDN18	ARHGAP26	exon 5	exon 8	1
CTNND1	ARHGAP26	exon 15	exon 12	1
CTNND1	ARHGAP26	exon 16	exon 13	1
OCLN	ARHGAP26	exon 4	exon 12	4

B. Low Group

Gene1	Gene2	Exon1	Exon2	Count
CLDN18	ARHGAP26	exon 5	exon 12	3

CLDN18.2 high expression group had higher CLDN18:*ARHGAP26* fusion positive rate (low vs high: 0.91% vs 5.5%, $q < .0001$). The most common fusion between *CLDN18* exon 5 and *ARHGAP26* exon 12.

CONCLUSIONS

Tumors expressing high *CLDN18*, especially 18.2, displayed distinct genomic and transcriptomic alterations in immune biomarkers and immune cell infiltration in the TME.

Anti-CLDN18.2 monoclonal antibodies are being tested in GC and CLDN18 is a target for ADC and CAR-T therapies, our data suggest that expression may play a role in guiding patient selection and treatment combinations.