14 CLAUDIN-6 AFFECTS THE CELL CYCLE AND P53 SIGNALING IN GASTRIC CANCER

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Background Claudin-6 (CLDN6) differentially overexpressed in Gastric Cancer (GC) is associated with poor prognosis and survival of patients. Uncovering affected pathways and genes associated with CLDN6 in GC can help in the identification of novel prognostic targets.

Methods CBioPortal^{1,2} was used to extract and analyze The Cancer Genome Atlas (TCGA) Stomach Adenocarcinoma Pan-Cancer Atlas Data (STAD). FunRich tool³ and Gene Ontology molecular signature database of Gene Set Enrichment Analysis (GSEA) were used for functional enrichment. CBioPortal was used to identify differentially expressed genes between groups. Graph pad Prism 8 was used to generate the graphics.

Results TCGA STAD PanCancer Atlas data was analyzed in terms of alterations in CLDN6. 34% of the GC samples (141 samples) were assigned to the CLDN6 alteration group while the rest of the samples (299) were assigned to the non-CLDN6 alteration group (figure 1). Major alterations of CLDN6 in GC included shallow deletion, diploid, gain, and differentially expressed mRNA (figure 2). Differentially overexpressed genes in the CLDN6 group with log-ratio cutoff ≥ 1 were used for functional enrichment in different biological pathway categories (figure 3); 18.1% of genes were associated with the transport of small molecules through the membrane, 14.6% mediated transmembrane transport and 12.5% were associated with lipid metabolism (figure 4). The Gene ontology molecular signature database of GSEA also confirmed that these genes were involved in lipid metabolism, transport activity, and epithelium development processes (table 1). Moreover, GC samples with CLDN6 alterations have higher mutations in p53 signaling (29% in TP53, 7% in CDKN2A) gene signature (figure 5) over samples in the non-CLDN6 alteration group (figure 6). Similarly, genes related with cell cycle control like CCNE1, MYC, SRC, and STAT3 showed higher mutations in the CLDN6 alteration group while JAK1 and E2F8 showed lower mutations than non-CLDN6 GC samples (figure 7). These observations indicate that CLDN6 in GC affects the transport of small molecules and lipid metabolism and that it is associated to tumors with higher mutations in p53 and cell cycle-related genes.

Abstract 14 Table 1 Functional enrichment of differentially expressed genes (log-ratio ≥ 1) in CLDN6 group GC samples in Gene ontology molecular signature database of GSEA

Gene Set Name [# Genes (K)]	# Genes in Overlap (k)	p-value	FDR q-value
GOBP EPITHELIUM DEVELOPMENT [1275]	60	9.32 e ⁻²¹	9.49 e ⁻¹⁷
GOCC APICAL PLASMA MEMBRANE [351]	31	1.33 e ⁻¹⁸	6.76 e ⁻¹⁵
GOCC APICAL PART OF CELL [414]	33	2.25 e ⁻¹⁸	7.66 e ⁻¹⁵
GOCC CLUSTER OF ACTIN BASED CELL PROJECTIONS [156]	22	6.87 e ⁻¹⁸	1.75 e ⁻¹⁴
GOMF TRANSPORTER ACTIVITY [1168]	52	4.5 e ⁻¹⁷	9.16 e ⁻¹⁴
GOBP LIPID METABOLIC PROCESS [1426]	57	1.49 e ⁻¹⁶	2.54 e ⁻¹³
GOCC BLOOD MICROPARTICLE [146]	20	3.93 e ⁻¹⁶	5.72 e ⁻¹³
GOCC BRUSH BORDER [101]	17	1.88 e ⁻¹⁵	2.4 e ⁻¹²
GOCC PLASMA MEMBRANE REGION [1208]	50	3.32 e ⁻¹⁵	3.36 e ⁻¹²
GOBP EMBRYO DEVELOPMENT [992]	45	3.43 e ⁻¹⁵	3.36 e ⁻¹²

Abstract 14 Figure 1 Distribution of GC samples and patients of TCGA STAD data between CLDN6 and non CLDN6 alteration groups

Abstract 14 Figure 2 Major alterations in CLDN6 in GC (TCGA STAD data)

Abstract 14 Figure 3 Volcano plot of differentially expressed genes in CLDN6 and non CLDN6 groups. Log10 p-Value cutoff ≥ 2