Prevalence of Claudin18.2 and PD-L1 Expression in Chinese Gastric/Gastroesophageal Junction Adenocarcinoma

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ABSTRACT

Background: Claudin18.2 (CLDN18.2), a tight junction protein highly specific to gastric mucosa, is a promising target for gastric cancer treatment[1]. Immunotherapy targeting PD-1 combined with chemotherapy has been approved as the first line treatment of gastric/gastroesophageal junction (G/GEJ) adenocarcinoma[2]. Understanding the expression profiles of CLDN18.2 and PD-L1 could offer guidance for the development of combination therapies that maximize the benefits of both agents. This study investigated the prevalence of CLDN18.2 expression from surgical resections of G/GEJ adenocarcinoma at diagnosis and its correlation with PD-L1 expression in Chinese patients.

Methods: Expression of CLDN18.2 in formalin-fixed, paraffin-embedded (FFPE) G/GEJ adenocarcinoma tissue samples was detected by immunohistochemistry (IHC) using an in-house anti-CLDN18.2 antibody (Clone14G11) on the Leica Bond III IHC stainer. Both the staining intensity (0: no visible tumor cell membrane staining; 1+: clearly visible membrane staining at 20x; 2+: clearly visible membrane staining at 10x; 3+: clearly visible membrane staining at 4x) and the percentage of positive tumor cells were evaluated. CLDN18.2 positivity was defined as expression of CLDN18.2 in ≥ 10% tumor cells with intensity ≥ 1+. Samples with moderate-to-strong CLDN18.2 membrane staining (intensity ≥ 2+) in ≥ 40% and in ≥ 70% tumor cells were also analyzed. PD-L1 expression was assessed based on combined positive score (CPS) using Agilent's PD-L1 IHC 28-8 pharmDx.

Results: A total of 300 G/GEJ resected adenocarcinoma tissue samples were assessed, 89 (30%) were histologically classified as intestinal, 158 (52%) diffuse, 33 (11%) mixed, and 20 (7%) others. 295 (98%, 286 GC, 9 GEJ) samples were from primary site, 5 (2%) samples were from metastatic site (ovary, lymph node, omentum or left adnexa). CLDN18.2 staining was positive in 216 (72%), and negative in 84 (28%) of the tissue samples. 136 (45%) samples showed moderate-to-strong CLDN18.2 membrane staining in ≥ 40% tumor cells, 79 (26%) samples showed moderate-to-strong CLDN18.2 membrane staining in ≥ 70% tumor cells. CLDN18.2 positivity prevalence was 75% (n = 119/158) in diffuse and 61% (n=54/89) in intestinal subtypes. Moderate-to-strong CLDN18.2 membrane staining in ≥ 40% tumor cells and in ≥ 70% tumor cells were observed in 48% (n=76/158), 30% (47/158) diffuse subtypes, and in 39% (n=35/89), 21% (19/89) intestinal subtypes respectively. For PD-L1 expression, 51 (17%) had PD-L1 CPS ≥ 5. 19% (n=41/216) of the CLDN18.2 positive samples also showed PD-L1 CPS ≥ 5. In the CLDN18.2 subgroups with moderate-to-strong CLDN18.2 membrane staining in ≥ 40% tumor cells and in ≥ 70% tumor cells, 21% (n=28/136), 18% (n=14/79) had PD-L1 CPS ≥ 5. The distribution of CLDN18.2 expression is independent of PD-L1 status.

Conclusions: High prevalence of CLDN18.2 expression in Chinese patients with G/GEJ adenocarcinoma was observed. About 80% CLDN18.2 positive tumors had PD-L1 CPS < 5. These results support the value of CLDN18.2-targeted therapy in gastric cancer, especially for those patients who may not benefit from anti-PD-1/PD-L1 immuno-checkpoint therapy.

Clinicopathological Features by CLDN18.2 Status

Characteristic	N (%)	CLDN18.2 ≥10%/≥1+	CLDN18.2 <10%/≥1+	*P*	CLDN18.2 ≥40%/≥2+	CLDN18.2 <40%/≥2+	*P*	CLDN18.2 ≥70%/≥2+	CLDN18.2 <70%/≥2+	*p*
All samples	300 (100%)	216 (72%)	84 (28%)	--	136 (45%)	164 (55%)	--	79 (26%)	221 (74%)	--
Location[1]				--			--			--
Stomach	286 (95%)	207 (72%)	79 (28%)	--	130 (45%)	156 (55%)	--	77 (27%)	209 (73%)	--
GEJ	9 (3%)	5 (56%)	4 (44%)	--	3 (33%)	6 (67%)	--	1 (11%)	8 (89%)	--
Lauren classification				0.016*			0.183			0.152
Diffuse	158 (52%)	119 (75%)	39 (25%)		76 (48%)	82 (52%)		47 (30%)	111 (70%)	
Intestinal	89 (30%)	54 (61%)	35 (39%)		35 (39%)	54 (61%)		19 (21%)	70 (79%)	
Mixed	33 (11%)	30 (91%)	3 (9%)	--	21 (64%)	12 (36%)	--	12 (36%)	21 (64%)	--
Others	20 (7%)	13 (65%)	7 (35%)	--	4 (20%)	16 (80%)	--	1 (5%)	19 (95%)	--
PD-L1 status				0.143			0.132			0.842
CPS≥5	51 (17%)	41 (80%)	10 (20%)		28 (55%)	23 (45%)		14 (27%)	37 (73%)	
CPS<5	249 (83%)	175 (70%)	74 (30%)		108 (43%)	141 (57%)		65 (26%)	184 (74%)	

Table 1. Correlation between CLDN18.2 expression and clinicopathological features. [1] 5 samples from metastatic site (ovary, lymph node, omentum or left adnexa) were not included. *represent for *p*<0.05, significant.

CLDN18.2 and PD-L1 Expression in Cases

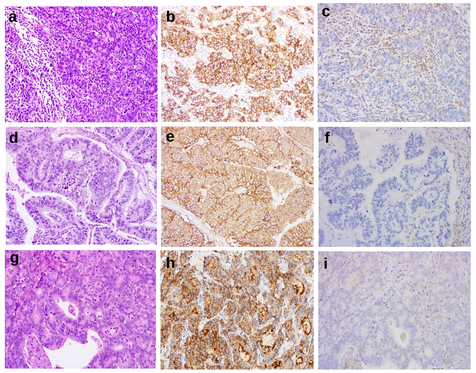

Figure 1. Representative images of CLDN18.2 (b, e, h) and PD-L1 (c, f, i) expression in gastric cancer cases with different histological types. Hematoxylin-eosin staining (a, d, g). F0210112006, gastric cancer with diffuse type (a, b, c), 100% tumor cells with CLDN18.2 staining ≥1+, PD-L1 CPS=35. F0210112004, gastric cancer with intestinal type (d, e, f), 35% tumor cells with CLDN18.2 staining ≥1+, PD-L1 CPS=2. F0210112008, gastric cancer with mixed type (g, h, i), 95% tumor cells with CLDN18.2 staining ≥1+, PD-L1 CPS=2. Original magnification 200x (a–i).

CLDN18.2 Scoring in Gastric Cancer

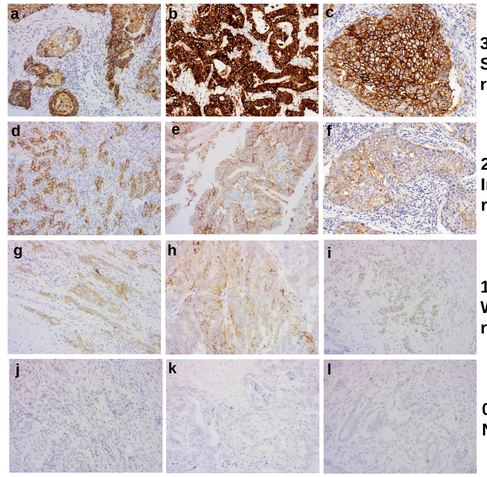

Figure 2. a–l Representative images of CLDN18.2 expression in gastric cancer cells with different histological types: diffuse (a, d, g, j), intestinal (b, e, h, k), and mixed (c, f, i, l). Membrane staining of tumor cells was scored as 3+/ strong (a–c), 2+/ intermediate (d–f), 1+/ weak (g–i), or 0/ none (j–l). Original magnification 200x (a–l).

CONCLUSIONS

- We have set up CLDN18.2 IHC assay using an in-house anti-CLDN18.2 antibody (Clone14G11) on the Leica Bond III IHC stainer.
- CLDN18.2 expression ≥10%/≥1+ was reported in the majority of G/GEJ adenocarcinoma samples, while PD-L1 CPS ≥ 5 was only observed in 17% of the total samples. No correlation between the two markers expression was observed.
- These results support the value of CLDN18.2-targeted therapy in gastric cancer, especially for those patients who may not benefit from anti-PD-1/PD-L1 immuno-checkpoint therapy.
- Limitation of this retrospective study: All tumor samples were from surgical resections of G/GEJ adenocarcinoma in Chinese patients, with limited samples from metastatic lesions and no clinical annotations. Further explorations of the expression of CLDN18.2, PD-L1 CPS and their correlation, the impact of stage of disease, biopsy location and ethnicity is required.

REFERENCES

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