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Claudin 18.2 in pancreatic neuroendocrine tumors: a potential therapeutic target

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BACKGROUND

There remains an unmet need for treatment options for advanced pancreatic neuroendocrine tumors (PanNETs). Claudin 18.2 (CLDN18.2) is a tight junction molecule of gastric epithelium, which becomes exposed on tumor cell surface following malignant transformation, making it a viable target for cancer therapy. Clinical trials with Zolbetuximab and other novel CLDN18.2 targeting therapeutic agents in several cancers are currently ongoing. Given CLDN18.2 is ectopically expressed in pancreatic adenocarcinoma, we sought to examine CLDN 18.2 as a potential biomarker in PanNETs.

METHODS

Paraffin embedded tissue microarrays (TMAs) with PanNET specimens from 110 patients were immunostained with anti-CLDN18.2 mAb (Abcam, ab314690). CLDN18.2 expression was quantified in each core by measuring the average intensity value, classified as low (0-84/1+), medium (85-170/2+), or high (171-255/3+). For patients noted to have high CLDN18.2 expression, we examined tumor grade (G) and SSTR2 expression. We then screened available PanNET cell lines (BON, QGP, NT-3) for CLDN18.2 expression using Western blot assay and assessed binding of Zolbetuximab (anti-CLDN18.2 mAb) with flow cytometry. The difference in CLDN18.2 positivity between QGP and BON cells was determined by a two-tailed unpaired t-test, with $p<0.05$ considered statistically significant.

RESULTS

Immunostaining of TMAs confirmed high membranous CLDN18.2 expression in 14% (n= 15/108) of PanNET specimens. Two CLDN 18.2 positive specimens were later noted to be G1 small bowel liver metastasis and G1 gastric primary. G1, G2 and G3 represented 67% (n=10), 27% (n=4) and 6% (n=1) of PanNET patients. SSTR immunostaining was available in 16 patients, and positive in all except one patient with G3 PanNET. All three of the screened PanNET cell lines exhibited CLDN18.2 levels detectable by Western blot with QGP cells displaying the greatest positivity. Flow cytometry further confirmed CLDN18.2 expression in BON and QGP cell lines. QGP cells exhibited 2-fold greater percentage of live CLDN18.2-positive cells than BON ($p = 0.0025$) with a 1.27 fold difference in median fluorescence intensity ($p<0.0001$).

CONCLUSIONS

CLDN 18.2 is a promising biomarker in PanNETs. Further studies are needed to assess CLDN 18.2 expression in gastrointestinal NETs and explore possible CLDN 18.2–targeted therapies in NETs.

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