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Translational potential of a receptor-targeted contrast agent for fluorescence-guided applications in pancreatic neuroendocrine tumors

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BACKGROUND

Accurate intraoperative localization of primary and metastatic pancreatic neuroendocrine tumors (pNETs) is challenging, and molecularly driven fluorescence-guided surgery could significantly improve surgical outcomes with given the overexpression of somatostatin receptor subtype-2 (SSTR2). We developed an optimized SSTR2-targeted fluorescent agent, MMC(FNIR-Tag)-TOC, which expressed excellent targeting specificity and pharmacokinetics, as the lead compound for clinical development. To bridge the gap between preclinical and clinical development of MMC(FNIR-Tag)-TOC, we implemented a fluorescence-guided pathology strategy to (i) examine the binding of our agent to human tumors and (ii) investigate its potential use for delineation of surgical margins.

METHODS

We obtained whole tissue sections (n=8) from pNET patients who underwent curative-intent pancreatectomy from the Institutional Tissue Bank at The University of Texas MD Anderson Cancer Center after Institutional Review Board approval. The tissues were snap-frozen and serially sectioned into 5 µm frozen sections for ex vivo staining with MMC(FNIR-Tag)-TOC as described in the supplemental file. The stained sections were scanned for fluorescence signal using a near-infrared fluorescence imaging system (Odyssey, LI-COR). Sequential sections from each specimen were also stained with standard hematoxylin and eosin (H&E) and immunohistochemistry (IHC) for SSTR2 (ab134152, Abcam, 1:1000 dilution) to allow morphologic evaluation of tumor and normal tissues and to assess SSTR2 expression in the samples, respectively. We performed qualitative analysis and evaluated the correlation between the fluorescence staining pattern and SSTR2 distribution in the tumor and surrounding normal areas of the sections.

RESULTS

Six tissue sections contained tumor only, and two samples contained both tumor and normal pancreas. SSTR2 IHC staining was positive in tumor cells, with strong and widespread staining intensity in all cases except one, where variable intensity was seen, as indicated by areas of both strong and weak staining in the tumor. SSTR2 staining showed minimal background staining in pancreatic acinar cells (normal pancreas), while highlighting islets of Langerhans.

Fluorescence imaging showed excellent co-localization of MMC(FNIR-Tag)-TOC with SSTR2-positive areas that was confined within the tumor boundary, as confirmed by H&E and IHC staining.

CONCLUSIONS

Our findings showed that MMC(FNIR-Tag)-TOC has high specificity for human pNET tissues. The observed fluorescence signal was largely correlated with SSTR2 IHC staining and accurately represented pNET tumor extension, which suggests strong utility for fluorescence-guided applications. Accordingly, we plan to extend our research into the clinical arena and initiate a first-in-human trial to investigate the feasibility of using MMC(FNIR-Tag)-TOC for FGS in patients with pNETs.

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