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Perspective of $\alpha_v\beta_6$-Integrin Imaging for Clinical Management of Pancreatic Carcinoma and Its Precursor Lesions

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Abstract

β_6-integrin immunohistochemistry analysis of a large number of pancreatic ductal adenocarcinoma (PDAC, 383 primary tumors, 7 lymph node, and 8 distant metastases) and 34 pancreatic intraepithelial neoplasia (PanIN) specimens revealed a high prevalence of $\alpha_v\beta_6$-integrin expression in PDAC primaries (88%) and in almost all metastases, as well as in PanIN (57%). These findings underscore the high potential of a novel $\alpha_v\beta_6$-integrin targeting positron emission tomography (PET) radiopharmaceutical, Ga-68-Avebehexin, for early diagnosis of pancreatic cancer.

Keywords

clinical translation of novel oncologic radiotracers, cancer detection imaging, cancer imaging, immunohistochemistry, integrin

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Pancreatic ductal adenocarcinoma (PDAC) is currently the fourth leading cause of cancer deaths in the United States with an overall 5-year survival rate of only 8%.[1] This poor outcome is particularly related to diagnosis at an advanced stage in the majority of cases. On the other hand, treatment at an early stage, or when tumors are still small sized, dramatically improves the therapeutic outcome,[2] which is underpinning the importance of an early and reliable diagnosis. [^{18}F]Fluorodeoxyglucose (FDG), the currently most widely used positron emission tomography (PET) tracer for metabolic tumor imaging, is not useful for the early detection of PDAC.[3] Especially high-risk individuals (ie, patients with genetic syndromes or a family history of PDAC, chronic pancreatitis, and others)[4] could therefore benefit strongly from improvement of noninvasive imaging strategies for early detection of PDAC or its most frequent precursor lesions, pancreatic intraepithelial neoplasia (PanIN).

Preliminary data from a small cohort of 34 cases suggested that the heterodimeric transmembrane receptor $\alpha_v\beta_6$-integrin is extensively expressed in the majority of PDAC specimen.[5] Consequently, this integrin subtype has been exploited earlier as a target for preclinical PET imaging in a murine model of pancreatic cancer.[6] Along these lines, we recently developed ^{68}Ga-Avebehexin (Figure 1),[7] a gallium-68-labeled derivative of the $\alpha_v\beta_6$-integrin selective cyclic nonapeptide c(FRGDLAFp[NMe]K) introduced by Kessler and coworkers,[8] which features the triazacyclononane-triphosphinate (TRAP) chelator for highly efficient Ga-68 complexation.[9] ^{68}Ga-Avebehexin is characterized by a high-$\alpha_v\beta_6$-integrin affinity (Inhibition concentration [IC_{50}] = 0.26 nM) and pronounced hydrophilicity (log D = –3.7), resulting

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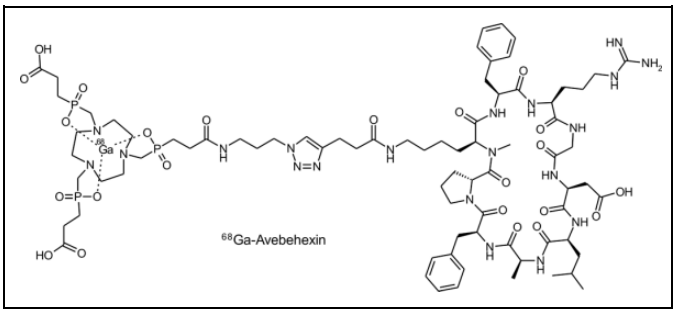

Figure 1. ^{68}Ga-Avebehexin, a gallium-68-labeled TRAP conjugate of the $\alpha_v\beta_6$-integrin selective cyclic nonapeptide c(FRGDLAFp[NMe]K), for noninvasive imaging of $\alpha_v\beta_6$-integrin expression by positron emission tomography (PET).

in fast renal clearance and low background signal. ^{68}Ga-Avebehexin was found suitable for highly sensitive detection even of moderate $\alpha_v\beta_6$-integrin expression levels, exemplified by high-contrast PET imaging of subcutaneous H2009 (lung adenocarcinoma) xenografts in severe combined immunodeficiency (SCID) mice.[7] Notably, we found a particularly low pancreatic uptake (0.07% of injected dose per gram tissue), resulting in a high tumor-to-pancreas ratio of 9.9 $\pm$ 1.6 which was exceeding all other tumor-to-organ ratios in that study.[7] Such low physiological uptake in the pancreas suggests particular suitability of ^{68}Ga-Avebehexin-PET for detection of intrapancreatic $\alpha_v\beta_6$-integrin expressing lesions.

Hence, in order to further substantiate the clinical potential of ^{68}Ga-Avebehexin-PET, we investigated the expression of β_6-integrin in a large cohort of PDACs (383 primary tumors, 7 lymph node, and 8 distant metastases) and 34 PanIN, in order to underpin the suitability of $\alpha_v\beta_6$-integrin as a target for detection of early-stage pancreatic cancer. β_6-integrin expression was investigated by means of immunohistochemistry according to our previously reported protocol,[7] using tissue microarrays that were constructed as described previously[10-12] containing PanIN and primary resected PDAC, their lymph node and distant metastases. Expression intensity and frequency were evaluated by an experienced pathologist (K.S.) according to the scoring scheme established by Sipos et al[5] with additional respect to the expression patterns. A slight and purely cytoplasmic expression was defined as negative (immunoreactive score 0.5 or below), an at least slight, membranous expression of β_6-integrin was defined as positive (immunoreactive score > 0.5). Median expression scores and standard deviations were calculated using Microsoft Excel.

In PanIN lesions, expression intensity increased from PanIN1 to PanIN3 (Figure 2) with a membranous staining pattern in 57% of PanIN3. Figure 3 shows that 87.8% of ductal adenocarcinoma of the pancreas in our large cohort displayed positivity for β_6-integrin. Moreover, all lymph node metastases (7 out of 7) and 88% of distant metastases (7 out of 8) were found to be strongly positive. β_6-integrin expression was always limited to the tumor cells and the directly adjacent peritumoral stroma.

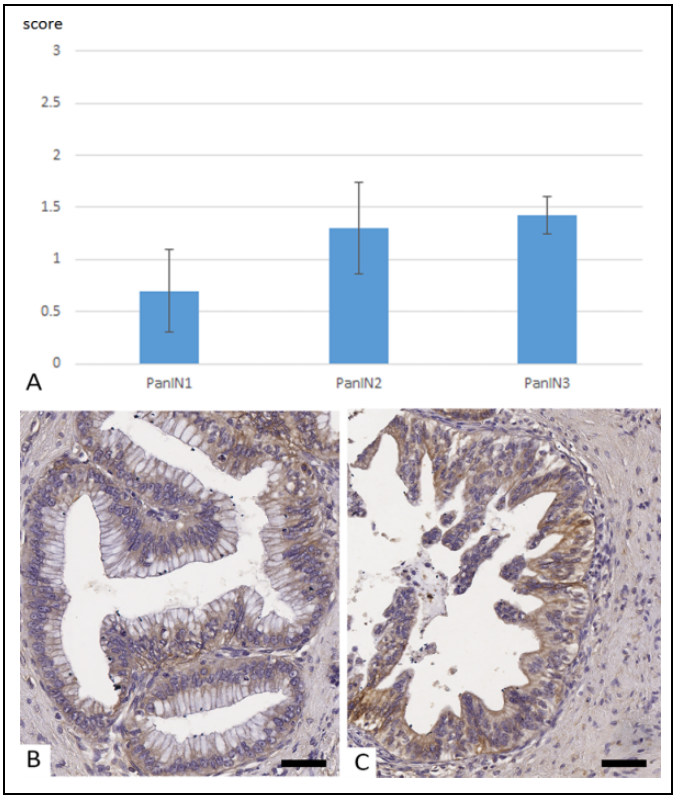

Figure 2. Median β_6-integrin expression intensity and standard deviation in human pancreatic intraepithelial neoplasia (PanIN) lesions (A) with representative examples for a slight basal expression in PanIN1 (B, score 0.8) and moderate cytoplasmic and membranous expression in PanIN3 (C, score 1.5). B and C, immunohistochemistry of β_6-integrin, scale bars 50 μm.

In view of such consistently high, frequent and tumor cell–specific $\alpha v\beta 6$-integrin levels in precursor lesions, primaries and metastases of PDAC, we anticipate a substantial value of $\alpha_v\beta_6$-integrin targeted imaging for early detection and clinical management of this type of neoplasia. ^{68}Ga-Avebehexin-PET in patients with PDAC might improve current clinical preoperative staging and monitoring of therapy response in this highly lethal malignancy, especially upon contrasting such a receptor-directed tracer approach with a metabolic imaging readout (ie, FDG-PET). This is because ductal adenocarcinomas of the pancreas frequently do not only consist of malignant tumor cells but may also comprise a very high percentage of metabolically less active, tumor-associated stromal cells (see Figure 3B and C), resulting in a low overall metabolic activity per tissue volume. Hence, a selective, cell surface receptor directed imaging method like ^{68}Ga-Avebehexin-PET, allowing to directly and specifically detect PDAC tumor cells, appears more suitable in the PDAC setting.

We conclude that $\alpha_v\beta_6$-integrin might be a potential tumor-specific imaging biomarker for the early detection of human PDAC and its metastases. Further studies will have to determine whether $\alpha_v\beta_6$-integrin imaging is also able to discriminate between cases of PDAC and chronic or autoimmune pancreatitis and whether ^{68}Ga-Avebehexin-PET fulfills the hope to be

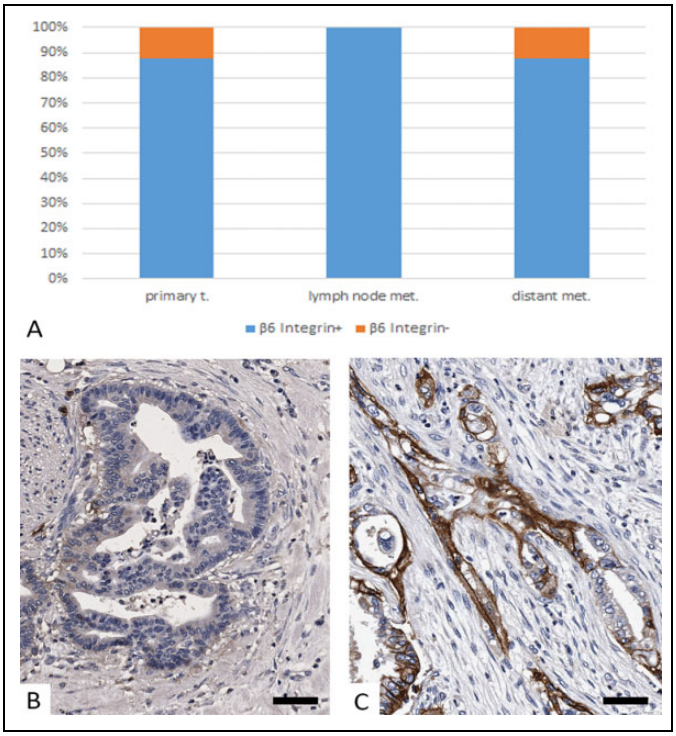

Figure 3. A high $ß_6$-integrin expression frequency is observed in human pancreatic ductal adenocarcinoma (PDAC; primary t.), their lymph node and distant metastases (met; A). A slight and purely cytoplasmic expression (B) was graded as negative (score 0.1), strong membranous and cytoplasmic expression in the majority of tumor cells (C) as positive (score 2.15). B and C, immunohistochemistry of $ß_6$-integrin, scale bars 50 μm.

better suited than FDG-PET for detecting PDAC lesions in the human setting. Although the prognostic relevance of $\alpha_v\beta_6$-integrin in PDAC has not been investigated yet, its role as a prognostic indicator in several cancers, among them colon[13] and gastric carcinoma,[14] implicates further potential applications of ^{68}Ga-Avebehexin as a prognostic in vivo molecular imaging tracer.

Declaration of Conflicting Interests

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