

Targeting Mesothelin in Pancreatic Ductal Adeno-Carcinoma (PDAC)

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Mesothelin as a Relevant Tumor Imaging and Therapeutic Target in Pancreatic Ductal Adeno-Carcinoma

Pancreatic Ductal Adenocarcinoma (PDAC) represents 90% of all pancreatic malignancies [1]. To date, PDAC is the fourth leading cause of cancer-related death and its incidence is rising to become the second one in the next decade [2]. Two major public health problems, obesity and type 2 diabetes, are important etiology factors involved in PDAC development [3]. Despite intense research efforts, PDAC is an aggressive tumor with a five-year survival rate of 5% [1]. The reasons for this dramatic prognosis are multiple; 1) PDAC are often resistant to chemo and or radiotherapy [4]; 2) 90% of PDAC are diagnosed at advanced stages, limiting therapeutic windows [5]; 3) most of the clinical trials investigating targeted therapies alone failed to demonstrate improvement of patients overall survival [6].

Identification of PDAC antigens for diagnosis and therapy is an urgent need to improve patient management. Relevant targets have been identified and included mesothelin. Mesothelin is a membrane-associated glycoprotein with limited expression in normal tissues including mesothelial cells of the pleura, pericardium and peritoneum [7]. Mesothelin is overexpressed in several solid tumors and accumulating evidences suggest its role as a diagnostic marker and as a relevant therapeutic target in ovarian cancer, mesothelioma and PDAC. Mesothelin expression has been reported in 80 to 85 % of PDAC [8]. A weak expression of mesothelin in normal tissues and an overexpression in cancer tissues make mesothelin an attractive target for therapy. Several antibodies-based

compounds targeting mesothelin and immunotherapies are under clinical investigations in several tumors [8,9]. However, the selection of patients eligible to these therapies needs a companion test detecting mesothelin expression.

In the October 2019 issue of *Cancers (Basel)*, we presented results from TCGA datasets [10]. Based on 179 PDAC patient samples, we showed a restricted expression of mesothelin in tumor specimens as compared to healthy pancreatic tissues. These results were recently confirmed by immunohistochemical analysis of PDAC samples and their healthy counterparts [11]. We further showed that high mesothelin expression was correlated with shorter overall survival. Moreover, an elevated expression in advanced stages of PDAC was observed suggesting a role of mesothelin in tumor progression. Consistently, the role of mesothelin in peritoneal metastasis of PDAC through an induction of angiogenesis was recently suggested [12].

We next investigated the potential of ^{99m}Tc-A1, a radiolabeled single-domain antibody (sdAb)-derived imaging agent, as a mesothelin-targeting probe [10]. This class of imaging agents specifically binds their target at early time point after injection, with elevated tumor-to-background ratio [13]. Currently, mesothelin-targeting agents are monoclonal antibodies (mAbs) or single-chain variable fragments (scFv) [14-16]. Although antibodies have been extensively considered for *in vivo* imaging, their slow blood clearance and their high non-specific background restricted their use. The smaller size of sdAb-derived imaging agents allows fast blood clearance and high target-to-background ratio at early time point. In this study, ^{99m}Tc-A1 showed a non-invasive imaging

of mesothelin-expressing PDAC, with elevated tumor-to-background ratio 1h post-injection. No signal was observed on SPECT images after ^{99m}Tc -A1 injection with the exception of tumor, kidney and bladder. Renal accumulation was observed in agreement with the general pattern of sdAb distribution [17].

Future directions of this work will include clinical translation of ^{99m}Tc -A1 as a companion marker to identify patients that should benefit of anti-mesothelin therapies. This theranostic approach will open new opportunities for the management of cancer patients. The incorporation of high-energy β^- (^{177}Lu) to anti-mesothelin sdAb will specifically kills mesothelin-expressing tumor cells.

This theranostic methodology will couple a molecular imaging to (i) predict response to the targeted radionuclide therapy and (ii) to follow up treatment efficacy. Radiolabeling with an imaging-dedicated radioisotopes (such as ^{68}Ga) or with a therapy-dedicated one (such as ^{177}Lu) can be performed with the same sdAb. This method has been successfully performed in preclinical model of breast cancer without any evidence of renal damage [18]. A better management of PDAC patients is also expected. Further development will therefore include DOTA- chelation chemistry to allow either ^{68}Ga or ^{177}Lu radiolabeling for diagnosis and therapy of PDAC.

Combining a therapeutic agent to a specific method of detection of aggressive tumor is the future of precision medicine.

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