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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO, World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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Nanotechnology and pancreatic cancer management: State of the art and further perspectives

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) represents a leading cause of cancer death and is often diagnosticated too late to allow adequate treatments. Lots of biomarkers have been discovered in lasts years but, to date, there is a lack of low-cost and non-invasive tools for PDAC early detection. Nonetheless, drugs commonly used in PDAC treatment do not allow achieving long-term satisfying results. Nanotechnology is gaining importance in both PDAC early detection and treatment. The main implications of nanotechnology in cancer diagnosis lay in the ability that nanoparticles have on concentrate the alteration in human proteome caused by cancer. Nanoparticle-enabled blood tests have been demonstrated to reach high rate of sensitivity (up to 85%) and specificity (up to 100%). In the field of cancer therapy nanoparticles can be used as nanocarriers able to reach specific tumour's cells and selectively release the drug they contain into them. A literature review was carried out with the aim to assess the state of the art and highlight the future perspectives of nanotechnology in PDAC early detection and therapy.

Key Words: Pancreatic ductal adenocarcinoma; Biomarkers; Nanotechnology; Nanoparticles; Protein corona; Early detection

Core Tip: Pancreatic ductal adenocarcinoma (PDAC) is very lethal. Surgery is the only effective treatment. Unfortunately, only 20% of PDACs can be radically resected because of the lack of tools for early diagnosis and since chemotherapy agents fail to reach satisfying prognosis. Nanoparticles can amplify the cancer-induced proteome

alteration allowing early cancer detection and can also be used in cancer treatment as carriers improving the effectiveness of chemotherapy. This review focuses the actual and futures implications of nanotechnology in PDAC diagnosis and treatment.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) represents a sneaky disease that often runs asymptomatic in its early stage. Symptoms as intense pain or jaundice that led to medical consult frequently occur when the tumour is already in an advanced stage. Therefore, PDAC first diagnosis is generally reached when the local invasion or distant metastases are present. This behaviour, in association with the biology of the tumour, account for the poor prognosis that affect the majority of PDAC patients[1].

Surgery may improve patient's prognosis; regrettably, radical resection is precluded to almost 80% of the affected because only a minority of PDACs are diagnosed early enough[2].

Chemotherapy, alone or in association with radiotherapy is commonly used in neoadjuvant or adjuvant settings or in presence of metastatic disease. Unfortunately, to date, PDAC responsivity to these treatments remains poor[3].

To date, there is a lack of cheap, user-friendly and non-invasive tools for PDAC early detection. Food and Drug Administration (FDA) approved only carbohydrate antigen (Ca) 19.9 for use in daily clinical practice; however, the American Society of Clinical Oncology does not recommend it in a diagnostic phase because of its poor sensitivity and specificity[4].

Over the last decade, a large number of different biomarkers have been identified; many proved their efficacy, alone or in combination with Ca 19.9, in detecting PDAC and/or distinguish PDAC from other pancreatic benign diseases (*e.g.*, chronic pancreatitis)[5].

Unfortunately, almost all of them failed to become reproducible in routinely practice since resulting from complex, expensive and laborious technology (*e.g.*, genetic sequencing, transcriptomic expression profiling, proteomic and metabolomic profiling) and not meeting the ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users) criteria requested by the World Health Organization (WHO)[6].

In the field of cancer treatment, immunotherapy represents the "newer kid on the block". This science is based on the enhancement of the immune system activity against cancer cells. Despite being promising, immunotherapy still has its "dark side" when considered for PDAC. PDAC microenvironment has been identified as a leading cause of failure of this therapeutic strategy[7].

On these bases, it is clear that both newer PDAC early diagnosis strategies and more efficient therapies represent the challenges to win and hot topics of research.

Since nanomedicine is gaining momentum in cancer management, aim of the present work was to assess the state of the art and to highlight the future perspectives of nanotechnology in PDAC early detection and therapy.

METHODS

To tackle the above-mentioned issue, PubMed database was queried for articles published up to December 2020. Terms pancreatic cancer, pancreatic adenocarcinoma, nanotechnology, nanomedicine, nanoparticles, diagnosis, detection, therapy and management have been used in different combinations. References reported in the selected articles have been also considered as other bibliographic sources. Only articles published in English with available full text and without limitation concerning article types (original articles, review, *etc.*), subjects involved in the research (*e.g.*, humans,

mice), experimental condition (*in vitro* or *in vivo*) and population size have been considered.

NANOTECHNOLOGY AND PDAC EARLY DIAGNOSIS

Nanotechnology is a multidisciplinary scientific field involving physics, engineering, chemistry and biology. This science is based on the use of objects whose dimensions are in the nanoscale (range 1 nm–100 nm) (http://data.europa.eu/eli/reco/2011/696/oj.): the nanoparticles (NPs). In recent years, this science is gaining more and more momentum opening interesting scenarios in the management of different types of tumours.

When NPs interact with organic fluids (*e.g.*, plasma), they are covered by a shell of biomolecules, forming the so-called biomolecular corona (BC). Since proteins represent the most abundant elements forming the BC, this structure is often called Protein Corona (PC) too.

The shape of PC depends on NPs' physiochemical properties (*e.g.* materials, size, electric charge, hydrophobicity)[8], environmental factors (temperature, incubation time)[9] and experimental source characteristics (*e.g.*, plasma, urine, human, murine)[10].

Actually, since NPs are able to concentrate even poorly abundant plasma proteins, characterization of PC may reveal changes in protein concentration that cannot be detected by common laboratory tests.

The main implications of nanotechnology in cancer diagnosis and treatment lay in the ability that NPs have to concentrate cancer-induced alteration in human proteome. Nevertheless, it has been proved that different patients affected by different pathological conditions have personalized PC[11].

On this basis and considering that proteins alterations are the hallmark of cancerogenesis, NP-enabled tools (NETs) have been investigated for early cancer detection. Moreover, by the use of common techniques (*e.g.*, light scattering, electrophoresis) nanotechnology proved to fully meet the above-mentioned WHO criteria.

Prostate cancer has been the first tumour investigated for early detection based on the development of NETs[12]. Further similar tests have been lately developed and applied to other solid neoplasms[13].

In 2014, a pilot study was conducted analysing plasma samples collected from 11 patients affected by untreated PDAC and 13 patients undergoing surgery for benign disease ("healthy controls"). The samples were let to interact with anionic liposomes (ALs) made of 1,2-dioleoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (DOPG); the obtained PCs general characteristics (*i.e.*, dimension, surface charge and protein composition) and their protein abundances were assessed by Dynamic Light Scattering and Laser Doppler Electrophoresis techniques. The Authors demonstrated significant differences in the surface charge (the zeta potential) and size between PCs formed after interaction of NPs with plasma of PDAC and healthy (*i.e.*, non-oncological) subjects. To explain these findings, different protein patterns constituting PCs of cancer patients and controls were hypothesized. Indeed, PCs of PDAC patients were significantly more enriched than those of healthy subjects. This enrichment was particularly due to a subset of plasma proteins with molecular weight comprised between 30 and 60 kDa. The lack of proteomics-based mass spectrometry investigations did not allow to fully characterize the proteins forming the PCs in the two groups[14].

Moreover, during the last recent years, different NPs have been tested in order to improve the accuracy of NETs in detecting PDAC. Among them, particular relevance gained graphene oxide (GO) nanoflakes. Differently from other NPs, GO nanoflakes bind low levels of the most abundant proteins present in human blood (*e.g.*, albumin) and have the ability to adsorb other poorly-concentrated plasma proteins. As shown by Papi *et al*[15], when PCs formed around GO nanoflakes of 25 pancreatic ductal adenocarcinoma patients were compared with those of 25 controls, PDAC patients PCs were significantly less enriched of proteins with molecular weight ranging between 20-30 kDa. This difference allowed distinguishing between cancer and non-cancer subjects with a sensitivity of 92%.

Nevertheless, the studies performed analyzing the PC of PDACs demonstrated that also the stage of the disease determines changes in PC composition[16]. Particularly, SDS-PAGE analysis of PCs formed around 1,2-dioleoyl-sn-glycero-3-phospho-(1'-rac-glycerol) liposomes allowed to distinguish patients affected by T1-T2 PDACs from T3s and metastatic ones. More in detail, PC intensity profiles of T1-T2 pancreatic ductal adenocarcinomas significantly differed from those of the T3s because of the dissimilar

abundance of a subset of proteins with molecular weight ranging between 25 and 50 kDa (p 0.04). Comparing T1-T2 to metastatic PDACs, significant differences in intensity profiles were also found in the subgroups of proteins with molecular weight of 25-50 kDa (p 0.01) and 50-120 kDa (p 0.04). The differences highlighted in the protein intensities would reflect the stage-related different expression of proteins (*e.g.*, VEGF, CDK2, adhesion molecules, *etc.*) already reported as result of more sophisticated and expensive technologies[14].

All the studies focused on PDAC early diagnosis and considered in this paper have been summarized in Table 1.

NANOTECHNOLOGY AND PDAC THERAPY

Due to the modest results commonly achieved by conventional drugs, nanotechnologies have been tested to improve the effectiveness of chemotherapy agents by increasing the availability of the drug in the tumour and decreasing the toxicity reducing its effects on host cells[17].

Essentially, NPs can be loaded with drugs and used as nanocarriers able to reach the tumour and selectively release the drug they contain into it.

Many NPs as liposomes, micelles, dendrimers, exomes, organic and inorganic NPs and different mechanisms of action as endocytosis, fusion with plasma membranes, active or passive targeting have been studied and increasingly used for solid cancer treatment[18].

In 2008, Patra *et al*[19] demonstrated, *in vitro* and *in vivo*, a significant inhibition of pancreatic cancer cells proliferation and growth using a formulation of gold NPs transporting cetuximab (C225) and gemcitabine.

In 2015, liposomal irinotecan (Onivyde®) was approved by the FDA for clinical use in metastatic PDAC, who already have received gemcitabine. The efficacy of Onivyde's® was demonstrated in a randomized trial performed on a series of 417 patients affected by metastatic PDACs. Patients who received the combination of Onivyde® and 5-fluorouracil (5-FU)/Leucovorin gained on average 2 mo of survival and showed an average delay in the time to tumor growth of 3.1 mo when compared to those who received only 5-FU/Leucovorin[20].

However, it has been demonstrated that these liposomal formulations lose their selectivity over the time, due to the exposure to blood proteins, and their toxic effect increases. As shown by Mirshafiee and colleagues, after exposure to plasma, NPs present significant inhibition (up to 94%) of their targeting ability. This inhibition is due to the formation of the PC that impairs the biodistribution and the cellular uptake of the NPs, and to the effect of the organic filters (liver and spleen)[21].

Nonetheless, Liu demonstrated in PDAC animal models that, when compared with liposomes, mesoporous silica nanoparticles (MSNs) improve irinotecan loading and efficacy[22]. More in detail, the Author developed a supported lipid bilayer coated MSN carrier with increased loading capacity and cancer cells killing ability when compared to the conventional liposomal formulation. Furthermore, these nanocarriers showed improved stability decreasing the irinotecan toxicity by the reduction of the systemic leakage of the drug. The MSN carrier developed by Liu and coworkers was also more efficient in the treatment of pancreatic cancer metastatic cells and, according to the Author opinion, could be used in FOLFIRINOX regimen treatment for PDAC.

NP albumin-bound paclitaxel, better known in clinical practice as nab-paclitaxel or abraxane, is the newest drug approved for PDAC treatment and is widely used in association with gemcitabine in gem-abraxane combined therapeutic settings[23].

As demonstrated in mice by Meng *et al*[24] in 2015, coated bilayer MSNs can also improve the synergic delivery of gemcitabine and paclitaxel in human PDACs.

In this paper, Meng also focused on the role that MSN nanocarriers have in overcoming the challenges of PDAC stromal barrier and abnormal perfusion that have been widely recognized among the main factors contributing to the failure of oncological treatments.

On the basis of the interesting results obtained using MSNs, these NPs have been tested also in the immunotherapy for PDAC. MSNs loaded with oxaliplatin and indoximod, an inhibitor of immunosuppressive indoleamine 2,3-dioxygenase, showed their ability in improving innate and adaptative immunity against PDAC in vaccination approaches, systemic and local administration[25]. The Authors also reported the innovation of using a nanocarrier to produce a synergistic immune response by the concomitant delivery of an immunogenic cell death stimulus and interfering in immune suppression.

Table 1 Nanotechnology and pancreatic ductal adenocarcinoma early diagnosis

Year	Ref.	NP type	Main findings
2012	Walkey *et al*[8]	Gold, Silica, Polystyrene	Characteristics of NPs (material, size, electric charge, hydrophobicity) influence the composition of the PC
2012	Monopoli *et al*[10]	Silica, Carbon, Iron oxide, Polystyrene	Different experimental sources (*e.g.*, plasma, urine), affect the composition of the PC
2013	Tenzer *et al*[9]	Silica, Polystyrene	Environmental factors (*e.g.*, incubation time) influence the composition of PC
2014	Caracciolo *et al*[14]	Liposomes	After interaction of NPs with plasma of PDACs and non-oncological subjects, differences in the electric charge (zeta potential) and size of the PCs allow to distinguish between the two groups
2015	Zheng *et al*[12]	Gold	Gold-NPs successfully used for early detection of prostate cancer
2017	Corbo *et al*[11]	Silica, Polystyrene, Gold, Liposomes	Different patients affected by different pathological conditions have "personalized" PC
2018	Caputo *et al*[16]	Liposomes	Analysis of PCs formed around DOPG liposomes allowed to distinguish patients affected by T1-T2 PDACs from T3s and metastatic ones
2019	Künzel *et al*[13]	Silica	Successful application of silica NPs in early diagnosis of the head and neck solid squamous carcinoma
2019	Papi *et al*[15]	GO	Analysis of BC formed around GO nanoflakes distinguished PDAC from healthy subjects (sensitivity 92%)

NP: Nanoparticle; PC: Protein corona; PDAC: Pancreatic ductal adenocarcinoma; DOPG: 1,2-dioleoyl-sn-glycero-3-phospho-(1'-rac-glycerol); BC: Biomolecular corona; GO: Graphene oxide; NET: NP-enabled tool.

Nevertheless, nanocarriers have been proposed for different gene therapies for PDAC. In this field, NPs can be used to improve the biological availability and selectivity of nucleic acids as small interfering RNA (siRNA) or microRNA and reduce the immune system activity against these therapeutic agents[26].

Despite the large number and the quality of advances in NP-based therapies for PDAC, the research for a safe, non-toxic stable, biocompatible and biodegradable nanovector is still the gap to fill. In this field, chitosan may pave the way for the development of efficient and not toxic drug delivery system[27]. As reported in the review of Sadoughi *et al*[27], chitosan proved its efficacy in PDAC therapy as nanocarrier of both gemcitabine and 5-FU.

All the studies focused on the application of nanotechnology in PDAC therapy considered in this paper have been summarized in Table 2.

CONCLUSION

According to this literature review and taking into account that potential bias due to possible missing analyzed articles cannot be excluded, NP-based tools seem to be promising in PDAC management.

If further confirmed on larger series, results obtained from original and pioneering experiences may lead to the development of fast and cheap tool that could be used for early PDAC detection.

Nonetheless, if PDAC tumour dimension and presence of metastases will be confirmed relevant in NP-enabled blood test accuracy, nanotechnology could also be used together with standard clinical and pathological staging system; this "molecular" staging may provide useful information for PDAC prognosis and therapy.

Nanotechnologies have already demonstrated their usefulness in improving the therapeutic response to pancreatic cancer. However, future research efforts in this area must on the one hand be aimed at improving nanotechnology interfaces and, on the other hand, answer the unresolved questions relating to the bioavailability and clearance of nanovectors in order to increase efficacy and reduce toxic effect.

A more accurate understanding of the interactions between NPs and biological fluids represents the prerequisite for ensuring that nanomedicines confirm to be a valid potential weapon against this lethal disease.

Table 2 Nanotechnology and pancreatic ductal adenocarcinoma therapy

Year	Ref.	NP type	Main Findings
2008	Patra *et al*[19]	Gold	Gold NPs used as nanocarrier improve the effect of cetuximab and gemcitabine in reducing the growth and the proliferation of pancreatic cancer cells in murine model.
2013	Mirshafiee *et al*[21]	Silica	The exposure to human plasma significantly reduces the targeting ability of NPs.
2015	Meng *et al*[24]	MSN	Coated bilayer MSNs improve the synergic delivery of gemcitabine and paclitaxel in PANC-1 injected in murine models.
2015	FDA[20]	Liposomal irinotecan (Onivyde®)	Approval of Onivyde® for clinical use in metastatic PDAC, who already have received gemcitabine.
2016	Liu *et al*[22]	MSN	In KPC pancreatic cancer cells injected into murine models, biocompatibility and therapeutic efficacy of MSNs-irinotecan formulation are superior to liposomal-irinotecan formulation.
2017	Lu *et al*[25]	MSN	MSNs improve oxaliplatin and indoximod bioavailability in KPC pancreatic cancer cells injected into murine models.
2017	Shi *et al*[23]	NP albumin	FDA approved the clinical use of NP albumin-bound paclitaxel (Abraxane) for pancreatic cancer.
2020	Sadoughi *et al*[27]	Chitosan	The use of chitosan as carrier of gemcitabine and 5-FU improves therapeutic effect decreasing toxicity in pancreatic cancer cells.

NP: Nanoparticle; MSN: Mesoporous silica nanoparticle; KPC: KrasLSL-G12D/+/Trp53LSL-R172H/+/Pdx-1-Cre; PANC-1: Pancreatic cancer cell; PDAC: Pancreatic ductal adenocarcinoma; 5-FU: 5-Fluorouracil.

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