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**Nanomaterials: applications in the diagnosis and treatment of pancreatic cancer**

Wang J *et al*. Nanomaterials: applications in the diagnosis and treatment of PC

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**Abstract**

Pancreatic cancer (PC) remains one of the leading causes of cancer-related death in human sowing to missed early and effective diagnosis. The inability to translate research into clinical trials and to target chemotherapy drugs to tumors is a major obstacle in PC treatment. Compared with traditional cancer detection methods, the method combining existing clinical diagnosis and detection systems with nanoscale components using novel nanomaterials shows higher sensitivity and specificity. Nanomaterials can interact with biological systems to efficiently and accurately detect and monitor biological events during diagnosis and treatment. With the advance of experimental and engineering technology, more nanomaterials will begin the transition to clinical trials for their validation. This paper describes a number of nanomaterials used in the diagnosis and treatment of PC.

**Key words**: Nanomaterials; Pancreatic cancer; Diagnosis; Treatment; Nanoparticles; Quantum dots

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**Core tip:** Pancreatic cancer remains one of the leading causes of cancer-related death in humans owing to missed early and effective diagnosis. Nanomaterials can interact with biological systems to efficiently and accurately detect and monitor biological events during diagnosis and treatment in pancreatic cancer.

**Introduction**

Pancreatic cancer (PC) is one of the most common malignancies of the digestive system. It is a highly fatal disease with a 5-year survival rate of less than 5%[1]. PC is highly aggressive and can easily invade adjacent tissues and metastasize to distant organs[2,3].Additionally, PC is significantly resistant to standard chemotherapy, so the most effective treatment for PC is surgical resection[4,5]. About 80% of PC patients are diagnosed at an advanced stage because of the lack of clinical symptoms at early stages of the disease. Surgical treatment at these late stages is suboptimal because of the high risk of metastasis[6]. computerized tomography and endoscopic ultrasonography with or without fine needle biopsy have been widely used for diagnosing and staging of PC and computerized tomography with pancreas protocol and endoscopic ultrasonography correlate moderately well in terms of mass detection, mass size, vascular involvement and lymph node involvement[7,8]. However, the two methods also have some drawbacks. The diagnosis results are related to the clinician's ability to read the image and the proficiency of endoscopic operation, which may lead to missed diagnosis. Therefore, a new method for early detection and diagnosis of PC is urgently needed.

The rapid development of new nanomaterials in recent years may lead to improvements in the diagnosis of PC and therefore benefit patients. In many tumor models, nanomaterials have been proved to be effective, and it is expected that these nanomaterials will be more widely applied to clinical applications in the future. Compared with traditional biosensor systems, nanomaterials have many advantages and great development potential. Using nanoscale components to construct nanomaterials can greatly improve detection sensitivity. In addition, by expanding the upper and lower limits of biomarker detection, the indications for surgical treatment are effectively expanded. Furthermore, advances in manufacturing technology can reduce the cost of producing these nanosensors, thereby reducing the medical costs of detecting and diagnosing cancer and reducing the burden on patients[9]. Recently, much academic research has been devoted to the testing and development of nanotechnology, which promises to improve the detection of existing diseases.

Nanomaterials work at the nanoscale, which is broadly defined as 1 to 500 nm, or about a billionth of a meter. Through multidisciplinary cooperation in the fields of medicine, biology, chemistry, physics, engineering and technology, the development of nanomaterials has achieved great success[10]. There are two main reasons for the characteristic properties of nanomaterials at such a small size. First, there is a large surface area to volume ratio, and many of the atoms that make up the material are very close to the surface. Second, since the size of the material is close to the wavelength that excites the components of the nanomaterial, it exhibits quantum forces[11]. This review will introduce the characteristics of some nanomaterials and their applications in the diagnosis or treatment of PC.

**Nano biomaterials**

***Nanoparticles***

To date, carbohydrate antigen (Ca) 19.9 is the only PDAC marker approved by the United States Food and Drug Administration. However, its use is discouraged in the diagnostic phase because of the poor sensitivity (60%-70%) and specificity (70%-85%)[12]. In many nanobiomaterials systems, nanoparticles (NP) are often key components in detecting cancers. These particles are made of a variety of materials, and each of them has unique properties which are designed specifically to enhance the ability to detect biomarkers. With advances in nanotechnology and our understanding of materials at the nanoscale, nanoparticles have been approved or entered clinical application, including diagnostic applications, such as imaging or biomarker testing, as well as therapeutic applications, or a combination of diagnostic and therapeutic applications, also known as therapeutic diagnostics[13].

***Quantum dots***

Quantum dots (QDs) are a class of nanoparticles used to detect cancer *in vitro* and *in vivo*. These nanocrystals are composed of semiconductor particles with inorganic elements at their core and surrounded by metal shells[14]. They are generally less than ten nanometers in diameter[15] and the strengths of quantum dots in cancer diagnosis and treatment and even the application in cancer study stem from their unique characteristics. The first is the ability to adjust the size and composition of quantum dots so that they have unique fluorescence excitation wavelengths, ranging from 400 nm to 2000 nm[16]. QDs can be tuned to any color to accommodate different wavelengths, making it possible to identify and track different biomarkers by applying only one single light source. In addition, the other one useful feature of quantum dots is that they are reusable and have a long lifespan, possibly due to their resistance to fading[17]. One problem with normal healthy tissue imaging is that it often exhibits autofluorescence, which interferes with signals coming from tissue in cancer[13]. Quantum dots are designed to combine with fluorescent properties in the near-infrared spectrum, so the autofluorescence interference can be eliminated[14]. One potential problem with using QDs *in vivo* is the risk of toxicity after injection. Some improvements have been made to reduce the potential toxicity, but more studies are needed to determine the appropriate clinical solutions.

***Carbon nanotubes***

Carbon nanotubes (CNT) are hexagonal structures composed of self-aligned single-walled or double-walled carbon molecules, with diameters ranging from 0.3 nm to 100 nm[18]. CNT have several properties that make them more suitable for use in nanomaterials. The characteristics of resistance to high heat and electrical conductivity permit CNT to function normally even when exposed to high temperatures or electrical currents. CNT also show high-tensile strength, making them resistant to permanent deformation due to physical forces. In general, CNT can be divided into two categories due to the different principles in recognizing biomarkers: one is based on electrochemical signals generated by redox reactions, and the other is based on detection signals of field effect transistors generated by surface charges of CNT[19]. In the first category, both single-walled and multi-walled CNT are used in a type of application called a nanotube forest. The technique requires the nanotubes to be lined up in parallel so that antibodies to specific biomarkers are attached to the surface. The second type of detection is the aforementioned field effect transistors method, in which nanotubes are connected to electrodes at either end by lithography and functionalized to bind biomarkers. Once these biomarkers are bound, a decrease in the conductivity of the nanotubes is detected, and is proportional to the amount of binding.

***Gold nanoparticles***

Gold nanoparticles make up another class of promising particles in diagnostics and are made from colloidal gold. These nanoparticles exist mainly in the form of gold nanospheres and exhibit a strong ruby color in aqueous solution. The intriguing optical properties of gold nanoparticles are due to local surface plasmon resonance, in which the valence electrons of gold nanoparticles oscillate with incident light at a specific frequency[20]. Some of the energy absorbed by gold nanoparticles is emitted as scattered light, which forms the basis of optical imaging of gold nanoparticles. The rest of the energy decays in a non-radioactive form, turning into heat that can be used to kill cancer cells, thus acting as photothermal therapy[21]. Gold nanoparticles have been found to be widely used in multiple potential tumor diagnosis and treatment fields.

***Liposomes***

Liposome, which can be applied to transport a drug to the location of tumors, is one type of nanoparticle consist of a lipid bilayer[22]. Like other types of nanoparticles, liposomes rely on enhanced permeability and retention (EPR effects) to enter tumor blood vessels and stay close to the tumor. The phenomenon of EPR stems from the structural characteristics of the vascular system in solid tumors. Nanoparticles increase the ability to exude through less tight endothelial connections. Once in the tumor microenvironment, the retention of nanoparticles increases due to inadequate lymphatic drainage. To take advantage of the EPR effect, liposomes are typically designed to be less than 200 nm in size to improve the amount of retention in the tumor[23]. Liposomes are able to be targeted with unique transport components to increase cellular uptake in the target tissue.

**Nano biomaterials and PC**

***Nanoparticles and PC***

One type of nanoparticle used to target PC cells was organically modified silica nanoparticles with a diameter of about 20 nm. The surface of these nanoparticles was functionalized with transferrin, stabilizer four and antimycin, and the fluorophore rhodamine B was used as the imaging agent. This technique is simple to operate and suitable for photobiological imaging research[24]. Similarly, another study indicated that mesoporous silica nanospheres functionalized with the target ligand and were covalently attached with a rare earth ion Gd(III) *via* a disulfide group. *In vitro*, that was shown to be an effective MRI contrast agent in models with PC. However, the disulfide was rapidly metabolized *in vivo*[25].

In addition, parvifloron D (PvD), a natural compound isolated from the Plectranthus genus, showed cytotoxicity and anti-proliferation activity on human leukemic cancer cells. However, PvD is a compound with very low water solubility, and nanotechnology was an effective strategy to solve this problem using albumin nanoparticles prepared by desorption. The nanoencapsulated PvD showed selective cytotoxicity towards PC cell lines. Further optimization that included glucose crosslinking resulted in PvD that was wrapped in nanoparticles that were molded to a similar size (100–400 nm) and shape. The coupling of erlotinib to these PvD nanoparticles, led to substantial antiproliferative activity in the BxPC-3 PC cell line[26].

Gemcitabine (GEM) is a first-line, standalone chemotherapy drug for PC, but tumor cells develop resistance to it after a few months. Multiple clinical and preclinical studies have shown that GEM in combination with other chemotherapy drugs can achieve better therapeutic results. However, this type of combination therapy often causes severe systemic toxicity. Hence, new treatment regimens need to be developed to safely deliver chemotherapeutic drug combinations to patients. Nanoparticles mediate drug delivery by incorporating drug combinations at the same time, similar to a “cocktail of drugs”, targeted to tumor cells[27].

***Quantum dots and PC***

Noninvasive acquisition of tumorigenesis and metastasis information requires nontoxic, long-acting fluorescent probes for tumor imaging. A biocompatible near infrared ray (NIR) fluorescent probe modified with glucose (Glc) on the surface of NIR Ag2Se quantum dots (NIR Ag2Se QDs) has been used to image tumors *in vivo*. These glucose-functionalized Ag2Se QDs (Glc-Ag2Se QDs) were observed *in vivo* for at least 7 d. In addition, the probe was excreted through the kidney, and the excretion capacity is conducive to the application of imaging *in vivo*. Furthermore, Glc-Ag2Se QDs were used for targeted imaging of human breast cancer cells (MCF-7) as well as imaging of SW1990 PC cells[28]. Detection of circulating tumor cells (CTCs) play a vital role in the diagnosis of tumors. CTCs disseminate from the primary tumor using the circulatory or lymphatic system and can form secondary tumor colonies. The number of CTCs has been used as an indicator of cancer progression. However, the population of CTCs is very heterogeneous and the identification of CTC subsets such as tumor stem cells with high metastatic potential is a very challenging task but has great importance for the diagnosis and management of tumors. With the help of quantum dots, CTCs with higher metastatic potential, such as CD24+ and CD133+ CTCs, have been identified in live animals and may reveal detailed mechanisms of metastasis, such as tumor cell extravasation into blood vessels[29]. ZnO QDs are also used for the detection of CA19-9 cancer biomarkers using an immunosandwich method, involving square wave extraction voltammetry and photoluminescence, to enable better detection of PC cells [30].

***CNT and PC***

CA19-9 is an important tumor antigen of pancreatic, bile duct, stomach, colorectal and liver cancer.CA19-9 has been used to construct a novel immune sensor consisting of CNT, gold nanoparticles and SiO2 nanoparticles. The process used to make the nanosensor involves the outer surface of the CNT being covered with bovine serum albumin molecules. Gold nanoparticles are then attached to bovine serum albumin-CNT, and the electrochemical deposition of gold provides nucleation sites for the first gold nanoparticles. These initial steps provide a large surface where the CA19-9 antibody can be immobilized and used as a sensing component. To improve the signal and the sensitivity of detection, SiO2 nanoparticles are modified as secondary antibodies for a sandwich immunoassay. Experiments at different concentrations of CA19-9, showed a detection threshold 100 times lower than the ELISA standard currently applied in clinical practice, and therefore could be more effective in diagnosing early PC[31]. Multi-walled CNTs have also been used to build genetic fingerprints of PC. Studies have shown that multiwalled CNT electrochemical sensing were combined with random amplified polymorphic DNA. This detected differences in guanine and deoxyguanine triphosphate between DNA samples in peripheral blood from PC patients and control patients[32].

***Gold nanoparticles and PC***

A recent study suggested that a drug delivery nanosystem based on gold nanoparticles (PEGAuNPs) was able to effectively deliver drugs to tumor cells. Adriamycin and volitinib an anthracycline and tyrosine kinase inhibitor respectively, were coupled with gold nanoparticles and modified for size, stability and morphology. The combination of PEGAuNPs with adriamycin and varlitinib proved effective in human cells, with PEGAuNPs further suppressing cancer cell proliferation and reducing the toxicity to normal cells[33]. Another study by Banstola *et al*[34] indicated that chemotherapeutic photothermal combination therapy could improve the efficacy of chemotherapeutic drugs in patients with PC. Specifically, the combination of paclitaxel-targeted polydopamine polymer microspheres and controllable gold nanoparticles suggested significant improvement in the efficacy of photothermal chemotherapy in PC cell lines[35].

***Liposomes and PC***

Extracellular matrix (ECM) overexpression in pancreatic ductal adenocarcinoma cells limits drug penetration into tumors and is associated with poor prognosis. A recent study demonstrated that a proteolytic enzyme, which underwent pretreatment based on the nanoparticle system, decomposed the dense extracellular collagen matrix of PC and increased the penetration of drugs in an orthotopic murine PC model. More specifically, this collagenase was a proteolytic enzyme encapsulated by a 100-nanometer liposome, which was designed to protect collagenase from premature inactivation, prolonging its release rate at the target site, and effectively improving the efficacy of the drug[34]. Interestingly, degradation of the extracellular matrix did not increase the number of circulating tumor cells or metastases. This strategy also has the potential to degrade the extracellular matrix in other diseases, such as liver fibrosis, and improve tissue permeability before administration[36]. Similarly, the effect of gemcitabine in pancreatic ductal adenocarcinoma is limited by dense fibrosis, as well as pharmacokinetics and low blood flow. To address this, activated liposomes that release drugs through local heating may enhance serum stability and circulatory effects; the released drugs also retain the ability to spread within the tumor. In a mouse model of more aggressive PC, local hyperthermia with liposomes combined with gemcitabine induced cell death and the formation of apoptotic areas[37]. The summary was showed in Table 1.

**Conclusion**

This article reviews some of the current developments in nanomaterials for the diagnosis and treatment of PC. The efficacy of nanomaterials depends on following factors, including targeted delivery of nanoparticles to tumor sites, EPR effects, tumor heterogeneity, tumor microenvironment and metastasis prevention, nanobiological interactions, and host-tumor immune crosstalk. The synthesis of nanomaterials is also important for the diagnosis and treatment of PC. With continued research and development efforts we expect targeted NPs to have a tremendous impact on human health for decades to come.

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**Figure Legends**

**Table 1 The summary of the application of nanomaterials in pancreatic cancer in this study**

|  |  |  |
| --- | --- | --- |
| Nanomaterials | Example | Function |
| Nanoparticles (NPs) | Silica NPs | Photobiological imaging research[24]  MRI contrast agent[25] |
| Albumin NPs | Wrap anti-proliferation drug (PvD) to target cancer cell[26] |
| Delivery NPs | Safely deliver Gemcitabine to tumor cells and eliminate toxic effects on normal cells[27] |
| Quantum dots (QDs) | Ag2Se QDs | Image pancreatic cancer (PC) *in vivo*[28] |
| CTC QDs | Identify CD24+ and CD133+ to detect CTCs[29] |
| ZnO QDs | Better detection of CA19-9 and PC cell[30] |
| Carbon nanotubes (CNTs) | CA19-9 CNTs | Construct a novel immune sensor and more efficient detection of early PC[31] |
| Multi-walled CNTs | Built genetic fingerprints of PC[32] |
| Gold nanoparticles | PEGAuNPs | Effectively deliver drugs to tumor cells.  Further suppressing cancer cell proliferation and reducing the toxicity to normal cells[33]  Improvement in the efficacy of photothermal chemotherapy in PC[34] |
| Liposome | Collagenase liposome | Prolonging drug release rate at the target site, and effectively improving the efficacy of the drug[35] |
| Gemcitabine liposome | Local hyperthermia with liposomes combined with gemcitabine induce cell death and the formation of apoptotic areas[37] |