Perspectives of gold nanoparticles and their applications in pancreatic cancer (Review)

ANAMARIA MAGDALENA TOMŞA[1], ANDREEA LIANA RĂCHIŞAN[1], ANDREEA ALEXANDRA ALDEA[1*] and LORENA CIUMĂRNEAN[2*]

[1]Department No. 9 Mother and Child, 2nd Clinic of Pediatrics and [2]Department of Internal Medicine IV, 'Iuliu Haţieganu' University of Medicine and Pharmacy, 400012 Cluj-Napoca, Romania

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Abstract. Nanoparticles (NPs) represent a major point of interest in the scientific field, with an increasing number of studies revealing promising results. Nano-oncology is a relatively new area of research that continues to expand, revealing new perspectives in both diagnosing and treating cancer. Treating pancreatic cancer (PC) remains a major challenge, with modest positive results, thus an increasing number of studies have focused on this disease. Out of all the NPs that have been used in experimental studies, gold NPs (GNPs) appear to be the most efficient, with little systemic toxicity. This review aims to summarize the latest studies that reveal the effects that GNPs have on PC cells, focusing on different ways in which they can be used to diagnose this disease, to induce apoptosis or cause cytotoxicity in cancer cells. Although literature has limited data concerning this specific topic, the results are promising. However more studies are required until GNPs can be used in clinical practice.

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Correspondence to: Dr Andreea Liana Răchişan, Department No. 9 Mother and Child, 2nd Clinic of Pediatrics, 'Iuliu Haţieganu' University of Medicine and Pharmacy, Crisan 3, 400012 Cluj-Napoca, Romania
E-mail: andreea_rachisan@yahoo.com

*Contributed equally

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1. Introduction

Malignancies represent a major health issue worldwide, with outcomes depending on numerous factors including the genetical background, environmental triggers, the tumor stage at the time of diagnosis, the clinical response to treatment, but most importantly, the type of tumor (1). One of the most aggressive cancers that remains difficult to treat, with a 5-year survival rate less than 5%, is pancreatic cancer (PC). Surgical resection remains the only curative treatment, with a success rate of only 18-25%. Furthermore, not all patients diagnosed with PC are candidates for surgery, but only for palliation (1-5).

Nanotechnology represents a major subject of interest with an impact in numerous fields including biology, material sciences, chemistry, as well as medicine. The traditional treatment for PC relies mostly on chemotherapy, radiotherapy and surgery, however new research in nano-oncology shows promising results. The oncological application of nanoparticles (NPs), especially gold NPs (GNPs) has emerged as a significant therapy in the diagnosis and treatment of PC (6,7).

Widely recognized as biocompatible, GNPs are still being studied as a potential treatment for different cancers, with great success (8). The aim of this review was to highlight the role that GNPs may play in the management of PC, from diagnosis to treatment. The latest studies on this topic which show how GNPs may be used to diagnose PC, but also the studies that explain the dynamics of GNPs inside the cells were summarized. Data on how GNPs induce apoptosis or cytotoxicity, both per se and in combination with other therapies and procedures were also included.

2. Materials and methods

An electronic literature search in the PubMed database was conducted and relevant articles published up to April 2020 containing information about the use of GNPs in PC were included. In our search the following terms were used: 'gold nanoparticles', 'pancreatic cancer', 'targeted drug therapy'. In order to write this review, data from numerous types of studies, mainly experimental, both *in vitro* and *in vivo* were collected, excluding review articles.

3. Overview of GNPs

GNPs have been extensively studied for their use in the treatment of cancer. They present a considerably high interest in the medical field due to their different uses, including photothermal therapies, radiosensitization, imagistic properties and targeted drug delivery. What makes them appropriate for these applications is their optical properties. Gold represents a system which has an equal number of positive ions (which have a fixed position) and conduction electrons (free and mobile) (8). When the surface of the metal is irradiated by an electromagnetic wave, the oscillating electric fields of the wave interact with the free electrons, causing the oscillation of the surface electrons in resonance with the frequency of visible light. Free electrons are conducted by the electrical field to oscillate coherently. The collective oscillations of the free electrons are also called 'plasmons', and those of the surface electrons are called 'surface plasmons'. Surface plasmons interact with visible light forming the phenomena known as 'surface plasmonic resonance' (SPR). SPR determines the formation of strong electromagnetic fields on the surface and enhances the properties of the GNP: Absorption, scattering and the conversion of light into heat. For medical imagistic purposes GNPs of larger dimensions are preferred for their better light scattering property, whereas smaller NPs are better used in photothermal therapy due to their higher efficiency in transforming light into heat (8,9). The way in which the cells internalize GNPs, their intracellular distribution in different cell compartments, as well as their toxicity are dictated by their dimensions, morphology and surface properties (10). GNPs can be designed into various shapes: Spherical, hemispherical, stellar, rods, branched as well as other shapes (10).

GNPs can be produced in large quantities, with well-established shapes and sizes. They can be also synthesized directly *in situ* by chemically reducing gold salts and initiating their growth by using growth-nuclei which help the NPs increase in size until the desired dimensions are reached. It has been demonstrated that this plays an important role on how the cell internalizes the NPs and also on the cytotoxic effects NPs have against the cell. The most toxic appear to be the GNPs of smaller dimensions (1-2 nm), their toxicity expressing on both malignant and healthy human cells. Larger GNPs (4.8-12 nm) present an important toxicity on cancer cells, but little toxicity on healthy cells, while GNPs which exceed 15 nm are considered to be non-toxic (10,11).

Despite all the advantages that GNPs present, there are still some problems that must be addressed. One inconvenience is that GNPs absorb certain proteins which leads to their instability. To stop this from happening, they are usually coated with one layer of hydrophilic biocompatible polymer-like dendrimer, polylysine, PEI or polyethylene glycol. Another problem that may occur is that once they get inside the organism, they can be retained by the macrophages and other cells of the reticuloendothelial system (RES). As foreign particles are eliminated by the RES, the challenge is to prevent GNPs, once *in vivo*, from being internalized by RES cells in order to prolong the time they spend inside the organism. An important role in this issue is played by the size of the NPs. It has been observed that smaller-sized particles have a considerably longer life in the blood stream compared to larger NPs (11).

Their most common sites of action are the nucleus, mitochondria and the endoplasmic reticulum. At the nuclear level, GNPs work by drug toxicity, gene expression modulation or direct toxicity, while at the mitochondrial level GNPs may produce ROS, may activate autophagy or may modify the membrane potential (12).

4. GNPs used in the treatment of PC

GNPs present a high radio-enhancing property, which has made them a candidate for radiotherapy studies. Ivošev *et al* studied the uptake mechanism, internalization and excretion of GNPs with a core size of 2 nm and hydrodynamic diameter of 4.5 nm (ultra-small GNPs) functionalized with dithiolated diethylenetriaminepentaacetic acid (GNPs-DTDTPA) in several cancer cell lines (Table I). They demonstrated that the dynamics of these GNPs are dependent on the cell line, concluding that they may be a promising candidate for the treatment of PC (13). Huay *et al* revealed that pre-treatment of PC cells with GNPs sensitized the cells to the effects of gemcitabine, decreasing gemcitabine-induced EMT, stemness and MAPK activation (14). Another study on photodynamic therapy focused on the effects of GNPs attached on the surface of silica NPs organically modified with photosensitizer methylene blue. Irradiating these NPs with 630 nm resulted in an enhanced O_2^- production, with various amounts that were dependent on the diameter of silica NPs (30/55/80 nm). A PC cell line (PANC-1) was used to study the dynamics of cellular uptake and photodynamic cytotoxicity. The study revealed that the effects were dependent on the attachment of GNPs to the surface of silica NPs, as well as to the size of silica NPs (15).

Since PC remains difficult to treat, different combined approaches are being studied. Zhang *et al* focused on a synergistic strategy in which honeycomb-like GNPs (HGNPs) were used together with interventional photo-thermal therapy (IPTT) combined with brachytherapy (BT) in two different types of PC cell lines (PANC-1 and SW1990). Firstly, they conducted a survival assay to evaluate the radiosensitization effectiveness of HGNPs *in vitro*, obtaining a higher apoptosis rate compared to cells without HGNPs. Then, they used tumor-bearing mice (SW1990) to study *in vivo* distribution and the effects of the NPs. They divided the mice into 5 groups, obtaining a significantly better tumor destruction in the HGNPs + IPTT and HGNPs + IPT-BT groups, with a lower rate of loco-regional recurrence in the HGNPs + IPT-BT group. Furthermore, the normal tissues appeared to present no side effects from this synergistic therapy (16).

Gold nano-cages (GNCs) have also been studied as potential treatment for PC. Qiu *et al* designed a theranostic NP using GNCs modified with hyaluronic acid, conjugated with anti-Glypican-1 (anti-GPC1) antibody, oridonin, gadolinium and Cy7 dye. The NPs were demonstrated to have a long-time stability and MRI and fluorescent properties, rendering them useful in the diagnosis phase of a cancer. Various cell lines (Table I) were used to study the dynamics of NPs, which were endocytosed only by PANC-1 and BXPC-3 cells, but not by 293T cells. While presenting insignificant toxicity, the designed NPs significantly promoted the apoptosis of PC cells *in vitro*, while *in vivo* they permitted multimodal imaging and targeted drug therapy (17).

Table I. Different designs of GNPs studied in pancreatic cancer.

Authors, year	Design of the NPs	Cell line	Results	(Refs.)
Ivošev *et al* 2020	-Ultrasmall GNPs (core size 2 nm, hydrodynamic diameter 4.5 nm) -Functionalized with dithiolated diethylenetriaminepentaacetic acid	-Pancreatic cancer (BxPC-3) -Glioblastoma (U87-MG) -Chordoma (UM-Chor1) -Cervix (HeLa) -Prostate (PC3) -Fibroblasts (dermal fibroblasts)	-Uptake and excretion dependent on the cell line -Concentrate preferentially in cancer cell lines, particularly in pancreatic cancer, prostate cancer and glioblastoma	(13)
Huay *et al* 2019	-20 nm GNPs	-Pancreatic cancer (PANC-1, AsPC-1, MIA PaCa-2, HPAFII)	-Pre-treatment with GNPs inhibits the upregulation of stem cell markers -Pre-treatment with GNPs reverses the epithelial -Mesenchymal transition, inhibits the stemness induced by gemcitabine and sensitizes gemcitabine-resistant pancreatic cancer to gemcitabine	(14)
Roy *et al* 2019	-GNPs attached to silica NPs modified with methylene blue	-Pancreatic cancer (PANC-1)	-Irradiation with 630 nm laser -Enhanced O_2^- production, dependent on the diameter of the silica NPs	(15)
Zhang *et al* 2019	-HGNPs (HGNPs) along with photothermal therapy and brachytherapy	-Pancreatic cancer (PANC-1, SW1990)	-*In vitro:* Higher apoptosis rate compared to cells that were not treated with HGNPs -*In vivo:* Significantly better tumor destruction in the HGNPs + IPTT and HGNPs + IPT-BT groups, with a lower rate of locoregional recurrence in the HGNPs + IPT-BT group -Normal tissues not affected by the combined therapy	(16)
Qiu *et al* 2018	-GNCs modified with hyaluronic acid and conjugated with anti-glypican-1 antibody, oridonin, gadolinium and Cy7 dye	-Pancreatic cancer (PANC-1, BXPC-3, SW1990) -human embryonic kidney (293 T-cell line)	-GNCs were endocytosed only by PANC-1 and BXPC-3, but not by 293 T-cells -*In vitro:* Promoted the apoptosis of pancreatic cancer cells -*In vivo:* Permitted multimodal imaging and targeted drug therapy	(17)

GNPs, gold nanoparticles; HGNPs, honeycomb-like GNPs; GNCs, gold nanocages; IPTT, interventional photo-thermal therapy; BT, brachy-therapy; IPT-BT, interventional photothermal-brachytherapy.

Table II. GNPs conjugated with chemotherapeutics and their effects on pancreatic cancer cells.

Authors, year	Design of the NPs	Cell line	Results	(Refs.)
Coelho *et al* 2019	-Polyethylene glycol-coated GNPs conjugated with doxorubicin/varlitinib (VAL-PEG-GNPs/DOX-PEG-GNPs)	-Healthy pancreatic cells (hTERT-HPNE) -Pancreatic cancer cells (S2-013, MIA PaCa-2)	-PEG-GNPs up to 1.0 nM are not toxic -DOX-PEG-GNPs are toxic for MIA PaCa-2, but not toxic for other cell lines -VAL-PEG-GNPs are toxic for both MIA PaCa-2 and S2-013, but not toxic for hTERT-HPNE	(23)
Steckiewicz *et al* 2020	-GNPs stabilized with reduced glutathione and conjugated with doxorubicin, gemcitabine and cytarabine	-Healthy pancreatic cells (hTERT-HPNE) -Pancreatic cancer cells (PANC-1) -Human osteosarcoma cells (143B) -Human osteoblast (hFOB1.19) -Breast cancer cells (MCF7) -Breast epithelial cells (MCF10A)	-GNPs present a cytotoxic effect dependent on their concentration -Low impact on the healthy cells	(24)
Banstola *et al* 2019	-GNPs linked using polydopamine to paclitaxel-loaded PLGA microspheres (GNPs-pD-PTX-PLGA-Ms)	-Pancreatic cancer cells (PANC-1)	-Enhanced ROS generation when using NIR -Downregulation of CATALASE and SOD2	(25)

rGNPs, gold nanoparticles; NPs, nanoparticles.

5. GNPs and targeted drug therapy in PC

Targeted Drug Delivery (TDD) represents the most advanced mode of substance transport through which the efficacy of the active substance is enhanced in a specific area, while at the same time the effect on the healthy cells is diminished (18,19). Nanotechnology has already demonstrated its efficacy in the TDD system and it has been suggested that the smaller the size of the NPs, the higher their specificity. Specific markers can be chemically modified or can be attached to the surface of the NPs in order to be able to directly interact with the cell-surface receptors and to easily penetrate the cell membrane layers (18-22).

Coelho *et al* evaluated the synergistic effect of two nano-conjugates [the polyethylene glycol-coated GNPs (PEG-GNPs) conjugated with doxorubicin (DOX-PEG-GNPs) and conjugated with varlitinib (VAL-PEG-GNPs) as *in vitro* targeted delivery against proliferation of cancer cells. In the study, a healthy pancreatic cell line (hTERT-HPNE) and two PC cell lines (S2-013 and MIA PaCa-2) were used. In the study, PEG-GNPs up to 1.0 nM were not toxic to either cell line (incubation period of 72 h). Concurrently, it was revealed that DOX-PEG-GNPs were toxic for MIA PaCa-2 cells (derived from primary pancreatic tumor), but not toxic for other cell lines. In addition, VAL-PEG-GNPs were not toxic for hTERT-HPNE, but they were toxic for both MIA PaCa-2 and S2-013 (derived from metastatic pancreatic tumors). Furthermore, the cells were treated for 24 h with DOX-PEG-GNPs, and then they were incubated for 48 h with VAL-PEG-GNPs, comparing the results with free antitumor drugs. It was concluded that the combined effect of the two antitumor drugs was only observed with the conjugates and it was higher for S2-013 cells. In addition, in the normal pancreatic cell line, the toxicity of drugs that were conjugated with PEG-GNPs was smaller compared with the toxicity induced by unconjugated free drugs (23).

Conjugating GNPs with chemotherapeutics represent a major point of interest in numerous studies (Table II). Steckiewicz *et al* assessed the safety and antitumor potential of GNPs stabilized with reduced glutathione (GSH) and conjugated with doxorubicin (DOX), gemcitabine (GEM) and cytarabine (CTA). The cytotoxic effect was assessed by MTT assay *in vitro* in different cell lines. It was revealed that GNPs presented a cytotoxic effect that was dependent on their concentration, with a lower impact on the healthy cell lines compared to the cancer cell lines, demonstrating that assessed GNPs present anticancer potential (24).

Banstola *et al* developed adherent GNPs linked using polydopamine to paclitaxel-loaded PLGA microspheres (GNPs-pD-PTX-PLGA-Ms) which they further assessed with and without NIR treatment in PANC-1 cells. It was revealed that using NIR resulted in more ROS generation and also in the downregulation of levels of two important antioxidant enzymes, CATALASE and SOD2. The effect of chemo-photothermal therapy was demonstrated to be synergistic in inducing the apoptosis of cancer cells (25).

6. Other perspectives on GNPs and PC

There are studies that focus on the role that NPs may play in the early detection of PC or even in the reversal of pancreatic desmoplasia. Nanotechnology is also studied through the prism of cancer detection. Alarfaj *et al* synthesized carbon quantum dots conjugated with gold nano-composite in order to detect CA 19-9, a tumor marker used in the rapid screening of PC (26). Han *et al* used pegylated polyethylenimine-coated GNPs to co-deliver heat shock protein HSP47 (targeting siRNA) and all-*trans* retinoic acid to re-educate activated pancreatic stellate cells (PSC). It was revealed that this nano-system induced PSC quiescence and inhibited extracellular matrix hyperplasia. In this context, the delivery of the drug to the tumor was enhanced, concurrently improving the effectiveness of chemotherapeutics (27). Similarly, another study revealed that miR-21 inhibitor can be co-delivered with gemcitabine by dendrimer-entrapped GNPs for PC therapy using new ultrasound-targeted micro-bubble destruction, with significant effects (28).

In recent years, the direction of GNP development had been towards obtaining an effective targeted therapy. Although experimental designs show promising results, a perfectly designed molecule with 100% bioavailability, significant antitumoral effects, no systemic side effects and at a low price has yet to be revealed. Nevertheless, researchers are making promising advances, increasingly focusing on combining different techniques, taking advantage of all the proprieties of gold, as aforementioned. However, as technology moves forward, newly developed quantum dots are becoming increasingly prevalent, perhaps even overtaking the interest from GNPs.

7. Conclusions

GNPs have been demonstrated to be suitable for diagnosing PC, inducing apoptosis in these cancer cells and even making PC cells more sensitive to chemotherapeutics (23-26,28). At present, the literature has limited but promising data on this topic. More studies are required in order to find the most efficient design for a GNP that can be safely used *in vivo* in PC patients with the intention to cure it. The studies presented in this review may be an ideal starting point for new studies to emerge that may provide more insights into this field.

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Authors' contributions

AMT and AAA conceived the review. AMT, ALR and AAA participated in the manuscript design and gathering of data. ALR, AAA and LC performed critical revision of the manuscript. All authors read and approved the final manuscript to be published.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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