Review article

The bioengineered and multifunctional nanoparticles in pancreatic cancer therapy: Bioresponisive nanostructures, phototherapy and targeted drug delivery

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ABSTRACT

The multidisciplinary approaches in treatment of cancer appear to be essential in term of bringing benefits of several disciplines and their coordination in tumor elimination. Because of the biological and malignant features of cancer cells, they have ability of developing resistance to conventional therapies such as chemo- and radio-therapy. Pancreatic cancer (PC) is a malignant disease of gastrointestinal tract in which chemotherapy and radiotherapy are main tools in its treatment, and recently, nanocarriers have been emerged as promising structures in its therapy. The bioresponsive nanocarriers are able to respond to pH and redox, among others, in targeted delivery of cargo for specific treatment of PC. The loading drugs on the nanoparticles that can be synthetic or natural compounds, can help in more reduction in progression of PC through enhancing their intracellular accumulation in cancer cells. The encapsulation of genes in the nanoparticles can protect against degradation and promotes intracellular accumulation in tumor suppression. A new kind of therapy for cancer is phototherapy in which nanoparticles can stimulate both photothermal therapy and photodynamic therapy through hyperthermia and ROS overgeneration to trigger cell death in PC. Therefore, synergistic therapy of phototherapy with chemotherapy is performed in accelerating tumor suppression. One of the important functions of nanotechnology is selective targeting of PC cells in reducing side effects on normal cells. The nanostructures are capable of being surface functionalized with aptamers, proteins and antibodies to specifically target PC cells in suppressing their progression. Therefore, a specific therapy for PC is provided and future implications for diagnosis of PC is suggested.

1. Introduction

The treatment of diseases cannot be provided by one discipline and it has been shown that combination of several disciplines is required to mediate effective treatment of diseases. One of the most well-known interdisciplinary approaches in disease therapy is nanomedicine that its aim is to combine nanotechnology science with medicine in treatment of human diseases (B. Hu et al., 2020). The development of novel nanostructures has been followed and various kinds of bio- and nano-materials with low particle size have been developed that display high safety, biocompatibility and high efficiency in overcoming the difficulties in treatment of human diseases (Mura and Couvreur, 2012). There are various kinds of nanoparticles that can be categorized into polymeric-, lipid-, metal- and carbon-based nanoparticles that each of them has its own ability in disease therapy. Moreover, nanomaterials can be used for immobilizing biomolecules and by this way, they serve as biosensors for analyzing biomarkers and diagnosis of diseases (El-Ansary and Faddah, 2010). The wearable or implantable devices having nanostructures can be employed to mediate real-time control of physiological status (Choi et al., 2016). In recent years, nanomaterials have been employed in treatment of cancer and their wide application has shown that they are promising agents for purpose of cancer therapy. The application of nanomaterials in cancer therapy is not limited to drug delivery, and they can mediate gene delivery, reversing chemoresistance, promoting cargo internalization in tumor cells, boosting anti-cancer immunity, biosensing and bioimaging, and development of stimuli-responsive nanocarriers has improved cancer suppression (Milad Ashrafizadeh, Shahin Aghamiri et al., 2022; Milad Ashrafizadeh, Masoud Delfi et al., 2021; Milad Ashrafizadeh, Ehsan Nazarzadeh Zare et al., 2022; M. Ashrafizadeh et al., 2023a,b). The nanomaterials have mainly particle size of 10–100 nm and they can easily internalize in tumor cells. The main way for internalization in tumor cells is endocytosis and when nanoparticle surface is modified with ligands, they bind to receptor to mediate receptor-induced endocytosis (Makvandi et al., 2021). Moreover, nanoparticles have large surface area, their physico-chemical properties are tunable and they can encapsulate both hydrophobic and hydrophilic drugs (S. Song et al., 2021).

There are several reasons for introduction of nanobiomaterials in cancer therapy. One of the most important reasons is that conventional therapies for cancer have not been able to cure cancer and there is still high morbidity and mortality of this malignant disease in patients. The conventional treatments have been able to improve prognosis and survival rate of patients and therapy failure in patients is observed when resistance occurs. Due to late diagnosis of patients, surgical resection is not an optimal option, and at the next step, radiotherapy, chemotherapy and immune checkpoint inhibitors are preferred that there is chance of resistance to the aforementioned therapies. Therefore, combination cancer therapy is suggested and nanomedicine allows to improve potential of therapeutics and prevent development of resistance. For instance, in case of chemoresistance, when chemotherapy and radiotherapy are utilized for repeated times, it could lead to resistance due to genomic mutations and epigenetic alterations in cancer cells (Ashrafizaveh et al., 2021; Mirzaei et al., 2021a,b,c,d,e). Moreover, there is chance of resistance to immunotherapy such as upregulation of PD-L1/PD-1 axis (Milad Ashrafizadeh, Ali Zarrabi, Kiavash Hushmandi et al., 2020). The nanostructures can induce photothermal ablation of cancer cells and this is due to the role of these particles as enzymes to stimulate apoptosis and ferroptosis in reducing tumorigenesis (Yuan et al., 2022). The cancer immunotherapy can be accelerated by nanostructures and biomimetic nanoparticles promote M1 polarization of macrophages through ROS generation to enhance immunotherapy-mediated glioblastoma ablation (T. M. Wang et al., 2022). The nanostructures have ability of combining chemotherapy and immunotherapy in effective tumor suppression (S. Liu et al., 2022). The manganese zinc sulfide nanoparticles have ability of stimulation of immunogenic cell death in treatment of metastatic melanoma (Z. J. Li

et al., 2022). The iron oxide@chlorophyll clustered nanostructures can stimulate photodynamic therapy to mediate ferroptosis and promote activity of immune system in suppression of bladder tumor (Chin et al., 2022). In another case, the photothermal and photodynamic therapies can be combined in suppressing tumorigenesis by nanoparticles (Chu et al., 2022). One of the newest strategies is combination of radiotherapy and immunotherapy by nanoparticles in cancer therapy (Shen et al., 2022). For reducing immunogenicity and elevating immune escape of nanostructures, their surface modification with cell membrane is suggested (Y. Zeng et al., 2022). The nanocarriers can deliver two compounds such as doxorubicin and erastin in providing synergistic cancer therapy and these drugs can be loaded in hydroxyethyl starch-polycaprolactone nanostructures (C. Xu et al., 2023). In order to stimulate cell death in tumor cells, the nanostructures should be able to reach cancer cells and therefore, they should evade being captured by macrophages (Z. Liu et al., 2023). Hence, targeted therapy of cancer has obtained much attention in recent years. In the present review, the state-of-art of using nanoparticles in pancreatic cancer (PC) therapy is followed and first, an overview of PC is provided to discuss its malignancy and problems in its treatment and then, an in-depth discussion of using nanoparticles for PC therapy is provided.

2. Pancreatic cancer: epidemiology and treatment challenges

After cardiovascular diseases, cancers are among the most common diseases around the world and development of effective therapeutics for these diseases is of interest (Mirzaei et al., 2021a,b,c,d,e). PC is a disorder of gastrointestinal tract in which its malignancy has caused significant problems for the prognosis of patients (Milad Ashrafizadeh et al., 2023). Although molecular profile of PC has been understood in recent years, its management and treatment are still problematic and the 5-year survival rate of patients is 5% (Milad Ashrafizadeh, Navid Rabiee et al., 2022; Pandol et al., 2012; Tanase et al., 2014). Based on histopathological profile, there are different types of PC that pancreatic ductal adenocarcinoma is the most common type. PC is the eighth or ninth leading cause of death worldwide and it is the fourth most common disease (Jemal et al., 2010; Krejs, 2010). In 2020, 481,000 new cases of PC were diagnosed and even in developed countries, the incidence rate and death rate of this malignancy are high (Khan et al., 2017). The 5-year survival rate of patients will be less than 10% and median overall survival of patients is 2–8 months (R. L. Siegel et al., 2017). The progressive nature of PC that is asymptomatic in early stages is a problematic issue for patients and after diagnosis of cancer in advanced stages, it has metastasis and therapeutic intervention is not that much effective for its treatment (Garrido-Laguna and Hidalgo, 2015; Khan et al., 2015; Kleeff et al., 2016). Biomarkers can be used for diagnosis, but their efficacy is under question and CA19-9 is an antigen that can be used for this purpose (Ballehaninna and Chamberlain, 2013). PC has four stages and, in each stage, the survival rate of patients is different that lowest 5-year survival rate is in IV stage that is 2% and highest survival rate is in stage I that is 13% (Lohse and Brothers, 2020). Although prognosis and survival of PC patients have not been improved in recent years, there have been attempts in understanding genomic mutations, risk factors and therapeutic strategies for this disease. PC commonly occurs in older people and in addition to late diagnosis, it shows high speed progression and is able to develop resistance to therapy (Seufferlein et al., 2012). PC is considered as a silent killer, since the only sign in early stages is pain and after diagnosis in higher stages, it shows metastasis to other tissues (Bapat et al., 2011; Cornman-Homonoff et al., 2017; D'Haese et al., 2014; di Mola and di Sebastiano, 2008). Table 1 summarizes some of dysregulated genes in PC. Fig. 1 is a schematic of PC.

Different strategies are used in treatment of PC including radiotherapy, chemotherapy, surgical resection and immunotherapy. In more recent approaches, plant derived-natural compounds have been employed to suppress progression of PC (Donald et al., 2012; Goldsmith

et al., 2015). Moreover, gene therapy has been emerged as a new tool in treatment of PC in which it can affect expression level of genes in a way to impair tumorigenesis in PC (Mirzaei et al., 2021a,b,c,d,e). However, there is still much space in treatment of cancer patients. Furthermore, there are also significant problems with aforementioned therapies, urging scientists to develop new type of therapies for cancer. About chemotherapy, the most important problem is development of drug resistance that can result from genomic mutations in tumors and is attributed to malignancy of cancer cells (Di et al., 2021; Meng et al., 2020). Moreover, phytochemicals have brought much hope in treatment of human cancers, but their poor bioavailability is a problem that requires nano-scale delivery systems (M. Ashrafizadeh et al., 2020a,b,c). The gene therapy approaches suffer from enzyme degradation and lack of specific internalization in tumor cells that requires nanoparticles for their targeted delivery (Mirzaei et al., 2021a,b,c,d,e; Mirzaei et al., 2021a,b,c,d,e). These drawbacks urge researchers to use nanoparticles for treatment of human cancers, especially PC that is aim of current review. Table 2 provides an overview of nanostructures used in PC therapy.

3. Smart nanocarriers

3.1. pH sensitive

The low pH level in tumor misgovernment (TME) has been considered as a promising tool in site-specific delivery of cargo for treatment of PC. The mesoporous silica nanoparticles (MSNs) and porous hollow silica nanostructures have appeared as promising factors for drug delivery due to their high safety confirmed in vitro and in vivo (Baeza et al., 2016; Y. Chen et al., 2014; Y. Chen and Shi, 2016; Shao et al., 2016; Shao et al., 2018; N. Singh et al., 2011; J. Wu et al., 2018; S. H. Wu et al., 2013; You et al., 2017). Although silica-based nanoparticles have been under attention in cancer theranostics, there have been some problems related to these nanostructures including presence of toxic silica framework decreasing biocompatibility and uncertain retention in vivo that diminish their clinical application (Y. Chen and Shi, 2016; X. Zeng et al., 2017). The introduction of disulfide bonds into silica-based nano-scale delivery systems is beneficial in achievement of organic/inorganic hybrid nanostructures (Du et al., 2018; N. Lu et al., 2018; N. Lu et al., 2016). In line with these discussions, hollow mesoporous

organosilica nanoparticles (HMONs) have been developed that are beneficial in treatment of PC. These nanocarriers were used for delivery of gemcitabine in PC therapy that enhance penetration of drug in tumor cells and they demonstrate high biocompatibility, degradability and low toxicity towards normal cells (F. Gao et al., 2019). In another experiment, pH-sensitive core-shell nanobombs have been developed for co-delivery gemcitabine and autophagy inhibitor, and degradation of calcium phosphate in low pH level leads to drug release. They increase cellular uptake of gemcitabine and then, autophagy inhibition suppressed tumor proliferation. Furthermore, in vitro and in vivo studies have shown that nanobomb reduces expression level of MMP-2 and paxillin in suppressing tumor progression (X. X. Chen et al., 2021).

The TME of PC is completely unique and it is dense containing 90% of stroma cells and 10% cancer cells (Erkan et al., 2012; Kota et al., 2017). Moreover, PC has been surrounded by stromal cells and extracellular matrix (ECM) and therefore, it is problematic for drugs to penetrate stroma in reaching tumor cells that is one of the main reasons for developing chemoresistance in PC cells (Erkan et al., 2012; Hosein, Brekken, Maitra, & hepatology, 2020). In order to achieve high internalization in TME of PC cells, it is suggested to develop membrane-disruptive nanostructures that can remove the stroma and other components in TME and ECM to suppress PC progression via drug release at tumor site (Fan et al., 2021). The pH-sensitive nanostructures have shown promising result in treatment of PC and one of their abilities is to deliver two drugs in synergistic cancer therapy. The co-delivery of gemcitabine and ERK inhibitor by polymeric nanostructures results in drug release in low pH level of TME, the nanoparticles are stable and they have particle size of 100–150 nm. These nanostructures suppress tumorigenesis in a synergistic way and they can overcome to limitations and drawbacks of ERK inhibitors in clinical application (Ray et al., 2021). Although pH-sensitive nanocarriers have been employed for co-delivery of two drugs, their particle size is still low (Ray et al., 2019).

Liposomes are one of the most promising nanocarriers in delivery of hydrophobic and hydrophilic drugs (Fanciullino and Ciccolini, 2009; Hofheinz et al., 2005; Hyodo et al., 2013). The discovery of liposomes was performed in 1960s by Alec Bangham (Laouini et al., 2012), the surface of these nanocarriers has been modified with PEG in improving their features (Graeser et al., 2009; Jantscheff et al., 2009; I.-Y. Kim et al., 2019; Perche and Torchilin, 2013). Liposomes are able to release drugs in cells via endocytosis (Hilbig and Oettle, 2008; H. H. Xu et al., 2014). Recently, pH-sensitive liposomes have been employed for co-delivery of curcumin and gemcitabine, and they enhanced cellular uptake of drugs. Furthermore, due to down-regulation of MRP5 by curcumin, an increase occurs in cellular uptake of gemcitabine (H. Xu et al., 2021). Moreover, the drug-loaded PAMAM dendrimers are also beneficial carriers for treatment of PC and pH-sensitive delivery of compounds. The nanoparticles demonstrate particle size of 80 nm in neutral pH and when they are penetrated into deep side of TME that has pH level of 6.5–7, it causes increase in size of nanostructures. This change in size of nanoparticles improves the extravasation and accumulation in tumor site via EPR effect and improves penetration in tumor tissue. Therefore, they are promising candidates in treatment of PC (H. J. Li et al., 2016). Therefore, pH-sensitive nanoparticles are can impair progression of PC in vitro and in vivo, and they improve potential of chemotherapy drugs in PC therapy (Iacobazzi et al., 2021; Kanamala et al., 2018; Pan et al., 2014; Zeiderman et al., 2016).

3.2. Redox sensitive

The redox is another stimulus used for release of drug at tumor site and redox-sensitive nanoparticles, especially micelles are promising in release of drug in response to GSH in TME (L. Zhu and Torchilin, 2013). Compared to normal cells and extracellular environment, the levels of GSH are higher in tumors (Bansal and Simon, 2018). Therefore, targeted delivery of drugs using GSH-sensitive nanoparticles has been of importance in PC therapy. The gemcitabine and miR-519c have been loaded

Table 1
The dysregulated molecular pathways in PC.

| Dysregulated signaling	Outcome	Reference
SAA1	Cancer-associated adipocytes increase SAA1 expression in tumorigenesis	Takehara et al. (2020)
EGFR	Single-cell transcriptomics highlights EGFR upregulation	(X. L. Zhao et al., 2021)
USP28/FOXM1/Wnt	USP28 increases FOXM1 stability in stimulation of Wnt	(L. L. Chen et al., 2021)
MST1/pyroptosis	MST1 stimulates ROS-mediated pyroptosis in PC elimination	Cui et al. (2019)
DIAPH3/TrxR1	DIAPH3 enhances TrxR1 levels to induce antioxidant activity	Rong et al. (2021)
SGLT2/Hippo	SGLT2 promotes Hippo expression in accelerating tumorigenesis	(D. D. Ren et al., 2021)
TRIM47/FBP1	TRIM47 stimulates ubiquitination of FBP1 in accelerating glycolysis	(L. Li et al., 2021)
TMEM43/PRPF3	TMEM43 promotes stability of PRPF3 in accelerating tumorigenesis	(J. Z. Li et al., 2022)
EIF3B	Silencing EIF3B diminishes progression and survival rate of cancer cells	(Zhu et al., 2021a)
ELK1/LGMN	ELK1 increases LGMN expression in poor prognosis	Yan et al. (2021)
S100A14	S100A14 enhances gemcitabine resistance	(Zhu et al., 2021b)
USP44/FBP1	USP44 increases FBP1 stability in reversing gemcitabine resistance	(C. Yang et al., 2019a,b,c)
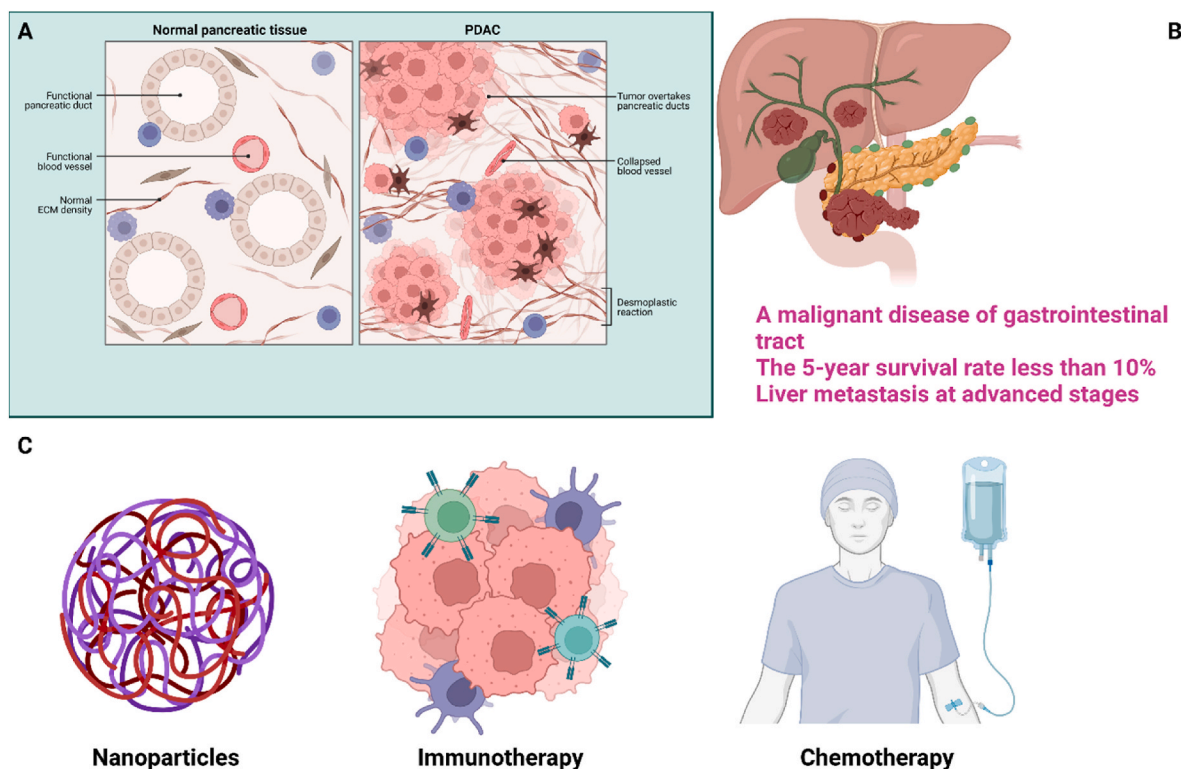
Fig. 1. A schematic depiction of PC.

on polymeric micelles that loading efficiency for gemcitabine was 14% and its drug release upon exposure to GSH was 90%. MiR-519c was chemically conjugated to polymeric micelles and in order to improve their selective targeting, they have been modified with GE11 peptide targeting EGFR. This leads to increase intracellular accumulation of micelles after systemic administration in animal models and by reducing HIF-1α expression and suppressing glucose metabolism, it can impair progression of PC c ells (Xin et al., 2020). In addition, DNA plasmid can be loaded on nanoparticles along with chemotherapy drugs in treatment of PC. After development of gelatin nanoparticles, p53-expressing plasmid and doxorubicin were loaded. Based on in vivo results, these nanoparticles suppressed tumor proliferation and due to selective targeting EGFR, their efficacy was higher compared to non-targeted nanostructures. The combination delivery increased potential in tumor suppression from 50-60%–77% and by increasing p53 expression in tumor cells, it caused cell death (J. Xu et al., 2014). In addition, redox-sensitive nanostructures have been used for co-delivery of drugs in PC therapy. Curcumin is a natural compound with chemopreventive activity (Abadi et al., 2022; Milad Ashrafizadeh, Ali Zarrabi, Farid Hashemi et al., 2020) and curcumin can suppress glycolysis mechanism in PC cells via down-regulation of HIF-1α (W. J. Guo et al., 2022). In order to increase potential of curcumin in cancer therapy, nanoparticles have been used in its delivery (Le et al., 2018). The co-delivery of curcumin and doxorubicin by redox-sensitive nanostructures leads to reduction in progression of PC cells up to 49% and they have high biocompatibility towards normal cells (Anajafi et al., 2017).

3.3. Light sensitive

The previous sections evaluated the response of nanoparticles to endogenous stimuli in TME and subsequent release of cargo in cancer therapy. The spatial modulation of nanoparticles can be provided by exposure to light and such nanostructures have been of importance in field of PC therapy. The light-activated monomethyl auristatin E (MMAE) prodrug nanoparticles have been prepared for co-delivery of chemotherapy drug and chlorin e6 as photosensitizer to mediate synergistic cancer therapy. When nanostructures exposed to irradiation, it caused increase in ROS generation and caspase-3 upregulation occurred that mediate release of drug from nanoparticles to induce cell death (Cho et al., 2022). The light-responsive nanocarriers can respond to wavelength of 405 nm (Ayala Orozco et al., 2020) and in spite of high potential of photo-responsive nanoparticles in PC therapy, there are no many experiments in this case (Table 3). Fig. 2 represents the function of stimuli-responsive nanocarriers in PC removal.

4. Photothermal and photodynamic therapy

4.1. Photothermal therapy

Gold nanoparticles can produce local heat after exposure to photons and this can lead to photothermal therapy (PTT) that is a non-invasive manner and is a spatiotemporal controllable process (Y. Li et al., 2014; Mallidi et al., 2009). In addition, since gold nanoparticles can improve pharmacokinetic of drugs, combination with PTT is beneficial in increasing drug sensitivity (Y. Guo et al., 2013a,b; D. H. Kim and Larson, 2015; Patino et al., 2015; Patra et al., 2010). A combination of mesoporous silica/gold nanoparticles have been developed and then, they have been modified with transferrin for targeted cancer therapy. These hybrid nanostructures have been used for targeted delivery of gemcitabine to improve potential of chemotherapy in PC suppression and due to PTT function of gold nanoparticles, exposure to laser irradiation leads to photo/chemo-therapy of PC (Zhao et al., 2017).

The gold nanoparticles are considered as good substances for SERS and they are utilized for purpose of therapeutic progression monitoring (de Moliner et al., 2021; Joseph et al., 2018; Panikkanvalappil et al., 2014). SERS is beneficial in improving selectivity, accuracy and specificity of multiplex detection and it is a good thing for molecular diagnosis (Langer et al., 2020). Moreover, SERS is beneficial in providing in-depth information regarding intracellular distribution (A. Ramya et al., 2015; A. N. Ramya et al., 2021; A. N. Ramya et al., 2016). A recent

Table 2

The application of nanocarriers for PC therapy.

Nanocarrier	Remark	Ref
iRGD-modified nanoparticles	Therapeutic delivery of Kras siRNA in impairing tumorigenesis	Lo et al. (2018)
Exosomes	Delivery of CRISPR/Cas9 system for down-regulation of Kras in PC therapy	McAndrews et al. (2021)
R8-dGR cationic liposomes	Therapeutic delivery of CRISPR/Cas9 system in reducing HIF-1α expression in cancer therapy	(M. M. Li et al., 2019)
siRNA-Loaded Hydroxyapatite Nanoparticles	Down-regulation of KRAS in impairing carcinogenesis	(D. Luo et al., 2021)
NIR-activated polymeric nanoplatform	Combination of phototherapy and chemotherapy in synergistic PC suppression	Zhan et al. (2020)
IR-780 Loaded Phospholipid Mimicking Homopolymeric Micelles	Long-circulation time and EPR effect in phototherapy of PC	(Yangjun Chen et al., 2016)
Black TiO2-based nanoprobes	MRI-guided photothermal therapy	(Wang et al., 2018a)
Peptide-conjugated hybrid lipid-mesoporous silica nanoparticles	Particle size of 160 nm Co-application of chemotherapy and phototherapy in tumor suppression	Thapa et al. (2017)
Catalase-loaded hierarchical zeolite	An implantable nanocapsule for PDT and impairing PC progression	(D. Hu et al., 2018)
Iron oxide nanoparticles	Combination of phototherapy and immunotherapy in synergistic cancer therapy	(M. T. Wang et al., 2022)
Injectable and Thermosensitive Liposomal Hydrogels	Light-responsive release of cargo in chemo-/photo-therapy of cancer	Kong et al. (2021)
Dual-functional melanin-based nanoliposomes	Targeted delivery of gemcitabine Co-application of chemotherapy and phototherapy	(J. Wang et al., 2019)
Iron-oxide core gold-shell nanoparticles	Photothermal ablation of cancer cells	(Yang Guo et al., 2013)
Prodrug Nanoparticles	Inducing anti-cancer immunity Phototherapy Suppressing glucose metabolism	Sun et al. (2021)
Phenylboronic acid modified nanoparticles	Amelioration of immunosuppression Suppressing cancer invasion and metastasis	(Zhengze Lu et al., 2021)
Prodrug nanoparticles	Delivery of calcipotriol and SN38 in PC therapy High blood circulation time Suppressing cancer invasion	(L. L. Wang et al., 2021)
Emodin-Conjugated PEGylation of Fe3O4 Nanoparticles	Targeting imaging in vivo	(S. S. Ren et al., 2021)
Undaria pinnatifida fucoidan nanoparticles loaded with quinacrine	Preventing proliferation and invasion of cancer cells Higher anti-cancer activity	(Etman et al., 2021)
Nimbolide-encapsulated PLGA nanoparticles	Down-regulation of Akt and mTOR in inducing MET in PC	(D. Singh et al., 2022)
Icariin-Loaded PLGA-PEG Nanoparticles	Apoptosis induction in cancer cells	Alhakamy (2021)
Thermosensitive and biodegradable hydrogel encapsulating targeted nanoparticles	Co-delivery of paclitaxel and gemcitabine in suppressing PC progression	Shabana et al. (2021)
Arsenic trioxide-loaded nanoparticles	Enhanced sensitivity of tumor cells to gemcitabine chemotherapy	(Y. H. Zhao et al., 2022)
Triptolide and celastrol loaded silk fibroin nanoparticles	Synergistic impact in tumor suppression	(B. Ding et al., 2017)

Table 2 (*continued*)

Nanocarrier	Remark	Ref
Peptide-Functionalized Polymeric Magnetic Nanoparticles	Selective internalization into tumor cells due to modification with CKAAKN peptide Specific diagnosis of cancer cells	(Xiuliang Zhu et al., 2019)
Diethyldithiocarbamate-copper complex loaded into hyaluronic acid decorated liposomes	Suppressing proliferation of cancer stem cells	Marengo et al. (2019)

Table 3

The stimuli-responsive nanocarriers in PC therapy.

Nanoparticle	Stimulus	Remark	Ref
Monomethyl Auristatin E Prodrug Nanoparticles	Light	Mediating chemo-/photo-therapy in impairing tumorigenesis	Cho et al. (2022)
Polymeric micelles	Redox	Co-delivery of miR-519c and gemcitabine in suppressing tumorigenesis Reducing HIF-1α expression	Xin et al. (2020)
Gelatin nanoparticles	Redox	Redox-responsive release of gemcitabine and p53 gene to induce apoptosis	(J. J. Xu et al., 2014)
Polymerosomes	Redox	Co-delivery of curcumin and gemcitabine in reducing survival rate of cancer cells	Anajafi et al. (2017)
Liposomes	pH	Hyaluronic acid modification of liposomes results in attachment into CD44 receptor Enhanced cellular uptake by 3.6 times	(M. Tang et al., 2019)
Liposomes	pH	Delivery of GGT1 inhibitors in suppressing proliferation of tumor cells	(J. Lu et al., 2015)
Liposomes	pH	Suppressing gemcitabine resistance	(H. Xu et al., 2016)
Clustered nanoparticles	pH	Co-delivery of TGF-β receptor inhibitors (LY2157299) and siRNA targeting PD-L1 (siPD-L1) for tumor microenvironment remodeling and providing anti-tumor immunity	(Y. L. Wang et al., 2020)

experiment has shown that MnO₂/Gold nanoparticles can be prepared and be modified with CCK peptide in presence of EDC to accelerate process of surface modification. Then, they can bind to receptors on the surface of cell for receptor-mediated endocytosis and after exposure to irradiation, they produce heat to stimulate apoptosis and this process can be monitored by SERS technology (Sujai et al., 2021).

Recently, thermally active nanotubes have brought much promise in treatment of PC (Antaris et al., 2013; Iancu and Mocan, 2011). However, a number of unexpected toxicities and biological interactions have prevented the clinical application of carbon nanotubes (Iverson et al., 2013; Mittal et al., 2011; Toyokuni, 2013). The first problem is identification of carbon nanotubes by reticuloendothelial system (RES) and the second one is lack of specificity towards a certain region (Patlolla et al., 2011). The surface modification of carbon nanotubes with PEG (PEGylation) has been beneficial in improving solubility of these nanostructures and it prevents enzymatic degradation and identification by macrophage, thus improving its blood circulation time (Ilie et al., 2013; M. Song et al., 2013; Tu et al., 2014). The multiwalled carbon nanotubes have been modified with PEG and then, exposure to irradiation (808 nm) results in mitochondrial membrane depolarization to induce apoptosis in PC cells (Mocan et al., 2014). In a recent effort,
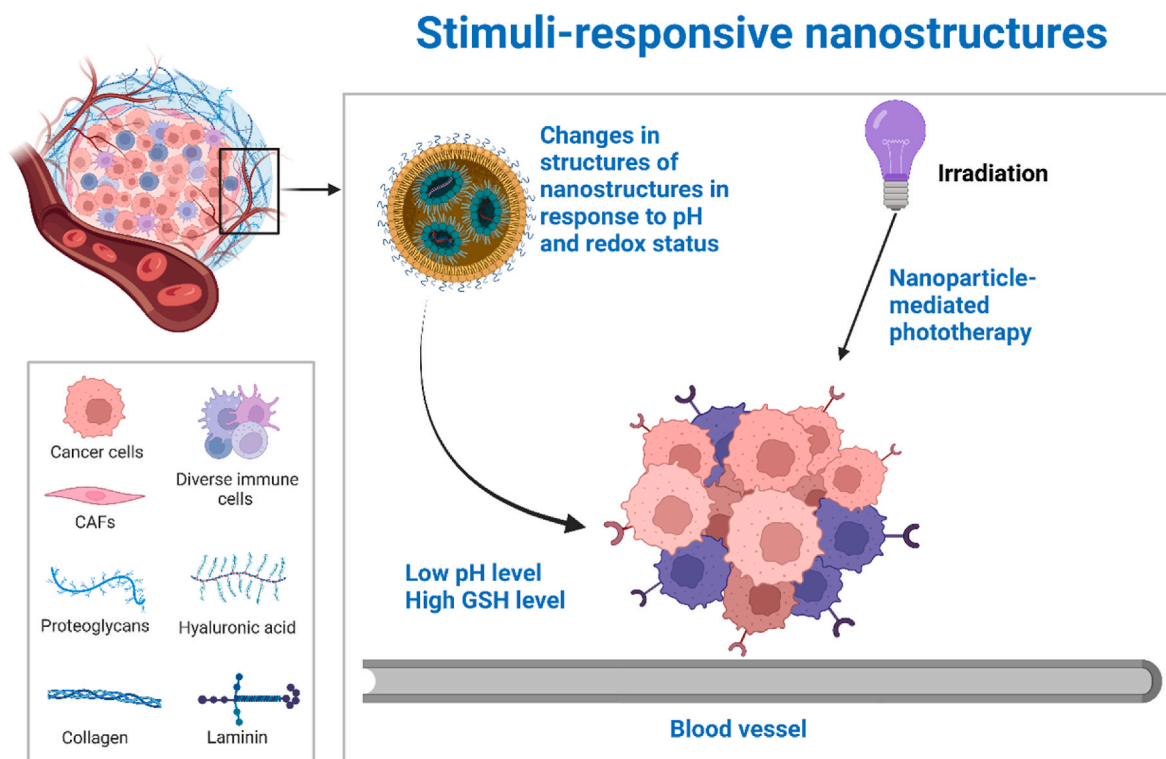
Fig. 2. The stimuli-responsive nanoparticles in PC therapy.

graphene@gold nanostar/lipid structures have been prepared. The graphene/gold nanostar has been modified with lipid membrane that has positive charge and then, whole nanosystem was modified with folic acid to specifically bind to folate receptors on the surface of PC cells. This nanosystem can provide specific delivery of gene and by absorbing irradiation, it can mediate gene therapy and PTT in suppressing PC progression (Jia et al., 2020). According to these studies, the nanostructures are promising agents in PC therapy that can absorb irradiation for PTT that is a non-invasive method. Moreover, such nanoparticles can be used for simultaneous drug delivery to mediate chemo-/-photo-therapy of PC cells. In order to improve some of the features of nanoparticles such as biocompatibility and long-circulation time, their surface modification with PEG can be provided (Poudel et al., 2017).

4.2. Photodynamic therapy

Photodynamic therapy (PDT) has appeared as new emerging tool for purpose of cancer therapy and when photosensitizers are placed at tumor site, exposure to irradiation can lead to energy transfer to surrounding oxygen molecules in increasing ROS generation for tumor ablation (H. Y. Zhao et al., 2022; L. X. Zhao et al., 2021). Three components are vital for purpose of PDT that include presence of photosensitizer, oxygen molecule and exposure to irradiation. Red and near infrared light can be used for purpose of PDT, as they have deep penetration into tissue and it results in destruction of chemical bonds to mediate monitored release of drug (H. S. Han and Choi, 2021; F. Wu et al., 2021). However, photosensitizer can be also adsorbed by normal tissues and this results in damage to both tumor and normal cells (Liu et al., 2019b; Y. Y. Wang et al., 2021). Therefore, targeted delivery of photosensitizers by nanoparticles can mediate specific PDT of tumor cells, especially in PC. The micellar nanoparticles have been used for delivery of paclitaxel, gemcitabine and porphine in PC therapy that nanoparticles had particle size of 135 nm, high stability and controlled release of drug. Micelles demonstrate high accumulation in PC tissue and after exposure to 650 nm laser irradiation, it causes PDT and due to

targeted delivery of paclitaxel and gemcitabine, it leads to chemo-/-photodynamic-therapy of PC (Q. Wu et al., 2022). Similar to PTT that can be used along with chemotherapy for synergistic cancer therapy, nanoparticle-mediated PDT can be used along with chemotherapy such as gemcitabine and after loading chlorin e6 (Ce6) as photosensitizer, it results in ROS overgeneration to mediate PDT in suppressing PC progression (L. Zhu et al., 2022).

The liquid crystalline nanoparticles (LCNPs) are promising factors for purpose of drug delivery and in recent years, they can be used for delivery of photosensitizers and chemotherapy agents in cancer therapy. Re(I) and gemcitabine were loaded in LCNPs that had particle size of 159–173 nm with zeta potential of −10 mV. Nanoparticles demonstrated 70% and 90% entrapment efficiency for gemcitabine and Re(I), and stimulated apoptosis in PC cells (Liew et al., 2022). Quantum dots (QDs) are colloidal semiconductors that have group II-VI or group III-V elements (Weaver et al., 2009). The optical property of QDs is unique and they have a number of characteristics including large absorption spectra, narrow emission bands and high molar extinction coefficient that make them proper agents for PDT (José-Yacamán et al., 2002; J. Liu et al., 2014). The ability of QDs for ROS generation has been beneficial for PDT (Anas et al., 2008). In an experiment, CdSe/ZnS QDs were prepared for suppressing growth rate of PC and by providing ROS generation, they mediate apoptosis to decrease cancer cell viability (S. J. He et al., 2016).

In addition, polymeric nanoparticles can be employed for encapsulation of Ce6 as photosensitizer. However, if Ce6 is solely used for PDT, its ability is low due to hyperactivation of ABCG2 in PC cells that mediates efflux of drug from tumor cells. Polymeric nanoparticles increase internalization of Ce6 into PC cells to increase its potential in PDT and impairing tumorigenesis (Roh et al., 2017). One of the important aspects is association between nanoparticle-mediated PDT and immune therapy in PC cells. PDT is capable of mediating immunogenic cell death (ICD) to induce dendritic cells (DCs) and mediate T cell infiltration for boosting immune response (Castano et al., 2006; Duan et al., 2019; L. Luo et al., 2018). An experiment has focused on development of oxygen-delivering

polyfluorocarbon nanovehicles that deeply penetrate into tumor tissue to oxygenate it and after exposure to irradiation, ROS generation occurs due to function of PF11DG to stimulate ICD in tumor cells and mediate gemcitabine release for improving anti-tumor immunity via increasing number of CD8$^+$ T and NK cells (Z. Z. Wang et al., 2021). Therefore, when it is brought into function of PDT in PC therapy, it is believed that similar to PTT, the mechanism of PDT is to induce cell death and it has also good efficacy in cancer therapy. However, there should be more attention into biocompatibility of these mechanisms and their effect on surrounding normal tissues as well as the impact of PDT and PTT on the immunotherapy in PC (Fig. 3).

5. Drug delivery

Nanotechnology is considered as an interdisciplinary field that aims in development of nanomaterials, nanoelectronis and nano-biotechnology. Nanotechnology has shown promising applications in healthcare, pharmaceuticals, biomimetics, materials, robotics and others (Miyazaki and Islam, 2007; Shea, 2005; Tratnyek and Johnson, 2006). One of the main applications of nanotechnology is in field of medicine and they promise important functions in cancer therapy via delivery of drugs (Nikezić et al., 2020). In addition to drug delivery, nanocarriers have been used for diagnosis and development of biocompatible nanomaterials in vitro and in vivo (Duncan, 2003; Ferrari, 2005). There are some questions related to drugs used for purpose of cancer therapy can be answered by nanoparticles. The first drawback is that in spite of promising results in vitro in regulation of molecular pathways, when ant-cancer agents are applied in vivo or in drug resistant-tumor cells, their ability in tumor suppression is not high. Moreover, there should be a nanosystem for targeted delivery of drugs in cancer therapy to provide specific accumulation of anti-cancer compounds in tumor site, reducing survival rate and also, enhancing potential in cancer elimination (M. Ashrafizadeh et al., 2022a,b,c,d,e; M. Ashrafizadeh et al., 2020a,b,c). The current section focuses on the application of nanostructures for purpose of drug delivery in PC. Although, it appears that most of the studies have focused on drug delivery approaches in PC therapy and this is the most important part. One of the problems related to nanoparticles in treatment of PC is their recognition by reticuloendothelial system (RES) that they are considered as foreign cells and cleared by immune system (Peng and Mu, 2016). The

biomimetic nanoparticles that have been modified with natural cell membranes, can elevate potential in targeted drug delivery (Ji et al., 2020; R. R. Li et al., 2019). The macrophage membrane-coated nanoparticles are capable of increasing the circulation in bloodstream, escaping RES system, escaping immune system and improving results in vivo for disease treatment (C. Gao et al., 2020; Liu et al., 2019a; Yu et al., 2020; Zhang et al., 2018). The camouflage can be diagnosed by cancer cells and then, they are internalized in them to release drug in a prolonged manner (Wang et al., 2018c; Zhang et al., 2018). In an effort, PLGA nanoparticles were prepared for delivery of gemcitabine in PC therapy and their surface was modified with macrophage membrane. This action improves biocompatibility of nanoparticles and enhances their accumulation in cancer cells. The combination use of nanoparticles and erlotinib led to suppressing of growth and DNA synthesis in impairing tumorigenesis in vitro and in vivo (Cai et al., 2021). In addition to surface modification, nanoparticles can be synthesized in a way that they are similar to cell membrane. For instance, phospholipids and cholesterol can be used for generation of liposomes that deliver gemcitabine to tumor cells and mimic cell membrane features in PC therapy (Bulanadi et al., 2020).

One of the most important progresses in PC therapy is development of nanocarriers for delivery of natural products. Berberine is a natural product that promotes levels of ROS to stimulate apoptotic cell death in PC (Park et al., 2015). Moreover, berberine stimulates DNA damage and cell cycle arrest in PC cells (Pinto-Garcia et al., 2010). The berberine- and irinotecan0loaded liposomal nanostructures have been beneficial in treatment of PC and by providing synergistic impact, they impair tumorigenesis (Cai et al., 2021). Furthermore, berbamine-loaded lipid nanoparticles are able to impair survival rate, growth and invasion of PC cells. These nanostructures stimulate apoptosis and they exert higher cytotoxic impact on tumor growth in vivo in animal model and reduced expression level of MMP-2, MMP-9 and Bcl-2 in PC (Z. Tang et al., 2022).

Oridonin is also a naturally occurring compound that is derived from Rabdosia rubescens (S. Gao et al., 2016) and it has important pharmacological activities including anti-bacterial, anti-inflammatory and anti-cancer (Xia et al., 2017; Yang et al., 2017). The GPC1-targeted gold nanoparticles have been applied for purpose of oridonin delivery in PC therapy and they induce apoptosis in PC cells and their ability is higher compared to non-targeted gold nanoparticles. Their biocompatibility was high and owing to important functions of gold nanoparticles, they
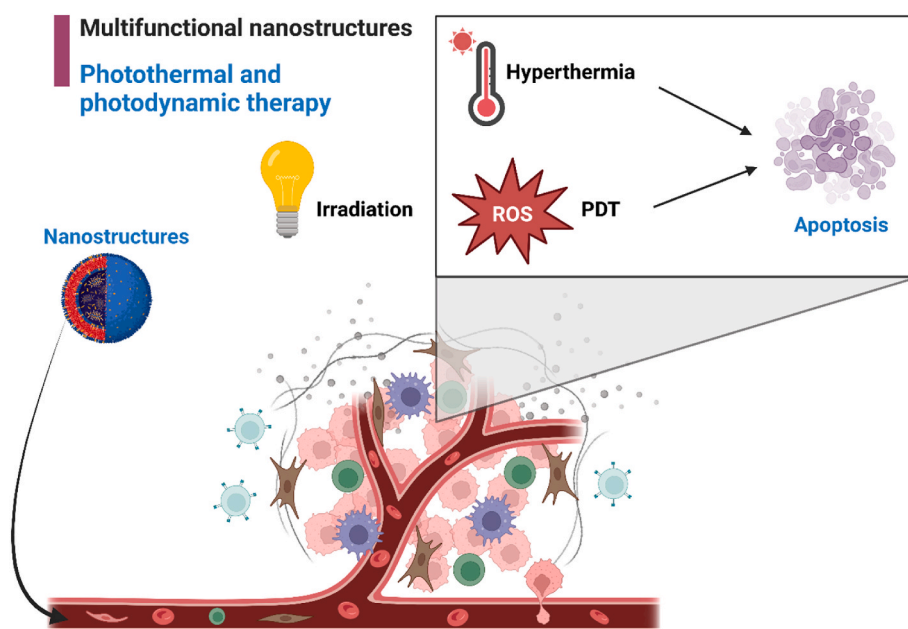

Fig. 3. The role of PDT and PTT mediated by nanostructures in PC therapy.

can be used for imaging of PC (Qiu et al., 2018). In addition to bioactive components, the leaf extracts can be loaded in nanoparticles for purpose of cancer therapy. Silver nanoparticles have been prepared for purpose of berberis thunbergii leaf delivery and they are able to effectively suppress viability of PC cells (J. W. Guo et al., 2022). However, it is suggested to load two anti-tumor compounds with various and distinct action mechanism in PC therapy. The PLGA nanoparticles have been fabricated for co-delivery of erlotinib and alantolactone in PC therapy and after endocytosis into tumor cells, PLGA nanoparticles release drugs. Then, erlotinib inhibits EGF/EGFR axis and alanolactone suppresses STAT3 pathway in impairing tumorigenesis. Moreover, alanto-lactone is able to increase ROS generation in p38 upregulation to induce apoptosis (Bao et al., 2021). According to these studies, it is highly suggested to use nanoparticles for delivery of drugs in PC therapy. After using nanoparticles, the internalization of drugs in tumor cells enhances and this improves cytotoxicity. The systemic toxicity of drugs decreases and nanoplatforms can mediate co-delivery for synergistic cancer therapy. Their particle size is low and their surface modification with cell membrane can significantly improve their biocompatibility and ability in PC therapy.

6. Gene delivery

When exogenous nucleic acid molecules are applied as agents for disease therapy to modulate genetic levels, it is known as gene therapy (Piperno et al., 2021). The main goal in using gene therapy method is to introduce genetic materials for therapeutic purposes with high biocompatibility. When a gene works improperly, gene therapy can be used to normalize its function and prevent disease progression. The gene therapy allows to introduce a proper gene and replace impaired gene with correct one in preventing disease pathogenesis (Sung and Kim, 2019). The use of genetic tools has a long story and in spite of providing satisfactory results, even in clinical trials for treatment of patients, the usefulness of gene therapy methods in cancer therapy has shown some drawbacks and problems. The TME in cancer cells display some similarities with inflammatory diseases and due to presence of cytokines and chemokines, it has an inflammatory environment. Moreover, due to proliferation of tumor cells in TME using glycolysis, high levels of lactate are generated that can reduce pH level and reach it to acidic level. Therefore, such acidic pH is able to negatively affect nature of genetic materials. Moreover, acidic pH is not the only factor that can affect genetic material, and the efficiency of gene therapy is compromised by RNase enzymes and degradation of genetic materials can negatively affect their potential in cancer therapy. Moreover, similar to drugs, genes lack specific delivery to tumor site and application of nano-scale delivery systems is beneficial in improving their accumulation in cancers (Mirzaei et al., 2021a,b,c,d,e; Mirzaei et al., 2021a,b,c,d,e). The current section focuses on the application of nanostructures for purpose of gene delivery in PC.

One of the problems in treatment of PC is development of immune escape in PC cells. The PD-L1 inhibition has been beneficial in improving anti-cancer immunity (Pacheco-Torres et al., 2021). Therefore, using genetic tool for down-regulation of PD-L1 can be used for anti-tumor immunity. PLGA nanostructures have been used for delivery of PD-L1-siRNA in PC therapy and the cellular uptake of nanoparticles was 99.2%. This gene therapy inhibited the upregulation of PD-L1 by IFN-gamma and enhanced sensitivity of PC cells to antigenic-specific immune cells. Moreover, siRNA delivery by PLGA nanoparticles suppressed tumor growth in vivo and increased CD8+T cells to mediate apoptosis (Jung et al., 2021). SiRNA has a negative charge and they can be degraded by enzymes in serum. Therefore, it is difficult for siRNA to penetrate into cell membrane (B. Kim et al., 2019). Therefore, it is suggested to use nanocarriers for delivery of siRNA and passing through biological barriers (Chengbin Yang, Guang Yang et al., 2019). There are two types of nanocarriers that can be used including viral and non-viral vectors (Setten et al., 2019; Chen et al., 2016). Due to low

biocompatibility and immune interaction of viral vectors, it is suggested to use non-viral vectors for this purpose (Thomas et al., 2003; Hao Yin et al., 2014). In a recent effort, carbon dioxide-derived biodegradable and cationic polycarbonates have been developed for siRNA delivery in PC therapy and they have high biocompatibility, low toxicity and high transfection efficiency. The endosomal escape of siRNA is provided by nanocarriers and they can protect against degradation to reduce K-ras expression in suppressing tumorigenesis (C. Han et al., 2021).

PRDM14 is one of the newly discovered factors in PC that before development of PC, its upregulation is observed in chronic pancreatitis (Moriya et al., 2018). The upregulation of PRDM14 enhances liver invasion of tumor cells and can also increase stemness of PC (Moriya et al., 2017). The PEGylated poly-L-ornithine (PLO)-based have been used for delivery of PRDM14-siRNA in PC therapy and after intravenous administration, the expression level of PRDM14 reduced that led to suppressed metastasis of tumor cells (Taniguchi et al., 2021). Moreover, single-wall carbon nanotubes have been used for siRNA delivery in suppressing PC progression (Anderson et al., 2014). However, one of the problems related to carbon nanotubes and also metal nanoparticles is their low biocompatibility and toxicity towards normal cells that can hamper their future application for PC therapy in clinical trials. Therefore, it is suggested to modify them with biocompatible polymers such as chitosan to pave their way for future clinical application. The cationic perfluorocarbon nanoemulsions are promising factors for delivery of siRNA in PC therapy. The nanoparticles penetrated deeply in tumor tissue and then, they released siRNA-NGF to reduce its expression leading to suppressed tumor progression in vivo (L. Ding et al., 2022). Based on these studies, it is suggested to use nanostructures for delivery of genes in PC therapy.

7. Functionalization of nanoparticles

7.1. Aptamers

Aptamer are single stranded nucleotides that their ability in binding to surface cell proteins and other small molecules with high affinity is of importance (Albanese et al., 2018; Zhou and Rossi, 2017Zhou and Rossi, 2017). Aptamer can have a DNA or RNA nature and their length is suggested to be 25–60 nts. The aptamers have been employed for targeted therapy of PC. XQ-2D is a newly developed aptamer that can bind to CD71 receptor, upregulated on the surface of PC cells to impair tumorigenesis (X. Wu et al., 2019). The SELEX method has been used to develop aptamers for increasing targeting ability in cancer therapy (F. He et al., 2020; Sefah, Shangguan, Xiong, O'donoghue, & Tan, 2010). Aptamers demonstrate important characteristics that their high affinity and specificity are among the most important ones. Due to high biocompatibility and efficacy of aptamers, they have been widely employed for drug delivery and clinical diagnosis as important fields in biomedicine (Keefe et al., 2010; Wang et al., 2018b). The polymeric nanostructures have been prepared from PCL-b-PEO and they have been decorated with aptamers to mediate targeted delivery of doxorubicin. Due to deep penetration of aptamer-modified polymeric micelles, they can increase doxorubicin delivery to PC cells and suppress their progression (Tian et al., 2021). Calcium phosphosilicate NanoJackets (NJs) are promising nano-scale delivery systems that demonstrate bioresorbable property and they have other features such as low toxicity, stability and protection of encapsulated cargo against degradation (Adair et al., 2010; Altinoğlu and Adair, 2010; Tabaković et al., 2012). They are inorganic nanomaterials and they are resistant to degradation in physiological status, but they are able to release their cargo in response to pH (Barth et al., 2010; Morgan et al., 2008). The NJs can be used for imaging of PC. However, in order to improve process of imaging, their surface modification should be provided. AP1153 as DNA aptamer was used for decoration of NJs that is capable of binding to CCKBR, as a receptor on the surface of tumor cells. Aptamer conjugation did not change the particle size of nanoparticles and moreover, after 36

h, high accumulation of nanoparticles in PC cells was observed, while there was no internalization in normal tissues. They displayed higher cellular accumulation compared to non-targeted nanoparticles and they were not internalized in normal pancreas tissue. They were able to exit from vasculature and distributed in PC tissue (Abraham et al., 2021). Regardless of modification of nanoparticles for targeted therapy of PC, aptamer can be directly conjugated to therapy agent in treatment of PC. However, this question may be raised that how aptamer can increase penetration of therapeutics to PC cells? An interesting experiment has shown that SQ2 as a nuclease-resistant aptamer is able to use clathrin-independent and caveolae-dependent (endocytosis pathways) in penetration into PC cells (Dua et al., 2015). The superparamagnetic iron oxide nanoparticles (SPIONs) have been emerged as promising agents for MRI imaging (Heydari Sheikh Hossein et al., 2020) and they can be coated by biocompatible compounds and they have functional groups on their surface (Laurent et al., 2014). The ability of SPIONs in cancer imaging, especially PC can be improved by surface modification by aptamer (Zou et al., 2019). The aptamer MUC1-SPIONs have particle size of 63.5 nm and their zeta potential is 10.2 mV. They had no cytotoxicity towards cells and by specific accumulation in animal model, they provided precise imaging of PC (Zou et al., 2019).

7.2. Peptides

Peptides are considered as sequences of amino acids that are connected to each other via amine bonds and they exert vital biological functions in cells. The peptides display ability in binding to receptors on the surface of cells and they have been used for generation of targeted nanoparticles in cancer therapy (Delfi et al., 2021). Although liposomes are promising nanocarriers in drug delivery due to their high biocompatibility, ease of synthesis and functionalization and low small size, there have been efforts in improving their targeted ability that one of them is development of stimuli-responsive liposomes (Milad Ashrafizadeh, Masoud Delfi et al., 2021) and another one is modification with peptides that is discussed in current section. Liposomes have been fabricated for co-delivery of paclitaxel and hydroxychloroquine, and then, they have been modified with TR in increasing their selectivity towards cancer cells. This co-delivery by peptide-modified liposomes prevents stromal fibrosis and simultaneously, enhances potential in PC elimination. The peptide-modified liposomes have demonstrated superior capacity both in vitro and in vivo. These liposomes were able to suppress autophagy in PC cells and cancer-associated fibroblasts to impair tumorigenesis (X. Chen et al., 2019). Since PC is a leading cause of death and its clinical progression is suggested to be rapid, cancer patients display survival rate less than 5% that is a great challenge for communities (Conroy et al., 2016; Gerritsen et al., 2016; R. Siegel et al., 2014). The mortality and morbidity of PC have shown enhancement in recent years (Guo and Cui, 2005). Due to this, multiple kinds of chemotherapy agents including paclitaxel, gemcitabine and 5-flourouracil have been utilized for purpose of cancer therapy (Cunningham et al., 2009). However, the results are partial and therefore, there has been focus on the combination therapy of PC (Deng et al., 2014; Lane, 2006; Xiong and Lavasanifar, 2011). Therefore, nano-scale delivery systems have been developed for targeted delivery of therapeutics in PC therapy. The dendrimers have been functionalized with PTP peptide and then, they have been loaded with paclitaxel and TR3 siRNA. Due to modification with PTP peptide, the dendrimers undergo receptor-mediated endocytosis in PC cells and after endosomal release, they deliver cargo in suppressing tumorigenesis (Y. Li et al., 2017). The benefit of modification with peptides is increased internalization in tumor cells compared to normal cells due to interaction with receptors on the surface of cancer cells (X. Zhu et al., 2019a,b).

7.3. Antibody and recombinants

Surface modification of nanoparticles with antibodies is also beneficial in improving targeted potential of nanoparticles in PC therapy. Death receptor 5 (DR5) is a membrane of TNF-α receptor that after upregulation, it stimulates apoptosis. TRAIL can antagonize DR5 and TRAIL has also affinity in binding to DR4, osteoprotegrin and decoy receptors 1 and 2 (Micheau et al., 2013). Since DR5 shows overexpression in various cancer cells and it is beneficial for TRAIL sensitivity, much attention has been directed towards its targeting in cancer therapy (Ashkenazi et al., 1999). The camptothecin has been loaded on nanoparticles and then, modification of these structures with αDR5 antibody (AMG 655) has been performed to target DR5. The antibody-targeted nanostructures stimulated apoptosis in PC cells, while naked nanoparticles had no potential. FLIP down-regulation elevated potential of antibody-conjugated nanoparticles in reducing PC progression. This effect is mediated by camptothecin that reduces FLIP expression and then, potential of antibody-modified nanostructures in PC apoptosis increases (Johnston et al., 2020). In another study, magnetic iron oxide nanoparticles have been prepared for doxorubicin delivery in PC and their modification with IGF1 has been performed. The intratumoral application of IGF1-modified nanoparticles can suppress growth and stimulate apoptosis in PC cells. Moreover, in vivo experiment revealed potential of drug-loaded nanoparticles in improving survival rate of animal models (H. Zhou et al., 2015). Enolase 1 (ENO1) protein is a glycolytic enzyme that has multiple functions (Capello et al., 2011; Cappello et al., 2009) and its overexpression is observed in PC cells that is responsible for increase in metastasis, invasion and progression (L. Wang et al., 2011; H. Yin et al., 2018). This cytoplasmic protein has enzymatic activity and has ability of being translated into MBP-1 in nucleus (Sedoris et al., 2010). ENO1-targeted SPIONs can be localized in cytoplasm and membrane, and due to selective internalization in PC cells, they can mediate proper imaging (L. Y. Wang et al., 2020).

7.4. Other ligands

The previous sections revealed potential of modification of nanoparticles with antibodies, peptides and aptamers in targeted treatment of PC. However, there are also other agents that can be used for this purpose and they demonstrate high selectivity towards PC cells. Hyaluronic acid (HA) is a polymer that is rich in hydroxyl and carboxyl functional groups that can be chemically modified and has ability of binding to CD44 receptor (Ganesh et al., 2013a,b; Misra et al., 2015). The previous studies have shown that HA-modified PEI nanostructures can delivery miR-125 b as a cargo in tumor microenvironment remodeling (Ganesh et al., 2013a,b; Ganesh et al., 2013a,b; Parayath et al., 2019; Parayath et al., 2018). A recent experiment has shed some light on the delivery of miR-125 b by HA-modified PEI/PEG nanoparticles leads to specific accumulation in tumor-associated macrophages to suppress M2 polarization and increase turnover of M2 to M1 macrophages in potentiating anti-tumor immunity (Parayath et al., 2021). The lipid nanocarriers can also be modified with HA to carry gemcitabine towards PC cells and such delivery enhances toxicity towards cancer cells and can impair progression in animal model (Z. Lu et al., 2017). In addition to delivery, HA-modified nanoparticles can specifically bind to CD44 receptor on the surface of PC cells and provide proper imaging of cancer (Y. Luo et al., 2019). According to these studies, small molecules, peptide, aptamers, antibodies and even polymers can be used for surface modification of nanoparticles in enhancing their selectivity towards PC cells (Table 4, Fig. 4).

8. Conclusion and remarks

The cancer treatment with only one discipline or field is an impossible task, since each field in cancer therapy has its own benefits and drawbacks. For instance, advancements in field of biology such as genetic tools and drug discovery have been beneficial in introducing new therapies for cancer to suppress them with higher ability. However,

Table 4
The functionalized nanoparticles in treatment of PC.

Nanostructures	Remarks	Ref
Aptamer-Targeted Calcium Phosphosilicate Nanoparticles	Specific targeting of tumor cells, selective accumulation and providing proper imaging	Abraham et al. (2021)
MUC-1 aptamer targeted superparamagnetic iron oxide nanoparticles	The in vivo and in vitro imaging of tumor cells	Zou et al. (2019)
Dual functional peptide-modified liposomes	Autophagy inhibition and targeting cancer-associated fibroblasts	(X. Chen et al., 2019)
Peptide Modified Dendrimer	CO-delivery of TR3-siRNA and paclitaxel in synergistic cancer therapy	(Y. Li et al., 2017)
Lactoferrin/Hyaluronic acid double-coated lignosulfonate nanoparticles	138 nm particle size −28 mV zeta potential Selective and sustained delivery of quinacrine	(S. M. Etman et al., 2020)

cancer therapy requires targeted delivery of cargo and specific accumulation of treatments in tumor cells that can be provided by nanostructures. Therefore, if such strategies are provided for each cancer therapy and the specific features of tumor cells is considered, there will be much improvement in cancer therapy. Due to development of precision medicine, it is of importance to evaluate property of nanoparticles in treatment of each cancer type to improve ability in treatment of cancer patients in future. Due to unique features of TME in PC, stimuli-responsive nanocarriers including pH-, redox- and light-responsive have been developed that they respond to endogenous or exogenous stimuli and sometimes, multifunctional nanocarriers have been developed that can be responded to both endogenous and exogenous stimuli. The benefit of light-responsive nanocarrier in PC is that they can also produce heat or ROS in suppressing progression of cancer cells and even they are used along with chemotherapy drug, they can enhance

chemotherapy-mediated cytotoxicity. The most popular part is delivery of drugs and genes by nanoparticles in PC therapy. The delivery of drugs by nanocarriers leads to increase in their internalization in tumor cells, prevents chemoresistance and increase cytotoxicity. The encapsulation of genes by nanoparticles avoids their degradation by enzymes and increases their potential in gene expression regulation to mediate effective cancer therapy. Moreover, when nanoparticles are used for delivery of both genes and drugs, synergistic cancer therapy is mediated. The modification of nanocarriers with ligands, peptides and enzymes enhances targeted potential.

The clinical application of nanomaterials relies on different factors and ability in cancer suppression is not the only factor. Although preclinical studies have confirmed that application of nanomaterials suppresses tumorigenesis in PC, regulates molecular pathways and decreases viability of tumor cells, the biocompatibility and large-scale production are also completely important factors for clinical application. The biocompatible nanomaterials such as liposomes and lipid-based nanostructures have been utilized for purpose of PC therapy and one of the limitations of studies is their ignorance towards surface modification with cell membranes. Although nanoparticles modified with macrophage membrane have been used in treatment of PC, others such as neutrophil membrane and exosomes can also be used in this purpose to improve biocompatibility of nanostructures. Moreover, large-scale production of nanoparticle is also of importance and in spite of development of complicated nanoparticles, their large-scale production is a problem that should be considered for clinical application. There is extensive view towards selective targeting of PC cells by their surface modification. However, the studies have ignored to carefully examine which endocytic mechanism is affected by these nanoparticles for internalization. Moreover, in addition to receptor-mediated endocytosis, there are other types such as caveolin- and caveolae-mediated endocytosis that have not been examined in these studies.

There is wealth evidence demonstrating that PDT and PTT are beneficial approaches in treatment of PC and their mechanism of action
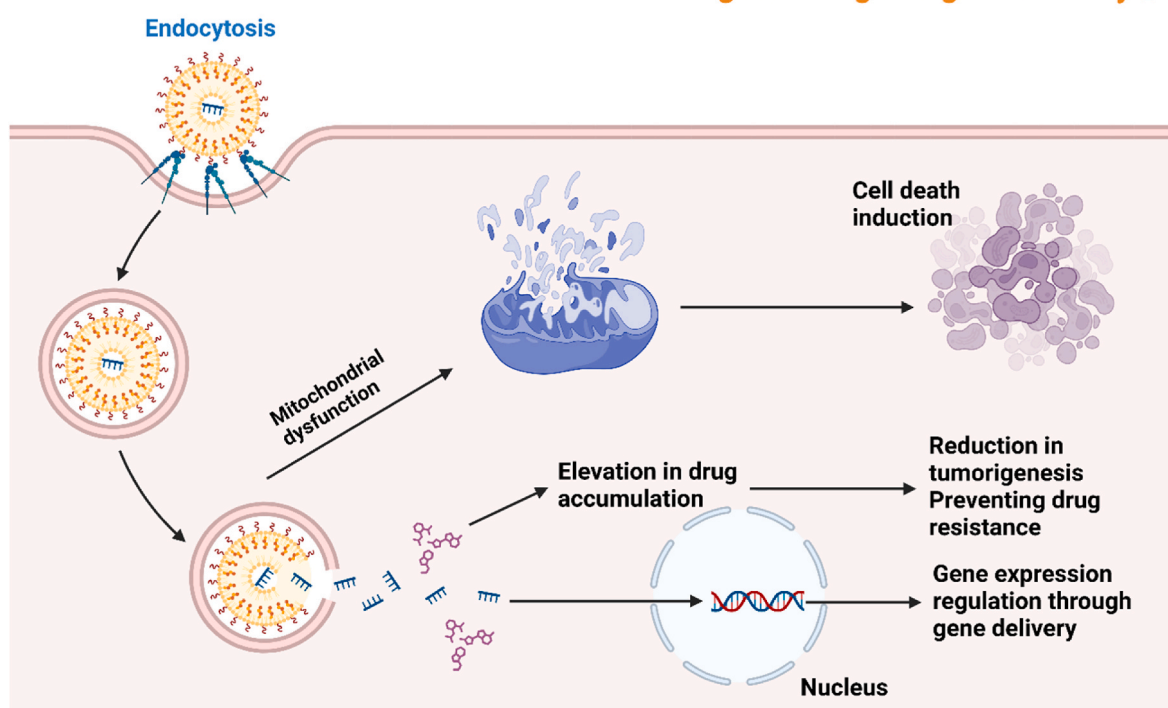

Fig. 4. The nanostructures for drug and gene delivery along with functionalized ones.

is different, but final effect on the tumor cell is similar. In PTT approach, light is transferred into heat, while in PDT, light is transferred into ROS to induce cell death in PC. Importantly, nanoparticles can carry photosensitizers into PC cells and then, they mediate phototherapy, and if gene or drug is also loaded on the nanostructures, it causes more reduction in progression and viability of cancer cells. However, since PDT can active anti-tumor immunity, more attention should be directed towards this aspect to evaluate potential of nanoparticle-mediated PDT in anti-cancer immunity. The gene delivery approaches have been beneficial in PC treatment and the most used one is siRNA, although there are also studies about using exosomes for delivery of CRISPR/Cas9 in PC therapy. Moreover, there is no experiment about shRNA delivery in PC therapy that can be focus of future studies. The nanoparticles used for gene delivery in PC therapy have shown high potential in cancer elimination and more novel nanoparticles should be developed in near future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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