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REVIEW

Immunotherapy-based novel nanoparticles in the treatment of gastrointestinal cancer: Trends and challenges

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Abstract

Gastrointestinal cancer (GIC) is the most common cancer with a poor prognosis. Currently, surgery is the main treatment for GIC. However, the high rate of postoperative recurrence leads to a low five-year survival rate. In recent years, immunotherapy has received much attention. As the only immunotherapy drugs approved by the Food and Drug Administration (FDA), immune checkpoint blockade (ICB) drugs have great potential in cancer therapy. Nevertheless, the efficacy of ICB treatment is greatly limited by the low immunogenicity and immunosuppressive microenvironment of GIC. Therefore, the targets of immunotherapy have expanded from ICB to increasing tumor immunogenicity, increasing the recruitment and maturation of immune cells and reducing the proportion of inhibitory immune cells, such as M2-like macrophages, regulatory T cells and myeloid-derived suppressor cells. Moreover, with the development of nanotechnology, a variety of nanoparticles have been approved by the FDA for clinical therapy, so novel nanodrug delivery systems have become a research focus for anticancer therapy. In this review, we summarize recent advances in the application of immunotherapy-based nanoparticles in GICs, such as gastric cancer, hepatocellular carcinoma, colorectal cancer and pancreatic cancer, and described the existing challenges and future trends.

Key Words: Gastrointestinal cancer; Gastric cancer; Hepatocellular carcinoma; Colorectal cancer; Pancreatic cancer; Immunotherapy-based novel nanoparticles

Core Tip: Recently, immunotherapy has received substantial attention. Although there are several Food and Drug Administration-approved immune checkpoint blockade (ICB) drugs, the efficacy remains limited, and the response rate is less than 20%. Because gastrointestinal cancer (GIC) is a group of immunosuppressive cancers, the efficacy of ICB treatment is also limited. Therefore, enhancing the immunogenicity of GIC or reversing the immunosuppressive microenvironment of GIC have become potential approaches for GIC immunotherapy. There are many studies on nanoparticle-based cancer therapy. However, there are only a few studies on immunotherapy-based nanoparticles in GIC. Here, we summarize recent advances in the application of immunotherapy-based nanoparticles in GIC and present our thoughts about this topic.

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INTRODUCTION

Gastrointestinal cancer (GIC) has been among the most commonly diagnosed cancers in recent decades [1-3]. In recent reports, the incidence and mortality rates have gradually decreased for gastric cancer (GC), hepatocellular carcinoma (HCC) and esophageal cancer in China; in contrast, the rates for colorectal cancer (CRC) have increased[4]. Regardless of the changes in the incidence and mortality rates of GIC, the disease has greatly affected the quality of life of many individuals.

Similar to other types of cancer, GIC has several therapies available. As the most conventional means of cancer treatment, surgery, chemotherapy and radiotherapy play important roles. Although traditional therapies effectively prolong survival for patients with GIC, there are still many drawbacks that cannot be ignored[5]. Surgery, especially minimally invasive surgery and radiotherapy, can effectively shrink the tumor and even make the local tumor disappear; chemotherapy can be administered systematically to kill cancer cells[6-8]. However, these treatments cannot prevent recurrence. Moreover, for GICs, the side effects of radiotherapy and chemotherapy on the digestive system seriously affect the quality of life of patients and cannot be ignored[9-11]. To improve the therapeutic effect and reduce the occurrence of adverse reactions, clinicians often try a variety of therapeutic combinations to achieve complementary advantages[12,13].

With progress in the concept of cancer treatment and the development of diagnosis and treatment technology, various precision treatment methods, such as targeted therapy, photodynamic therapy (PDT), photothermal therapy (PTT) and immunotherapy, have emerged as new sources of hope for patients[14-19]. Some scholars believe that the characteristics of the GIC immune microenvironment are related to the high mortality of patients with GIC; therefore, treatments that target the GIC immune microenvironment are gradually being recognized[20]. As one of the therapeutic methods that targets the cancer immune microenvironment, immune checkpoint blockade (ICB) treatment has achieved great success in clinical practice, laying a good foundation for the development of cancer immunotherapy[21].

Recently, a variety of nanobased drugs (such as Eligard[22], Marqibo[23], Onivyde[24], Doxil[25], Abraxane[26], Ontak[27] and Nanotherm[28]) have been widely used in clinical practice due to several characteristics, including their low toxicity, long circulation and passive targeting ability[29,30]. However, most of the nanobased drugs mentioned above are liposomes. In addition to liposomes, there are also other types of nanoparticles that possess the same potential for clinical translation. Similar to liposomes, small extracellular vesicles and cell membrane vesicles also have lipid bilayers, and they have better biocompatibility than liposomes due to their origin[31-34]. Furthermore, due to their simple production process and high drug loading efficiency, polymersomes are also considered candidate nanoparticles for clinical translation[35-37]. There are also many kinds of novel nanoparticles, such as gold nanoparticles, manganese dioxide nanoparticles, upconversion nanoparticles (UCNPs), metal organic framework nanoparticles and mesoporous silica nanoparticles (MSNPs), which can also play important roles in different diseases or cancers through their own characteristics[38-42]. Here, among the GICs, we focus on GC, HCC, CRC and pancreatic cancer and summarize the application trends of immunotherapy-based novel nanoparticles in these cancers as well as the challenges and opportunities

in the future.

IMMUNOTHERAPY-BASED NOVEL NANOPARTICLES IN GC

GC remains one of the most common causes of cancer-related death globally. Although a variety of treatments have been developed, the main treatment for GC is still surgery or endoscopic resection. The probability of patients experiencing recurrence after surgery is approximately 60%[43]. Currently, the median overall survival time with fluoropyrimidine-based combination chemotherapy is less than one year. In general, the overall clinical therapeutic effect of GC is not satisfactory[44,45]. In addition, immunotherapy for GC will become an important treatment option in the future, and nanoparticles, as highly efficient drug carriers, have played an important role in clinical practice[46-48]. Whether the combination of immunotherapy and nanoparticles can produce improved therapeutic effects is also worth examining.

Immune checkpoint inhibitors (ICIs), such as anti-programmed death receptor-1 (anti-PD-1) antibody and anti-programmed death receptor-ligand 1 (anti-PD-L1) antibody, can effectively block the PD-1/PD-L1 pathway and enhance the anticancer immune response[49]. Based on ICI treatment, Xu *et al*[50] prepared a novel nanoparticle named docetaxel (DOC)-PEG-PCL-monoclonal antibody (mAb) NP, which contained DOC as the chemotherapeutic drug and conjugated PD-L1 mAb on the surface of the nanoparticle. This nanodrug delivery system (NDDS) can effectively improve drug delivery efficiency and the solubility of hydrophobic drugs such as DOC. In addition, the system can target PD-L1-positive GC cells, exhibiting clinical translation potential. Recently, scientists found that a gradually acquired heritable *de novo* methylation program inhibited T-cell proliferation and clonal diversity during PD-1 blockade therapy[51]. Inspired by this study, Hu *et al*[52] designed copolymers loaded with the epigenetic agent 5-Aza-20-deoxycytidine (DAC), and an anti-PD-1 antibody was conjugated to the surface of the nanoparticles. The nanoparticles increased the stability of DAC and improved the therapeutic effect of ICI treatment *in vivo*.

Due to the characteristics of the cancer immune microenvironment, T-cell infiltration in GC patients is insufficient, which limits the effect of ICB treatment in GC[53]. Guo *et al*[54] constructed an NDDS named HMON@IR820/Pt-NPs, which coencapsulated platinum nanoparticles (chemo-prodrugs) and IR820 (photosensitizer) into hollow mesoporous organosilica nanoparticles. IR820-mediated PDT can lead to the release of oxidative mitochondrial DNA (mitoDNA). In addition, this oxidative process can oxidize Pt(0) to cytotoxic Pt(II), which can lead to the dysfunction of nuclear DNA (nDNA). The dual damage of mitoDNA and nDNA can activate the c-GAS/stimulator of interferon genes (STING) pathway, which can directly stimulate innate immunity and increase the infiltration of $CD8^+$ T cells, thus improving the efficacy of immunotherapy for GC.

Multiple studies have confirmed that tumor-associated macrophages (TAMs) are also involved in the composition of the tumor immune microenvironment. Moreover, M2-like macrophages can inhibit tumor immunity and promote tumor immune escape[55,56]. Zhang *et al*[57]'s group designed a novel human serum albumin (HSA)-Au(III) thiosemicarbazone agent nanoparticle delivery system for chemotherapy and immunotherapy in GC. This NDDS can simultaneously directly kill GC cells and polarize TAMs into M1-like macrophages, providing a new immunotherapy strategy for clinical translation.

The majority of cancer patients are often unable to activate adequate levels of anticancer immunity, whereas therapeutic tumor vaccines can help patients proactively generate adequate anticancer immune responses against tumor-specific antigens (TSAs) and tumor-associated antigens[58]. Among the different types of tumor vaccines, dendritic cell (DC)-based tumor vaccines have been explored in clinical experiments[59,60]. Kohnepoushi *et al*[61] prepared poly(lactic-co-glycolic) acid nanoparticles to protect the human gastric tumor antigen against proteolytic enzymes. In addition, nanoparticles that contain human gastric tumor antigen can facilitate DC maturation and further enhance the efficacy of DC vaccines in clinical practice.

In addition to ICB treatment and other therapies that can improve the cancer immune microenvironment, immunoadjuvants can act as a potential adjunctive therapy to stimulate anticancer immunity [62,63]. Zhang *et al*[64] developed a gold nanoshell-based NDDS that can convert near-infrared (NIR) light into thermal energy, enabling PTT. Moreover, high temperature can also break thiol bonds to release gene therapy agents and oligooxynucleotides that contain cytosine-guanine (CpG) motifs (which are also known as immunoadjuvants). This study designed a novel NDDS combined with hyperthermia, gene therapy and immunotherapy, which exhibited encouraging anticancer efficacy against GC *in vitro* and *in vivo* (Table 1).

IMMUNOTHERAPY-BASED NOVEL NANOPARTICLES IN HCC

Primary liver cancer is among the most commonly diagnosed cancers, most of which are HCC[65,66]. Due to the high infection rate of hepatitis B virus, the incidence of HCC in China remains high[67].

Table 1 Overview of immunotherapy-based novel nanoparticles in the treatment of gastric cancer [PubMed Search (immunotherapy) AND (nanoparticle) AND (gastric cancer)]

Type of nanoparticle	Treatment strategy	Drugs or active substance involved	The main involvement of immune cells	Ref.
Copolymers	ICIs, chemotherapy	DOC, PD-L1 mAb	T cells	Xu *et al*[50]
Copolymers	ICIs, epigenetic treatment	DAC, nivolumab	$PD1^+CD8^+$ TILs	Hu *et al*[52]
Hollow mesoporous organosilica nanoparticles	Dual-damage to nDNA and mitoDNA activates the c-GAS/STING pathway to stimulate innate immunity	Platinum, IR820	$CD8^+$ T cells, DCs	Guo *et al*[54]
HSA nanoparticles	Targeted chemotherapy and immunotherapy	Au(III) thiosemicarbazone agent	TAMs	Zhang *et al*[57]
Polymers	DC vaccine	Human gastric tumor antigens	DCs	Kohnepoushi *et al*[61]
Gold nanoshell	Gene therapy, hyperthermia and immunoadjuvants therapy	HER-2 targeted siRNA, gold, CpG	DCs, T cells	Zhang *et al*[64]

ICIs: Immune checkpoint inhibitors; DOC: Docetaxel; PD-L1: Programmed cell death ligand 1; mAb: Monoclonal antibody; DAC: 5-Aza-20-deoxycytidine; TILs: Tumor-infiltrating T cells; DCs: Dendritic cells; HSA: Human serum albumin; TAMs: Tumor-associated macrophages; HER-2: Human epidermal growth factor receptor-2; CpG: Cytosine–guanine.

Surgical resection of the liver is the main treatment for HCC. However, the prognosis after surgery is still poor. Recently, the development of molecular targeted therapy and immunotherapy for HCC has gained recognition in clinical studies[68]. Moreover, NDDSs can improve the efficiency of drug delivery into the tumor area and reduce side effects[69-71]. At present, a large number of studies using immunotherapy-based NDDSs have shown great potential for clinical translation.

ICB treatment has also emerged as a new option for advanced HCC[72]. However, ICB treatment alone has limited efficacy against HCC. Therefore, how to combine other kinds of therapies to improve the efficiency of ICB treatment has become a new academic topic. For example, Food and Drug Administration (FDA)-approved sorafenib-experienced patients used ipilimumab (anti-CTLA-4) combined with nivolumab (anti-PD-1) in March 2020[73]. In the last two decades, scientists have found that chemotherapeutic drugs, radiotherapy, PDT and some other treatments can induce immunogenic cell death (ICD), which can lead to the release of TSAs and increase tumor antigenicity[74]. Hence, ICD can improve the efficacy of ICB treatment by increasing tumor immunogenicity. According to the therapeutic strategies mentioned above, Xu *et al*[75] designed a cyclic arginine-glycine-aspartic acid peptide-modified self-assembling polymer-based NDDS. Cancer cells were damaged by PDT and chemotherapy, while induced ICD and enhanced tumor immunogenicity provided a suitable immune microenvironment for ICB treatment. Previous studies found that a lack of the p53 tumor suppressor gene leads to tumorigenesis and drug resistance[76-78]. With the development of research on the p53 tumor suppressor gene, an increasing body of evidence indicates that the p53 protein plays an important role in anticancer immunity by regulating the cancer immune microenvironment[79-81]. Furthermore, a recent study suggested that ICD induced by cytotoxic agents, such as chemotherapy drugs, may be involved in the activation of the p53 pathway[82]. Xiao *et al*[83] developed a novel lipid-polymer hybrid nanoplatform for mRNA delivery that can induce the expression of p53, effectively reprogramming the immune microenvironment of HCC. Moreover, combination with anti-PD-1 therapy can reverse the inhibitory immune microenvironment of HCC. To solve the problem of HCC recurrence after surgery, Li *et al*[84] designed a bionic NDDS consisting of MSNPs loaded with anti-PD-L1 and sorafenib and coated with platelet membranes at the surface of the MSNPs. This NDDS can target wounds and generate potent anti-HCC immunity, providing a new therapeutic idea for preventing recurrence in postsurgery HCC patients.

As we mentioned before, chemotherapy-based ICD can cause cancer cells to be more easily recognized by the immune system. However, the effect of single-drug-mediated ICD is very limited. Some studies have attempted to enhance the effect of ICD by combining two different ICD inducers to solve this problem. Yu *et al*[85] evaluated the potential of icaritin as an ICD inducer and utilized NDDS to deliver low doses of icaritin and doxorubicin simultaneously to the tumor area. This NDDS can reprogram the immune microenvironment and induce satisfactory anti-HCC effects. Furthermore, NDDS can lower the dose of chemotherapy to reduce the side effects.

TAMs play a major role in the immunosuppressive microenvironment of HCC[86]. Wang *et al*[87] screened chemokine C-C motif ligand (CCL)2 and CCL5 as two major chemokines responsible for the polarization of M2-like macrophages and designed a CCL2 and CCL5 dual-target lipid nanoparticle system. The combination of TAMs targeting lipid nanoparticles with ICB treatment achieved long-term survival in HCC mice. Similarly, as a common feature of the tumor microenvironment, hypoxia is also

common in HCC. Hypoxia can lead to radioresistance and the formation of an immunosuppressive microenvironment, including the accumulation of TAMs and depletion of effector T cells, which are closely related to the occurrence and development of cancer[88-90]. Dai *et al*[91] synthesized polydopamine-nanoparticle-stabilized oxygen microcapsules that can deliver oxygen to the tumor region and rapidly increase the concentration of oxygen. In this study, oxygen microcapsules increased HCC sensitivity to radiotherapy and polarized M2-like macrophages into M1-like macrophages, consequently activating anti-HCC immunity. In addition to conventional immune cells, liver sinusoidal endothelial cells (LSECs) can also play a significant role in immunosuppressive regulation[92]. Yu *et al*[93] designed a simvastatin-loaded NDDS to target LSECs in HCC patients. This NDDS can reduce the capillarization of LSECs to improve the stromal microenvironment and recruit natural killer T cells to inhibit tumor progression.

Cationic lipid nanoparticles have been suggested to be suitable delivery vectors for RNA, and several messenger RNA vaccines are based on lipid nanotechnology that was approved by the FDA during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic[94-97]. Zhang *et al*[98] developed a total HCC-derived RNA-loaded lipid nanoparticle vaccine to target DCs and activate anticancer immunity (Figure 1 and Table 2).

IMMUNOTHERAPY-BASED NOVEL NANOPARTICLES IN CRC

CRC is the third leading cause of cancer-related deaths globally[99]. CRC is the only cancer that can be reduced by screening. Most CRC patients can be screened by flexible sigmoidoscopy or guaiac-based fecal occult blood tests[100]. However, approximately 25% of CRC patients are at stage 4, and the 5-year survival rate is only 11%[101,102]. To improve the survival rate of advanced CRC patients, immunotherapy and nanoparticle-based drug delivery systems have become the focus of basic and clinical research for the past few years[103-105].

Similar to GC and HCC, ICB treatment is more widely used in CRC patients, but its curative effect is extremely limited, especially for mismatch repair-proficient/microsatellite stability/microsatellite instability-low CRC patients[106]. As we reported earlier, ICB treatment combined with ICD can achieve a "1 + 1 > 2" effect. A similar treatment strategy has also been applied in CRC research. For example, Yuan *et al*[107] utilized the ability of PDT to induce ICD and developed a photosensitive NDDS combined with ICB treatment that can enhance the response rate of anti-PD-L1 therapy in CRC. Zhu *et al*[108] also designed an oxaliplatin prodrug-conjugated photosensitive NDDS that can be stimulated by the NIR-II window (1000-1700 nm) for PTT, which is a proven to induce ICD. Moreover, oxaliplatin, a chemotherapy drug, is also known as an ICD inducer. This novel NDDS can induce ICD through both PTT and chemotherapy, which may provide a promising immunotherapy strategy for advanced CRC treatment. Shikonin (SK), a major active ingredient isolated from traditional Chinese medicine, has also been proven to induce ICD. Li *et al*[109] designed a versatile nanoparticle that can deliver knockdown siRNA for both the ICD inducer SK and PD-L1, which presents potential for CRC immunotherapy. Recently, ferroptosis was discovered as a nonapoptotic form of regulated cell death [110]. In addition, Duan *et al*[111]'s group proved that dihydroartemisinin (DHA), as a reactive oxygen species (ROS)-producing drug and ferroptosis inducer, can also induce ICD to potentiate anticancer immunity. Therefore, the same research group developed a Zn-pyrophosphate core-shell NDDS codeliver DHA and pyropheophorbide-iron (pyro-Fe). Glutathione and other thiol-based reductants in cancer cells can reduce Pyro-Fe^{III} to Pyro-Fe^{II}, which can catalyze the decomposition of DHA to induce ICD and ferroptosis. This novel NDDS overcame the deficiency of iron in solid tumors, enhanced the ability of DHA to induce ferroptosis and ICD, and increased the infiltration of $CD8^+$ T cells in CRC.

In addition to actively increasing the immunogenicity of CRC, stimulating immune cells can also activate anti-CRC immunity. Immune cells can be activated by stimulating toll-like receptors (TLRs), such as DCs and macrophages. Several TLR agonists have been approved by the FDA. However, none are currently approved for CRC treatment. The major problem for TLR agonists is the small size of the drugs, which allows the drugs to spread rapidly from the administration site and cause severe systemic side effects (Figure 2)[112]. Fortunately, nanoparticle-based delivery systems can solve this problem. Bahmani *et al*[113] prepared a platelet membrane-coated nanoparticle loaded with the TLR7 agonist R848. This biomimetic NDDS enhanced the retention of the drug in the tumor and effectively stimulated the maturation of DCs, resulting in complete tumor eradication in a murine model of CRC.

Notably, long noncoding RNAs (lncRNAs) have recently been reported to be involved in the formation of the immunosuppressive cancer microenvironment and have become a potential immunotherapy target[114-116]. Liu *et al*[117] designed a bioscaffold loaded with a lncRNA-targeting biomimetic NDDS that modulated the cancer immune microenvironment against CRC recurrence after surgery. The biomimetic NDDS coated with a CRC membrane, which provides NDDS with a tumor-homing capacity and carries TSAs into the tumor area, promotes the maturation of DCs. Moreover, a plasmid-encoding short hairpin RNA against Pvt1 was encapsulated inside the NDDS to enhance ICD and ameliorate granulocytic-myeloid-derived suppressor cell (G-MDSC)-mediated immunosuppression. This work provides a new perspective for NDDS-based lncRNA-targeted immunotherapy.

Table 2 Overview of Immunotherapy-based novel nanoparticles in the treatment of hepatocellular carcinoma [PubMed Search (immunotherapy) AND (nanoparticle) AND (hepatocellular carcinoma)]

Type of nanoparticle	Treatment strategy	Drugs or active substance involved	The main involvement of immune cells	Ref.
Nano-micelles	ICD, chemotherapy, PDT	PTX, TPABDTO	CTLs, MDSCs, Tregs, DCs	Xu *et al*[75]
Polymers	p53 gene reprograms the immune microenvironment	p53 mRNA	T cells, NK cells	Xiao *et al*[83]
MSNPs	Anti-angiogenic drugs, ICIs	Sorafenib, PD-L1 antibody	T cells	Li *et al*[84]
Copolymers	ICD, chemotherapy	Icaritin, DOX	T cells, DCs	Yu *et al*[85]
Lipid nanoparticle	CCL2 and CCL5 dual-target	BisCCL2/5i mRNA	TAMs	Wang *et al*[87]
Microcapsules	Improving hypoxia	Oxygen	TAMs	Dai *et al*[91]
Copolymers	Mitigates LSEC capillarization	Simvastatin	NKT cells	Yu *et al*[93]
LNPs	Antigen specific vaccine	Tumor-derived RNA	T cells, DCs	Zhang *et al*[98]

ICD: Immunogenic cell death; PDT: Photodynamic therapy; CTLs: Cytotoxic T lymphocytes; PTX: Paclitaxel; MDSCs: Myeloid-derived suppressor cells; DCs: Dendritic cells; CCL2: Chemokine C-C motif ligand 2; CCL5: Chemokine C-C motif ligand 5; DOX: Doxorubicin; PD-L1: Programmed cell death ligand 1; NK cells: Natural killer cells; TAMs: Tumor-associated macrophages; Tregs: Regulatory T lymphocytes; MSNPs: Mesoporous silica nanoparticles; LSEC: Liver sinusoidal endothelial cells; LNPs: Lipid nanoparticles; NKT: Natural killer T.

In recent years, as an important component of the immunosuppressive cancer microenvironment, MDSCs have also been identified as potential targets for cancer immunotherapy. Additionally, recent studies reported that MDSCs could be selectively enlarged because of the enrichment of *Fusobacterium nucleatum* (Fn) in CRC tissue, resulting in a cancer immunosuppressive microenvironment[118-121]. Dong *et al*[122] proposed a phage-based antibacterial system that used the broad-spectrum antibacterial effect of silver nanoparticles (AgNPs) for antibacterial activity and then transported phage M13 into the tumor and utilized the recognition mechanism of phages to selectively kill Fn, thus preventing the recruitment of MDSCs. In addition, phages are highly immunogenic and can directly stimulate the maturation of DCs and promote the activation of M1-like macrophages, significantly enhancing the anti-CRC immune response.

Over the years, CRC vaccines have been a focus of scientific research. Zhang *et al*[123] designed an in situ cancer vaccine. They reported a supramolecular assembled programmable immune activation nanomedicine (PIAN) that can produce strong and durable anticancer immunity in situ. PIAN entered the tumor area through enhanced permeability and retention (EPR) after tail vein injection and was then disassembled by the high ROS within the tumor tissue. The release of poly-[(N-2-hydroxyethyl)-aspartamide]-Pt(IV)/beta-cyclodextrin simultaneously mediated tumor cell death and antigen release. In addition, CpG/polyamidoamine (CpG/PAMAM) captured the released antigen and entered the tumor draining lymph node to stimulate DC maturation, thus activating anti-CRC-specific immunity. This excellent work provides a new idea for designing nanomedicine-based programmable *in situ* cancer vaccines for cancer immunotherapy (Table 3).

IMMUNOTHERAPY-BASED NOVEL NANOPARTICLES IN PANCREATIC CANCER

As one of the most aggressive and fatal cancers, pancreatic cancer has been the leading cause of cancer-related deaths worldwide in the last few decades[124,125]. Most patients experience no obvious symptoms during the development of the disease. Therefore, it is difficult to diagnose the disease in the early stage, and patients often miss the optimal treatment time after they have been diagnosed with pancreatic cancer. Moreover, the majority of patients eventually relapse, even if they receive potentially radical treatment[126]. In contrast to other malignant tumors, stromal hyperplasia is the main feature of the pancreatic cancer microenvironment[127]. As a result, pancreatic cancer does not have a sufficient blood supply, so antiangiogenic drugs are not suitable for pancreatic cancer[128]. In addition, the tumor stroma of pancreatic cancer acts as a natural physical barrier between the tumor tissue and the body's immune system, which also limits the application of immunotherapy[129,130]. Until now, most phase I and II clinical trials of immunotherapy in pancreatic cancer have failed. Interestingly, ICB treatment combined with chemotherapy and/or radiotherapy has shown encouraging clinical efficacy[131]. In recent years, with the continuous development of nanotechnology, scientists have proposed a variety of nanodelivery systems aimed at the unique pathological characteristics of pancreatic cancer. They attempted to utilize NDDSs to achieve synergistic therapy and improve the tumor microenvironment to reverse the current situation of pancreatic cancer[132].

Table 3 Overview of Immunotherapy-based novel nanoparticles in the treatment of colorectal cancer [PubMed Search (immunotherapy) AND (nanoparticle) AND (colorectal cancer)]

Type of nanoparticle	Treatment strategy	Drugs or active substance involved	The main involvement of immune cells	Ref.
Copolymers	PDT induces HIF-1α expression, leading to the upregulation of PD-L1 expression, ICIs	Photosensitizer, PD-L1 antibody	DCs, $CD8^+$T cells, memory T cells	Yuan *et al*[107]
Polymeric nanoparticle	PTT, chemotherapy, ICD	PBOXA, donor–spacer–acceptor–spacer–donor type fluorophore	DCs, T cells, CTLs	Zhu *et al*[108]
Copolymers	ICD, ICIs	SK, PD-L1 knockdown siRNA	DCs, TAMs, Tregs, T cells	Li *et al*[109]
Polymers	ICD, ferroptosis	DHA	DCs, T cells	Duan *et al*[111]
Platelet membrane-coated nanoparticle	TLR7 treatment	R848	DCs	Bahmani *et al* [113]
Liposomes with cell membrane	ICD, chemotherapy, lncRNA-targeting therapy	Oxaliplatin, shPvt1	DCs, MDSCs, $CD8^+$T cells	Liu *et al*[117]
Silver nanoparticles	Anti-Fn	Phage M13	MDSCs, DCs, TAMs	Dong *et al*[122]
Supramolecular assembled programmable immune activation nanomedicine	*In-situ* cancer vaccine, ICD	PPCD, CpG/PAMAM	DCs, $CD8^+$T cells	Zhang *et al*[123]

ICIs: Immune checkpoint inhibitors; HIF-1α: Hypoxia-inducible factor 1α; PDT: Photodynamic therapy; PTT: Photothermal therapy; ICD: Immunogenic cell death; PD-L1: Programmed cell death ligand 1; PBOXA: Oxaliplatin prodrug; SK: Shikonin, DHA: Dihydroartemisinin; TLR: Toll-like receptor; shPvt1: Short hair-pinned RNA against Pvt1; Fn: *Fusobacterium nucleatum*; PPCD: Poly-[(N-2-hydroxyethyl)-aspartamide]-Pt(IV)/beta-cyclodextrin; PAMAM: Polyamidoamine; MDSCs: Myeloid-derived suppressor cells; DCs: Dendritic cells; CTLs: Cytotoxic T lymphocytes; TAMs: Tumor-associated macrophages; Tregs: Regulatory T lymphocytes; MDSCs: Myeloid-derived suppressor cells.

As we mentioned above, the tumor stroma of pancreatic cancer limits the efficacy of immunotherapy. Wang *et al*[133] reported a pH-responsive clustered nanoparticle (iCluster) loaded with both siPD-L1 and transforming growth factor-β (TGF-β) receptor inhibitors (LY2157299). iCluster can deliver siPD-L1 and LY2157299 to tumor blood vessels and then release small PAMAM at acidic tumor extracellular pH (pH_e). Therefore, siPD-L1 can penetrate into tumor tissue as deeply as possible to activate anticancer immunity, and a TGF-β receptor inhibitor can reduce the barrier function of the tumor stroma to help more drugs penetrate into the tumor tissue, further promoting the activation of anticancer immunity. Similarly, Yu *et al*[134] designed a size-adjustable nanoparticle consisting of IR780 containing the thermosensitive ICB drug (BMS-202) conjugated to HSA-BMS. Under mild hyperthermia therapy, this novel nanoparticle releases the small HSA-BMS into the tumor site and relieves the immunosuppressive environment to normalize immunity. In recent years, some studies have reported that RNA interference (RNAi) has emerged as a better agent for inducing anticancer immunity than antibodies or small molecules *in vivo*[135]. PLGA polymers have been proven to be a potentially excellent siRNA delivery vector exhibiting low toxicity, sustained release and the EPR effect[136,137]. Jung *et al*[138] developed a poly(lactic-co-glycolic) acid (PLGA)-based siRNA nanoparticle named siPD-L1@PLGA. siPD-L1@PLGA increased the infiltration of $CD8^+$ T cells and significantly inhibited tumor growth.

The poor immunogenicity and excessive immunosuppressive cancer microenvironment of pancreatic cancer result in a lack of adequate antigen-presenting cells in the tumor microenvironment. Lorkowski *et al*[139] reported a dual-immunostimulatory nanoparticle that was simultaneously loaded with a STING agonist and TLR4 agonist. These dual-immunostimulatory nanoparticles can be taken up by DCs in the tumor site to significantly increase the number of mature DCs and activate anticancer immunity in pancreatic cancer. Theoretically, cancer immunosuppressive cells mainly include TAMs, MDSCs and regulatory T cells (Tregs). Recent studies have shown that MDSCs are the major inhibitory immune cells in the immunosuppressive microenvironment of pancreatic cancer[140]. A previous study found that low-molecular-weight heparin-D-α-tocopheryl (LMWH) could significantly inhibit G-MDSC recruitment[141]. Therefore, Lu *et al*[142] designed a paclitaxel-loaded 3-aminophenylboronic acid-modified LMWH-based nanoparticle. This novel LMWH-based nanoparticle can inhibit the recruitment of MDSCs and weaken the immunosuppressive state.

Pyroptosis is a mode of programmed cell death[143]. Recent studies have shown that pyrophosis can induce powerful anticancer immunity[144-146]. However, pyrophosis is usually induced by chemotherapeutic drugs, which limits the applications of pyrophosis in drug-resistant tumors[147]. Ding *et al* [148] designed biodegradable K3ZrF7:Yb/Er UCNPs (ZrNPs) as self-therapeutic agents and pyrophosis

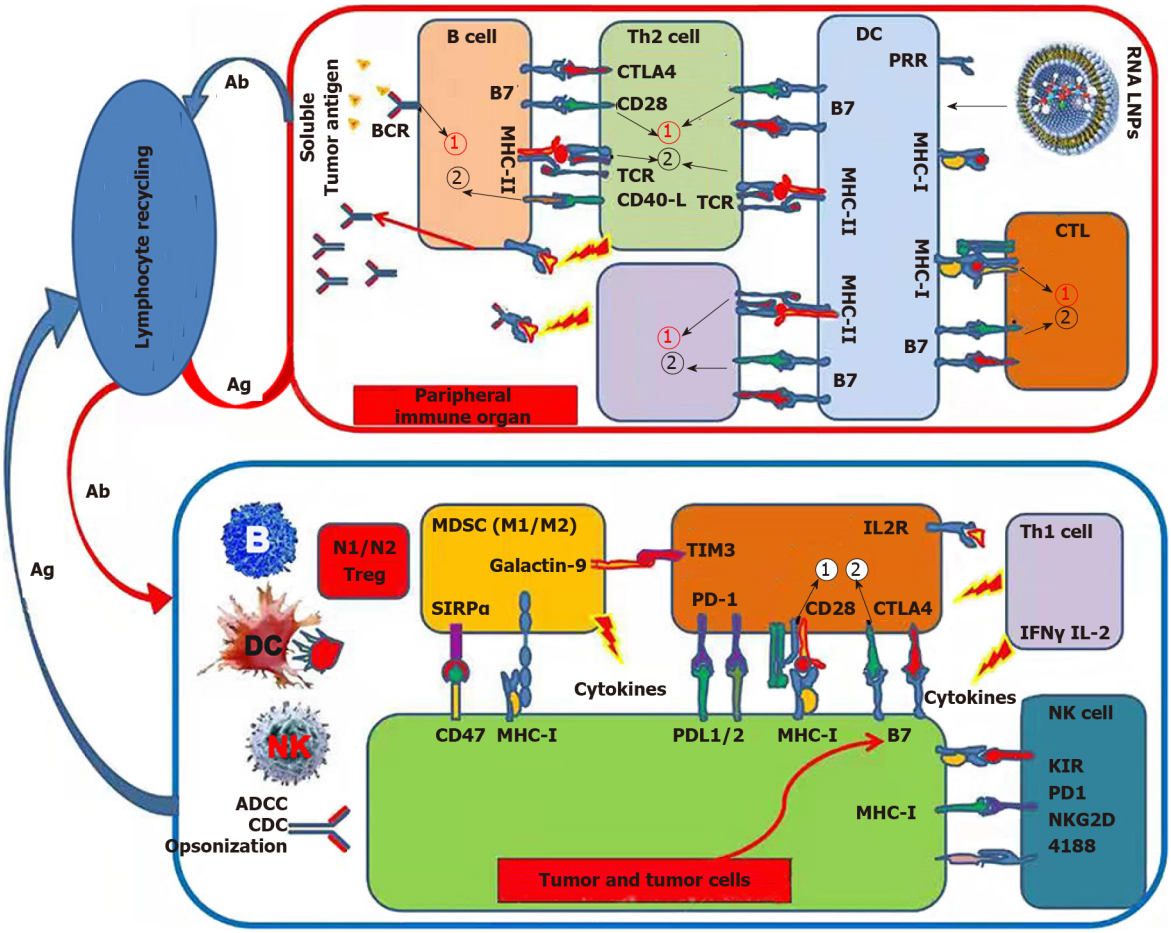

Figure 1 Tumor vaccine and tumor immunotherapy. Total tumor RNA was extracted and mixed with an immune adjuvant to formulate tumor vaccine. Tumor antigen was expressed and presented or cross-presented to Th and Tc cells by antigen presenting cells in lymph node to generate specific anti-tumor response. Citation: Zhang Y, Xie F, Yin Y, Zhang Q, Jin H, Wu Y, Pang L, Li J, Gao J. Immunotherapy of Tumor RNA-Loaded Lipid Nanoparticles Against Hepatocellular Carcinoma. Int J Nanomedicine 2021; 16: 1553-1564. Copyright ©The Authors 2011. Published by Dove Medical Press. The authors have obtained the permission for figure using from the Dove Medical Press Publishing Group (Supplementary material). Ab: Antibody; Ag: Antigen; BCR: B cell receptor; TCR: T-cell receptor; MHC: Major histocompatibility complex; PRR: Pattern recognition receptors; Th1/2: T helper type 1/2; CTL: Cytotoxic T-lymphocyte; CTLA4: Cytotoxic T-lymphocyte-associated protein 4; Treg: Regulatory T cell; DC: Dendritic cell; NK: Natural killer cell; MDSC: Mmyeloid-derived suppressor cell; ADCC: Antibody-dependent cellular cytotoxicity; CDC: Complement-dependent cytotoxicity; SIRPα: Signal regulatory protein α; LILRB1: Leukocyte immunoglobulin like receptor B1; TIM-3: T-cell immunoglobulin and mucin domain-3; PD1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; IL-2: Interleukin-2; IFNγ: Interferon γ; KIR: Killer cell immunoglobulin-like receptor; NKG2D: Natural killer group 2 member D.

inducers for the first time. ZrNP can lead to osmotic pressure disorder and further result in an increase in ROS, the activation of caspase-1 protein, the cleavage of gasdermin, the maturation of interleukin-1β, and ultimately cytolysis. ZrNP-induced pyrophosis can lead to DC maturation and activate effector memory T cells, as well as inhibit tumor growth and metastasis.

Gemcitabine is among the most effective FDA-approved chemotherapy drugs to prolong survival in patients with pancreatic cancer. However, the immunosuppressive cancer microenvironment, especially the presence of TAMs, significantly weakens the efficacy of gemcitabine. It has even been reported that gemcitabine can induce an increase in TAMs and promote the establishment of a tumor-suppressive immune microenvironment, which further increases gemcitabine drug resistance[149]. Furthermore, gemcitabine can even induce an increase in TAMs and promote the establishment of an immunosuppressive tumor microenvironment, which further leads to gemcitabine drug resistance[150]. Thus, Wang *et al*[151] developed a biomimetic nanoparticle named PG@KMCM consisting of gemcitabine-loaded PLGA nanoparticles coated with stable M2-like macrophage targeting peptides (M2pep). Pancreatic cancer cell membranes can deliver PG@KMCM to pancreatic cancer and target M2-like macrophages by M2pep to reprogram TAMs and reverse gemcitabine drug resistance. Cao *et al*[152] also considered TAMs to be a therapeutic target and reported a reduction-responsive RNAi NDDS to regulate the function of TAMs and reprogram tumor lipid metabolism. On the one hand, this novel NDDS can block the activity of monoacylglycerol lipase (MGLL) by MGLL siRNA to reduce the production of free fatty acids and thus cut off the tumor's nutrition supply. On the other hand, MGLL blockade may lead to the accumulation of 2-arachidonoylglycerol, which can be secreted into the cancer microenvironment and activate the endocannabinoid receptor-2 (CB-2), which can transform TAMs into M2-like macrophages.

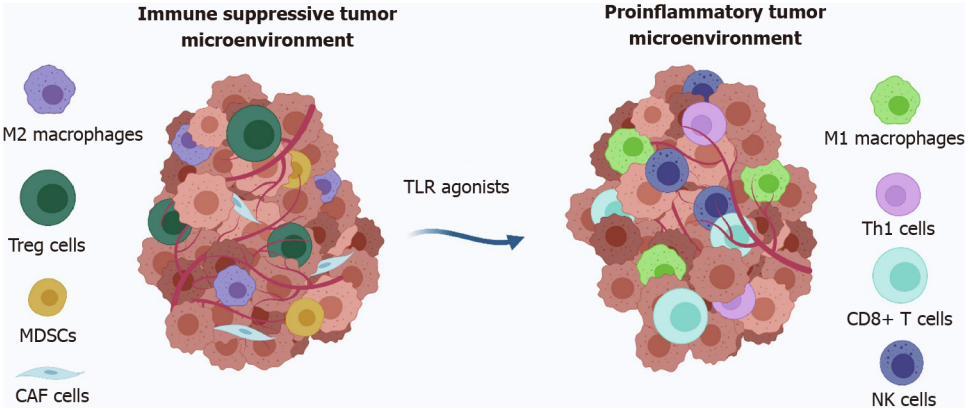

Figure 2 Altering an immunosuppressive tumor microenvironment into a pro-inflammatory microenvironment with the use of toll-like receptor agonists. Citation: Haegebaert RMS, Kempers M, Ceelen W, Lentacker I, Remaut K. Nanoparticle mediated targeting of toll-like receptors to treat colorectal cancer. Eur J Pharm Biopharm 2022; 172: 16-30. Copyright ©The Authors 2022. Published by Elsevier. The authors have obtained the permission for figure using from the Elsevier Publishing Group (Supplementary material). Treg: T regulatory cell; MDSCs: Myeloid-derived suppressor cells; CAF: Cancer-associated fibroblast; Th1: T-helper 1; $CD8^+$ T cells: Cytotoxic T cells; NK: Natural killer; TLR: Toll-like receptor.

Therefore, they prepared CB-2 siRNA to block CB-2 expression, preventing the transition of M2-like macrophages. The dual-RNAi NDDS developed in this research shows significant enhancement of the immunological environment in pancreatic cancer.

PTT has achieved satisfactory results in animal experiments, but it is difficult to apply widely in the clinic. The main reason is poor light penetration. It is harder to achieve the desired therapeutic effect for pancreatic cancer due to the depth of pancreatic cancer and the presence of the tumor stroma. To solve this conundrum, Wang *et al*[153] proposed magnetic resonance imaging (MRI)-guided interventional PTT (IPTT). They designed an iron oxide-based nanoparticle loaded with indocyanine green for PTT and imiquimod (IMQ) as an immunostimulant. IPTT can induce *in situ* cancer vaccination, which can be amplified by IMQ. In addition, iron oxide is a widely used MRI contrast agent. A recent study reported that iron oxide can modulate the cancer microenvironment by transforming M2-like macrophages into M1-like macrophages[154]. Overall, these novel iron oxide-based nanoparticles can improve therapeutic effects by directly killing cancer cells and activating the long-lasting immune effect by *in situ* vaccination and regulation of the immune microenvironment (Table 4).

FUTURE DIRECTIONS

In recent years, the increased development of immunotherapy has provided hope to patients with advanced cancer. Several ICB drugs have been approved by the FDA for clinical application in cancer treatment. However, due to the immunosuppressive microenvironment, only approximately 20% of patients can benefit from ICB treatment. In addition to ICB treatment, some conventional therapies, such as chemotherapy and radiotherapy, are also closely related to the immunosuppressive tumor microenvironment. The facts we mentioned above also exist in GIC. Therefore, we believe that in addition to ICB treatment, we should focus on reversing the immunosuppressive microenvironment in the future. Moreover, advances in nanotechnology have made drug delivery more efficient, allowing us to deliver drugs at specific times and locations based on the characteristics of the cancer and the drugs. We wondered whether the combination of nanotechnology and immunotherapy could achieve satisfactory therapeutic efficacy in GIC. Here, we summarize recent advances in immunotherapy-based novel nanoparticles in the treatment of GIC.

Since GC, HCC and CRC share similar tumor immune microenvironments, we will discuss the application of immunotherapy-based nanoparticles in these three kinds of GICs in the following paragraphs. Due to the limited monotherapy effect of ICB treatment, nanoparticles, as drug delivery vehicles, cannot significantly improve the therapeutic effect of ICB treatment. Thus, basically all ICB-based nanoparticles are combined with other therapeutic strategies. ICB treatment can reverse tumor immune escape from T cells. However, the low immunogenicity of the tumor results in insufficient T-cell infiltration in the tumor tissue. Hence, most studies have attempted to promote the therapeutic effect of ICB-based nanoparticles by inducing ICD.

ICD can increase tumor immunogenicity, but similar to ICB treatment, the immune-stimulating effect of ICD is limited. To amplify the ICD effect, some studies utilized the drug-loading capacity of nanoparticles and adopted a combination of multiple ICD inducers to enhance the immune response. Even so, we still do not recommend the combination of multiple ICD inducers to promote anticancer immunity. On the one hand, this strategy does not solve the problem of insufficient T-cell infiltration; on

Table 4 Overview of Immunotherapy-based novel nanoparticles in the treatment of pancreatic cancer [PubMed Search (immunotherapy) AND (nanoparticle) AND (pancreatic cancer)]

Type of nanoparticle	Treatment strategy	Drugs or active substance involved	The main involvement of immune cells	Ref.
Clustered nanoparticle	ICIs, TGF-β receptor inhibitors	LY2157299, siPD-L1	T cells	Wang *et al*[133]
HAS-Liposomes	ICD, ICIs, PTT	BMS-202, IR780	DCs, CTLs, T cells	Yu *et al*[134]
Copolymers	ICIs	siPD-L1	$CD8^+$T cells, NK cells	Jung *et al*[138]
LNPs	STING and TLR4 therapy	STING agonist, R4 agonist	DCs, Tregs, TAMs	Lorkowski *et al*[139]
Micellar nanoparticle	Inhibit G-MDSCs recruitment, chemotherapy	LMWH, PTX	G-MDSC, $CD8^+$T cells, $CD4^+$T cells	Lu *et al*[142]
UCNPs	Pyroptosis	K3ZrF7:Yb/Er UCNPs	DCs, memory T cells	Ding *et al*[148]
Cancer cell membrane with copolymers	ICIs, M2-macrophages targeting	M2pep, TAAs, PD-L1 antibody	TAMs, $CD8^+$T cells	Wang *et al*[151]
PDSA-based nanoplatform	Suppression of FFAs, repolarization of TAMs	siMGLL, siCB-2	TAMs	Cao *et al*[152]
Copolymers	PTT, immunotherapy	ICG, IMQ, IONs	TAMs, $CD8^+$T cells, $CD4^+$T cells, $CD4^+$T cells	Wang *et al*[153]
IONs	Repolarization of TAMs	Ferumoxytol	TAMs	Zanganeh *et al*[154]

ICIs: Immune checkpoint inhibitors; PD-L1: Programmed cell death ligand 1; TGF-β: Transforming growth factor-β; ICD: Immunogenic cell death; DCs: Dendritic cells; STING: Stimulator of interferon genes; LMWH: Low molecular weight heparin; MDSCs: Myeloid-derived suppressor cells; G-MDSCs: Granulocytic myeloid-derived suppressor cells; UCNPs: Upconversion nanoparticles; M2pep: Peptides targeting M2-like macrophages; TAAs: Tumor-associated antigens; PDSA: Poly (disulfide amide); FFAs: Free fatty acids; siMGLL: MGLL siRNA; siCB-2: CB-2 siRNA; ICG Indocyanine green; IMQ: Imiquimod; IONs: Iron oxide nanoparticles; PTX: Paclitaxel; PTT: Photothermal therapy; TAMs: Tumor-associated macrophages; Tregs: Regulatory T lymphocytes; TLR: Toll-like receptor.

the other hand, ICD inducers themselves can directly kill tumor cells. It is difficult to determine whether tumor inhibition is due to cytotoxicity or ICD-induced anticancer immunity.

Compared with ICD and ICB treatment, we believe that reprogramming the immunosuppressive tumor microenvironment by targeting inhibitory immune cells (*e.g.*, TAMs, Tregs and MDSCs) will be a revolutionary breakthrough in cancer immunotherapy in the future. Recently, many studies have attempted to successfully reprogram the tumor immune microenvironment by polarizing M2-like macrophages into M1-like macrophages. However, few reports have designed NDDSs to target Tregs and MDSCs in the tumor microenvironment. Therefore, it is of great significance to develop NDDSs for Tregs and MDSCs. In addition, the relationship between the intestinal flora and the immunosuppressive microenvironment of CRC also deserves future attention.

TLR agonists have also emerged as a promising treatment for cancer immunotherapy. However, due to the lack of targeting of TLR agonists, free TLR agonists often lead to serious systemic side effects. Therefore, it is necessary to deliver TLR agonists by nanoparticles. Numerous TLR agonists have been proven to be effective in stimulating anticancer immunity. In addition, combination therapies of TLR agonists with other immunotherapies are also anticipated. However, how to deliver TLR agonists to the tumor site stably and accurately and reduce serious systemic side effects are still problems that need prompt solutions.

With the successful large-scale clinical application of SARS-CoV-2 mRNA vaccines, research on cancer vaccines is also imminent. Due to the high heterogeneity of cancer, RNA vaccines are the best option. However, RNA is highly unstable. Liposomes, as mature NDDSs, can prepare cancer vaccines by encapsulating RNA. In addition, to improve the vaccine effect, NDDSs can be encapsulated with immune adjuvants to promote immune activation. RNA-based cancer vaccines, as a personalized cancer treatment strategy, can effectively improve anticancer immunity.

Next, we will discuss the application of immunotherapy-based nanoparticles in pancreatic cancer. Pancreatic cancer has several characteristics that are not found in other kinds of GICs, including the following: (1) Pancreatic cancer is surrounded by a tumor stroma, resulting in a physical barrier that isolates pancreatic cancer from the surrounding immune microenvironment; (2) Due to the anatomic position of the pancreas, pancreatic cancer is located deep in the abdominal cavity and therefore is not sensitive to PDT and PTT; and (3) Unlike other GICs, pancreatic cancer lacks blood supply and can adapt to nutrient deficiency and in a long-term hypoxic state.

To pass through the physical barrier of pancreatic cancer, size-adjusted NDDSs are the best option. Due to the deep location of pancreatic cancer, PTT has limited efficacy. Inspired by a previous study, we believe that IPTT and interventional PDT can be widely applied in the treatment of pancreatic cancer.

Additionally, interventional light-mediated therapy can be extended to GC, esophageal cancer and CRC, as well as HCC.

Compared with GC, HCC and CRC, pancreatic cancer has a similar immunosuppressive microenvironment, and the immunosuppressive situation is even worse. Most of the treatment strategies mentioned in GC, HCC and CRC can also be applied in pancreatic cancer. In previous reports, immunotherapy-based nanoparticles mainly used liposomes and copolymer nanoparticles, which are chemical synthesis products. Therefore, the nanoparticles can be designed according to demand. To increase biocompatibility and deliver tumor antigens, some literature has used tumor cell membranes to prepare biomimetic NDDSs, which have also achieved good results. In addition to the abovementioned nanoparticles, we particularly recommend small extracellular vesicles (also known as exosomes) as immunotherapy-based nanoparticles. First, exosomes are naturally nanosized. Second, similar to cell membrane vesicles, exosomes derived from tumor cells can carry tumor antigens. Third, exosomes can use surface modification to achieve biological functions, such as targeting. Last, exosomes have a certain drug delivery capacity. Thus, exosomes are potential immunotherapy-based nanoparticles for GIC that have not been reported in previous studies.

CONCLUSION

GIC is a common tumor worldwide. The immune microenvironments of GC, HCC, CRC and pancreatic cancer have similarities and differences. There are still many mechanisms of immune escape in GIC that are not well understood. Therefore, we need an in-depth understanding of the characteristics of each kind of GIC to take advantage of its characteristics and design immunotherapy-based nanoparticles.

FOOTNOTES

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