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Nanomedicine-based targeting delivery systems for peritoneal cavity localized therapy: A promising treatment of ovarian cancer and its peritoneal metastasis

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ABSTRACT

As one of the most common gynecological malignancies, peritoneal metastasis is a common feature and cause of high mortality in ovarian cancer (OC). Currently, the standard treatment for OC and its peritoneal metastasis is maximal cytoreductive surgery (CRS) combined with platinum-based chemotherapy. Compared with intravenous chemotherapy, traditional intraperitoneal (IP) chemotherapy exhibits obvious pharmacokinetic (PK) advantages and systemic safety and has shown significant survival benefits in several clinical studies of OC patients. However, there remain several challenges in traditional IP chemotherapy, such as insufficient drug retention, a lack of tumor targeting, inadequate drug penetration, gastrointestinal toxicity, and limited inhibition of tumor metastasis and chemoresistance. Nanomedicine-based IP targeting delivery systems, through specific drug carrier design with tumor cells and tumor environment (TME) targeting, make it possible to overcome these challenges and maximize local therapy efficacy while reducing side effects. In this review article, the rationale and challenges of nanomedicine-based IP chemotherapies, as well as their *in vivo* fate after IP administration, which are crucial for their rational design and clinical translation, are firstly discussed. Then, current strategies for nanomedicine-based targeting delivery systems and the relevant clinical trials in IP chemotherapy are summarized. Finally, the future directions of the nanomedicine-based IP targeting delivery system for OC and its peritoneal metastasis are proposed, expecting to improve the clinical development of IP chemotherapy.

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1. Introduction

Currently, ovarian cancer (OC) remains the second most common gynecological malignancy and the eighth-leading cause of cancer-related death among women worldwide [1]. It is high mortality largely refers to late diagnosis and treatment resistance [2]. The absence of specific symptoms and the lack of effective screening or diagnostic methods during the early stage (the International Federation of Gynecological Oncology (FIGO) stages I and II) largely contribute to the poor five-year survival rate [1,3], which is 70%–95% in early stages (I and II) and only 15%–30% at late stages (III and IV) [4,5]. Almost 70% of patients are diagnosed with advanced disease that has metastasized to the peritoneal cavity and/or retroperitoneal lymph nodes [6,7]. Epithelial ovarian cancer (EOC) accounts for 90% of OC; its common feature is peritoneal metastasis that is mainly through the transcoelomic pathway [7,8] and eventually develops into peritoneal cancer and malignant ascites [9,10]. Currently, the standard treatment for OC is maximal cytoreductive surgery (CRS), followed by adjuvant platinum-based chemotherapy [3]. Platinum-based chemotherapy has been proven for the first-line regimen of OC, achieving a response rate of 80% and a complete response of 40%–60% [1,11]. However, the majority of patients after chemotherapy will relapse within 18 months with ever shorter disease-free intervals and eventually die from the drug resistance of platinum-based chemotherapy, causing the poor five-year survival rate [2,12,13].

In recent years, large numbers of experimental therapies and clinical trials about OC have been carried out, and it is hoped that these can be added to platinum-based chemotherapy to achieve an OC cure or at least transform it into a chronic disease with

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prolonged disease-free intervals. In particular, intraperitoneal (IP) chemotherapy has been developed in the past decade, and multiple studies have shown that CRS combined with IP chemotherapy has yielded some benefits in advanced OC patients [14]. Compared with intravenous therapy, IP chemotherapy has significant pharmacokinetic (PK) advantages, contributing to high drug exposure in peritoneal carcinomatosis and reduced systemic toxicity [14]. However, there are some limitations before it becomes a standard treatment, mainly in terms of its safety and efficiency. The rapid clearance of high IP chemotherapy doses, the lack of tumor-targeting, and the constant administration of physical damages lead to greater gastrointestinal toxicity and a higher risk of infection [14]. In addition, studies have also shown that IP chemotherapy has a better prognosis in smaller tumors (<0.5 cm) while lacking efficacy in larger (>2 cm) bulky tumors, which is probably related to chemotherapeutics' tumor penetration [15-21]. Moreover, the tumor microenvironment (TME) within the abdominal cavity mainly consists of the peritoneum (solid state) and malignant ascites (fluid state), including tumor cells, stromal cells, vasculature, and extracellular matrix (ECM), which play critical roles in the OC invasion, metastasis, and platinum resistance; thus, single chemotherapeutics acting on tumor cells might not achieve effective tumor elimination [7,22,23].

The good news is that nanomedicine-based delivery systems for IP chemotherapy have been gradually developed, which could overcome these limitations, promoting the development of IP chemotherapy in OC and other peritoneal cancers (Table S1 in Supporting information) [24-39]. For instance, the long-term retention of chemotherapy drugs could be achieved through designing a sustained release system such as hydrogel, and targeting tumor tissues could be achieved through surface modification. In addition, because of complex pathological mechanisms, synergistic combination therapy of multiple chemotherapeutics or other therapies may be more appropriate than monotherapy. Nanomedicine-based IP delivery systems could achieve the above synergistic combination therapies so as to act on tumor cells and TME simultaneously, inhibiting metastasis and chemoresistance.

Based on the limitations of current IP chemotherapy, designing the optimal nanomedicine-based IP targeting delivery system is of importance for their clinical development. Furthermore, wonderful nanomedicine-based IP chemotherapies are inseparable from the understanding and control of their *in vivo* fate, which is crucial for their rational design and clinical translation [14,40-42]. Thus, in this review, the rationale and challenges of nanomedicine-based IP chemotherapy, as well as their *in vivo* fate following administration, will be discussed; then, current designation strategies and the relevant clinical trials of nanomedicine-based IP targeting delivery systems will be summarized, as well as the discussion about the future directions, expecting to promote the development of nanomedicine-based IP chemotherapy for OC and other peritoneal cancers.

2. Rationale and challenges of nanomedicine-based IP chemotherapy

2.1. Rationale of IP chemotherapy

The peritoneum that covers visceral, abdominal, and pelvic organs is composed of mesothelial cells, the sub-mesothelial basement membrane, and endothelial cells (ECs), which could defend against invasion by macromolecules [40]. The peritoneal-plasma barrier is composed of the peritoneum and cellular-interstitial matrix, in which the major resistances to macromolecules transportation are the blood capillary endothelium and cellular-interstitial matrix, and the barrier properties of the mesothelium are insignificant compared with the former two (Fig. 1). IP chemotherapy

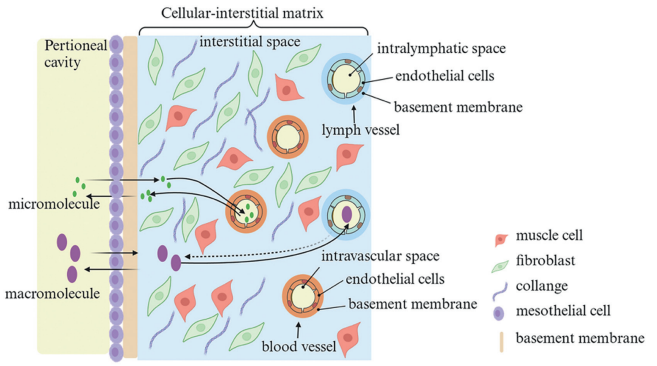

Fig. 1. Schematic illustration of the peritoneal-plasma barrier and the drug molecules transportation between the peritoneal cavity and the systemic systems. Micromolecular drugs can easily penetrate through the peritoneum and redistribute to the blood circulation; macromolecular drugs (including particles) are drained by the lymphatic system.

delivers a high concentration of chemotherapeutics directly into tumor tissues in the peritoneal cavity, which has certain advantages compared with intravenous administration. On one hand, the peritoneal-plasma barrier can limit the transport of macromolecular drugs between the peritoneal cavity and systemic circulation, offering the PK advantages and reduced systemic toxicity of IP therapy [4]. On the other hand, IP chemotherapy could increase the concentration of drugs in the small peritoneal metastases that are less than 1 mm in diameter and lack established vasculatures for intravenous delivery [43]. Several clinical studies in OC patients have shown that there is a survival benefit to IP over intravenous chemotherapy [44].

2.2. The in vivo fate and challenges of nanomedicine-based IP chemotherapy

Nanoparticles (NPs) are particles with a size of 1–1000 nm that have various advantages, including smaller size, multifunctionality, flexibility of design and modification, which are excellent drug delivery vehicles for the treatment of complex and heterogeneous diseases such as cancer [40]. For designing rational nanomedicines for IP chemotherapy, understanding the *in vivo* fate of them following IP administration is necessary, which is closely associated with their delivery efficiency and thus significantly affects their therapeutic efficacy. The compositions and physicochemical properties of nanomedicines (*e.g.*, particle size, surface charge, and surface modification) can influence their interactions with the peritoneal TME and thus affect their *in vivo* fate. Therefore, in this section, we will mainly focus on the *in vivo* fate of nanomedicines following IP administration, the relevant influence factors and challenges, providing references for their design, and thus promoting their clinical translation.

2.2.1. The in vivo fate and key influence factors of NPs after IP administration

(1) Physiological conditions in the peritoneal cavity (faced by NPs)

The peritoneum and peritoneal fluid (ascites) are the two major peritoneal cavity components [7]. The peritoneum is composed of mesothelial cells, the sub-mesothelial basement membrane, and ECs, which could defend against invasion by macromolecules [40]. Generally, only a small volume of peritoneal fluid (approx. 10–100 mL in physiological conditions) exists in the peritoneal cavity, which contains various components such as growth factors, nutrients, cytokines, chemokines, leukocytes, proteins (*e.g.*, albumin and

transferrin), degrading enzymes, all of which are continuously exchanged between the peritoneal fluid and blood [40,45]. Moreover, both the peritoneum and peritoneal fluid share similar stromal cell types, including mesenchymal cells, adipocytes, immune cells [6,7]. The omentum also contains unique vascularized structures called "milky spots" that contain various immune cells, such as lymphocytes, neutrophils [6,7]. In addition, the peritoneum that covers the diaphragm is characterized by lymphatic "stomata", cavities with a diameter of 3–12 μm between the mesothelial cells, which can provide direct access to an underlying network of lymphatic vessels that allow to clear particulate matter, bacteria, and cells from the peritoneal cavity into the circulation [45].

(2) Pharmacokinetics, biodistribution and penetration of NPs and the relevant influence factors

Following IP administration, in spite of the direct distribution/penetration into the tissues and organs in the peritoneal cavity, drugs are absorbed in the peritoneum capillaries (for small molecules with MWs <20 kDa) or are drained by the lymphatics (for larger molecules or particles) (Fig. 2) [14]. For molecules greater than 20 kDa and particles larger than 20 nm, the lymphatic system is the major drainage pathway; most of them are drained through lymphatic duct openings (stomata) on the subdiaphragmic surface that connects to the lymphatic vessels of deep diaphragmic tissues, and their lipophilicity and molecular weight/particle size are the key determinants [14,42]. Following being directly distributed or re-distributed on the tumor tissues of the peritoneal cavity, the next process is tumor interstitial transport of drug molecules or particles, which is mainly through two pathways: (1) convection driven *via* a pressure gradient; and (2) diffusion based on a concentration gradient [45]. According to the Péclet number, small molecules transport mainly through diffusion, while large substances transport mainly through convection [45].

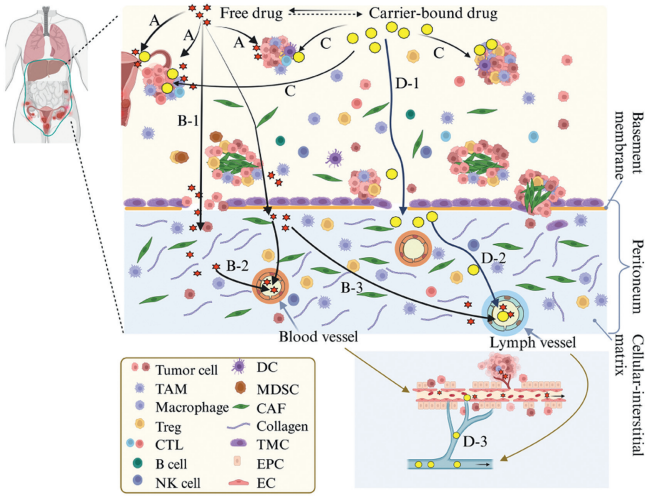

Fig. 2. The PK behavior of free drugs and carrier-bound drugs after IP administration. For free drugs, on one hand, they can directly be absorbed in the tissues and organs in the peritoneal cavity (A); on the other hand, some of them with small molecular weight can permeate through the peritoneum (B-1) and then be absorbed in the blood circulation (B-2), and the larger ones (especially those with high lipophilicity) are drained by the lymphatic system (B-3). For carrier-bound drugs, except for those that are directly absorbed in the tissues and organs in the peritoneal cavity (C), the rest are directly drained by the lymphatics (D-1, D-2), then some of them with small particle sizes (<50 nm) can pass through lymph nodes and be absorbed into the blood circulation (D-3), the bigger ones (>500 nm) are trapped in lymph nodes, and then the released free drugs can redistribute to the blood circulation and the surrounding tissues and organs in the peritoneal cavity. TAM, tumor associated macrophage; Treg, regulatory T cells; CTL, cytotoxic T lymphocyte; NK cell, natural killer cell; DC, dendritic cell; MDSC, myeloid-derived suppressor cell; CAF, cancer associated fibroblast; TMC, tumor associated mesothelial cell; EPC, epithelial cell; EC, endothelial cell.

Moreover, studies showed that drug transport convective or diffusion degree depends on temperature, the viscosity of the interstitial fluid, the stromal architecture (*e.g.*, stromal cells, density, viscoelasticity, geometrical arrangement), and their own physicochemical properties (*e.g.*, molecular weight, size, and surface charge) [45-48]. Several studies on the *in vivo* fate of micro/nanoparticles following IP administration and the relevant influence factors have been conducted (Table S2 in Supporting information) [14,41,42,49-55]. Studies have shown that for particles with a diameter less than 50 nm, they can pass through lymph nodes and ducts and end up in the blood circulation; for large particles with a particle size >500 nm, which are mostly trapped in lymph nodes, then free drugs are released from the particles; for larger particles with a size that exceeds or is close to the diameter of lymphatic duct openings, they are not easily cleared by the blood or lymphatic systems [4,14,56]. Especially for microparticles larger than 12 μm, they can escape lymphatic drainage, thus increasing their peritoneal retention time, and due to their lower surface area/volume ratio, the drug release is slower than that of the smaller particles, resulting in better peritoneal distribution [4,57]. In addition, Rie Ando-Matsuoka *et al.* investigated the *in vivo* fate of small-sized (~100 nm) cationic liposomes (CLs) with or without PEGylated in a peritoneally disseminated tumor model [41]. The results showed that, after IP injection, CLs retained in the peritoneal cavity for at least 3 days and efficiently accumulated in the targeted disseminated tumor cells without in other abdominal organs (*e.g.*, liver, spleen, and kidney), while PEGylated CLs were rapidly cleared from the peritoneal cavity to the blood system within 3 h following injection [41]. The different *in vivo* behaviors of CLs and PEGylated CLs might be due to the CLs clustering with ascites fluid proteins (albumin) and the lymphatic drainage system [41]. For a detailed discussion about the influence of the key factors on peritoneal retention and penetration, please see Section 3.2.

2.2.2. Challenges of nanomedicine-based IP chemotherapy

Up to now, none of the available chemotherapeutics have been approved for IP chemotherapy; there are still various challenges that need to be overcome before it becomes a standard treatment.

(1) The instability of nanomedicine under peritoneal physiological conditions

Compared with intravenous delivery, upon IP administration, NPs are directly delivered to the target sites, thus, interactions between NPs and blood components that might induce stability or immune issues could be avoided [58,59]. However, as mentioned above, there are also various components in the peritoneal cavity, especially in the peritoneal fluid, such as proteins and degrading enzymes, which can interact with drug molecules or NPs and thus influence their stability and biological activity [40]. For instance, studies have shown that, following IP administration, NPs tend to bind/interact with proteins to form the aggregation called "protein corona", which has been regarded as a crucial determiner of NPs' *in vivo* fate [59,60]. Reports showed that the absorption of certain amounts of proteins on the cationic NPs is associated with macrophage uptake and clearance [61,62]. Moreover, some ligand-modified NPs might lose their targeting ability due to the shielding effect of the protein corona, and the formation of the protein corona might change the cellular uptake pathway or uptake efficiency of NPs [60,62-68]. In short, the proteins, degrading enzymes, and other factors in the peritoneal fluid can lead to NPs' aggregation, disintegration, cargoes' premature release, off-target, and cellular uptake limitation, eventually resulting in reduced biological activity and increased systemic or local toxicity [40].

(2) Insufficient drug retention and drug penetration within tumor tissues

The good efficiency of IP chemotherapy requires a high local concentration of drugs for long duration and deep tissue penetration, which is associated with the PK and tissue distribution of drugs and the size of peritoneal carcinomatosis [45,56,69]. Studies showed that larger free drugs or some particles (with a diameter less than 50 nm) can pass through lymph nodes, followed by entering the blood circulation; while larger particles with a particle size >500 nm, after being trafficked by the lymphatic duct openings, are mostly trapped in lymph nodes, and then free drugs are released from the particles in the lymphatic system or further enter the blood circulation [4,14,56]. Thus, after IP administration, the majority of drug molecules or small-sized particles are cleared by the blood or lymphatic systems, resulting in higher systemic absorption and lower peritoneal retention.

Actually, the anti-tumor efficiency of chemotherapeutics is not determined by the concentration of drugs in the peritoneal cavity but by their concentration in tumor tissues, more specifically in tumor tissue centers [45]. Studies showed that postsurgical residual tumor size is associated with the efficiency of IP therapy, and a better prognosis and longer survival intervals in OC patients result from smaller tumors ($\leq$0.5 cm) over larger tumors ($\geq$2 cm) [14]. The related studies showed that these results were due to the drugs' permeability within the tumor mass [21,70,71]. Thus, adequate tumor penetration is important for IP chemotherapy. As reported, chemotherapeutics' tumor interstitial transport is mainly driven by convection or diffusion that is associated with their physicochemical properties and the stromal architecture [45-48]. Therefore, although small molecules (with low molecular weight) have penetration advantages, tumor stroma is also a critical obstacle. For instance, studies showed that the density of collagen fibers deposited in the tumor ECM could affect the stiffness and rigidity of the stroma, combined with the geometric arrangement of these collagen fibers, to jointly affect drug diffusion [45]. Moreover, tumor cells and stromal cells could contribute to a high cellular density and solid stress [45,72], and peritoneal mucus provides an additional barrier for IP chemotherapeutics [45,73]. For example, cancer-associated fibroblasts (CAFs) can contribute to physical barriers and microvascular compression to prevent the transportation of chemotherapeutics and immune cells, generating resistance to chemotherapy and immune therapy [74,75].

(3) Lack of tumor cell targeting and safety

Lack of tumor specificity is also a key restriction in IP chemotherapy. After IP administration, peritoneal tumors and healthy tissues/organs are exposed to high concentration of chemotherapeutics, which might cause hematologic and/or local (*e.g.*, gastrointestinal) toxicity. Peritoneal cavity tumor targeting can promote preferential uptake of chemotherapeutics by tumor cells, resulting in enhanced therapeutic effects and reduced side effects. Moreover, the safety of IP chemotherapeutics is not only associated with agents' targeting but also with their PK. For example, cisplatin, carboplatin, melphalan, and etoposide are rapidly absorbed into the systemic circulation, easily inducing systemic toxicity, while paclitaxel, mitoxantrone, and doxorubicin (DOX) are absorbed slowly, easily leading to dose-limited local toxicity [70,76-81]. Besides, mitomycin, 5-fluorouracil, and oxaliplatin can induce chemical peritonitis, and docetaxel causes ileus [82-85]. Administration procedures of traditional IP chemotherapy, such as placing IP catheters in patients' abdomens and frequent dosing, could induce infection and physical damage to peritoneal tissues [14,86,87].

(4) Limited inhibition of tumor metastasis and chemoresistance

The limited inhibition of metastasis and chemoresistance is also a challenge for IP chemotherapy [88]. The TME within the abdominal cavity plays vital roles in the metastasis and chemoresistance of OC cells. Interactions between malignant cells and the TME can be mediated by direct cell-cell contact, secreted molecules, or the transmission of exosomes [7]. Based on the "seed and soil" hypothesis, stromal cells and ECM provide a suitable soil for the peritoneal metastasis of OC (detailed discussions about the effects of the TME on OC development and peritoneal metastasis are elaborated in Section 1 in Supporting information) [6,22]. Besides, except for biophysical barriers in the TME, the interactions between the TME and OC cells could also contribute to the chemoresistance. Several cytokines secreted from stromal cells are associated with the activation of tumors' anti-apoptotic pathways and the exchange of drug efflux proteins, thus promoting drug metabolism, ECM formation, and the maintenance of cancer cell stemness, eventually resulting in chemotherapy resistance [23,89]. For instance, tumor ECs overexpress ATP-binding cassette (ABC) transporters (*e.g.*, multidrug resistance protein 1 and P-glycoprotein), which are associated with the chemoresistance of tumor cells [90-92]. Besides, it was reported that resistance to antiangiogenic therapy and an induction of tumor cell stemness could be mediated by proangiogenic TAMs [93]. Thus, single IP chemotherapeutics used for tumor cells might have limited effects and cannot effectively inhibit tumor progress, metastasis, and chemoresistance, while the peritoneal TME might be a potential therapeutic target.

3. Current strategies for nanomedicine-based IP chemotherapy

The application of nanomedicine-based delivery systems could combine numerous anti-tumor functionalities in a nanostructure-based therapy approach to overcome the above challenges, resulting in enhanced treatment effect, decreased side effects, inhibited metastasis and chemoresistance, reduced dosing frequency, and improved patient compliance [4,40,94]. Current strategies (Fig. 3) for nanomedicine-based targeting delivery systems are discussed and summarized below.

3.1. Improving the colloid stability

NPs' colloid stability in biofluids (*e.g.*, blood and peritoneal fluid) after administration is critical for their biological activity maintenance and therapeutic effect. Although some studies on NP's colloid stability in the blood have been conducted, relevant investigations in the peritoneal fluid are scarce. Dakwar *et al.* systematically studied the effects of surface charge and PEGylated on the colloid stability of liposomes and polystyrene (PS) NPs in mouse peritoneal fluid, human ascites fluid, and human serum [59]. In this study, they first determined the content and type of proteins in these three biofluids. The result demonstrates that protein content is human serum (6244 mg/dL) > human ascites fluid (3296.4 mg/dL) > mice peritoneal fluid (183.84 mg/dL), and the major protein type in the three biofluids is albumin. Then, they investigated the colloid stability of PS NPs (cationic, PEGylated, and anionic) and liposomes (cationic, 5 mol% PEGylated, and 10 mol% PEGylated). The results showed that both cationic and anionic non-PEGylated NPs tend to form large aggregates through binding to different proteins upon incubation with peritoneal fluids or human serum, and the aggregation tendency is proportional to the protein concentration in these biofluids (except for cationic PS NPs, which show the greatest aggregation in mice peritoneal fluid with the lowest protein content). Importantly, the result showed that PEGylation has a crucial impact on NPs' colloid stability in the three biofluids; a suitable PEGylated degree is necessary to avoid the formation of aggregation in peritoneal fluids, whether cationic or anionic liposomes. In addition, it is worth noting that only consider-

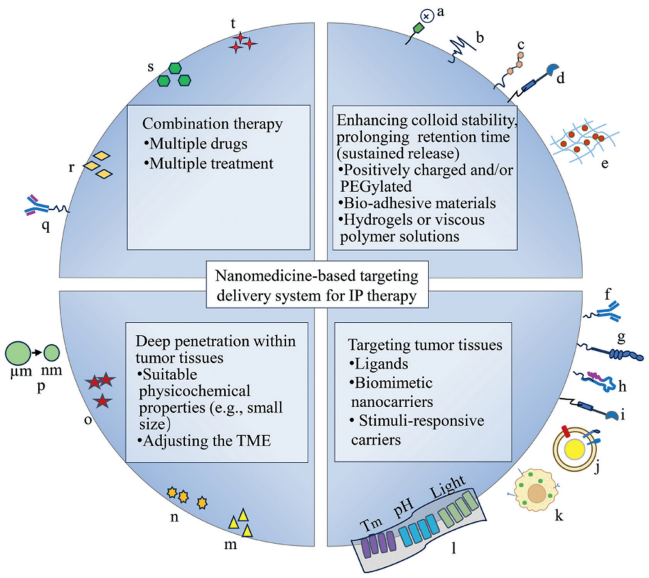

Fig. 3. Strategies of nanomedicine-based targeting delivery system for IP therapy. (a–e) Strategies for improving colloid stability, prolonging peritoneal retention time and achieving sustained release: (a) using the positively charged materials; (b) PEGylated; (c, d) conjugated with bio-adhesive molecules such as chitosan and lectin; (e) nanoparticles dispersed in hydrogels or polymer solutions. Strategies for targeting tumor tissues: (f–i) nanoparticles modified with antibodies, glycoproteins, peptides, and lectins, respectively; (j, k) biomimetic nanocarriers such as nanoparticles coated by bio-membranes and loaded in cells or exosomes; (l) nanoparticles composed with stimuli-responsive materials. Strategies for deep penetration within tumor tissues: (m–o) nanoparticles loaded with drugs that can modulate the TME, such as vascular normalizing drugs, stroma-degrading drugs, or tumor cells apoptosis-inducing drugs; (p) decreasing the particle size of nanoparticles. Strategies for combination therapy: (q, r) immunotherapy such as nanoparticles conjugation with antibodies and loading with small molecule immune drugs; (s) nanoparticles loaded with photosensitizer or photothermal agents; (t) nanoparticles loading with multiple chemotherapeutics.

ing NPs' ascites stability is not enough; their good colloidal stability in the blood is also important, since following IP administration, some NPs might enter the systemic circulation through the lymphatics, which may block capillaries if aggregation occurs.

3.2. Promoting peritoneal retention and tumor tissue penetration

As mentioned above, following IP administration, the determinants involving NPs' *in vivo* fate mainly involve their compositions, physicochemical properties (*e.g.*, particle size, surface charge, PEGylated), and the TME (*e.g.*, proteins, enzymes, stromal cells, the ECM); all of these can impact their peritoneal retention time and tumor penetration [40-42].

3.2.1. Prolonging peritoneal retention time

The peritoneal retention time of NPs could be prolonged by changing their compositions, particle size, surface charge, and surface modification. Some researchers (Table S2) have focused on the impacts of these factors on NPs' peritoneal retention, whereas some different conclusions were reached that might be associated with the NPs' types and colloid stability, healthy or diseased animal models, and the mutual influence between these factors.

If ignoring other factors, only considering the particle size, larger particles might be beneficial for longer peritoneal retention and lower systemic absorption. Lu *et al.* determined the PK of three paclitaxel formulations with different particle sizes: Cremophor micelles (13 nm), gelatin NPs (~600 nm), and PLG microparticles (~4 μm) [14]. The result demonstrated rapid clearance of the Cremophor micelles and gelatin NPs (remaining <0.1% after 24 h) and much longer retention (also much higher peritoneal concentration, 17–700 times) of the PLG microparticles; and in spite of the 50-times larger particle size, the clearance of the gelatin NPs is more rapid (approximately 10-times) than the Cremophor micelles [14]. These confirmed that microparticles have stronger peritoneal retention ability, and drug release is rate-limiting for the clearance of small particles (with a size smaller than the lymphatic openings) [14]. Moreover, Mirahmadi *et al.* investigated several different-sized neutral liposomes with the same compositions (100, 400, 1000, and 3000 nm) [42]. They indicated that neutral liposomes with 1000 nm had the greatest peritoneal retention and level (even more than neutral liposomes with 3000 nm), which might be due to the sediment of 3000 nm on abdominal organs [42]. Though larger particles are beneficial for longer peritoneal retention, large microparticles are easy to cause abdominal adhesion; hydrogels could overcome this and have been studied in IP therapy for many years [95-99]. Especially for thermosensitive hydrogels, which are temperature-sensitive and could undergo sol-gel transformation after IP administration, achieving sustained drug release and being minimally invasive [100]. Shen *et al.* prepared a sustained injectable thermosensitive polymer-platinum (IV) conjugate hydrogel to co-delivery cisplatin and paclitaxel, which could sustain drug release for 2.5 months *in vitro*, exhibiting excellent anti-tumor efficiency and significant safety compared with the free drug cocktail in the SKOV3 OC xenograft mouse model [101].

Because of the complex components (*e.g.*, proteins, enzymes, macrophages) in the peritoneal TME, considering particle size alone is not sufficient when designing NPs, and compositions, potential zeta, and surface modification are also associated with their peritoneal retention and sustained release degree [14,102-104]. Studies showed that cationic liposomes and lipid-based micro/nanoparticles have less lymphatic drainage and longer peritoneal retention compared with anionic or neutral particles, which might be associated with the fact that cationic particles can interact with negatively charged peritoneal mesothelial cells and their aggregation in the peritoneal cavity, as well as the higher uptake of negatively charged particles by peritoneal macrophages [4,51,105,106]. Sadzuka *et al.* investigated the peritoneal retention, distribution, and therapeutic effect of DOX-encapsulating liposomes with different lipid types, particle sizes, and surface charges in mouse models with solid tumors outside the abdominal cavity and peritoneal dissemination tumors [49]. The result showed that larger liposomes had a greater peritoneal retention level and were more effective against peritoneal dissemination in the abdominal cavity than small liposomes, and lipid composition had no effect on liposomes' peritoneal retention and distribution but on their side effects [49]. Moreover, they indicated that PEG modification of negatively charged liposomes had no effects on their peritoneal retention, while PEG modification of positively charged liposomes might reduce their abdominal retention, which might be because the abdominal tissues are negatively charged, and the decrease in the zeta potential by PEGylation reduced the adsorption of the cationic NPs by the abdominal tissues [49]. However, it is worth noting that the outer aqueous phase of the cationic liposomes in this research is 9.0% sucrose-lactate buffer (10 mmol/L, pH 4.0) [49]. Because of the different pH between the outer aqueous phase and peritoneal fluid, it is difficult to determine if the positive surface charge of the cationic liposomes is maintained when being exposed to the peritoneal physiological environment. Dadashzadeh *et al.* studied the effects of liposome composition, PEG coating, and surface charge on the peritoneal retention time of liposomes at two sizes of 100 and 1000 nm similarly, but came to different conclusions [50]. They showed that cationic liposomes have greater peritoneal levels and retention than neutral or anionic liposomes (cationic liposome composed with DSPC are greater than those prepared with 1,2-dipalmitoyl-*sn*–glycero-3-phosphocholine

(DPPC) and 1,2-dimyristoyl-*sn*–glycero-3-phosphocholine (DMPC) [50]. Cationic liposomes at 1000 nm have the greatest peritoneal retention; then there is the positively charged PEGylated small-size liposome (100 nm) that has a more uniform peritoneal distribution, greater peritoneal retention, slower drug release, and stronger resistance to peritoneal macrophages compared to the cationic conventional small-size liposome; the incorporation of PEG into the liposomes augmented the peritoneal level of these liposomes, especially for the anionic liposomes (except for protecting the vesicles against peritoneal macrophages, PEGylation can also decrease the repulsion between the negative surface of liposomes and the peritoneal mesothelium) [50].

In addition, the effect of particle size and surface charge on the NPs' peritoneal retention may be mutual. For example, a report showed that the effect of size on peritoneal retention was dependent on the surface charge of liposomes; 100 and 1000 nm negatively charged liposomes were equally rapidly cleared; while for the cationic liposomes, the 1000 nm cationic liposomes had the greatest peritoneal retention, followed by 100 nm cationic liposomes [40]. Besides, a report showed that, following IP administration, relatively large (>100 nm) anionic NPs can be preferentially taken up by tumor-associated macrophages (TAMs), while particles that were smaller than 100 nm or cationic showed no such tendency [51].

3.2.2. Promoting deep penetration within tumor tissues

To ensure the maximal efficacy of IP chemotherapy, in addition to the long retention time in the peritoneal cavity, achieving deep penetration of drugs within tumor tissue (to expose more central tumor cells to drugs) is also crucial. After IP administration, nanomedicines or drug molecules penetrate into tumor tissue mainly through two ways: (1) The minority is systemic circulation after clearance from the IP cavity; (2) The majority is directly diffusion or convection through the interstitial space within a tumor mass [14,40]. However, the TME of solid tumors is characterized by dense stromal tissue (including ECM and stromal cells) and abundant and leaky vasculature systems, which result in a narrow interstitial space, a high interstitial fluid pressure (IFP), and complex interactions between stromal cells and tumor cells, thereby counteracting penetration of nanomedicines and drug molecules [40,107]. Currently, there are mainly two strategies for enhancing tumor tissue penetration: one is designing NPs with suitable physicochemical properties, including particle size, surface charge, and surface modification (PEGylation); the other is regulating the TME, such as reducing solid tumor stromal density and IFP. Both of these can be used either alone or in combination.

Studies have demonstrated that NPs of smaller size could penetrate tumor tissues more efficiently than larger ones [40]. Moreover, surface charge also has important effects on their tumor penetration, whereas recent studies about the effect of surface charge on their tumor penetration are controversial. Several studies showed that neutral NPs (±10 mV or −2∼−5 mV) can penetrate more deeply and distribute more homogeneously within tumor tissue than charged analogs due to the fact that cationic materials tend to interact with negatively charged matrix polymers (*e.g.*, hyaluronan) and anionic materials tend to interact with positively charged matrix (*e.g.*, collagen), resulting in reduced penetration and homogenous distribution [108-110]. However, Wang *et al.* demonstrated that 100 nm cationic PEGylated NPs outperformed their anionic or neutral counterparts in tumor penetration ability, resulting in their superior treatment efficacy [111]. In addition to particle size and surface charge, surface modification also has effects on nanoparticle tumor tissue penetration. As mentioned above, the PEGylated cation liposome at 100 nm demonstrated a more uniform distribution in the peritoneal cavity compared to the positively charged conventional liposome [50]. Besides, Lee *et al.* showed that the 27 nm epidermal growth factor receptor (EGFR)-modified micelles exhibited reduced tumor penetration compared to the non-modified micelles due to the "binding site barrier" effect, that is, specific binding and/or cellular internalization of antibodies by targeted cells halts their penetration in solid tumors [107,112].

Approaches about adjusting the TME for nanomedicines or drug molecules deep penetration within tumor tissues mainly include reducing IFP and depleting tumor stroma, specific for decreasing vasculatures and debulking ECM and stromal cells in tumor tissues [40,107]. Murakami *et al.* constructed a docetaxel-conjugate nanoparticle (Cellax), which could target tumor stroma and perform more efficaciously than docetaxel and nab paclitaxel [113]. In this study, Cellax can interact selectively with CAFs (α-smooth muscle actin (α-SMA) high expression) and be internalized *via* an albumin-SPARC (secreted protein acidic and rich in cysteine) dependent mechanism, resulting in the depletion of CAFs, increased tumor perfusion, decreased tumor matrix, and suppressed tumor interstitial fluid, compared with other treatments [107,113]. The anti-stromal effect of Cellax corresponded to the significantly enhanced antimetastatic effect, manifesting lung nodules reduced by 7- to 24-fold [113]. Besides, "tumor priming", a technology that uses tumor cell apoptosis-inducing agents to expand interstitial space and/or reduce the IFP, will also promote the penetration of nanomedicines and drug molecules within tumor tissues [14]. The report showed that tumor priming is tumor-selective owing to the greater susceptibility of tumor cells to apoptosis compared with normal cells [14]. Tumor priming with chemotherapeutics such as paclitaxel and DOX can decrease tumor cell density, expand interstitial space, decompress tumor vasculatures, and enhance extravasation and convection-mediated transport, resulting in enhanced penetration and dispersion of drug molecules and NPs in solid tumors [14,114-120]. Based on the above methods of regulating the TME to promote drug penetration within tumor tissues, nanomedicine-based delivery systems that simultaneously deliver TME-regulating drugs and chemotherapeutics or the relevant sequential treatments may be a feasible strategy for cancer therapy. In addition, some small molecules with IFP reduction and tumor stroma depletion ability, such as Bevacizumab (an anti-angiogenic drug), Imatinib (a prostaglandin inhibitor), and collagenase or hyaluronidase (ECM degradation enzymes), can also be used for TME regulation [40,107,121-123].

3.2.3. Keeping the balance between peritoneal retention and tumor tissue penetration

When constructing nanomedicine-based delivery systems, the influence of particle size, surface charge, and other factors on tumor penetration and abdominal retention should be comprehensively considered. It is worth noting that small NPs generally penetrate deeply within tumor tissues with a short abdominal cavity retention time, while large particles are just the opposite. For this mission, some strategies might be available: constructing hydrogel-based sustained release nanocomposites, using bio-adhesive materials (*e.g.*, chitosan, lectin), or designing stimulus-responsive carriers whose physicochemical properties (*e.g.*, particle size, surface charge) can change with the TME or external environment [105,124-126]. Bio-adhesive NPs are composed of natural biopolymers (*e.g.*, chitosan, gelatin, lectin, dopamine) or synthetic/semi-synthetic polymers (*e.g.*, hyperbranched polyglycerol, polyacrylic acid) that could interact with biological substrates to prolong drug retention time as well as promote particle uptake and local drug delivery [126,127]. For example, Deng *et al.* designed a bio-adhesive nanoparticle that could interact with aldehydes and proteins on mesothelial cells in the peritoneal cavity, significantly extending its peritoneal retention time and thus enhancing its anti-tumor efficiency [39]. In addition, the nanoparticle-hydrogel com-

bination system can also prolong abdominal cavity retention and promote tumor tissue penetration. Xiao *et al.* prepared a norcantharidin NPs and oxaliplatin co-encapsulating thermosensitive hydrogel nanocomposite for IP administration, which could prolong peritoneal retention and allow drug sustained release, resulting in significant anti-tumor efficiency [128].

3.3. Combination therapy, targeting tumor cells and the TME

In addition to extending retention time and enhancing tumor tissue penetration, combination therapy can also be achieved by nanomedicine-based delivery systems that can be designed to deliver various drugs with different physicochemical properties (*e.g.*, hydrophilic, hydrophobic) or pharmacological mechanisms (*e.g.*, apoptosis-promoting, anti-angiogenesis, immunoregulation). The combination of multiple chemotherapeutics or treatments can overcome the defects of monotherapy, effectively inhibit tumor progression and metastasis, and reduce the generation of chemotherapy resistance. Besides, as mentioned above, IP TME is associated with OC IP metastasis and chemoresistance. Therefore, nanomedicine-based IP delivery systems for targeting peritoneal tumor cells and TME will be a feasible and promising chemotherapy strategy. Meanwhile, it is of importance that the combination therapy takes into account the physicochemical properties of drugs and their PK and tissue distribution after IP administration, as well as the TME (*e.g.*, biological barriers), so as to produce synergistic effects and avoid significant adverse effects. In the following section, we will discuss the relevant strategies for targeting OC cells and the TME. Due to the limited research on the IP delivery of tumor cells and TME-targeting nanomedicine-based delivery systems in OC therapy, relevant research on targeting other cancers and the TME through intravenous or subcutaneous administration is also introduced, which may have implications or the potential to be applied in OC IP therapy.

3.3.1. Targeting tumor cells

Nanomedicine-based delivery systems could passively or actively target tumor sites without affecting the functions of healthy tissues and organs. Traditional passive targeting involves the enhanced permeability and retention (EPR) effect, and active targeting associates with the ligand-receptor interactions [129,130]. In OC peritoneal metastasis cancers, tumor lesions differ in size and location with poor vascularization and blood perfusion, which is incapable of conforming to the EPR effect, and the peritoneal-plasma barrier also prevents NPs from taking advantage of the EPR effect [4,131]. However, active targeting strategies might play significant roles in IP chemotherapy since IP administration brings the drugs directly to the peritoneal cavity and because of the lower protein content and macrophages in the peritoneal fluid, both of which reduce their tendency to bind to plasma proteins and blood cells, increasing the chance of carrier contact with tumor cells and reducing the risk of drug off-target, which is more efficient than intravenous active targeting [129,132]. Moreover, active targeting can allow specific recognition of the receptors on target sites, thus enabling better delivery efficiency and safety [133]. Nanomedicine-based active targeting delivery systems could be NPs or biomimetic nanocarriers modified by surface-specific ligands (*e.g.*, antibodies, aptamers, glycoproteins, lectins, peptides) to recognize cellular overexpressed receptors and/or take advantage of the intrinsic properties of carrier cells (*e.g.*, homotypic targeting, adhesion to tumor cells, tumor homing capability, long-term circulation) [13,130,134,135].

Currently, various ligands that target specific or overexpressed elements on OC cells have been modified on NPs (Table S3 in Supporting information) [24,27,136-153]. Folate receptors are overexpressed in OC cells and are rarely found in healthy cells, which makes αFR (folate receptor) antibody one of the most common ligands targeting OC cells [13]. Corbin *et al.* prepared αFR-antibody-targeted high-density lipoprotein NPs (HDL NPs) for near-infrared fluorescent imaging of peritoneal metastatic OC. The results demonstrated that IP administration of FR-α-targeted NPs could selectively target OC cells, resulting in enhanced therapy efficacy and safety compared with intravenous administration [154].

In addition to directly modifying ligands on NPs, biomimetic nanocarriers with or without ligand modifications are also effective tumor-targeted drug delivery systems; various cell membranes have been used for nanoparticle coating (*e.g.*, erythrocyte membrane, platelet membrane, leucocyte cell membrane, stem cell membrane, immune cell membrane, cancer cell membrane, and fibroblast membrane), as well as extracellular vesicles such as exosomes [134,135,155]. However, up to now, studies on the application of biomimetic nanocarriers to IP drug delivery are scarce, most of which are used for systemic administration or other methods (*e.g.*, intra-tumoral injection) [156-159]. Qian *et al.* prepared an injectable hydrogel-encapsulating paclitaxel-loaded red blood cell membrane nanoparticle for local chemotherapy (Fig. S1A in Supporting information) [158]. The combination of red cell membrane NPs and hydrogel significantly prolonged drug retention time locally, and due to the encapsulation of the cell membrane, the therapeutic effect at tumor sites and safety were greatly improved [158].

Additionally, a stimulus-responsive nanomedicine-based delivery system could also be employed to indirectly target tumor cells. Through specific materials or the surface conjugation of stimuli-responsive moieties, the physicochemical properties (*e.g.*, particle size, surface charge, shape) of the stimuli-responsive NPs could be changed (*e.g.*, size change, surface charge reversal, ligand hidden or exposed) under intrinsic (involving pH value, redox potential, enzyme concentration, and GSH concentration in the TME) or extrinsic (including temperature, light, *etc.*) stimuli, resulting in tumor tissue targeting accumulation and drug's spatiotemporally and quantitatively specific release [4,129,133]. Therefore, compared to conventional NPs, stimulus-responsive nanomedicines can successfully decrease drugs' release tendency in normal tissues and maintain drug concentrations in tumor cells for a more extended period, enabling obvious clinical advantages [160]. Li *et al.* designed matrix metalloproteinases (MMPs) and adenosine triphosphate (ATP)-responsive DOX-loaded nano-micelles (PCL-DNA/DOX-Peptide-PEG), which exhibit significantly enhanced cellular uptake levels compared with free drug in mouse ovarian epithelial tumor cells (ID-8) [161]. Fu *et al.* designed a reactive oxygen species (ROS)-responsive composite nano-hydrangea loaded with allicin and platinum (IV) prodrug (DTP@AP NPs) for comprehensive chemosensitization [162]. In this study, DTP@AP NPs can preferentially accumulate in tumor sites through the EPR effect followed by tumor cell uptake, then allicin and platinum (IV) prodrugs were responsively released triggered by tumor ROS for synergistic chemosensitization and tumor cell apoptosis, eventually resulting in marked tumor suppression and reduced side effects in an OC patient-derived tumor xenograft model [162]. Besides, Wang *et al.* designed a functional enzyme infrared QDAU5 NPs (FEIRQ NPs), which degraded under the high concentration of glutathione (GSH) in the TME, then β-galactosidase (β-Gal) and EQ were released [163]. The biological evaluation results indicated that FEIRQ NPs could induce ferroptosis, endoplasmic reticulum stress, and antigen pre-conditioning and maturation of dendritic cells and $CD8^+$ T cells, leading to excellent antitumor efficacy in the absence of cytotoxic drugs; and FEIRQ NPs also showed high fluorescence intensity upon exposure to the β-Gal enzyme expressed in OC, enabling real-time monitoring of therapeutic effects [163]. For more research about stimulus-responsive nanomedicines (also

called self-adaptive nanomaterials), please see a review by Yang *et al.* [160].

Moreover, in order to avoid off-target effect and achieve better targeting efficiency, combinations of multiple strategies were developed, such as dual targeting NPs and stimuli-responsive nanocarriers modified with bio-membranes or ligands [133,164]. Yan *et al.* developed DOX-loaded CD44 and folate receptor dually targeted NPs based on a direct conjugate of HA and folic acid (HA/FA-NP-DOX) [165]. In this study, HA/FA-NP-DOX possessed high selectivity to both CD44 and FR, resulting in strong killing of CD44 and FR-positive SKOV3 cells while low toxicity against CD44 and FR-negative L929 fibroblast cells, and the *in vivo* studies revealed the significant elevated tumor accumulation and survival benefits of HA/FA-NP-DOX compared to free DOX (Fig. S1B in Supporting information) [165]. Simón-Gracia *et al.* prepared an iRGD peptide (target transmembrane glycoprotein neuropilin 1 (NRP-1) and $\alpha_v\beta_3$ integrins (overexpressed in tumor cells)) conjugated pH-sensitive polymersome for paclitaxel IP delivery, which demonstrated enhanced tumor selection and penetration, contributing to enhanced inhibition of peritoneal tumor growth and local dissemination compared to the pristine paclitaxel-polymersomes or Abraxane (Fig. S1C in Supporting information) [4,164]. Gong *et al.* constructed a pH-responsive nanoparticle (H/D@FA-CaP NPs) in which hemin and cisplatin were encapsulated in hydrophobic 1,2-distearoyl-*sn*–glycero-3-phospho-ethanolamine (DSPE) to form a tight core, hydrophilic polyethylene glycol 2000 (PEG 2000) and calcium phosphate formed the outside shell, and FA was modified on the surface of NPs [142]. In this study, folic acid (FA) modification could target OC cells; hemin could inhibit BACH1 as well as down-regulate CD47, promoting the apoptosis of tumor cells and inducing phagocytosis of tumors by macrophages; and hemin also has a synergistic effect with cisplatin to promote apoptosis of tumor cells [142]. Besides, Zheng *et al.* developed a DOX-loaded cRGD-decorated pH-responsive polyion complex (PIC) micelle [143]. In this study, due to cRGD decoration, PIC micelles could actively target tumors through the specific recognition of $\alpha v\beta 3$integrin on the membrane of tumor cells, and then DOX was released under an intracellular acidic microenvironment after being internalized by tumor cells. The tumor active-targeting and TME stimulation-response eventually resulted in enhanced inhibition efficacy toward hepatoma and reduced side effects compared with the insensitive controls [143].

In addition to the targeting strategies mentioned above, a novel spatiotemporally targeted method has emerged. Yang *et al.* designed a spatiotemporally targeted polycystine-based nanoantidote that served as a neutralizer of cisplatin to decrease its toxicity without affecting its anticancer efficacy [166]. The nanoantidotes were administered before cisplatin (CDDP), which can selectively accumulate in the liver and kidney, and then firmly bound to CDDP during subsequent chemotherapy. The nanoantidotes and two-step administration strategy could maintain the anticancer efficacy of CDDP after reducing systemic toxicity, having great potential for expanding the clinical application of CDDP [166].

3.3.2. Targeting IP TME (or both TME and tumor cells)

The stromal cells and ECM in the intraperitoneal TME of OC can generate high-density matrix barriers, blocking the infiltration of chemotherapeutics, oxygen, and immune cells [167]. Besides, stromal cells with pro-tumor phenotypes could promote the development of tumor cells and affect angiogenesis and immune effects, ECM also plays important roles in stabilizing the typical tissue structures and regulating the cells' behaviors, both of which are associated with tumor progression, metastasis, and therapy resistance [7,168-173]. Moreover, since the identification of specific targets in tumor cells might fail due to intrinsic genomic instability, TME is emerging as an attractive target for nanomedicine-based delivery systems [174]. Thus, in the following sections, we will discuss the nanomedicine delivery strategies targeting these stromal cells and the ECM.

(1) Targeting CAFs

In addition to the pro-tumor effects, CAFs comprise a large portion of tumor mass and are more stable and uneasy to develop into chemoresistance [175]. All of these indicate CAFs are attractive targets for OC therapy. Currently, strategies about targeting CAFs for cancer therapy mainly include two aspects: one is the inhibition of the signaling pathways between CAFs and tumor cells or other stromal cells to improve the sensitivity to antitumor treatments; the other is inhibiting the production of ECM by CAFs to reduce the solid pressure and IFP, promoting the diffusion and deep penetration of drugs in tumors [176,177]. Detailed strategies for nanomedicine-based CAFs targeting are discussed in Section 2.1 (Supporting information).

(2) Targeting ECs and angiogenesis

Currently, targeting ECs and angiogenesis for antiangiogenic therapy has been a frequently applied strategy for OC treatment with various advantages: (i) Directly binding to their receptors after treatment (for systemic administration); (ii) the genetic stability of ECs reduces the potential risk of therapy resistance; (iii) most of ECs markers are expressed whatever the tumor type, involving an ubiquitous approach and a broad application spectrum [178,179]. Conventional anti-angiogenic agents such as monoclonal antibodies (mAbs), small-molecule inhibitors, and fusion proteins (*e.g.*, Bevacizumab, Ramucirumab) could inhibit angiogenesis and tumor growth. However, these agents are not always leading to therapeutic breakthroughs, and in some cases, are associated with toxicity, instability, and the generation of a relative hypoxic TME and therapy resistance [180-182]. Therefore, some new therapeutic strategies have been developed, including enhancing the safety and stability of anti-angiogenic agents, combining anti-neovascularization with chemotherapy or immunotherapy, or normalizing the structure and function of vessels [182]. In this context, serval nanomedicine-based delivery systems have been developed for anti-angiogenic therapy, including lipid-based, polymeric, and inorganic NPs, which can effectively function as anti-angiogenic drug carriers or have intrinsic anti-angiogenic properties [182]. Detailed strategies for nanomedicine-based ECs and angiogenesis targeting are discussed in Section 2.2 (Supporting information).

(3) Targeting TAMs

As one of the most abundant immune cells in the TME of OC associated with tumor progression, angiogenesis, metastasis, and therapy resistance, TAMs, especially M2-like TAMs, are becoming an attractive target for OC therapy. Relevant strategies mainly include inducing TAMs ablation (survival interference *via* inhibiting the CSF1-CSF1R signaling pathway, such as anti-CSF1R mAbs), limiting TAMs recruitment (inhibiting the CCL2-CCR2 signaling pathway, such as anti-CCL2 antibodies), and reprogramming (repolarizing TAMs from an M2 to M1 phenotype, such as Toll-like receptor (TLR) agonists) [183-188]. Detailed strategies for nanomedicine-based TAMs targeting are discussed in Section 2.3 (Supporting information).

(4) Targeting MDSCs and Tregs

MDSCs are vital immune cells in the TME of OC, which are associated with tumor progression, metastasis, and chemoresistance, as well as contributing to the formation of the immunosuppressive TME. Consequently, targeting MDSCs has emerged as

a research focal point, and the major strategies focus on depleting the MDSCs, inhibiting their immunosuppressive activity, blocking recruitment and expansion, and inducing differentiation [189]. Moreover, the depletion of Tregs to regulate the TME is also an attractive therapeutic direction for OC therapy. Recently, lots of studies have demonstrated the immunotherapeutic effect of Tregs-targeting nanomedicine strategy [190]. Detailed strategies for nanomedicine-based MDSCs and Tregs targeting are discussed in Section 2.4 (Supporting information).

(5) Targeting ECM

Studies focused on using collagenase and hyaluronidase to degrade collagen against cancer progression are in development, and various nanomedicine delivery systems that transport ECM-degrading agents targeting the ECM in tumor tissues have been constructed. Detailed strategies for nanomedicine-based ECM targeting are discussed in Section 2.5 (Supporting information).

4. Ongoing clinical studies for nanomedicine-based IP chemotherapy

Currently, 14 nanomedicines have been approved for systemic administration of cancer treatment, but none for IP chemotherapy [4,191]. Fortunately, with the understanding of IP chemotherapy and the development of nanomedicine-based delivery systems, lots of nanomedicine-based delivery systems are being designed and studied for IP therapy. Despite this, currently only four nanomedicine-based IP therapies have entered clinical trials; all of these are for peritoneal cancers or other cancers with peritoneal metastasis. Details of the four clinical trials are discussed in Section 3 (Supporting information).

5. Conclusion and future perspectives

CRS, followed by platinum-based chemotherapy, is the standard treatment for OC and its peritoneal metastasis or other peritoneal cancers. Multiple studies have shown that IP chemotherapy has clinical benefits in peritoneal cancer patients compared with intravenous therapy. However, there are no products specifically designed or approved for IP therapy, and the current practice is the off-label use of drugs designed for intravenous therapy. Consequently, some problems followed, such as short retention of drugs in the abdominal cavity, high drug exposure in a short time, a lack of tumor tissue targeting, inadequate penetration within tumor tissues, and chemoresistance, eventually resulting in severe gastrointestinal toxicity and reduced efficacy. Therefore, reasonable designs of drug delivery systems are necessary for IP chemotherapy. Furthermore, rational drug delivery systems are inseparable from the understanding and control of their *in vivo* fate, which is crucial for their design and clinical translation and is associated with drug carriers' physicochemical properties and peritoneal physiological environment. Therefore, studies on the *in vivo* fate of drug carriers following IP delivery are also important for the development of IP chemotherapy.

The optimal delivery system for IP therapy should have a long peritoneal retention time or sustained release, specifically target tumor tissues, and penetrate deeply within the tumor mass, which can maintain stability under a normal peritoneal physiological environment and rapidly degrade and release drugs at tumor sites. Besides, due to the complex pathological mechanisms of tumors and the pro-tumoral components in the TME, multi-drug or multi-therapy combinations are also necessary. Nanomedicine-based IP targeting delivery systems can well address the above problems and needs of IP chemotherapy. It's worth noting that the IP TME plays vital roles in the progression, metastasis, and chemoresistance of peritoneal cancers. Thus, nanomedicine-based delivery systems dually targeting tumor cells and the TME might have better therapeutic effects than single anti-tumor chemotherapy drugs, which is a feasible direction.

Moreover, nanomedicine-based IP targeting delivery systems could be applied not only in conventional IP chemotherapy (intraperitoneal chemotherapy (IPEC) or hyperthermic intraperitoneal chemotherapy (HIPEC)), but also in the new IP chemotherapy technologies, such as depot systems (*e.g.*, hydrogel) and PIPAC. Thermosensitive hydrogels are temperature-sensitive and can undergo sol-gel transformation after IP administration, achieving sustained drug release and being minimally invasive, the nanoparticle-thermosensitive hydrogel combination system can achieve the functions mentioned above. In addition, because of the prolonged peritoneal retention time, IP catheter might be avoided, thus patients' compliance and quality of life can be significantly improved. PIPAC also has many advantages compared to conventional IP chemotherapy, including homogeneous drug distribution, enhanced tumor penetration, decreased dosing, and improved patient compliance and quality of life. The combination of nanomedicine-based IP targeting delivery systems with these new IP chemotherapy technologies could play synergistic roles to further improve efficacy and safety, which is a promising direction for IP chemotherapy and its combination with other treatments such as anti-angiogenesis and immune therapies used for OC and its peritoneal metastasis or other peritoneal cancers.

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.

CRediT authorship contribution statement

Boyuan Liu: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Zixu Liu:** Formal analysis, Data curation. **Ping Wang:** Formal analysis, Data curation. **Yu Zhang:** Visualization, Formal analysis. **Haibing He:** Visualization, Formal analysis. **Tian Yin:** Visualization, Formal analysis. **Jingxin Gou:** Writing – review & editing, Visualization, Formal analysis. **Xing Tang:** Supervision, Resources, Project administration, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110229.

References

[1] S. Lheureux, M. Braunstein, A.M. Oza, CA. Cancer J. Clin. 69 (2019) 280–304.
[2] D. Holmes, Nature 527 (2015) S217.
[3] A.J. Cortez, P. Tudrej, K.A. Kujawa, K.M. Lisowska, Cancer Chemother. Pharmacol. 81 (2018) 17–38.
[4] S. Breusa, S. Zilio, G. Catania, et al., Front. Oncol. 13 (2023) 1125868.
[5] L.C. Peres, K.L. Cushing-Haugen, M. Köbel, et al., J. Natl. Cancer Inst. 111 (2019) 60–68.
[6] E. Schoutrop, L. Moyano-Galceran, S. Lheureux, et al., Semin. Cancer Biol. 86 (2022) 207–223.
[7] S. Mei, X. Chen, K. Wang, Y. Chen, Cancer Cell Int. 23 (2023) 11.
[8] M.A. Lisio, L. Fu, A. Goyeneche, Z.H. Gao, C. Telleria, Int. J. Mol. Sci. 20 (2019) 952.
[9] J. Krugmann, C. Schwarz, B. Melcher, et al., Arch. Gynecol. Obstet. 299 (2019) 515–523.

[10] D.S. Tan, R. Agarwal, S.B. Kaye, Lancet Oncol. 7 (2006) 925–934.
[11] T.A. Yap, C.P. Carden, S.B. Kaye, Nat. Rev. Cancer 9 (2009) 167–181.
[12] G.C. Jayson, E.C. Kohn, H.C. Kitchener, J.A. Ledermann, Lancet 384 (2014) 1376–1388.
[13] F. Delie, E. Allemann, M. Cohen, J. Drug Deliv. Sci. Technol. 22 (2012) 421–426.
[14] Z. Lu, J. Wang, M.G. Wientjes, J.L. Au, Future Oncol. 6 (2010) 1625–1641.
[15] E. Gitsch, P. Sevelda, S. Schmidl, H. Salzer, Eur. J. Gynaecol. Oncol. 11 (1990) 19–22.
[16] F.O. Recio, M.S. Piver, R.E. Hempling, D.L. Driscoll, Gynecol. Oncol. 68 (1998) 267–273.
[17] M.S. Piver, F.O. Recio, T.R. Baker, D. Driscoll, Cancer 73 (1994) 1693–1698.
[18] R.R. Barakat, P. Sabbatini, D. Bhaskaran, et al., J. Clin. Oncol. 20 (2002) 694–698.
[19] E. Topuz, P. Saip, A. Aydmer, et al., Eur. J. Gynaecol. Oncol. 19 (1998) 265–270.
[20] D.S. Alberts, P.Y. Liu, E.V. Hannigan, et al., N. Engl. J. Med. 335 (1996) 1950–1955.
[21] M. Markman, B. Reichman, T. Hakes, et al., J. Cancer Res. Clin. Oncol. 118 (1992) 235–237.
[22] Z. Luo, Q. Wang, W. Lau, et al., Cancer Lett. 377 (2016) 174–182.
[23] M. Castells, B. Thibault, J.P. Delord, B. Couderc, Int. J. Mol. Sci. 13 (2012) 9545–9571.
[24] X. Huang, M. Qiu, T. Wang, et al., J. Nanobiotechnol. 20 (2022) 93.
[25] A.H. Colby, S.M. Berry, A.M. Moran, et al., ACS Nano 11 (2017) 1466–1477.
[26] B.T. Surikutchi, R. Obenza-Otero, E. Russo, et al., Int. J. Pharm. 622 (2022) 121828.
[27] A. Oseledchyk, C. Andreou, M.A. Wall, M.F. Kircher, ACS Nano 11 (2017) 1488–1497.
[28] K. Yamaguchi, O. Hiraike, H. Iwaki, et al., Mol. Pharmaceutics 18 (2021) 4090–4098.
[29] K. Qian, H. Qian, J. Cai, et al., Patho. Res. Pract. 215 (2019) 755–760.
[30] J. Luo, Z. Wu, Y. Lu, et al., Int. J. Biol. Macromol. 152 (2020) 718–726.
[31] J. Kim, M.K. Shim, Y.J. Cho, et al., Biomaterials 279 (2021) 121189.
[32] M. Qiu, J. Chen, X. Huang, et al., ACS Appl. Mater. Interfaces 14 (2022) 21954–21965.
[33] V. Mulens-Arias, A. Nicolás-Boluda, A. Pinto, et al., ACS Nano 15 (2021) 3330–3348.
[34] R. Liu, A.H. Colby, D. Gilmore, et al., Biomaterials 102 (2016) 175–186.
[35] S. Xu, H. Fan, L. Yin, et al., Eur. J. Pharm. Biopharm. 104 (2016) 251–259.
[36] D. Hargrove, B. Liang, R. Kashfi-Sadabad, et al., J. Control. Release 328 (2020) 846–858.
[37] D.H. Shin, G.S. Kwon, J. Control. Release 268 (2017) 176–183.
[38] M. Shariati, G. Lollo, K. Matha, et al., ACS Appl. Mater. Interfaces 12 (2020) 29024–29036.
[39] D. Yang, Y. Fan, C. Emiliano, et al., Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 11453–11458.
[40] G.R. Dakwar, M. Shariati, W. Willaert, et al., Adv. Drug Deliv. Rev. 108 (2017) 13–24.
[41] R. Ando-Matsuoka, H. Ando, A.S. Abu Lila, et al., J. Control. Release 341 (2022) 524–532.
[42] N. Mirahmadi, M.H. Babaei, A.M. Vail, S. Dadashzadeh, Int. J. Pharm. 383 (2010) 7–13.
[43] X.F. Li, S. Carlin, M. Urano, et al., Cancer Res. 67 (2007) 7646–7653.
[44] L. Kuroki, S.R. Guntupalli, BMJ 371 (2020) m3773.
[45] W. Ceelen, H. Braet, G. Van Ramshorst, et al., Expert Opin. Drug Deliv. 17 (2020) 511–522.
[46] P.A. Netti, D.A. Berk, M.A. Swartz, A.J. Grodzinsky, R.K. Jain, Cancer Res. 60 (2000) 2497–2503.
[47] R.K. Jain, Cancer Res. 47 (1987) 3039–3051.
[48] E.W. Young, Integr. Biol. 5 (2013) 1096–1109.
[49] Y. Sadzuka, S. Hirota, T. Sonobe, Toxicol. Lett. 116 (2000) 51–59.
[50] S. Dadashzadeh, N. Mirahmadi, M.H. Babaei, A.M. Vali, J. Control. Release 148 (2010) 177–186.
[51] T. Haber, Y.R. Cornejo, S. Aramburo, et al., Proc. Natl. Acad. Sci. U. S. A. 117 (2020) 19737–19745.
[52] Y. Kai, G. Hua, S. Xiaoze, et al., Biomaterials 34 (2013) 2787–2795.
[53] D.S. Kohane, J.Y. Tse, Y. Yeo, et al., J. Biomed. Mater. Res. A 77 (2006) 351–361.
[54] K. Hirano, C.A. Hunt, J. Pharm. Sci. 74 (1985) 915–921.
[55] P. Maincent, P. Thouvenot, C. Amicabile, et al., Pharm. Res. 9 (1992) 1534–1539.
[56] G. Bajaj, Y. Yeo, Pharm. Res. 27 (2010) 735–738.
[57] K. De Clercq, C. Schelfhout, M. Bracke, et al., Biomaterials 96 (2016) 33–46.
[58] B.S. Zolnik, Á. González-Fernández, N. Sadrieh, M.A. Dobrovolskaia, Endocrinology 151 (2010) 458–465.
[59] G. Dakwar, E. Zagato, J. Delanghe, et al., Acta Biomater. 10 (2014) 2965–2975.
[60] Q. Jianping, Z. Jie, L. Yi, et al., Drug Discov. Today 22 (2017) 166–172.
[61] K. Saha, M. Rahimi, M. Yazdani, et al., ACS Nano 10 (2016) 4421–4430.
[62] C. Zhi-Ting, G. Li-Qin, J. Wei, et al., ACS Nano 14 (2020) 3563–3575.
[63] G. Caracciolo, L. Callipo, S.C. De Sanctis, et al., Biophys. Acta 1798 (2010) 536–543.
[64] G. Caracciolo, F. Cardarelli, D. Pozzi, et al., ACS Appl. Mater. Interfaces 5 (2013) 13171–13179.
[65] S. Schöttler, G. Becker, S. Winzen, et al., Nat. Nanotechnol. 11 (2016) 372–377.
[66] M. Tonigold, J. Simon, D. Estupiñán, et al., Nat. Nanotechnol. 13 (2018) 862–869.
[67] V. Mirshafiee, M. Mahmoudi, K. Lou, J. Cheng, M.L. Kraft, Chem. Commun. 49 (2013) 2557–2559.
[68] A. Salvati, A.S. Pitek, M.P. Monopoli, et al., Nat. Nanotechnol. 8 (2013) 137–143.
[69] R. Dedrick, Semin. Oncol. 12 (1985) 1–6.
[70] S. Zimm, S.M. Cleary, W.E. Lucas, et al., Cancer Res. 47 (1987) 1712–1716.
[71] M. Markman, Intraperitoneal chemotherapy, in: A. Altchek, L. Deligdisch, N.G. Kase (Eds.), Diagnosis and Management of Ovarian Disorders, 2nd Edition, Academic Press, San Diego, 2003, pp. 505–513.
[72] V.P. Chauhan, R.M. Lanning, B. Diop-Frimpong, et al., Biophys. J. 97 (2009) 330–336.
[73] J. Leal, H.D. Smyth, D. Ghosh, Int. J. Pharm. 532 (2017) 555–572.
[74] M. Zhang, Z. Chen, Y. Wang, H. Zhao, Y. Du, Cancers 14 (2022) 2637.
[75] A. Garcia-Gomez, J. Rodríguez-Ubreva, E. Ballestar, Clin. Immunol. 196 (2018) 64–71.
[76] F. Elferink, W. Van Der Vijgh, I. Klein, et al., Cancer Chemother. Pharmacol. 21 (1988) 57–60.
[77] J.D. Nagel, F.J. Varossieau, R. Dubbelman, W.W. ten Bokkel Huinink, J.G. McVie, Cancer Chemother. Pharmacol. 29 (1992) 480–484.
[78] M. Markman, E. Rowinsky, T. Hakes, et al., J. Clin. Oncol. 10 (1992) 1485–1491.
[79] D.S. Alberts, E.A. Surwit, Y.M. Peng, et al., Cancer Res. 48 (1988) 5874–5877.
[80] R. Demicheli, G. Bonciarelli, A. Jirillo, et al., Tumori 71 (1985) 63–68.
[81] S.B. Howell, C.E. Pfeifle, R.A. Olshen, Ann. Intern. Med. 101 (1984) 14–18.
[82] B.J. Monk, E.A. Surwit, D.S. Alberts, V. Graham, Semin. Oncol. 15 (1988) 27–31.
[83] R.J.Morgan Jr, J.H. Doroshow, T. Synold, et al., Clin. Cancer Res. 9 (2003) 5896–5901.
[84] J.L. Speyer, J.M. Collins, R.L. Dedrick, et al., Cancer Res. 40 (1980) 567–572.
[85] D.M. Elias, L. Sideris, Surg. Oncol. Clin. N. Am. 12 (2003) 755–769.
[86] L.B. Wenzel, H.Q. Huang, D.K. Armstrong, J.L. Walker, D. Cella, J. Clin. Oncol. 25 (2007) 437–443.
[87] J.L. Walker, D.K. Armstrong, H.Q. Huang, et al., Gynecol. Oncol. 100 (2006) 27–32.
[88] Y. Minareci, O.A. Tosun, H. Sozen, S. Topuz, M.Y. Salihoglu, Medeni. Med. J. 35 (2020) 202–211.
[89] A. Ghoneum, S. Almousa, B. Warren, et al., Semin. Cancer Biol. 77 (2021) 83–98.
[90] L. Huang, C. Perrault, J. Coelho-Martins, et al., J. Hematol. Oncol. 6 (2013) 49.
[91] K. Hida, N. Maishi, Y. Sakurai, Y. Hida, H. Harashima, Adv. Drug Deliv. Rev. 99 (2016) 140–147.
[92] D.A. Annan, H. Kikuchi, N. Maishi, Y. Hida, K. Hida, Int. J. Mol. Sci. 21 (2020) 3238.
[93] C.A. Penn, K. Yang, H. Zong, et al., Mol. Cancer Ther. 17 (2018) 96–106.
[94] J. Wang, Y. Li, G. Nie, Nat. Rev. Mater. 6 (2021) 766–783.
[95] K. Stratakis, T. Arkoumanis, A. Liakea, et al., Chirurgia 117 (2022) 585–593.
[96] G.U. Ruiz-Esparza, X. Wang, X. Zhang, et al., Nanomicro Lett. 13 (2021) 212.
[97] E.M. Ahmed, J. Adv. Res. 6 (2015) 105–121.
[98] Y. Huang, J. Zheng, G. Zeng, et al., Mater. Today Bio 24 (2024) 100931.
[99] M. Norouzi, B. Nazari, D.W. Miller, Drug Discov. Today 21 (2016) 1835–1849.
[100] Z. Li, J. Guan, Expert Opin, Drug Deliv. 8 (2011) 991–1007.
[101] W. Shen, X. Chen, J. Luan, et al., ACS Appl. Mater. Interfaces 9 (2017) 40031–40046.
[102] M. Longmire, P.L. Choyke, H. Kobayashi, Nanomedicine 3 (2008) 703–717.
[103] M.F. Flessner, J.D. Fenstermacher, R.G. Blasberg, R.L. Dedrick, Am. J. Physiol. Heart Circ. Physiol. 248 (1985) H26–H32.
[104] A. Supersaxo, W.R. Hein, H. Steffen, Pharm. Res. 8 (1991) 1286–1291.
[105] G. Lee, S. Han, I. Inocencio, et al., Mol. Pharm. 16 (2019) 4987–4999.
[106] Y. Aramaki, K. Akiyama, T. Hara, S. Tsuchiya, Eur. J. Pharm. Sci. 3 (1995) 63–70.
[107] M.J. Ernsting, M. Murakami, A. Roy, S.D. Li, J. Control. Release 172 (2013) 782–794.
[108] T. Stylianopoulos, M.Z. Poh, N. Insin, et al., Biophys. J. 99 (2010) 1342–1349.
[109] O. Lieleg, R.M. Baumgärtel, A.R. Bausch, Biophys. J. 97 (2009) 1569–1577.
[110] T. Nomura, N. Koreeda, F. Yamashita, Y. Takakura, M. Hashida, Pharm. Res. 15 (1998) 128–132.
[111] H.X. Wang, Z.Q. Zuo, J.Z. Du, et al., Nano Today 11 (2016) 133–144.
[112] H. Lee, H. Fonge, B. Hoang, R.M. Reilly, C. Allen, Mol. Pharm. 7 (2010) 1195–1208.
[113] M. Murakami, M. Ernsting, E. Undzys, et al., Cancer Res. 73 (2013) 4862–4871.
[114] J.H. Zheng, C.T. Chen, J.L. Au, M.G. Wientjes, AAPS PharmSci 3 (2001) E15.
[115] H.J. Kuh, S.H. Jang, M.G. Wientjes, J.R. Weaver, J.L. Au, J. Pharmacol. Exp. Ther. 290 (1999) 871–880.
[116] S.H. Jang, M.G. Wientjes, J.L. Au, J. Pharmacol. Exp. Ther. 296 (2001) 1035–1042.
[117] C.T. Chen, J.L. Au, M.G. Wientjes, Clin. Cancer Res. 4 (1998) 277–282.
[118] D. Lu, M.G. Wientjes, Z. Lu, J.L. Au, J. Pharmacol. Exp. Ther. 322 (2007) 80–88.
[119] S.H. Jang, M.G. Wientjes, J.L. Au, Invest. New Drugs 19 (2001) 113–123.
[120] G. Griffon-Etienne, Y. Boucher, C. Brekken, H.D. Suit, R.K. Jain, Cancer Res. 59 (1999) 3776–3782.
[121] K. Pietras, Semin. Oncol. 31 (2004) 18–23.
[122] K. Pietras, A. Ostman, M. Sjöquist, et al., Cancer Res. 61 (2001) 2929–2934.
[123] R. Cairns, I. Papandreou, N. Denko, Mol. Cancer Res. 4 (2006) 61–70.
[124] Y. Yeo, T. Ito, E. Bellas, et al., Ann. Surg. 245 (2007) 819–824.
[125] F. Mohamed, O.A. Stuart, P.H. Sugarbaker, J. Surg. Res. 113 (2003) 114–120.
[126] L. Yu, Z. Luo, T. Chen, et al., Int. J. Mol. Sci. 23 (2022) 2370.
[127] S.K. Nethi, S. Das, C.R. Patra, S.J.B.S. Mukherjee, Biomater. Sci. 7 (2019) 2652–2674.
[128] S. Xiao, Y. Wang, W. Ma, et al., Drug Deliv. 29 (2022) 2713–2722.
[129] Q. He, J. Chen, J. Yan, et al., Asian J. Pharm. Sci. 15 (2020) 416–448.
[130] T.M. Allen, Nat. Rev. Cancer 2 (2002) 750–763.

[131] L. Zhao, W. Yuan, J. Li, et al., Adv. Funct. Mater. 28 (2018) 1806162.
[132] R.K. Jain, Adv. Drug Delivery Rev. 64 (2012) 353–365.
[133] W. Chen, K. Shi, Y. Yu, et al., Chin. Chem. Lett. 35 (2023) 109159.
[134] R.H. Fang, W. Gao, L. Zhang, Nat. Rev. Clin. Oncol. 20 (2023) 33–48.
[135] C. Guido, G. Maiorano, B. Cortese, S. D'Amone, I.E. Palamà, Bioengineering 7 (2020) 111.
[136] C. Andreou, A. Oseledchyk, F. Nicolson, et al., J. Visualized Exp. 145 (2019) e58389.
[137] H.D. Han, L.S. Mangala, J.W. Lee, et al., Clin. Cancer Res. 16 (2010) 3910–3922.
[138] U.K. Nässander, P.A. Steerenberg, H. Poppe, et al., Cancer Res. 52 (1992) 646–653.
[139] M. Satpathy, L. Wang, R. Zielinski, et al., Small 10 (2014) 544–555.
[140] V. Shah, O. Taratula, O.B. Garbuzenko, et al., Clin. Cancer Res. 19 (2013) 6193–6204.
[141] Y. Yang, X. Zhao, X. Li, et al., Oncol. Lett. 13 (2017) 99–104.
[142] K. Gong, J. Liao, J. Lin, et al., Chin. Chem. Lett. 35 (2024) 108888.
[143] P. Zheng, Y. Liu, J. Chen, et al., Chin. Chem. Lett. 31 (2020) 1178–1182.
[144] D. Kim, Z.G. Gao, E.S. Lee, Y.H. Bae, Mol. Pharm. 6 (2009) 1353–1362.
[145] Y. Zheng, Z. Cai, X. Song, et al., Int. J. Pharm. 382 (2009) 262–269.
[146] M.H. Vingerhoeds, P.A. Steerenberg, J.J. Hendriks, et al., Br. J. Cancer 74 (1996) 1023–1029.
[147] A. Cirstoiu-Hapca, F. Buchegger, N. Lange, et al., J. Control. Release 144 (2010) 324–331.
[148] W. Chen, R. Bardhan, M. Bartels, et al., Mol. Cancer Ther. 9 (2010) 1028–1038.
[149] L. Ceppi, N.M. Bardhan, Y. Na, et al., ACS Nano 13 (2019) 5356–5365.
[150] C. Schumann, S. Chan, J.A. Millar, et al., Nanomedicine 14 (2018) 1395–1405.
[151] L.B. Mensah, S.W. Morton, J. Li, H. Xiao, et al., Bioeng. Transl. Med. 4 (2019) e10131.
[152] A.C. Khayrani, H. Mahmud, A.K.K. Oo, et al., Int. J. Mol. Sci. 20 (2019) 1042.
[153] F. Delie, P. Ribaux, P. Petignat, M.J.B. Cohen, Biochimie 94 (2012) 2391–2397.
[154] I.R. Corbin, K.K. Ng, L. Ding, A. Jurisicova, G. Zheng, Nanomedicine 8 (2013) 875–890.
[155] A. Li, Y. Zhao, Y. Li, et al., Drug Deliv. 28 (2021) 1237–1255.
[156] B. Bahmani, H. Gong, B.T. Luk, et al., Nat. Commun. 12 (2021) 1999.
[157] Y. Li, R. Yuan, Y. Luo, et al., Adv. Mater. 35 (2023) 2300216.
[158] H. Qian, K. Qian, J. Cai, et al., ACS Biomater. Sci. Eng. 5 (2019) 1100–1112.
[159] J. Wang, H. Pan, J. Li, et al., Chin. Chem. Lett. 34 (2023) 107828.
[160] G. Yang, Y. Liu, J. Chen, J. Ding, X. Chen, Acc. Mater. Res. 3 (2022) 1232–1247.
[161] G. Li, W. Xu, Y. Shi, M. Chen, D. Peng, J. Biomed. Nanotechnol. 18 (2022) 718–728.
[162] H. Fu, P. Liang, Q. Chen, et al., Chin. Chem. Lett. 35 (2024) 109241.
[163] J. Wang, X. Pan, J. Zhang, et al., Chin. Chem. Lett. 35 (2024) 109187.
[164] L. Simón-Gracia, H. Hunt, P. Scodeller, J. Gaitzsch, et al., Biomaterials 104 (2016) 247–257.
[165] Y. Yan, Y. Dong, S. Yue, et al., ACS Appl. Mater. Interfaces 11 (2019) 46548–46557.
[166] J. Yang, T. Su, H. Zou, et al., Angew. Chem. 134 (2022) e202211136.
[167] Y. Feng, Z. Liao, H. Zhang, et al., Chem. Eng. J. 452 (2023) 139506.
[168] Y. Jiang, C. Wang, S. Zhou, Biochim. Biophys. Acta Rev. Cancer 1873 (2020) 188361.
[169] M. Cummings, C. Freer, N. Orsi, Semin. Cancer Biol. 77 (2021) 3–28.
[170] P. Lu, V.M. Weaver, Z. Werb, J. Cell Biol. 196 (2012) 395–406.
[171] T.Y. Yu, G. Zhang, X.X. Chai, et al., Life Sci. 332 (2023) 122084.
[172] K. Dzobo, C. Dandara, Biomimetics 8 (2023) 146.
[173] Y. Brown, S. Hua, P.S. Tanwar, Matrix. Biol. 118 (2023) 16–46.
[174] L. Pascual-Antón, P. Sandoval, G.T. González-Mateo, et al., J. Pathol. 261 (2023) 238–251.
[175] J.M. Hansen, R.L. Coleman, A.K. Sood, Eur. J. Cancer 56 (2016) 131–143.
[176] H. Peng, X. He, Q. Wang, Front. Immunol. 13 (2022) 1035997.
[177] J. Guo, H. Zeng, Y. Chen, Mol. Pharm. 17 (2020) 1028–1048.
[178] J. Schmitt, D. Matei, Cancer Treat. Rev. 38 (2012) 272–283.
[179] F. Danhier, O. Feron, V. Préat, J. Control. Release 148 (2010) 135–146.
[180] D. Ribatti, T. Annese, S. Ruggieri, R. Tamma, E. Crivellato, Transl. Oncol. 12 (2019) 981–986.
[181] K. Yoncheva, G. Momekov, Expert Opin. Drug Deliv. 8 (2011) 1041–1056.
[182] R. Giordo, Z. Wehbe, P. Paliogiannis, et al., Semin. Cancer Biol. 86 (2022) 784–804.
[183] G. Hu, M. Guo, J. Xu, et al., Front. Immunol. 10 (2019) 475392.
[184] M. Ovais, M. Guo, C. Chen, Adv. Mater. 31 (2019) 1808303.
[185] P.S. Kirk, T. Koreckij, H.M. Nguyen, et al., Int. J. Mol. Sci. 14 (2013) 10483–10496.
[186] D.E. Sanford, B.A. Belt, R.Z. Panni, et al., Clin. Cancer Res. 19 (2013) 3404–3415.
[187] F.J. Van Dalen, M.H. Van Stevendaal, F.L. Fennemann, M. Verdoes, O.J.M. Ilina, Molecules 24 (2018) 9.
[188] E.B. Glass, A.A. Hoover, K.K. Bullock, et al., BMC Cancer 22 (2022) 497.
[189] E.L. Yang, Z.J. Sun, Adv. Healthc. Mater. 13 (2024) e2303294.
[190] S.B. Yong, J.Y. Chung, Y. Song, et al., Biomaterials 219 (2019) 119401.
[191] F. Rodríguez, P. Caruana, N.De la Fuente, et al., Biomolecules 12 (2022) 784.