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Application of tumor microparticles in tumor prevention and treatment

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Abstract

Tumor microparticles (T-MPs) are vesicles released from tumor cells when they receive apoptotic or stimuli signals. T-MPs, which contain some proteins, lipids and nucleic acids from tumor cells, contribute to the exchange of material, energy and information between cells. T-MPs contain both tumor antigens and innate immunostimulatory signals, making T-MPs as a new form of tumor vaccine. Meanwhile, T-MPs can be used as natural carriers to transport "cargoes", such as chemotherapy drugs, oncolytic viruses, nucleic acids, and metal nanoparticles to treat tumors. In addition, T-MPs enhance the effect of chemotherapy. This review introduces the application of T-MPs as vaccines, delivery systems and chemosensitizers in tumor prevention and treatment, with a focus on the mechanisms, clinical applications, and influencing factors of drug-loaded T-MPs in tumor treatment.

Keywords: Tumor microparticles, Tumor vaccine, Drug delivery, Immunotherapy

Introduction

Tumor is a large class of diseases, which can occur in almost any organ or tissue of the body when abnormal cells grow uncontrollably. Traditional tumor treatment methods, e.g., chemotherapy and radiotherapy, have the disadvantages of strong side effects and easy recurrence after treatment (Falzone et al. 2023). Surgical treatment is only suitable for early stage tumors, as advanced tumors often have metastasized and are difficult to be completely cut off by surgery (Megyesfalvi et al. 2023). Tumor is characterized not only by overgrowth of malignant cells but also by suppression and reprogramming of the immune system (de Visser and Joyce 2023). It is hoped to prevent and treat tumors by activating the immune system. More than 100 years ago, William Coley used microbes to treat tumors, which was the beginning of tumor immunotherapy (Feld and Mitchell 2018). In the past 20 years, tumor immunotherapy mainly focused on adoptive cell therapy, immune checkpoint inhibitors and therapeutic tumor vaccines (Finck et al. 2022; Robert 2020; Saxena et al. 2021). However, the efficacy of immunotherapy on most tumors remains limited (Wang et al. 2022a). How to combine tumor immunotherapy

with traditional tumor treatment methods to improve efficacy and reduce side effects is currently a concern for researchers.

Extracellular vesicles (EVs), as carriers of material, energy and information between cells, have become the hotspot of various researches (Rädler et al. 2023). Microparticles (MPs), also known as microvesicles, ectosomes, shedding vesicles, belong to the family of EVs (Bian et al. 2019; Kubo 2018). MPs are vesicles that encapsulate a part of cytosolic contents within the cellular membrane when cells undergo apoptosis or stimulants. The diameter of MPs is between 100 ~ 1000 nm (Marar et al. 2021; Minciacchi et al. 2015). After being released into extracellular space, MPs exert various biological functions (Li et al. 2021; Wang et al. 2022c; Wei et al. 2021b).

Tumor microparticles (T-MPs) are MPs released by tumor cells which receive apoptotic or stimuli signals (Tang et al. 2022). T-MPs carry a portion of contents from tumor cells and can transmit information at the release site, as well as to distant cells through blood circulation (Ma et al. 2020; Zhang et al. 2018; Zhu et al. 2021). Compared with synthetic carriers such as liposomes, T-MPs have unique advantages as natural carrier. First, T-MPs have a good histocompatibility and can be maintained in the body for a long time (Meng et al. 2020). Second, T-MPs are extremely stable. In vitro experiments, T-MPs which have lipid raft structure can effectively resist the damage of some detergents, such as Triton-X100, indicating that the structure of T-MPs is remarkably stable (Tang et al. 2012). Third, T-MPs have tumor-homing property. The average size of T-MPs is 100–300 nm, and they have strong deformation ability, allowing them to easily pass through the leaky tumor blood vessels and enter the tumor tissues (Clancy et al. 2022; Zhang et al. 2020). Fourth, T-MPs can transport "cargoes" such as chemotherapy drugs, oncolytic viruses, or circular DNA into tumor tissues to directly kill tumor cells, and mobilize the immune system to participate in tumor treatment, making tumor treatment more thorough (Hu et al. 2022).

Exosomes are another type of EVs with a diameter of 30 ~ 150 nm, also used as natural carriers (Ruan et al. 2022). Compared with exosomes, T-MPs as natural carriers might possess the following merits. First, MPs have a larger diameter than exosomes and can load more cargo (Zhang et al. 2020). Second, MPs feature better tumor-targeting property. After intravenously injecting exosomes into mice for 24 h, less than 10% of the total exosomes were accumulated in the tumor (Qi et al. 2016). However, MPs could achieve 19% (Yu et al. 2017). Third, compared with exosomes derived from tumor cells, T-MPs could more effectively trigger T cell anti-tumor immune response (Zhang et al. 2020).

Based on their characteristics, T-MPs have been developed as prophylactic tumor vaccines, therapeutic tumor vaccines, natural delivery systems and chemosensitizers (Liu et al. 2017; Zhang and Huang 2015), which may provide tumor immunologists and oncologists with novel approaches to the prevention and treatment of tumors in the coming clinical settings. This review analyzes and summarizes the application of T-MPs in tumor prevention and treatment.

Collection and characterization of T-MPs

T-MPs are produced when tumor cells become apoptotic or receive stimulating signals. In order to obtain T-MPs, it is customary to irradiate tumor cells with UV, then put the tumor cells back into CO_2 incubator to make them slowly release MPs,

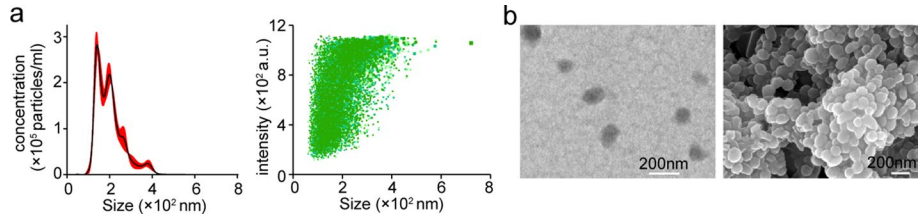

Fig. 1 Characterization of T-MPs (Sun et al. 2023). **a** NTA detection results of H22 hepatocarcinoma cell-derived MPs (H22-MPs). **b** Morphology of H22-MPs under transmission electron microscope and scanning electron microscope

Table 1 Summary of T-MPs served as prophylactic tumor vaccines

Administration	Activated immunocytes	Prevented tumors	References
s.c	DCs, T cells	s.c. H22, B16, CT26	(Zhang et al. 2015)
Oral	DCs, T cells	s.c. H22, B16, CT26	(Dong et al. 2017)
i.m.	Monocytes, macrophages, T cells	i.m. H22, B16, B16-OVA, CT26	(Sun et al. 2023)
i.v.	Neutrophils, macrophages	Metastatic LLC, B16	(Zhai et al. 2022)

and then obtain T-MPs by differential centrifugation (Ma et al. 2021). To be specific, tumor cell suspension is first exposed to 300 J/m^2 UV for 1 h, then the cells are placed in a CO_2 incubator for 24 h. Next, the tumor cells and media are centrifuged at 1000 ×*g* for 10 min to remove apoptotic cells, followed by centrifugation at 14,000 ×*g* for 2 min to remove cell debris. Finally, the supernatant is centrifuged at 14,000 ×*g* for 1 h to collect T-MPs (Ma et al. 2021, 2016b). In addition, methods such as X-ray (Timaner et al. 2020; Wan and Sun, 2020), hypoxia (Berchem et al. 2016; Zhang et al. 2018), and starvation (Jiang et al. 2019; Zhao et al. 2016) can also induce tumor cells to release MPs.

The diameter and concentration of T-MPs can be measured by nanoparticle tracking analysis (NTA) (Timaner et al. 2020; Wang et al. 2014). To visualize the morphology of T-MPs more visually, transmission electron microscope and scanning electron microscope can be used (Fig. 1). The Zeta potential of T-MPs can be detected by dynamic light scattering (Jiang et al. 2022; Zhao et al. 2016). Protein in T-MPs can be analyzed by western blot, and nucleic acids in T-MPs can be tested by PCR or RT-PCR (Chen et al. 2020; Pasquier et al. 2012). The chemotherapeutic drug content in T-MPs can be measured by high-performance liquid chromatography (Tang et al. 2012).

T-MPs serve as prophylactic tumor vaccines

Tumor antigens in T-MPs could be processed by dendritic cells (DCs) and cross-presented to CD8$^+$ T cells, suggesting that T-MPs had the potential to become tumor vaccine (Battisti et al. 2017; Dionisi et al. 2018; Rughetti et al. 2014). Follow-up researches showed that T-MPs could significantly inhibit tumorigenesis by subcutaneous (s.c.) injection, oral administration, intramuscular (i.m.) injection or intravenous (i.v.) injection in mice (Dong et al. 2017; Sun et al. 2023; Zhai et al. 2022; Zhang et al. 2015), revealing that T-MPs were expected to be novel tumor vaccine (Table 1).

s.c. injection vaccine

Mice were immunized three times by s.c. injection with T-MPs, followed by a challenge with tumor cells via s.c. injection. It was found that 50% (3/6) of the mice inoculated with T-MPs were tumor-free, indicating that s.c. injection of T-MPs could effectively prevent tumor growth (Zhang et al. 2015). Another study further explained the mechanism of T-MPs as tumor vaccine (Ma et al. 2018). DCs took up T-MPs into lysosomes, where pH value increased via reactive oxygen species (ROS) produced by NOX2, so that the tumor antigens were effectively degraded into antigenic peptide. Meanwhile, T-MPs drew lysosome to endoplasmic reticulum, promoting the formation of MHC class I-tumor antigen peptide complexes. T-MPs also activated the lysosomal Ca^{2+} channel Mcoln2, triggering Ca^{2+} release. The released Ca^{2+} activated TFEB, which directly bound with CD80/CD86 promoter region, thereby promoting the expression of CD80/86. Mature DCs enabled full activation of tumor-specific $CD8^{+}$ T cells which could kill tumor cells (Fig. 2). The above two studies confirmed that T-MPs could prevent tumorigenesis by s.c. injection, providing a new form of tumor vaccine.

Oral vaccine

Oral vaccines have been used for hundreds of years, which have successfully prevented severe viral and bacterial infections. The advantage of oral vaccine is its ease, safety, and the possibility to mediate both mucosal and systemic immune responses (Carlsen et al. 2023; Vela Ramirez et al. 2017). However, the use of oral vaccine is still limited to intestinal mucosal pathogen infections, with little exploration in tumor prevention (Durán-Lobato et al. 2020). Previous research suggested that T-MPs could be used as oral vaccine to prevent tumorigenesis (Dong et al. 2017). In this work, mice were orally inoculated with T-MPs, followed by a challenge with tumor cells via s.c. injection. The results showed that oral immunization of mice effectively suppressed tumorigenesis (Fig. 3). This study suggested that it was possible to develop oral tumor vaccines for human use based on T-MPs in the future.

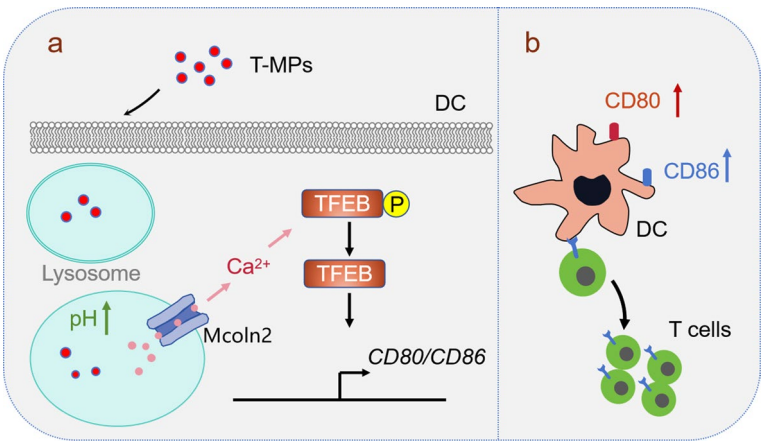

Fig. 2 The schematic diagram of mechanism by which T-MPs activated DCs (Ma et al. 2018). **a** T-MPs increased DC lysosomal pH, causing Ca^{2+} release through lysosomal Ca^{2+} channel Mcoln2. Ca^{2+} induced the activation of TFEB, thus promoting the expression of CD80/86; **b** mature DCs enable full activation of tumor-specific $CD8^{+}$ T cells

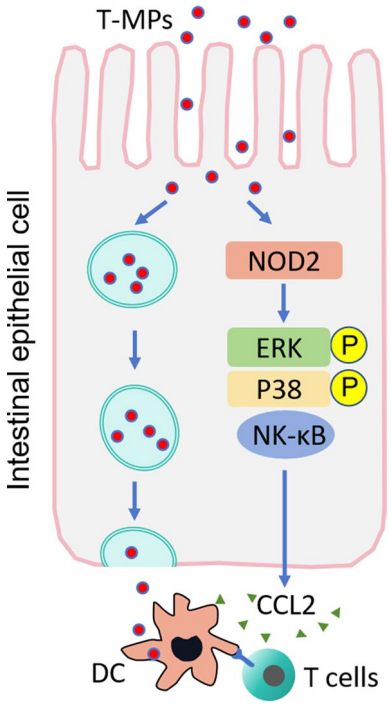

Fig. 3 Schematic showing mechanism of T-MPs as oral tumor vaccine (Dong et al. 2017). Orally administered T-MPs could not only activate the NOD2 signaling for CCL2 production in intestinal epithelial cell and DC recruitment, but also be transported to the basolateral site by intestinal epithelial cell and captured by DC, inducing T cell anti-tumor immunity

i.m. injection vaccine

Another study showed that i.m. vaccination of T-MPs could also effectively inhibit tumorigenesis (Sun et al. 2023). Mice were intramuscularly immunized with T-MPs three times, and then subjected to an i.m. injection of tumor cells. The results showed that 66.7% (4/6) of mice were tumor-free, indicating that i.m. injection of T-MPs could also effectively prevent tumorigenesis. The team further analyzed the mechanism by which T-MPs inhibited tumorigenesis and found that after T-MPs were injected into mice, macrophages first engulfed them and upregulated CCL2 expression, thus drew monocytes in blood to the vaccine injection site, increasing the phagocytosis of T-MPs. Monocytes subsequently entered the draining lymph nodes and differentiated toward monocyte-derived DCs (moDCs). moDCs presented tumor antigens in T-MPs to $CD8^+$ T cells, thereby delivering a strong anti-tumor immune response (Fig. 4).

i.v. injection vaccine

In another study, mice were immunized with T-MPs via i.v. injection, followed by a challenge with tumor cells through tail vein (Zhai et al. 2022). The results showed that pretreatment with T-MPs could significantly reduce the number of tumor nodules in lung and prolonged the survival of mice, indicating that T-MPs could prevent tumor lung metastasis. Mechanically, T-MPs injected into mice through tail vein could reach lung and be taken up by neutrophils and macrophages. After uptake of

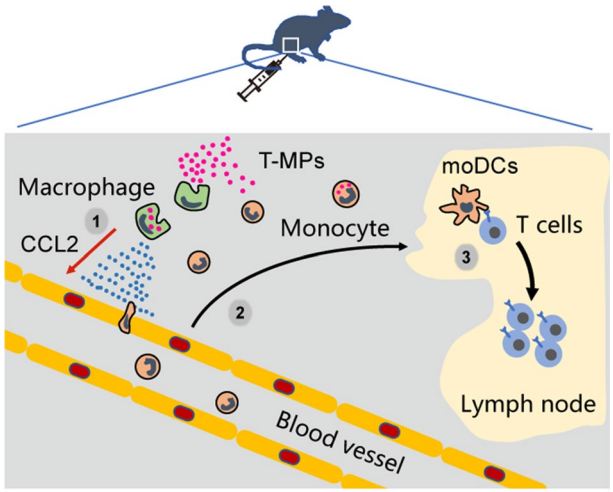

Fig. 4 Schematic showing mechanism by which T-MPs served as i.m. injection vaccine (Sun et al. 2023). (1) After T-MPs were injected into mice, macrophages first took up them and upregulated CCL2 expression. (2) CCL2 drew monocytes in blood to vaccine injection site, increasing the uptake of T-MPs. (3) Monocytes entered draining lymph node, and differentiated into monocyte-derived DCs (moDCs), which promoted T cell-specific proliferation

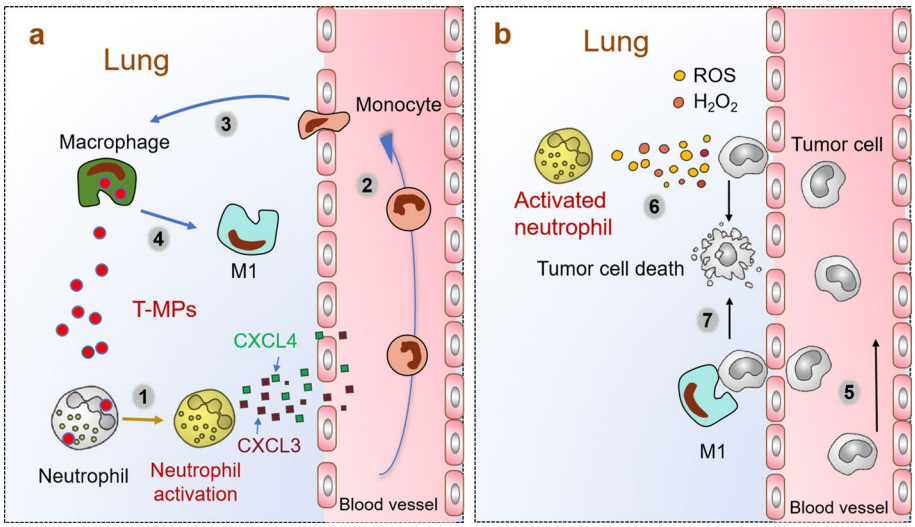

Fig. 5 The schematic diagram of mechanism by which T-MPs prevented tumor lung metastasis (Zhai et al. 2022). **a** Steps 1–4; **b** steps 5–7. (1) Neutrophils which endocytosed T-MPs were activated, and secreted CCL3 and CCL4. (2) CCL3 and CCL4 attracted monocytes to lung. (3) Monocytes differentiated into macrophages. (4) Macrophages endocytosing T-MPs polarized to anti-tumor M1 type. (5) Tumor cells circulating in blood entered lung through the gaps between vascular endothelial cells. (6) Activated neutrophils which produced ROS and H_2O_2 killed tumor cells in lung. (7) M1 macrophages destroyed tumor cells in lung

T-MPs, neutrophils were activated, and secreted CCL3 and CCL4, which attracted monocytes to lung. These monocytes further differentiated into macrophages. Macrophages endocytosing T-MPs polarized to anti-tumor M1 type. M1 macrophages and activated neutrophils which produce ROS and H_2O_2, killed the tumor cells in lung, thereby preventing lung metastasis (Fig. 5).

Collectively, T-MPs can trigger a strong anti-tumor immune response and significantly inhibit tumorigenesis or tumor lung metastasis. Different vaccine injection methods enable different cells to first take up T-MPs. For example, oral T-MPs were endocytosed by ileal epithelial cells but intramuscularly administered T-MPs by macrophages (Sun et al. 2023; Dong et al. 2017). However, all aforementioned T-MP vaccination methods can activate immune cells, thus preventing tumorigenesis or lung metastasis (Table 1).

T-MPs serve as therapeutic tumor vaccines

At present, therapeutic vaccines are more meaningful than prophylactic vaccines for tumors (Antonarelli et al. 2021). Since T-MPs can deliver tumor-specific immunity to prevent tumorigenesis, it is considered whether T-MPs can be used as therapeutic tumor vaccines. Several therapeutic vaccines have been designed based on T-MPs (Table 2).

DCs phagocytosing T-MPs can be used to treat tumors

DCs are the most important antigen-presenting cells in the body (Balan et al. 2019; Lu et al. 2022). On the basis of demonstrating that s.c. inoculation of T-MPs could prevent tumors, Zhang et al. conceived that T-MPs might also be used as therapeutic vaccines (Zhang et al. 2015). However, the direct injection of T-MPs into tumor-bearing mice did not effectively inhibit tumor growth, and the authors suggested that it might be due to the inability of DCs in tumor-bearing mice to efficiently take up T-MPs. Therefore, they incubated mouse bone marrow-derived DCs with T-MPs in vitro and then injected them through tail vein into tumor-bearing mice, finding the tumor growth was significantly inhibited. Meanwhile, many $IFN\gamma^{+}CD8^{+}$ T cells were found in tumors, indicating that DCs engulfing T-MPs could trigger $CD8^{+}$ T cell-specific proliferation and kill tumor cells (Zhang et al. 2015). With DCs as an adjuvant, T-MPs could be used for therapeutic tumor vaccines, providing a new approach to tumor immunotherapy.

Monocytes that engulf T-MPs can serve as therapeutic tumor vaccines

Monocytes are the largest immunocytes in blood and an important part of the body's defense system (Guilliams et al. 2018; Olingy et al. 2019). After co-incubation with T-MPs, monocytes could upregulate HLA-DR expression, increase the secretion of reactive oxygen intermediates, TNF, IL-10, IL-12p40, and enhance cytotoxic effect on tumor cells, suggesting that monocytes taking up T-MPs had the potential to treat tumors (Baj-Krzyworzeka et al. 2007). In another study, based on investigation of the mechanism by which T-MPs serve as prophylactic tumor vaccine, tumor-bearing mice were subjected to an injection of monocytes co-incubated with T-MPs in vitro through tail vein, and

Table 2 Summary of T-MPs served as therapeutic tumor vaccines

Administration	Activated immunocytes	Treated tumors	References
i.v.	DCs, T cells	s.c. H22, CT26	(Zhang et al. 2015)
i.v.	Monocytes, T cells	i.m. H22, B16; Metastatic B16-OVA	(Sun et al. 2023)
Intrapleural	Macrophages, T cells	LLC with MPE	(Wan et al. 2020)
s.c	T cells	s.c. C6	(Pineda et al. 2019)

the results showed that T-MP-loaded monocytes could effectively inhibit tumor development (Sun et al. 2023). This study also found that T-MP-loaded monocytes effectively inhibited B16-OVA tumor lung metastasis, and many IFNγ-producing SIINFEKL specific $CD8^+$ T cells were found in mouse spleen, indicating that T-MP-loaded monocytes could process the tumor antigens and cross-present to $CD8^+$ T cells which specifically multiplied and effectively killed tumor cells.

T-MPs were used to treat malignant pleural effusion (MPE)

Radiotherapy is a routine method for treating tumors. When the irradiated tumor cells undergo damage or die, the surrounding unirradiated tumor cells can also undergo the effect of radiation, which is known as the radiation-induced bystander effect (RIBE), but the mechanism under RIBE is not well defined (Daguenet et al. 2020; Zhang et al. 2022). Wan et al. found that radiation-irradiated tumor cells could release T-MPs, which mediated RIBE by inducing ferroptosis of tumor cells. This study then tried to use T-MPs for anti-tumor therapy. Mice with MPE were subjected to an intrapleural injection of T-MPs into pleural cavity. The researchers found that when T-MPs induced ferroptosis of tumor cells, extracellular calreticulin expression and released ATP from tumor cells increased, thus tumor cells were more easily recognized and cleared by macrophages. T-MPs induced the polarization of macrophages toward M1 type, and enhanced the anti-tumor function of macrophages, thus significantly inhibiting the progression of MPE and prolonging the survival of mice (Wan et al. 2020).

T-MP treatment for glioma

Glioma is the most common malignant tumor in the central nervous system, and the average survival of glioma patients is only 14 months (Yang et al. 2022). Researchers used C6 cell derived microparticles (C6-MPs) to treat glioma-bearing rats (Pineda et al. 2019). Compared with the control group, tumor growth in C6-MPs group rats was significantly inhibited, and the percentage of infiltrative helper T cells, cytotoxic T cells, regulatory T cells, and apoptotic cells in tumor increased, indicating that C6-MPs treatment of glioma was based on the body's immune response.

The above studies suggested that T-MPs could be used as therapeutic tumor vaccines by activating immune cells (Table 2). Although T-MPs as therapeutic vaccines have not yet been clinically tested, it is foreseeable that this kind of therapeutic tumor vaccine has bright prospects.

T-MPs serve as delivery systems and chemosensitizers

Platelet-derived MPs catalyzed the production of the anti-inflammatory mediator lipoxin A4 by transferring 12-lipoxygenase to mast cells (Tang et al. 2010), indicating the possibility of MPs as delivery systems. Considering the similarity in size, structure, and carrier function between MPs and artificial nanoparticles, it was speculated that MPs could serve as natural delivery systems (Saari et al. 2015). At present, T-MPs are used to transport chemotherapy drugs, oncolytic viruses (OAs), nucleic acids, metal nanoparticles, etc., and have shown good efficacy in tumor treatment (Table 3). In addition, T-MPs could serve as chemosensitizers to enhance the effect of chemotherapy (Jin et al. 2017).

Table 3 Summary of T-MPs served as delivery systems for tumor treatment

Cargo carried by T-MPs	Tumor models	Achievements	References
Flu	s.c. LLC	Inhibited tumor growth	(Chen et al. 2022)
MTX	H22 ascites	Reduction in ascites	(Tang et al. 2012)
Cis	i.p. A2780	Inhibited tumor growth	(Tang et al. 2012)
DOX	s.c. H22 /metastatic B16	Inhibited tumor growth/tumor lung metastasis	(Liang et al. 2019)
5-FU	s.c. H22	Inhibited tumor growth	(Liang et al. 2019)
Bi_2Se_3 + DOX	s.c. H22	Inhibited tumor growth	(Wang et al. 2020)
NAP	s.c. CT26	Inhibited tumor growth and liver metastasis	(Jing et al. 2023)
YM155 + MTX	s.c. Saos-2	Inhibited tumor growth	(Wei et al. 2021a)
PTX + *Bcl-2* siRNA	s.c. MDA-MB-231	Inhibited tumor growth	(Zhu et al. 2017)
OAs	s.c. A549/i.p. A549, A2780, CMT64	Inhibited tumor growth	(Ran et al. 2016)
MC DNA	4T1 in situ tumor	Inhibited tumor growth	(Kanada et al. 2019)
Fe_3O_4	s.c. B16, CT26	Inhibited tumor growth	(Zhao et al. 2019)

T-MPs as natural carriers for tumor treatment

Generally, two methods can be used to load cargo into T-MPs (Yong et al. 2022). One method is to first allow the cargo to enter tumor cells, and when the tumor cells release T-MPs, the cargo is sorted into T-MPs (Tang et al. 2010). There are several means to load cargo to tumor cells. Incubation (Guo et al. 2019; Wei et al. 2021a; Zhao et al. 2019) or electroporation (Wang et al. 2020) can introduce chemotherapy drugs and/or nanoparticles into tumor cells. DNA can be transfected into tumor cells using liposomes (Kanada et al. 2019), and OAs can enter tumor cells through transfection (Ran et al. 2016). The second method is to first stimulate tumor cells to release MPs, and then directly load cargo to T-MPs through electroporation (Zhu et al. 2017) or incubation (Jing et al. 2023).

Drug-loaded T-MPs can be used to treat tumor

Multiple studies have shown that drug-loaded T-MPs could effectively treat tumors. T-MPs loaded with chemotherapy drugs such as methotrexate (MTX) or doxorubicin (DOX), could directly kill tumor cells in vivo and in vitro (Tang et al. 2012). Interestingly, adding 0.6 mg MTX to tumor cell suspension could only kill 2% of tumor cells, while adding T-MPs loaded with 0.6 mg MTX could kill 23% of tumor cells, indicating that drug-loaded T-MPs had stronger tumor killing efficiency compared to simple chemotherapy drugs. The results also indicated that drug-loaded T-MPs presented a good safety in killing tumors (Tang et al. 2012). Another study suggested that T-MPs carrying cisplatin (Cis) combined with low dose irradiation could improve the survival rate of tumor-bearing mice without affecting liver and kidney functions (Sun et al. 2017).

Monocarboxylic acid transporter4 (MCT4) is a high affinity lactate transporter protein responsible for the efflux of intracellular lactate, and the high expression of MCT4 is associated with poor prognosis in various tumors (Benjamin et al. 2018;

Payen et al. 2020). Fluvastatin (Flu), an inhibitor of MCT4, has been screened as a drug for lung adenocarcinoma treatment (Wang et al. 2022b; Yang et al. 2017). The lung cancer-bearing mice were treated with intrapleural injection of Flu or Flu-loaded T-MPs. The results showed that T-MPs loaded with 0.4 μg Flu could effectively inhibit tumor growth, while 20 μg Flu was required to achieve the same effect, suggesting that low-dose Flu delivery through T-MPs could achieve the effect of tumor treatment (Chen et al. 2022). This study revealed that lung adenocarcinoma could be treated by targeting tumor lactate transport and immune response.

T-MPs carrying DOX or 5-FU could significantly inhibit the growth of H22 hepatocarcinoma s.c. tumor, and prolonged the survival of tumor-bearing mice. DOX-loaded T-MPs could also inhibit pulmonary metastasis of melanoma, and had a good safety in mice (Liang et al. 2019).

Bi_2Se_3 can convert light energy into thermal energy under near-infrared (NIR) irradiation, and is used in tumor photothermal therapy (Li et al. 2020). T-MPs carrying Bi_2Se_3 and DOX (Bi_2Se_3/DOX-loaded T-MPs) showed promising efficacy in treating H22 liver cancer s.c. tumor in mouse models. Bi_2Se_3/DOX-loaded T-MPs could penetrate into the interior of tumor. Under NIR irradiation, Bi_2Se_3/DOX-loaded T-MPs played a dual role of tumor photothermal therapy and chemotherapy, effectively inhibiting tumor growth and showing a good safety (Wang et al. 2020).

Cancer stem cells (CSCs) are cells with self-renewal ability and high tumorigenicity, which can drive tumor proliferation, metastasis and recurrence (Swati et al. 2023; Trumpp and Haas 2022). Napabucasin (NAP) inhibits CSCs through directly inhibiting gene transcription triggered by STAT3 (Bitsch et al. 2022; Li et al. 2015). T-MPs carrying NAP were used to treat colon cancer-bearing mice (Jing et al. 2023). The results showed that compared to using NAP alone, NAP-loaded T-MPs group achieved better efficacy. In addition, NAP-loaded T-MPs could significantly inhibit liver metastasis of colon cancer. This work also indicated that NAP-loaded T-MPs had no significant toxicity to normal tissues.

Survivin is overexpressed in most tumor cells, which closely related to the differentiation, proliferation, infiltration, and metastasis of tumor cells (Nozaki et al. 2022). T-MPs carrying survivin inhibitor YM155 and chemotherapy drugs could effectively reverse the multidrug resistance of osteosarcoma, thereby improving the anti-tumor effect and reducing systemic toxicity (Wei et al. 2021a).

T-MPs carrying paclitaxel (PTX) and siRNA targeting anti-apoptosis gene *Bcl-2* were modified with folate in T-MP surface to treat folate receptor positive MDA-MB-231 breast cancer (Zhu et al. 2017). The modification of folate promoted T-MPs targeting MDA-MB-231 breast cancer cells, and the loaded PTX and *Bcl-2* siRNA enabled T-MPs to have a synergistic therapeutic effect on tumor. Both at the cellular level and in tumor-bearing models, this drug-loaded T-MPs exhibited strong tumor killing ability and achieved satisfactory tumor therapeutic effects.

T-MPs carrying OAs for tumor treatment

OAs are genetically modified virus that can selectively replicate in tumor cells and kill them (He et al. 2022; Liu et al. 2022). However, OAs are easy to be recognized and neutralized by body's immune system, which makes it difficult for OAs to kill tumor cells

(Lin et al. 2023; Mantwill et al. 2021). T-MPs could deliver OAs, and protect OAs from being recognized by neutralizing antibody, so that OA-loaded T-MPs were able to effectively kill tumor cells. Since T-MPs do not rely on Coxsackievirus and adenovirus receptor (CAR) to enter tumor cells, OVs with downregulated CAR still killed tumor cells through T-MPs delivery (Ran et al. 2016).

T-MPs carrying minicircle (MC) DNA were used to treat tumor

Kanada et al. prepared MC DNA-loaded T-MPs, which could transport genes to tumor cells and make tumor cells express thymidine kinase (TK) and nitroreductase (NTR) that both are prodrug converting enzymes (Kanada et al. 2019). TK led to early termination of DNA synthesis in tumor cells through activating the prodrug Ganciclovir, and NTR prevented DNA replication by reducing the prodrug CB1954, thus effectively inhibiting the growth of mammary cancer cells. In tumor-bearing mouse models, T-MPs containing MC DNA were injected into 4T1 in situ tumor, and TK-NTR synthesized by tumor cells transformed the co-delivered prodrugs into cytotoxic agents, which not only killed the targeted cells, but also led to the death of surrounding tumor cells, significantly inhibiting tumor development.

T-MPs carrying metallic material were used to treat tumor

The surface of T-MPs carrying Fe_3O_4 nanoparticles was connected to dense CpG adjuvant liposomes to obtain tumor vaccine (Fe_3O_4/T-MPs-CpG/Lipo) (Zhao et al. 2019). The vaccine could polarize TAMs into M1 phenotype, induce infiltration of cytotoxic T cells, and reverse "cold" tumor into "hot" tumor. In addition, by combining Fe_3O_4/T-MPs-CpG/Lipo vaccine with PD-L1 monoclonal antibody, approximately 83% (5/6) of tumor-bearing mice received treatment became tumor-free.

The above researches suggested that using T-MPs as natural delivery systems could provide a novel tumor treatment strategy.

Application of drug-loaded T-MPs in clinical treatment of tumors

Some preclinical researches have shown that drug-loaded T-MPs could effectively kill tumor cells and mobilize anti-tumor immune cells to jointly inhibit tumor growth (Jing et al. 2023; Liang et al. 2019; Tang et al. 2012). Based on these studies, drug-loaded T-MPs have been used in clinical therapy of tumors and achieved satisfactory benefits (Table 4).

Table 4 Summary of T-MPs served as drug carrier for clinical treatment of tumors

Drug carried by T-MPs	Patients	Clinical remission rate	References
Cis	Lung cancer with MPE	100% (3/3)	(Ma et al. 2016a)
MTX	Lung cancer with MPE	90.9% (10/11)	(Guo et al. 2019)
MTX	Lung cancer with MPE	84.4% (27/32)	(Xu et al. 2020)
MTX	Lung cancer with MPE	82.5% (33/40)	(Dong et al. 2022)
MTX	ECCA	100% (20/20)	(Gao et al. 2020)

MPE is a common complication in the late stage of tumor patients with lung cancer, breast cancer or gastric cancer (Bibby et al. 2018). MPE is often accompanied by dyspnea, chest pain, dry cough and other symptoms, which reduce life quality and survival of patients (Bashour et al. 2022; Ferreiro et al. 2021). The treatments of MPE, such as catheter drainage, promotion of pleural adhesion and infusion of chemotherapy drugs, have unsatisfactory efficiency and strong side effects (Feller-Kopman et al. 2018). New treatment method of MPE needs to be developed. Ma et al. used T-MPs carrying Cis for the treatment of advanced lung cancer patients with MPE (Ma et al. 2016a). After treatment, one patient achieved complete remission and two patients achieved partial remission, with an objective clinical remission rate of 100% (3/3).

Guo et al. made use of MTX-loaded T-MPs to treat advanced lung cancer patients with MPE (Guo et al. 2019). The results showed the objective clinical response rate was 90.9% (10/11), and no significant normal tissue toxicity was observed. This small clinical study indicated that intrathoracic administration of MTX-loaded T-MPs could produce positive clinical reactions and have a good safety.

In another clinical study, 32 lung cancer patients with MPE were treated with MTX-loaded T-MPs, and the objective clinical remission rate reached 84.4% (27/32) (Xu et al. 2020). After treatment with drug-loaded T-MPs, the patients' MPE was significantly reduced, which changed from turbid faint red to clear faint yellow. Dong et al. used MTX-loaded T-MPs to treat advanced lung cancer patients with MPE (Dong et al. 2022). Among 40 patients who received drug-loaded T-MP therapy, 10 patients achieved complete remission, 23 patients achieved partial remission, and the objective clinical remission rate reached 82.5%.

Cholangiocarcinoma is located at the key position of bile drainage and normal operation of liver function, and the "shell" of this tumor is hard (Razumilava and Gores 2014; Rizvi et al. 2018). Patients with cholangiocarcinoma, especially those with extrahepatic cholangiocarcinoma (ECCA), are insensitive to radiotherapy and chemotherapy. Once they lose the opportunity of radical surgery, these patients will face the situation of "no medicine available", making ECCA as one of the most difficult tumor types in clinical treatment (Montal et al. 2020; Vithayathil and Khan 2022). For patients with ECCA, MTX-loaded T-MPs were injected into bile duct above the ECCA through drainage tube (Gao et al. 2020). The results showed that 25% (5/20) of patients relieved biliary obstruction, and 100% (20/20) of patients had a change in bowel color from clay to yellow. The majority of patients had improved dietary conditions and quality of life. There were no significant changes in the patients' blood routine, liver and kidney function, and no discomfort symptoms such as abdominal pain, nausea, vomiting, etc. This study suggested that drug-loaded T-MPs could serve as an effective treatment method for ECCA.

The above results revealed that T-MPs could be used as drug delivery systems in the clinical treatment of tumors (Fig. 6).

The mechanisms of drug-loaded T-MPs in tumor treatment

Why can chemotherapy drugs encapsulated in T-MPs be more effective in killing tumors? Some studies have analyzed the mechanisms of drug-loaded T-MPs in tumor treatment.

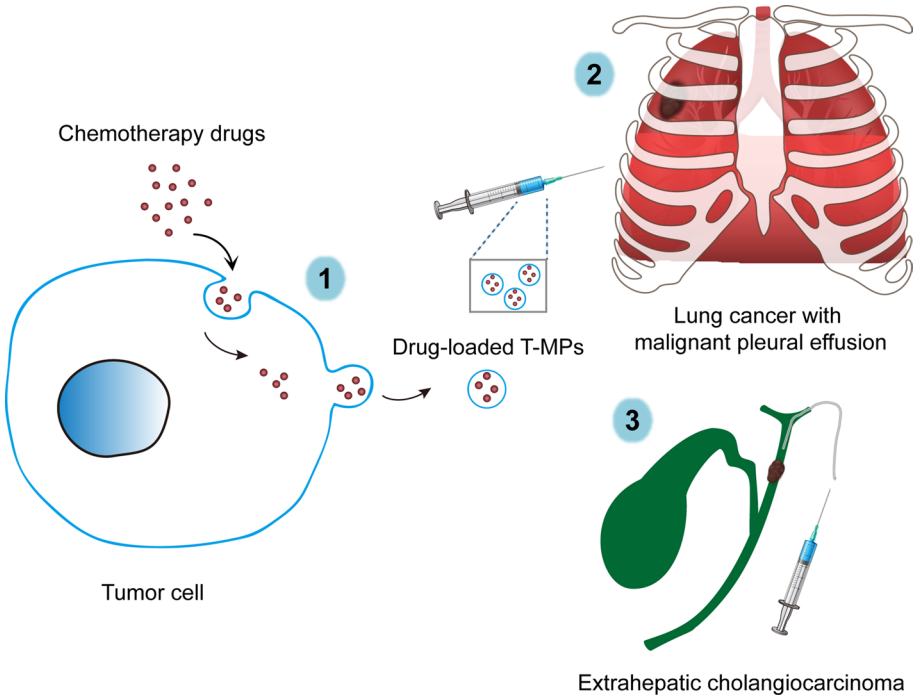

Fig. 6 The schematic diagram of drug-loaded T-MP application in clinical treatment of tumors. (1) Tumor cells were co-incubated with chemotherapy drugs, followed by release of drug-loaded T-MPs. (2) Lung cancer patients with malignant pleural effusion were treated with drug-loaded T-MPs by intrathoracic injection. (3) For patients with ECCA, drug-loaded T-MPs were injected into bile duct above the extrahepatic cholangiocarcinoma through drainage tube

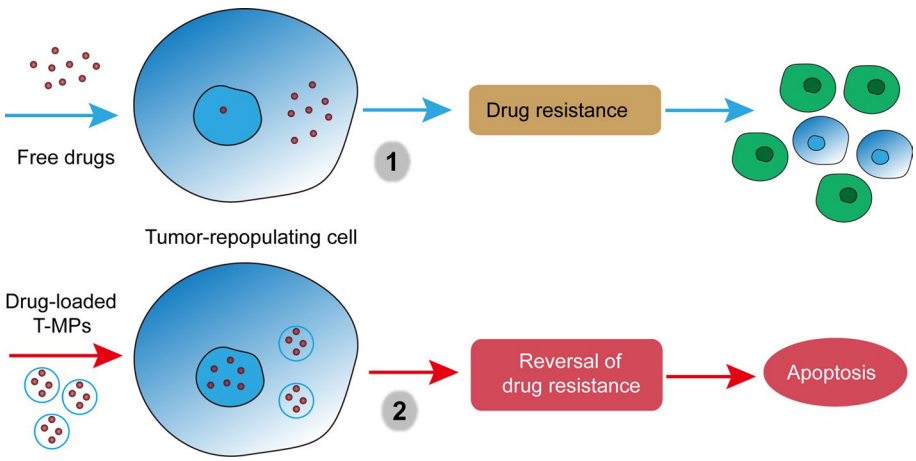

Fig. 7 Schematic showing mechanism by which drug-loaded T-MPs killed tumor-repopulating cells (Ma et al. 2016a). (1) Conventional chemotherapy drug treatment induced tumor-repopulating cell drug resistance. (2) Drug-loaded T-MP therapy reversed tumor-repopulating cell drug resistance and induced cell apoptosis

Drug-loaded T-MPs kill tumor-repopulating cells

Tumor cells isolated from 3D fibrin gels have the characteristics of CSCs, which are functionally defined as tumor-repopulating cells (TRCs) (Liu et al. 2012, 2018; Lv et al. 2021). TRCs were softer and easier to deform than differentiated tumor cells, so TRCs could take up drug-loaded T-MPs more efficiently (Ma et al. 2016a). T-MPs could deliver

drugs into lysosomes of TRCs, and mediate the movement of lysosomes to nucleus, thereby transporting drugs into nucleus of TRCs. Meanwhile, T-MPs interfered with the ABC transporter system to prevent drug efflux, thus effectively killing TRCs (Fig. 7). The elucidation of this mechanism was expected to promote the clinical transformation of T-MPs as natural drug delivery systems.

Drug-loaded T-MPs treat tumors by recruiting neutrophils

Neutrophils are the most abundant immune cells in blood, which contribute to both natural and adaptive immunity (Liew and Kubes 2019; Subhan and Torchilin 2021). Cytokines and epigenetics signals in the tumor microenvironment (TME) can trigger the formation of anti-tumor neutrophils (N1) and pro-tumor neutrophils (N2) (Jaillon et al. 2020). N1 neutrophils can directly kill tumor cells by releasing ROS and reactive nitrogen species, which also promote T cell activation and recruit pro-inflammatory macrophages to kill tumors (Giese et al. 2019; Gungabeesoon et al. 2023; Hedrick and Malanchi 2022). When T-MPs carrying MTX were used to treat MPE, a large number of neutrophils migrated to pleural cavity, and the number of attracted neutrophils was positively correlated with the regression of MPE (Xu et al. 2020). In animal models, it was found that drug-loaded T-MPs induced macrophages to release CXCL1 and CXCL2, which drew neutrophils to pleural cavity. This chemotaxis process endowed neutrophils with anti-tumor properties. Activated neutrophils killed tumors by releasing ROS and neutrophil extracellular traps (NETs). At the same time, the released NETs covered the gaps between vascular endothelial cells and reduced fluid leakage from blood vessels, thus achieving the benefits of killing tumor cells and reducing MPE (Fig. 8).

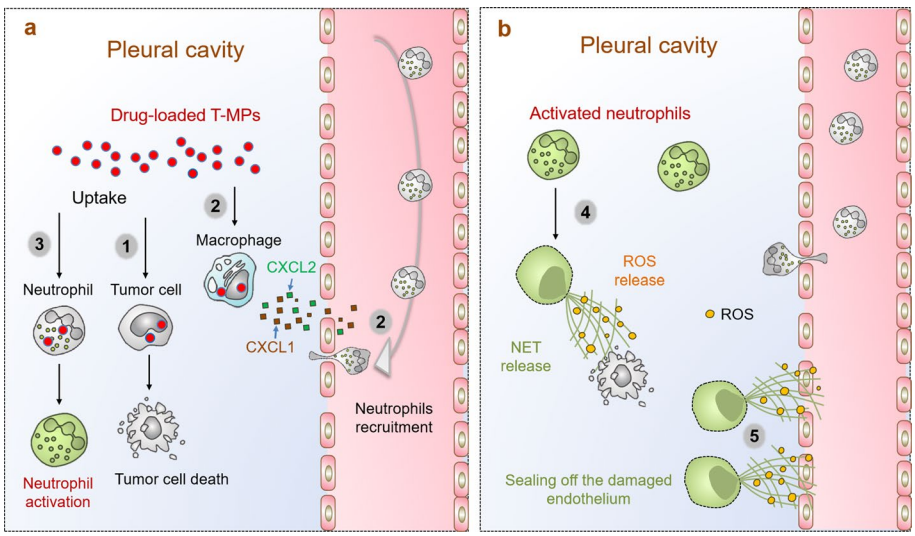

Fig. 8 Schematic showing drug-loaded T-MP treatment of MPE (Xu et al. 2020). **a** Steps 1–3; **b** steps 4–5. (1) Tumor cells were directly killed by uptake of drug-loaded T-MPs which were injected into pleural cavity. (2) Macrophages took up drug-loaded T-MPs and released CXCL1 and CXCL2, thus drawing neutrophils in blood into the pleural cavity. (3) The microenvironment of pleural cavity was remolded by drug-loaded T-MPs and neutrophils were activated. (4) Activated neutrophils released ROS and NETs to kill tumors. (5) Neutrophils released NETs to cover the gaps between vascular endothelial cells, preventing the production of pleural effusion

Gao et al. found that when drug-loaded T-MPs reached the bile duct above ECCA, a large number of neutrophils were recruited, and then the matrix around ECCA was destroyed, exposing tumor cells, which were killed by drug-loaded T-MPs (Gao et al. 2020). The dead ECCA cells further stimulated neutrophils, which also attacked tumor cells, achieving the benefit of ECCA treatment.

Drug-loaded T-MPs can transform M2 macrophages into M1 phenotype

Tumor-associated macrophages (TAMs) are the largest number of immune cells in TME, which can trigger the occurrence, development and metastasis of tumors (Kloosterman and Akkari 2023; Ngambenjawong et al. 2017). TAMs have the ability to polarize toward M1 or M2 phenotype. M1 TAMs mediate anti-tumor immunity, while M2 TAMs promote the growth of tumors (Boutilier and Elsawa 2021; Cassetta and Pollard 2023; Gunassekaran et al. 2021). Drug-loaded T-MPs could serve as anti-tumor immune modulator which transformed TAMs into IFNβ-producing M1 phenotype, thus enhancing the anti-tumor immune response (Wei et al. 2023). Mechanically, drug-loaded T-MPs entered lysosomes of macrophage, and led to Ca^{2+} release, thereby polarizing macrophages to M1 phenotype. Meanwhile, drug in lysosome entered nucleus and activated the DNA receptor hnRNPA2B1 to produce IFNβ. These findings suggested that drug-loaded T-MPs could serve as a new immunotherapy method by activating macrophages.

Drug-loaded T-MPs remold TME

Tumors represent complex ecosystems formed by tumor cells, surrounding normal cells and various immune cells in the process of continuous struggle and mutual adaptation (Bader et al. 2020; Bejarano et al. 2021). The type and quantity of immune cells in TME affect the development and treatment of tumors (Barkley et al. 2022; Qin et al. 2023). Composition of cells in MPE of mice treated with MTX-loaded T-MPs was analyzed, and the results showed an abatement in the proportion of $CD45^{-}$ cells, indicating a decrease in tumor cell infiltration (Guo et al. 2019). At the same time, an increase in T cells and neutrophils was observed. In addition, there was a significant decrease in TAMs, indicating that MTX-loaded T-MPs had selective toxicity to TAMs. These results suggested that MTX-loaded T-MP therapy not only significantly reduced the number of tumor cells and TAMs in MPE, but also increased the proportion of anti-tumor immune cells, thereby resisting the immune suppression microenvironment in pleural cavity.

Another study also found that Flu-loaded T-MPs attracted $CD8^{+}$ T cells, Th1 cells, NK cells, M1 macrophages and other anti-tumor immune cells, while reduced Treg cells, myeloid suppressor cells and other immunosuppressive cells, thus triggering the reversal of immunosuppressive TME (Chen et al. 2022).

Drug-loaded T-MPs induce PD-1 downregulation in neutrophils

Neutrophils in TME upregulated PD-1, which inhibited T cell activation through PD-1/PD-L1 axis (Xu et al. 2023). Drug-loaded T-MPs mediated the internalization and degradation of PD-1 in neutrophils, thereby reducing the inhibition of T cells. Meanwhile, neutrophils activated by drug-loaded T-MPs could release ROS and elastase, which induced the tumor cell apoptosis. In addition, elastase hydrolyzed tumor matrix, triggering the infiltration of cytotoxic T cells, and thus enhancing the anti-tumor effect (Fig. 9).

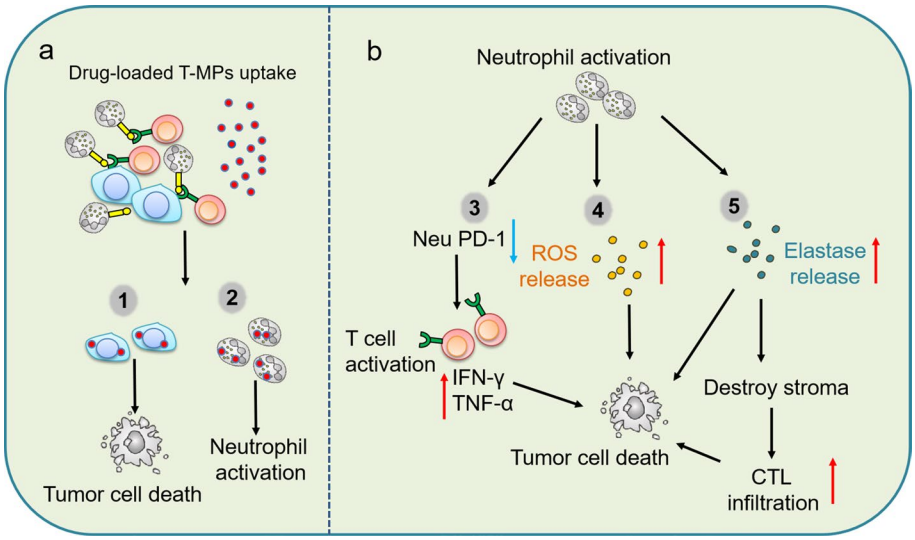

Fig. 9 Schematic showing drug-loaded T-MP enhancement of anti-tumor responses (Xu et al. 2023). **a** Steps 1–2; **b** steps 3–5. (1) Drug-loaded T-MPs were endocytosed by tumor cells and destroyed tumor cells effectively; (2) Neutrophils were activated after endocytosis of drug-loaded T-MPs; (3) Activated neutrophils reduced the expression of PD-1 and promoted T cell activation; (4) Activated neutrophils released ROS and induced the tumor cell apoptosis; (5) Activated neutrophils released elastase to kill tumor cells and destroy matrix, promoting the infiltration of T cells and enhancing anti-tumor response. The red arrow indicates an increase expression, and blue arrow indicates a reduced expression

To sum up, compared to other immunotherapies, drug-loaded T-MPs have the dual advantages of chemotherapy and immunotherapy. Drug-loaded T-MPs can not only directly kill tumor cells, but also activate anti-tumor immune cells, and reshape the tumor immune microenvironment, thereby possessing the feature of low toxicity and high efficiency.

Factors affecting the efficacy of drug-loaded T-MPs

The diameter distribution of drug-loaded T-MPs is wide, ranging from 100 to 1000 nm (Hood 2019; Rädler et al. 2023; Zhao et al. 2023). Meanwhile, there are differences in softness of drug-loaded T-MPs derived from different tumor cells (Liang et al. 2019). These factors may affect the effectiveness of T-MPs in tumor treatment.

The softness of drug-loaded T-MPs affects efficacy

Applying TRCs cultured in soft 3D fibrin gel, Liang et al. prepared MPs derived from TRCs (3D-MPs) (Liang et al. 2019). Compared with ordinary tumor cell derived MPs (2D MPs), 3D-MPs were softer and more prone to deformation. Drug-loaded 3D-MPs had a stronger ability to enter into the depths of tumor, and were more easily absorbed by TRCs, thus achieved better tumor treatment outcomes. This study indicated that the softness of drug-loaded T-MPs directly affected the anti-tumor effect.

The particle size of drug-loaded T-MPs affects efficacy

Differences of characterization, in vivo distribution, and anti-tumor efficacy between small T-MPs (SMPs, $\leq$200 nm) and large T-MPs (LMPs, >200 nm) loaded with MTX had been compared (Jiang et al. 2022). The results indicated that dosage of drug carried

by SMPs was more suitable, and SMPs were more stable in tumor tissue. SMPs could be better engulfed by DCs which presented tumor antigens to T cells and stimulate them specific proliferation. For the treatment of solid tumors in mice, SMPs had higher concentrations in tumors, stronger immune activation ability, and better tumor treatment effects compared to LMPs, suggesting that the particle size of drug-loaded T-MPs should be an important quality control factor when preparing them.

T-MPs enhance the effect of chemotherapy

Nonmuscle-invasive bladder cancer (NMIBC) is often treated by surgical resection combined with intravesical chemotherapy (Ho and Modi 2023; Pietzak et al. 2017). However, TRCs with multidrug resistance in NMIBC cannot be eliminated by drugs, which eventually leads to the recurrence of bladder cancer (Liu et al. 2018). Jin et al. combined chemotherapy drugs and T-MPs for the treatment of NMIBC (Jin et al. 2017). The bladder of mice with NMIBC was perfused with T-MPs. After 12 h, DOX solution was instilled into mouse bladder. The results showed that T-MPs could significantly enhance the efficacy of DOX. This study also explored the mechanism of T-MPs as chemosensitizers to enhance chemotherapy efficacy: tumor cells taking up T-MPs enhanced drug uptake by reducing the expression of multidrug-resistant proteins. At the same time, T-MPs could elevate the pH value of lysosomes in tumor cells, and promote the migration of lysosomes carrying drug toward nucleus. Finally, drugs enter the nucleus, thus enhancing the killing of bladder cancer cells. This study provided a new strategy for treatment of bladder cancer.

Summary and perspectives

T-MPs carry some proteins, lipids, nucleic acids and other components of tumor cells (Hu et al. 2022). The proteins in T-MPs contain tumor antigens and can be presented by antigen-presenting cells. The nucleic acid and other components in T-MPs can serve as natural immune stimulants to enhance the body's immune response (Sun et al. 2023; Zhang et al. 2015). These characteristics of T-MPs give them the potential as prophylactic tumor vaccines. Although some studies have shown that s.c. inoculation, oral administration, i.m. inoculation or tail vein inoculation could stimulate the body's strong anti-tumor immune response and effectively prevent the occurrence or metastasis of tumors, there is no clinical study on T-MPs as a prophylactic tumor vaccine at present.

When antigen-presenting cells and T-MPs are co-incubated in vitro and then injected into tumor-bearing mice, tumor was reduced. Similar to the principle of T-MPs as prophylactic vaccines, antigen-presenting cells which have endocytosed T-MPs can present tumor antigens to $CD8^+$ T cells through MHCI molecules, and stimulate the specific proliferation of $CD8^+$ T cells which were transformed into cytotoxic T cells to kill tumors (Sun et al. 2023; Zhang et al. 2015). Meanwhile, T-MPs can be directly used to treat MPE or glioma (Pineda et al. 2019; Wan et al. 2020). The existing studies have highlighted the efficacy of T-MPs as therapeutic vaccines in tumor-bearing mice. In the future, T-MPs are expected to become a novel approach for tumor immunotherapy.

T-MPs can serve as natural carriers for transporting chemotherapy drugs, OAs, MC DNA, etc., into tumor cells, which will be killed effectively. Drug-loaded T-MPs can also attract immune cells to participate in tumor treatment, making tumor treatment

more efficient and thorough. At present, drug-loaded T-MPs have been used in clinical treatment of MPE and ECCA, and achieved good efficacy (Gao et al. 2020; Guo et al. 2019; Xu et al. 2020).

Many studies have confirmed that drug-loaded T-MPs are safe for tumor treatment. However, since T-MPs are derived from tumor cells, reintroducing DNA, RNA and protein wrapped in T-MPs into the human body may still has certain risks (Clancy et al. 2015; Kalluri and McAndrews 2023). The long-term effects of this new carrier on patients require long-lasting monitoring in follow-up.

In order to more rationally utilize drug-loaded T-MPs for tumor treatment, many details require further research. The first issue worth noting is the preparation of drug-loaded T-MPs: (i) *Selecting more suitable chemotherapy drug for T-MP delivery.* At present, there is no comparison regarding the therapeutic effects of T-MPs carrying different drugs on the same type of tumor, which means that the drugs carried by T-MPs for tumor treatment may not be optimal. In the future, it is necessary to determine the optimal chemotherapy drug carried by T-MPs for a certain tumor treatment. (ii) *Ascertaining the optimal drug loading dose.* Currently, the drug-loaded T-MPs injection dosage used in clinical trials is converted from animal experiment results, and the optimal injection dosage for tumor patients needs further research. (iii) *More precise particle size control of drug-loaded T-MPs.* The size distribution of drug carrier is an important feature that can affect the circulatory dynamics, tissue distribution, and safety of intravenous systemic applications (Niu et al. 2018; Sen Gupta 2016; Vallet-Regí et al. 2022). Although drug-loaded T-MPs with a wide size distribution have shown good therapeutic efficacy and safety in clinical studies, it should be noted that these studies are limited to local administration (Dong et al. 2022; Gao et al. 2020; Guo et al. 2019; Xu et al. 2020). Once considering the i.v. administration of this new carrier for clinical treatment, a narrower size distribution of drug-loaded T-MPs is essential. Correspondingly, determining the optimal size distribution range and optimizing the process to obtain drug-loaded T-MPs are urgent issues that need to be addressed for full body application in the future. (iv) *Standardizing the preparation method of drug-loaded T-MPs.* The preparation method for drug-loaded T-MPs is not unified so far. Some studies co-incubate tumor cells with chemotherapy drugs, irradiate them with UV, and then extract drug-loaded T-MPs (Chen et al. 2022; Gao et al. 2020; Xu et al. 2023). While other studies first irradiate tumor cells with UV, then co-incubate chemotherapy drugs with tumor cells, and finally extract drug-loaded T-MPs (Ma et al. 2021; Wei et al. 2023). Although both methods have achieved ideal therapeutic effects, a unified operating procedure is more conducive to promote the standardized use of drug-loaded T-MPs in clinical practice.

In addition, the following two issues need to be noted. Firstly, the beneficiaries of drug-loaded T-MPs should be identified. Based on patient's drug sensitivity and tumor type, screening patients who are more likely to benefit from drug-loaded T-MP treatment, is the key problem that needs to be addressed. Secondly, systemic application of drug-loaded T-MPs through i.v. injection should be explored. At present, clinical trials of drug-loaded T-MPs are limited to tumors that can be injected T-MPs into cavity nearby the tumor through catheter or syringe, such as MPE and ECCA (Dong et al. 2022; Gao et al. 2020; Guo et al. 2019; Xu et al. 2020). For other tumors, e.g.,

liver cancer and breast cancer, whether they can be treated by i.v. infusion of drug-loaded T-MPs is an issue of future research.

In summary, T-MPs have good biocompatibility, stability, and targeting properties, showing unique advantages as vaccines, natural delivery systems and chemosensitizers for tumor prevention and treatment. T-MPs are expected to provide new avenues for humans to conquer tumors in the future.

Abbreviations

MPs	Microparticles
EVs	Extracellular vesicles
T-MPs	Tumor microparticles
NTA	Nanoparticle tracking analysis
DCs	Dendritic cells
moDCs	Monocyte-derived DCs
s.c.	Subcutaneous
i.m.	Intramuscular
i.v.	Intravenous
ROS	Reactive oxygen species
RIBE	Radiation-induced bystander effect
MPE	Malignant pleural effusion
OAs	Oncolytic viruses
MTX	Methotrexate
DOX	Doxorubicin
Cis	Cisplatin
MCT4	Monocarboxylic acid transporter4
Flu	Fluvastatin
CSCs	Cancer stem cells
NAP	Napabucasin
PTX	Paclitaxel
TK	Thymidine kinase
NT	Nitroreductase
ECCA	Extrahepatic cholangiocarcinoma
TRCs	Tumor-repopulating cells
NETs	Neutrophil extracellular traps
TAMs	Tumor-associated macrophages
TME	Tumor microenvironment
NMIBC	Nonmuscle-invasive bladder cancer

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Author contributions
WS wrote the manuscript. WS and PX created the tables. PX, PP, SG, RL, GJ, HH, WL, and LD drew the figures. PX and PP revised the manuscript. SG, RL, GJ, HH, and WL checked the references. All authors have reviewed the manuscript.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All the authors agree to the publication of this manuscript.

Competing interests
The authors declare that they have no competing interests.

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