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Review article

# Dual identity of tumor-associated macrophage in regulated cell death and oncotherapy

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ABSTRACT

Tumor-associated macrophage (TAM) affects the intrinsic properties of tumor cells and the tumor microenvironment (TME), which can stimulate tumor cell proliferation, migration, and genetic instability, and macrophage diversity includes the diversity of tumors with different functional characteristics. Macrophages are now a central drug target in various diseases, especially in the TME, which, as "tumor promoters" and "immunosuppressors", have different responsibilities during tumor development and accompany by significant dynamic alterations in various subpopulations. Remodelling immunosuppression of TME and promotion of pre-existing antitumor immune responses is critical by altering TAM polarization, which is relevant to the efficacy of immunotherapy, and uncovering the exact mechanism of action of TAMs and identifying their specific targets is vital to optimizing current immunotherapies. Hence, this review aims to reveal the triadic interactions of macrophages with programmed death and oncotherapy, and to integrate certain relationships in cancer treatment.

## 1. Introduction

A highly sophisticated tumor immunosuppressive microenvironment (TIME) consisting of tumor cells, infiltrating immune cells, and stromal cells is a fundamental cause of the poor therapeutic efficiency of tumor chemotherapy and immunotherapy [1]. Critical components of the ecological cancer niche are inflammatory cells, and an essential link between inflammation and cancer is the tumor-associated macrophage (TAM) [2–4].

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One group of macrophages widely present throughout our body, immune cells used for host defence at different polarizations, mediates inflammation through their distinct functions of phagocytosis and exocytosis, ROS production, and cytokine secretion at different polarizations. Macrophages initiate immune responses and moderate metabolism to maintain ecological homeostasis in our body [5–7].

Macrophages from bone marrow monocytes in cancer are double-edged, reflecting their malleability to the environment and disease onset [8,9]. It was realized that macrophages could be activated by bacteria and gained the ability to kill tumor cells through products and cytokines; on the other side, it was rapidly admitted that TAM promotes tumor metastasis and growth from malignant metastatic tumors [10,11]. Therefore, we aim to provide more convenience for tumor treatment by integrating the available information on macrophages and considering more oncological diversity within the tumor.

Regulated cell death (RCD) pathways are designed to drive the clearance of functionally dispensable, infected, or potentially tumorigenic cells in order to function as essential players in improving homeostasis *in vivo*, as the host carries out defense against cancer, pathogens and a host of other pathologies [12]. It has been described a couple of typologies of RCD pathways, involving apoptosis, necrosis, and pyroptosis, among others, which adopt diverse cellular and molecular procedures and have distinct consequences, like the ability to initiate an inflammatory response, but all are ultimately for the stability of the organism [13,14]. Therefore, combining macrophages and RCD to organize the discourse can pave the ground for a greater insight into the treatment of tumors (Fig. 1).

Using nanomedicines to systematically target TAMs can be an exceedingly compelling methodology [15], as TAMs make desirable therapeutic targets not only because of their substantial propensity to phagocytose nanoparticles but also because the application of macrophages into drug delivery significantly increases intra-tumor drug accumulation and better tumor killing [16]. Effective exploitation of effective nano-drugs may l result in a groundbreaking in tumor immunotherapy [17], and a deeper appreciation of the complexity of the role of TAM within the modulation of immunotherapy could yield novel insight into tumor microenvironment (TME). Strategies for using macrophages for cancer therapeutic tools and targets will be reviewed, and the therapeutic potential of targeting TAM will be further discussed to provide insight for the following works.

## 2. Macrophages for RCD

Macrophages, known as human scavengers, are dependent on natural immunity. Most macrophages in adult tissues are seeded before birth, are derived from the yolk sac during embryonic development, are self-renewing, and are maintained independently of

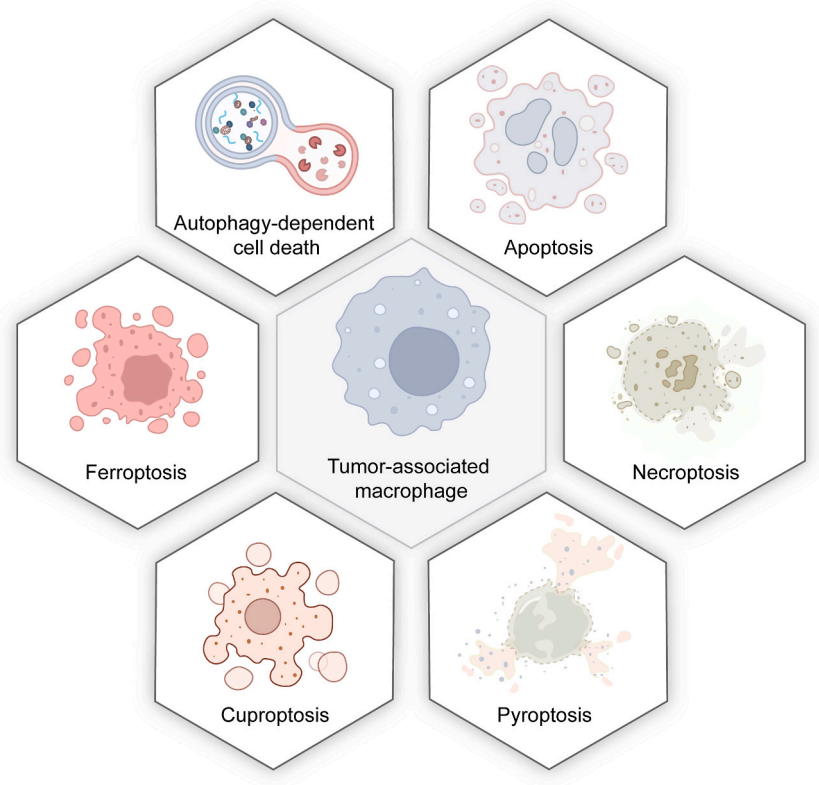


**Fig. 1.** TAM action in regulatory death affects tumor progression.
TAM has multiple roles in tumor development and can influence the occurrence of RCD.

monocytes; in addition, each organ has its own unique combination of macrophages of embryonic and adult origin. Macrophages are distributed throughout the body, including blastocytes (in the liver), splenocytes (in the spleen), bone marrow-derived macrophages (in bone), and dust cells (in the lungs) [18] (Fig. 2). Individual organs in the body possess their specific population of resident macrophages that are interconnected with stromal and functional tissues [19] and perform different functions such as different types of macrophages in the intestine, with different phenotypes and functions, but working together to maintain tolerance to normal intestinal flora and oral antigens; macrophages in the marginal zone of the spleen, which suppress natural and adaptive immunity to apoptotic cells; and sinusoidal macrophages in the sub-envelope of the lymph nodes, which clear viruses from the lymph and initiate antiviral immune responses etc. TAMs, which are among the most abundant tumor-infiltrating leukocytes, are innate immune cells and antigen-presenting cells that specifically engage with tumor organization [19]. Macrophages are specialized phagocytes that maintain the dynamic balance in the body by internalizing bulky detritus as debris, pathogens and apoptotic cells.

TAMs are mainly classified into M1-type macrophages that inhibit tumor growth and M2-type macrophages that promote tumor growth; secreted factors from cancer cells in TME are released and affect the polarization of different TAM phenotypes [20] (Fig. 3). Early stages of cancer, in TME, M1-type macrophages in TME anti-tumor reactions and initiate inflammatory, express high-level pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-α (TNF-α) [21], which directly kill cancer cells and have the ability to activate the adaptive immune system, thereby making M1-type macrophages critical for tumor therapy. Macrophages polarized to the M2-type, which have anti-inflammatory effects, primarily perform essential roles in promoting tumor growth, vascularization, tumor metastasis, and immune escape [22]. Inhibition of M2-type macrophages or conversion of M2-type macrophages to M1-type macrophages is a common strategy for the treatment of solid tumors [23].

When regular or abnormal cell death occurs in the human organism, it will be swallowed and degraded by macrophages very rapidly [24]. Physiological conditions under which cell death takes place proceed primarily through apoptosis, a non-inflammatory process that mainly is acted upon in a cascade by caspases-3, a significant family of Caspases. Apoptosis is mediated by a caspase 3 activation cascade that kills tumor cells, recruits macrophages, and delivers “eat me” signals. Removal of apoptotic cells are not eliminated promptly, and necrosis continues to occur within dying tumor cells along with the release of intracellular substances into

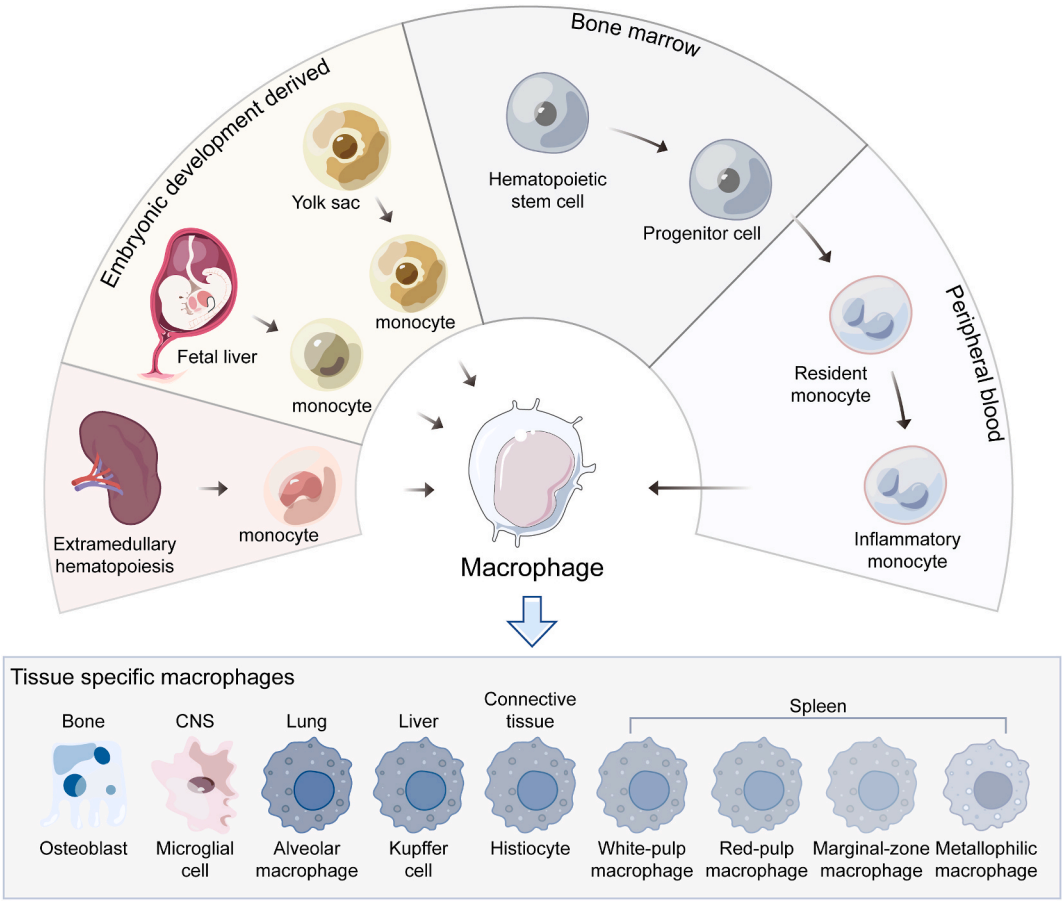


**Fig. 2.** The origin of macrophages and their classification in the organism.
Macrophages can be differentiated from distinct cells and exist simultaneously in various locations of the body, performing diverse functions and actions. Abbreviations: Central Nervous System (CNS).

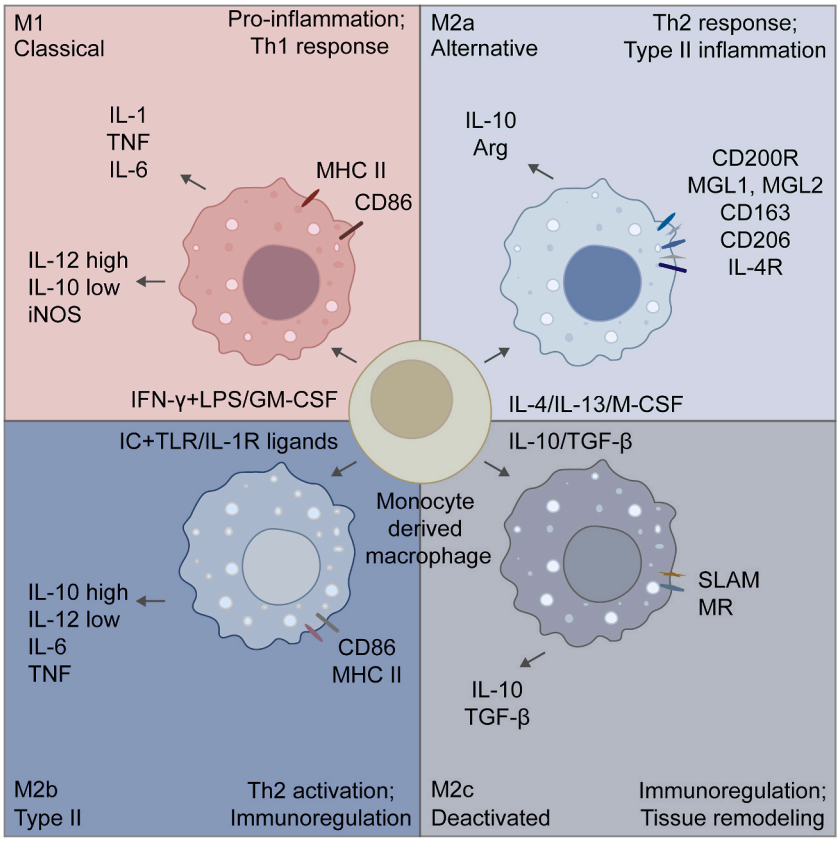


**Fig. 3.** Types of tumor-associated macrophages and their main functions and roles.
TAM is a double-edged sword in tumor therapy, where monocytes are induced by different stimulating factors in the tumor microenvironment to play different roles as TAM and secrete different cytokines to influence tumor progression. Abbreviations: tumor necrosis factor (TNF); interferon (IFN); monoacylglycerol (MGL); transforming growth factor (TGF); major histocompatibility complex (MHC); toll-like receptors (TLR); signaling lymphocytic activation molecule (SLAM); nuclear receptor (MR); colony stimulating factor (CSF).

the interstitial matrix, representing a damage-associated molecular pattern that may lead to necrosis or pyroptosis. When macrophages act in RCD, they accelerate the death of tumor cells and improve the therapeutic effect, but there are also conditions in which the presence of differently polarized macrophages produces two opposite results on treatment, allowing tumor cells to escape.

### *2.1. Apoptosis*

Efferocytosis is the process by which phagocytes remove apoptotic cells that are programmed to death, a process by which apoptotic cells are "buried", hence the term efferocytosis. Moreover, macrophages will be involved in and may influence this process, mostly negatively, in all tissue development, maintenance of endostasis, and disease processes (Fig. 4A).

Yu Jiali et al. found that activated antigen-specific FasCD8$^+$ T cells interacted with FasLCD11b$^+$F4/80$^+$ monocyte-derived macrophages and underwent apoptosis to promote liver metastasis [24]. M2-type TAMs inhibit apoptosis and promote cancer metastasis [25]. In hepatocellular carcinoma, M2-type TAMs increase the level of Cancer stem cells (CSC) and thus reduce sorafenib-induced apoptosis [26]. In the triple negative breast cancer (TNBC) mouse model, surgical trauma accelerated primary tumors exhibiting an increase in TAMs, particularly M2-type macrophages, which accelerated tumor progression and lung metastasis [27].

Macrophages, immune cells that are essential in the tumor microenvironment, may be cultured by tumor cells into a pro-tumor phenotype to promote tumor progression and metastasis [28,29]. The mechanisms mediating the interrelationship with tumor cells and macrophages in the TME remain challenging to describe [5]. It was shown that α-ketoisovalerate (KIV) and α-keto-β-methylpentanoic acid promote macrophages to become pro-tumorigenic, while KIV promotes pro-inflammatory effects in macrophages, affecting inflammatory signaling pathways, phagocytosis, apoptosis and redox homeostasis [30]. M2-type TAMs also play an oncogenic role in lung adenocarcinoma (LUAD) promoting tumor progression [31]. The macrophage atlas was constructed, and the infiltration rate of M2-type TAM subpopulations was found to be higher in the proficiency of mismatch repair (pMMR)-colorectal cancer (CRC) tumor tissues than in mismatch repair deficiency (dMMR)-CRC tumor tissues [32], and M2 polarization trajectories revealed apoptosis of M2-type TAM in dMMR. These findings suggested a potential function of apoptosis in tumor suppression and enhancement of immunotherapeutic effects.

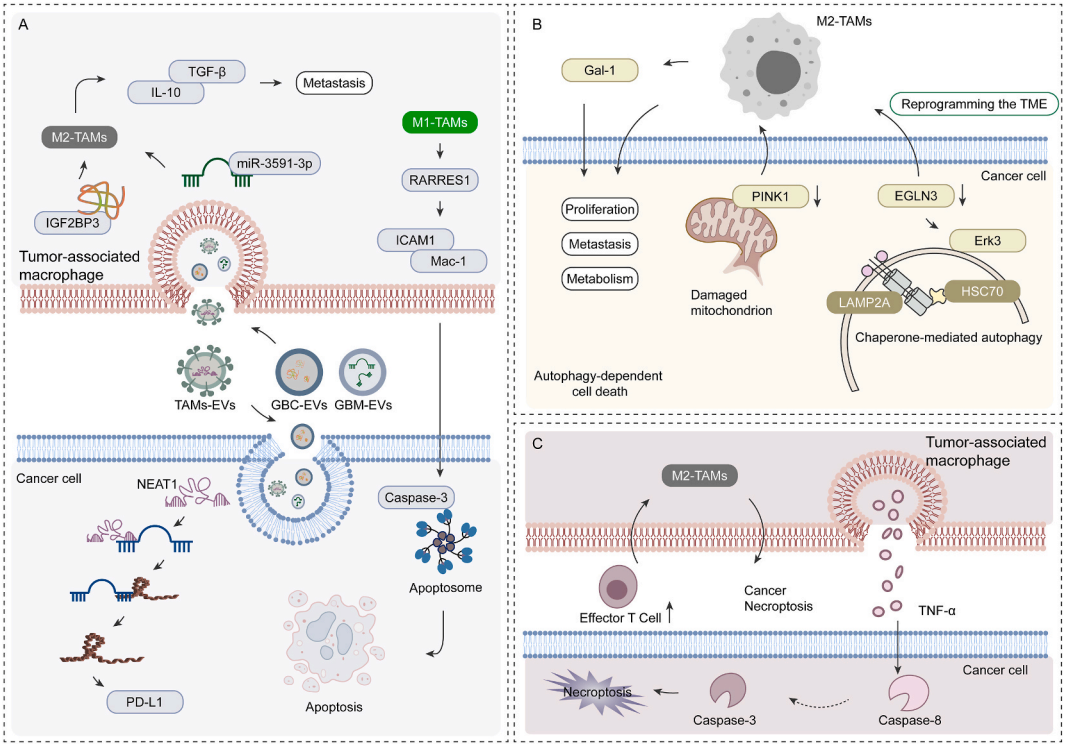


**Fig. 4.** Schematic diagram of the molecular mechanisms by which tumor-associated macrophages regulate tumor cell apoptosis, autophagy-dependent cell death and necroptosis.
(**A**) Macrophages are involved in tumor cell apoptosis and may influence this process with a dual role. (**B**) Macrophages play an important role in the autophagy-associated mode of tumor cell death. (**C**) Cell necrosis is the primary mechanism of cell death and usually leads to an opposite immune response. Abbreviations: tumor-associated macrophages (TAMs); transforming growth factor (TGF); insulin like growth factor 2 mRNA binding protein 3 (IGF2BP3); retinoic acid receptor responder 1 (RARRES1); intercellular adhesion molecule 1 (ICAM1); intercellular adhesion molecule 1 (NEAT1); programmed cell death 1 ligand 1 (PD-L1); galactokinase-1 (Gal-1); PTEN induced kinase 1 (PINK1); tumor microenvironment (TME); egl-9 family hypoxia inducible factor 3 (EGLN3); mitogen-activated protein kinase 12 (Erk3); lysosomal-associated membrane protein 2 (LAMP2A); heat shock cognate 70 (HSC70); tumor necrosis factor (TNF); Gallbladder Cancer (GBC); glioblastoma (GBM); extracellular vesicles (EVs).

Exosomes selectively secrete distinct metabolites from cells to maintain cellular homeostasis, particularly in the immune microenvironment where complex crosstalk occurs between exosomes and TAMs. Current studies have found that M2-polarized TAMs can stimulate the immune escape of cancer cells by secreting extracellular vehicles (EVs) that affect the proliferation of ovarian cancer (OC) cells and apoptosis of $CD8^{+}$T cells [33]. Gallbladder cancer (GBC) cell-derived exosomes significantly promote macrophage M2 polarization by carrying IGF2BP3, and then the polarized macrophages promote the malignant behavior of GBC cells [34]. Studies have reported that glioma-derived exosomes (GDEs) affect macrophage polarization, and glioma progression, while miR-3591–3p from GDEs could remarkably induce M2-type macrophages polarization and increase IL10 and TGFβ1 secretion, in turn promoting glioma invasion and migration [35].

Nevertheless, M1-type macrophages are also capable of promoting apoptosis, and in melanoma can act as enhancers of increased apoptosis in cancer cells by regulating M1-type macrophage polarization [36]. M1-type macrophages are induced to activate by RARRES1 through promoting ICAM1 expression, thereby causing apoptosis in renal clear cell carcinoma (KIRC) [37]. Combining the cell surface death receptor CD95 with its cognate ligand CD95L transmits a series of downstream signals leading to apoptosis [38], which is essential for immune homeostasis and monitoring. Macrophages expressing CD95L can induce apoptosis in tumor-infiltrating lymphocytes, thereby recognizing and destroying cancer cells. Macrophages are mononuclear CD34 antigen-presenting cells with defense mechanisms that function in a dual role in neoplastic progression. β-Defensin 2 exerts its anti-neoplastic action in breast cancer by regulating macrophage immunity and thus regulating the induction of apoptosis (Annexin-V), inhibiting the cell cycle in phagosomes, and reducing the proliferation of C127i cells.

### 2.2. *Autophagy-dependent cell death*

Macrophages to interact at TME with other immune cells through guiding intercellular contacts or secreting various effector molecules. TAM has an integral part to play in tumor progression, autophagy, and angiogenesis owing to its heterogeneity and intense plasticity [39–41]. Similarly, combining tumor cells with other immune cells can drive the recruitment and polarization of macrophages [42] (Fig. 4B). LC3-associated phagocytosis (LAP) contributes to various cellular processes, especially in immunity. Stabilizing

phagosomes through a macroautophagy mechanism in human macrophages can maintain antigen presentation on MHC class II molecules [43,44]. Erk3 was found to bind to HSC70 (70 kDa) and lysosomal-associated membrane protein type 2 A (LAMP2A), which are two core components mediating chaperone molecular autophagy (CMA). EGLN3-catalyzed hydroxylation antagonizes CMA-dependent Erk3 destruction, and inactivated EGLN3 inhibits macrophage migration, efferent cell increases and M2-type polarization, and improves LLC cancer growth by reprogramming the TME [45].

PTEN-induced kinase 1 (PINK1) mediates an essential pathway for mitophagy, and PINK1 deficiency in gastric cancer (GC) cells promote TAM polarization toward an M2-type phenotype and mediates GC cell growth, metabolism, and metastasis. Research reveals the action of LAP from macrophages in TMEs derived from AML, where targeted inhibition of LAP in TMEs promotes the accumulation of apoptotic cells and apoptotic vesicles, and accelerates leukemia growth [46]. Gal-1, a well-known soluble tumor-promoting factor in TME, is actively secreted by macrophages in response to stimulation of HCC cells, and Gal-1 produced in TAMs leads to HCC tumor growth in mice *in vivo* [47].

### 2.3. Necroptosis

Cell death determines the response of the surrounding environment, while immune activation against cell death depends on the activation of the mortality pathway. Apoptosis and necroptosis are the main cell death mechanisms and usually lead to an opposite immune response. Apoptotic death usually leads to an immunosilencing answer, while necroptosis death releases molecules that promote inflammation, a process known as necroinflammation [48] (Fig. 4C). Macrophages induce tumor necroptosis via derived TNFα *in vivo*, a process that also requires programmed cell death ligand 1 (PD-L1), GSDMC, and caspase-8, all of which are needed for the induction of tumor necrosis by macrophage-derived TNFα *in vivo* [49].

As a pan-cancerous feature associated with partial necroptosis, intra-tumor high potassium (K) has shown immunosuppressive potency against T cells [50], and some of the studies demonstrated that intra-tumor high K inhibits the anti-tumor capacity of TAMs. DNA hypomethylating drugs increase tumor infiltrating effector T cells, increase M2-type macrophages and lead to increased tumor necroptosis in a pancreatic cancer model [51].

### 2.4. Pyroptosis

Immunogenic cell death (ICD) is a highly inflammatory form of death, pyroptosis provided to alleviate immunosuppression and facilitate a systemic immune response in solid tumors [52] (Fig. 5A). Gasdermin-E (GSDME) in tumors enhanced anti-tumor immunity by activating pyroptosis, and GSDME expression simultaneously enhanced phagocytosis of TAMs on tumor cells, along with the number and function of tumor-infiltrating $CD8^{+}$T lymphocytes and natural killer cells [53]. Gasdermin-D (GSDMD) activated by inflammatory vesicles in macrophages is cleaved by caspase-1 to produce *N*-GSDMD fragments, which are then aggregated in the plasma membrane to form pores that increase membrane-permeability, resulting in IL-1β release and pyroptosis [54]. Previous studies have shown that amino acid metabolism in colon cancer produces pivotal enzymes that are involved in regulating colorectal cancer through cell death and that these key metabolic enzymes may lead to immune escape from colorectal cancer through pyroptosis leading to macrophage death [55].

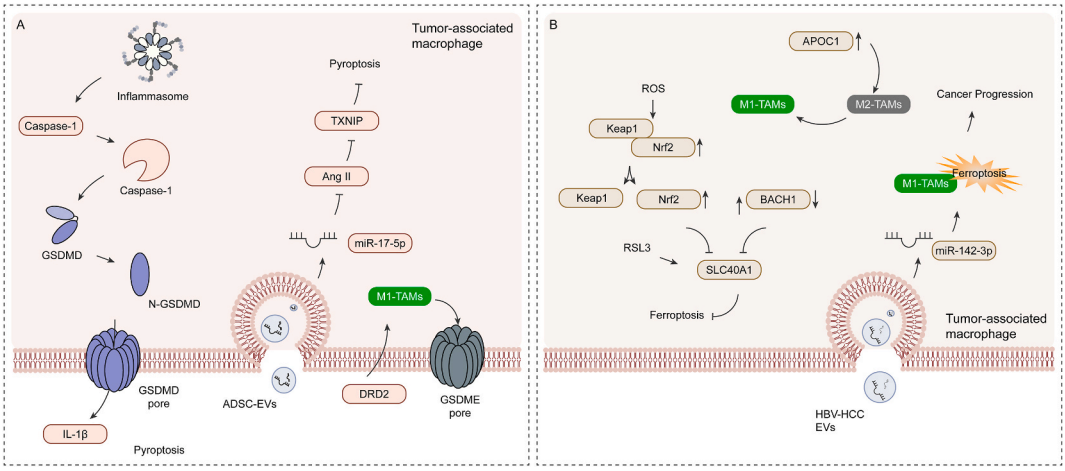


**Fig. 5.** Schematic representation of the molecular mechanisms by which tumor-associated macrophages regulate tumor pyroptosis and ferroptosis. (**A**) Macrophage involvement in pyroptosis provides an excellent opportunity to alleviate immunosuppression and promote systemic immune response in solid tumors. (**B**) Macrophages produce cytokines that can help induce or inhibit the process of ferroptosis in different ways. Abbreviations: tumor-associated macrophages (TAMs); dopamine receptor D2 (DRD2); gasdermin (GSDM); adipose-derived stem cell (ADSC); extracellular vesicles (EVs); apolipoprotein C1 (APOC1); kelch like ECH associated protein 1 (Keap1); NFE2 like bZIP transcription factor 2 (Nrf2); BTB domain and CNC homolog 1 (BACH1); solute carrier family 40 member 1 (SLC40A1); hepatitis B virus (HBV); Hepatocellular carcinoma (HCC).

Pyroptosis-releasing factor activates GSDMD-cleaved caspase-1 in macrophages, leading to cytokine release and subsequent cytokine release syndrome (CRS), which inhibits chimeric antigen receptor (CAR) T cell therapy for patients [56]. Sorafenib induces macrophage pyroptosis and triggers natural killer cell-mediated cytotoxicity against hepatocellular carcinoma [57]. *In vitro* trials have shown that adipose-derived mesenchymal stem cells (ADSCs)- derived exosomes were absorbed by macrophages, and miR-17–5p in ADSC exosomes reduced Ang II-induced TXNIP and decreased the triggering of macrophage pyroptosis [58], thereby affecting abdominal aortic aneurysm (AAA) progression. Inhibition of macrophage pyroptosis activation and inflammation can inhibit the development of Xanthoma [59]. DRD2 triggers programmed cell death in breast cancer by regulating the tumor microenvironment, promoting M1 polarization of macrophages, and triggering GSDME to perform pyroptosis [60].

### 2.5. Ferroptosis

Ferroptosis is thought to be a novel form of discovery differing in that it is not a form of apoptosis and is iron-dependent lipid hydroperoxides, involving iron, lipid, and amino acid metabolism [61]. Cytokines, some produced mainly by macrophages, have been reported to be able to induce or inhibit the procedure of ferroptosis in different manners [62–65] (Fig. 5B). Periodic studies related to the influence of macrophage function by amino acid metabolism found that there are eight critical enzymes involved in amino acid metabolism in colonic TAMs [55], namely ACADM, ACADS, GPX4, GSR, HADH, HMGCL, HMGCS1 and IDH1, are closely associated with GPX4, a critical protein of ferroptosis, which may regulate metabolism in colorectal cancer through ferroptosis. APOC1 is expressed highly in TAMs of HCC tissues [66], and inhibition of its expression can reverse the M2-type to M1-type through the ferroptosis in TAMs of HCC, thereby reshaping TIME and improving immunotherapy for HCC.

Macrophages, in contrast to tumor cells, are inherently passive to iron-dependent cell death triggered by lipid peroxidation [67,68]. Single-cell RNA sequencing (scRNA-seq) provides a deeper understanding of cellular behavior in the complicated tumor microenvironment by analyzing single-cell populations [69]. Recently, human primary macrophages were found to be able to respond to RSL3, an inhibitor of ferroptosis against GPX-4, by upregulating the expression of the iron transport protein ferritin, and the interaction of Nrf2 and BACH1 was able to induce ferritin expression and enhance the *anti*-ferroptosis effect of human macrophages [70]. Nuclear factor-erythroid 2-related factor 2 (NFE2L2) is specifically expressed in tumor macrophages and is associated with ferroptosis and occurrence in cervical squamous cell carcinoma (CESC) [71]. Studies on HBV-positive hepatocellular carcinoma cells found that their secreted exosome miR-142–3p promotes HCC progression by inducing ferroptosis in M1-type macrophages [72].

### 2.6. Cuproptosis

Microelements, which are indispensable in living organisms, also exhibit cytotoxicity when their concentrations exceed the threshold for maintaining homeostatic mechanisms. But what few people know is that there are actually many metal-induced deaths, besides ferroptosis [73], there is also zinc death [74] (excess zinc can trigger non-apoptotic cell death by inhibiting adenosine triphosphate (ATP) synthesis), and cuproptosis [75–78]. Researchers have named this mechanism of copper ion-induced cell death "Cuproptosis" [79], new and unique form of regulated cell death that is closely related to immunity and occurs in a variety of cancers [80–84]. In head and neck squamous cell carcinoma (HNSCC), a strong correlation between macrophages and cuproptosis was found by analysis of RNA-seq data and relevant clinical data [85].

## 3. Macrophage's multiple identities in tumor treatment

### 3.1. Drug directly regulates TAMs-mediated tumor killing

#### 3.1.1. Affects macrophage function or signal

Alisol B23 acetate (AB23A) targets CD11b/CD18 and improves macrophage polarization, thus affecting the invasion, migration, and apoptosis of non-small cell lung cancer (NSCLC) [86]. Ecteinascidin interacts with the tumor microenvironment to reduce the number of TAMs and inhibit the secretion of cytokines and chemokines, thus causing ovarian and endometrial carcinoma apoptosis [87]. Oligo-Fucoidan [88], an oligofucose gum, induced immune activity and anti-tumor M1-type macrophages and attenuated the side effects of olaparib, such as promoting immunosuppression and pro-tumor M2-type macrophages, which inhibited postoperative TNBC recurrence and metastasis.

Promethazine enhances autophagy in glioblastoma multiforme (GBM) cancer cells and accidently reprograms immunosuppressive TAMs by inhibiting histamine receptor signaling, making them immunostimulatory [89]. Studies have found that erastin in macrophages increases IL-8 production through STAT3-mediated macrophage M2 polarization, which would have implications as a potential target for *anti*-ferroptosis ovarian cancer (OC) cells to improve the overall anti-tumor effect [90].

Many of natural products have good antitumor effects [91,92], and dihydroartemisinin (DHA) [93] has been shown to remodel TAM to an antitumor M1 phenotype at certain concentrations, and previous studies demonstrated the finding that DHA remodels TAM to an M1 phenotype while DHA triggers ferroptosis in TAM and leads to a DNA damage response and NF-κB activation. M1-type macrophages upregulate ferritin to promote intracellular iron retention, while M2-type macrophages upregulate iron transport proteins to enhance iron drainage [94]. Iron chelation therapy has been shown to reverse the iron processing function of M2-type macrophages [95,96], switching from iron release to chelation and blocking the tumor-promoting effects of macrophages. Iron supply outward by administering iron oxide nanoparticles has also been shown to inhibit tumor growth and metastasis by stimulating pro-inflammatory macrophage polarization and ROS production [97].

Bisphosphonates were among the first anti-cancer drugs approved for use in humans and have activity against TAMs. Clodronates belong to the family of non-nitrogenous bisphosphonates [98]. In early studies, clodronate-loaded liposomes (clodrolip) were commonly used to deplete hepatic macrophages. Afterwards, intracellular release and accumulation of clodronate induced apoptosis in macrophages [99], and the liposomes were artificially prepared vesicles that were phagocytosed by macrophages after injection. The first generation of nitrogen-containing bisphosphonates [100,101] (etidronate, clodronate, and tiludronate) is converted intracellularly to non-hydrolyzable ATP analogues, leading to apoptosis. Bisphosphonates (zoledronic acid) bind mainly to microcalcifications present in breast tumors and are subsequently phagocytosed by TAM to induce apoptosis and promote M2-type to M1-type repolarization [101,102]. Bisphosphonates are often formulated as liposomes or nanoparticles [103,104], and TAM depletion by clodronate liposomes (clodrolip) improves survival, and some of the drugs that benefit from TAMs depletion by bisphosphonates include anti-angiogenic therapies (sorafenib and *anti*-VEGF antibodies) and liposomal adriamycin (Doxil) [99,105]. Not all therapies benefit from macrophage/TAM depletion [106,107], and indeed, indiscriminate depletion of systemic macrophages, such as through the administration of clodronate liposomes may sometimes exacerbate disease progression.

AFS98 and M279 anti-mouse CSF–1R antibodies [108,109], which block CSF-1 and IL-34, have been widely used to explore the effects of macrophage depletion in mouse tumor models and have been shown to reduce tumor size and improve survival in the MMTV-PyMT spontaneous mammary tumor model during early and long-term administration. Colony-stimulating factor 1 receptor (CSF–1R) is a tyrosine kinase receptor expressed on mononuclear phagocytes [110]. Intraperitoneal injection of *anti*–CSF–1R antibodies systemically depletes resident macrophages in several major organs and compromises tumor outcome [111]. Small molecule CSF–1R kinase inhibitor (BLZ945) has been shown to be effective in mouse models of glioma, breast and cervical cancer [112,113], enriching TAM with a CD206 M2-type phenotype and leading to tumor recurrence in mouse glioma models [114]. New developments of additional CSF-1R-specific inhibitors (e.g., PLX3397, PLX7486, BLZ945, and ARRY-382) are also being studied in clinical trials, showing improved efficacy in the treatment of a variety of tumors [115,116].

Rapamycin [117,118], a mTORC1-specific inhibitor, has been shown to have antitumor effects in a mouse model of Huh-7 liver cancer, stimulating macrophages to an M1-type phenotype, a potential target for anticancer therapy [119]. Other signaling molecules upstream of mTOR, such as PI3kγ, PI3kγ inhibitor (IPI-549) retarded tumor growth in a TAM-dependent manner in implanted human tumor virus-positive head and neck squamous cell carcinoma (HPVHNSCC), lung cancer and breast cancer models by promoting TAM immunostimulatory responses [120]. Similarly, expression of PTEN (PI3k inhibitor) or silencing of Akt1 promoted antitumor M1-type macrophage polarization [121]. CAY10526 and celecoxib effectively inhibited the proliferation of myeloid and bladder cancers, while co-culture with celecoxib further showed the ability to reduce the expression of T-cell inhibitory PD-L1 in MBT-2 cells and also promoted the M2 to M1 polarization of TAM [122–124] (Table 1).

### *3.1.2. Downstream pathways through upstream molecules that affect macrophage polarization*

FPS1M [125], a stimulator of TLR4, enhances macrophage glycolysis and regulates macrophage differentiation to the M1 phenotype through activation of the TLR4-mediated PI3K/AKT/mTOR signaling axis, and this transformation promotes apoptosis of colorectal cancer cells *in vitro* and *in vivo*. Dehydroepiandrosterone (DHEA) [126] is recognized as an FDA-approved dietary supplement or over-the-counter drug with anti-inflammatory and immunomodulatory properties. It was found that DHEA exerts anti-tumor effects by exacerbating Nig-induced abnormal autophagy and pyroptosis through activation of lipopolysaccharide (LPS)-triggered GPER in macrophages. The Lmdd-MPFG (LM) vaccine activates the NF-κB pathway in TAM via the Toll-like receptor (TLR)2-MyD88 pathway and recruits p62 to activate the autophagic pathway [127,128]. The overall effect of LM tilts TAM from an M2-type state to an M1-type state [129]. Such a dramatic transformation of TAM also enhanced the adaptive immunity of TME and significantly inhibited tumor progression [120].

RON (Recepteur d'Origine Nantais) is a receptor tyrosine kinase expressed on tissue-resident macrophages, and RON signaling in macrophages promotes cell spreading and phagocytosis and enhances M2-type polarization by stimulating arginase expression and

**Table 1**
Summarizes drugs that act by affecting macrophage function or signaling.

| Name | Type | Test Model | Function |
|---|---|---|---|
| Alisol B23 acetate | Compound | *In vitro* | Targeting CD11b/CD18 in TAMs |
| Ecteinascidin | Compound | *In vitro* | Reduce the number of TAMs |
| Oligo-Fucoidan | Compound | *In vitro* | Induced immune activity and anti-tumor M1-type macrophages |
| Promethazine | Compound | *In vitro* | Reprograms immunosuppressive TAMs |
| Erastin | Compound | *In vitro* | Increases IL-8 producted in macrophage |
| Dihydroartemisinin | Compound | *In vitro* | Remodel TAM to an antitumor M1 phenotype |
| AFS98 | Antibody | Mouse | Block CSF-1 and IL-34 |
| M279 | Antibody | Mouse | Block CSF-1 and IL-34 |
| BLZ945 | Compound | Clinical trial | Small molecule CSF–1R kinase inhibitor |
| PLX3397 | Compound | Clinical trial | Small molecule CSF–1R kinase inhibitor |
| PLX7486 | Compound | Clinical trial | Small molecule CSF–1R kinase inhibitor |
| ARRY-382 | Compound | Clinical trial | Small molecule CSF–1R kinase inhibitor |
| Rapamycin | Compound | Mouse | mTORC1-specific inhibitor |
| IPI-549 | Compound | *In vitro* | PI3kγ inhibitor |
| CAY10526 | Compound | *In vitro* /Mouse | Reduce the expression of T-cell inhibitory PD-L1 |

attenuating responses to pro-inflammatory stimuli (e.g., IFN-γ and LPS) [130–132]. RON signaling in macrophages promotes growth and metastatic growth in prostate and breast cancers [133–135]. Blockade of RON kinase by the inhibitor BMS-777607/ASLAN002 increases the number of pro-inflammatory TNF-α secreting macrophages and reduces lung metastatic growth in the PyMT-MSP breast tumor model [134].

Anti-cancer monoclonal antibodies such as rituximab and trastuzumab have been shown to exert their therapeutic effects primarily or partially through macrophage-mediated antibody-dependent cell-mediated phagocytosis (ADCP) [136,137]. Evidence suggests that trogocytosis-induced cell death is complementary to whole-cell phagocytosis [138]. A small molecule CCR2 inhibitor (PF-04136309) effectively reduces the recruitment of inflammatory monocytes to tumors, thereby reducing tumor growth and liver metastasis in a mouse model of pancreatic cancer [139]. Blocking the CCL2-CCR2 axis has been shown to inhibit the recruitment of TAMs to tumor sites. Preliminary studies using antibody inhibition of CCR2 have shown reduced tumor growth and improved chemotherapeutic efficacy in multiple mouse tumor models [140]. CXCR4 inhibitor (AMD3100) inhibits the formation of neoplastic vascular system and tumor recurrence stimulated by vascular endothelial growth factor A (VEGF-A) secreted by TAM in the recruitment and differentiation of monocytes expressing its receptor CXCR4 and differentiating them into tumor-infiltrating TAM [141]. CXCL12 binding to CXCR4 is involved in a variety of biological processes, such as cancer proliferation, angiogenesis, and metastasis [142]. AMD3100/plerixafor inhibition of CXCR4 has been tested in clinical trials in patients with colorectal or pancreatic cancer [143].

Mazzieri et al. demonstrated that therapeutic blockade of ANG2 with an anti-ANG2 antibody prevented the association between TEM and angiogenic vessels as well as inhibited TEE2 expression in TEM, thereby reducing angiogenesis and tumor growth in breast and pancreatic tumor models [144], and that ANG2 upregulation is one of the mechanisms of resistance to anti-VEGF therapy [145, 146]. Vascular disruptor 5,6-dimethoxyketone-4-acetic acid (DMXAA) has also been shown to activate the immunostimulatory function of TAM, thereby coordinating the antitumor response of $CD8^+$ T cells [147] (Table 2).

### 3.2. Indirect effect of macrophages on drug antitumor

Oxaliplatin (OXA), a first-line chemotherapy drug for gastric cancer, showed that Circ0008253 from the M2 macrophage exosome could be transferred directly from tumor-related macrophages to gastric cancer cells, thus enhancing OXA resistance and avoiding apoptosis of gastric cancer cells [148]. M2-type TAMs increase CSC levels but decrease SOR-induced apoptosis and upregulate SOR resistance in HCC cells through the release of potential paracrine factors CXCL1 and CXCL2 [26]. Fluvoxamine [149], an antidepressant, inhibits 5-hydroxytryptamine reuptake. It was found that fluvoxamine significantly decreased the expression level of PD-L1, promoted T lymphocyte and M1-type macrophages infiltration in tumor tissues, and could treat colon cancer by inhibiting proliferation, migration and inducing apoptosis.

Further studies revealed that co-inhibition of MEK [150] (with dimethylphenidate) and autophagy (with mefloquine) activated the STING/type I interferon pathway in tumor cells, which in turn activated paracrine TAMs to form an immunogenic M1-type phenotype, thereby enhancing anti-tumor immunity. Enhanced secretory autophagy in glioblastoma (GB) promotes M1-type polarization of TAM to enhance temozolomide (TMZ) sensitivity of GB cells [151]. Multiple chemotherapeutic agents also modulate the macrophage response to tumors [152–154]. Microtubule stabilizers such as docetaxel and paclitaxel have been shown to promote the polarization of myeloid-derived suppressor cells (MDSC) into macrophages with an anti-tumor M1 phenotype by inhibiting STAT3 phosphorylation in mouse fibrosarcoma and mammary tumors [155]. Cyclophosphamide treatment inhibits the production of pro-tumor M2-type macrophage-associated cytokines and promotes macrophage infiltration [156]. Paclitaxel and doxorubicin induce cell cycle arrest and eventually cancer cell death, which stimulates TAMs to induce pro-inflammatory genes and repolarize them into M1-type TAMs with antitumor effects [157]. Cisplatin (CIS) and carboplatin inhibit DNA replication leading to cancer cell death, and dead cancer cells express more CSF1, which attracts large numbers of $CSF1R^+$ TAMs (M2-type) [158]. Adriamycin inhibits RNA and DNA synthesis and induces ICD in cancer cells, leading to the repolarization of TAMs to an M1-type phenotype [159]. Furthermore, 5-fluorouracil and gemcitabine also disrupt RNA and DNA synthesis, thereby promoting the M1 phenotype in TAMs [157]. Through the secretion of growth factors and inhibition of tumor cell death signaling pathways, TAMs can also actively promote chemoresistance. To a certain extent, chemotherapy can be considered counterproductive because it causes attraction of M2-type macrophages, which will lead to tumor progression [154] (Table 3).

**Table 2**
Summarize drug exerts downstream pathways through upstream molecules that affect macrophage polarization.

| Name | Type | Test Model | Function |
|---|---|---|---|
| FPS1M | Compound | *In vitro*/Mouse | Stimulator of TLR4 |
| Dehydroepiandrosterone | Compound | *In vitro* | Induced abnormal autophagy and pyroptosis |
| Lmdd-MPFG | Vaccine | *In vitro* | Activates the NF-κB pathway in TAM |
| BMS-777607/ASLAN002 | Compound | *In vitro*/Mouse | Blockade of RON kinase |
| Rituximab | Antibody | Clinical trial | Mediated ADCP via macrophages |
| Trastuzumab | Antibody | Clinical trial | Mediated ADCP via macrophages |
| PF-04136309 | Compound | Mouse | Small molecule CCR2 inhibitor |
| AMD3100 | Compound | Mouse | Small molecule CXCR4 inhibitor |
| AMD3100/plerixafor | Compound | Clinical trial | Inhibition of CXCR4 |
| *Anti*-ANG2 | Antibody | Mouse | Blockade of ANG2 |
| DMXAA | Compound | Mouse | Activate the immunostimulatory function of TAM |

Although these limitations have not been reported in completed or ongoing clinical trials, it is critical that they must be considered in the design of future clinical trials, and alternative targets that overcome these limitations may be required to achieve an optimal and consistent therapeutic response.

### 3.3. Macrophage for drug delivery

Macrophages, classically activated by IFN-γ and/or LPS, have been optimized for cancer therapy in the 1990s owing to the exceptional ability to kill tumor cells and the ability to accumulate in solid tumors within the region of necrosis/hypoxia due to antigen presentation properties [160,161]. During the same period, the enhanced permeability and retention effect (EPR) triggered the emergence of a field of nanoparticle research that relied heavily on the "passive targeting" provided by this effect [162]. Many strategies for drug delivery have been devised to supply the nanoparticles used with complementary "active targeting" components, that is, the addition of specific ligands that target cancer cells or overexpressed receptors in the TME [163,164].

Macrophages act differently from erythrocytes, cancer cells and neutrophils as drug carriers. Loading of nanoparticles (NPs) into erythrocytes enhances their blood circulation but does not give them active tumor targeting ability, rather cancer cell based vectors can target the source cancer cells. Neutrophils target inflammation, not tumors, primarily through LFA-1, LL-6 receptor and TNF-α receptor, which are surface adhesion molecules. Macrophage-based drug carriers are more versatile compared to these carriers. Not only do they recycle in the bloodstream like erythrocytes and neutrophils, but also specifically target tumor tissues through α4 and β1 integrins of macrophages that bind vascular cell adhesion molecule-1 (VCAM-1) of various cancer cells.

Targeted drug delivery is mainly focused on organs, tissues, or cells, while the drug acts primarily at the material (target) points of proteins and nucleic acids in subcellular organelles of cells [17]. Rather than smaller loops like drugs, antibodies and nanoparticles, which are able to enter the TME without relying on passive diffusion, more giant immune cells use complex cellular mechanisms to navigate to and cross the tumor-associated endothelium and occupy specific areas within the TME [165–167].

#### 3.3.1. Macrophages as direct anti-cancer drug carriers

Macrophages can develop a typical distribution pattern by intravenous injection into mice [168]. In addition, it was previously shown that injected macrophages could enter the lung metastases of melanoma with B16 cells [169]. Also, it has been indirectly demonstrated that intraperitoneal injection of macrophages may be much more efficient in targeting intraperitoneal organs than systemic injection. Lately, macrophages have been able to enter the inflamed pancreas by intraperitoneal injection to induce formation [170], demonstrating that they have potential utility in the majority of inflammation-related pathologies. However, mouse macrophage lines such as RAW264.7 can similarly achieve this similar inflammatory site targeting effect compared to primary macrophages, and therefore a rather non-selective accumulation of macrophages is suspected under this experiment [171].

Incubation of drugs with hepatic macrophages can construct drug-loaded macrophages [172] (Fig. 6A). Fu et al. developed RAW 264.7 macrophages capable of loading DOX for the treatment of mesostasis 4T1 tumors and found that macrophage targeting and viability were not affected by DOX. DOX-loaded macrophage treatment was effective in extending the life span of mice with breast cancer tumors. Guo et al. found that loading DOX on M1 macrophages inhibited tumor invasion, while liposome-DOX had no such effect. Furthermore, they found that macrophages loaded with DOX could actively transport drugs to ovarian cancer cell y through the tunneling nanotube pathway [173].

#### 3.3.2. Macrophages as indirect anti-cancer drug carriers

*3.3.2.1. Combine drug with exosome.* Macrophage-derived exosomes are indispensable in the intercommunication between cancer cells and macrophages. Macrophages can be classified into M1 and M2 types according to their activation status. M1-type macrophages have pro-inflammatory effects, participate in positive immune response and destroy tumor tissue, and their anti-tumor effects are mainly derived from their surface markers such as major histocompatibility complex-II (MHC-II), CD80, CD86, etc.; M2-type macrophages have anti-inflammatory effects, down-regulate immune response and promote tumor growth [174]. Exosomes possess almost all the properties of the cell of origin, and therefore the functions of M1-type and M2-type macrophage exosomes are not identical [175] (Fig. 6B).

Zhang et al. reduced the semi-inhibitory concentration (IC50) of the drug after encapsulation of CIS with M1-Exos, which resulted in a significantly higher killing rate of drug-resistant breast cancer cells compared to the control group with direct CIS; and at low CIS concentrations, M1-Exos can be powerfully lethal to tumor cells, which may be related to the unique nature of exosomes [176]. It was

**Table 3**
Summarize drugs exerts indirect effects of macrophage anti-tumor.

| Name | Type | Test Model | Function |
|---|---|---|---|
| Oxaliplatin | Compound | *In vitro*/Mouse | First-line chemotherapy drug for gastric cancer |
| Fluvoxamine | Compound | Mouse | Decreased the expression level of PD-L1 |
| Dimethylphenidate + Mefloquine | Compound | *In vitro* | Activated the STING/type I interferon pathway |
| Cisplatin | Compound | *In vitro* | Inhibit DNA replication leading to cancer cell death |
| Carboplatin | Compound | *In vitro* | Inhibit DNA replication leading to cancer cell death |
| Adriamycin | Compound | *In vitro* | Inhibits RNA and DNA synthesis and induces ICD |

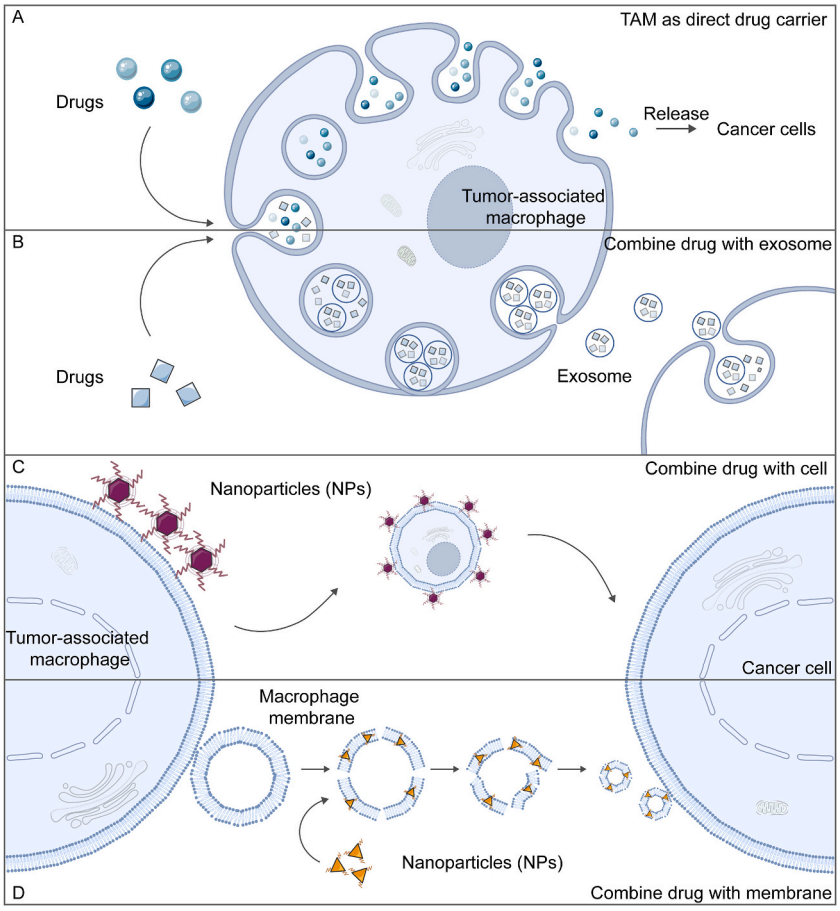


**Fig. 6.** Macrophages in drug delivery to inhibit tumor progression.
(**A**) Drugs are able to be phagocytosed directly by TAM or otherwise delivered to tumor cells via TAM in the tumor microenvironment. (**B**) Drug is phagocytosed by TAM and enters the exosome of TAM, which is delivered to the tumor cells with the secretion of exosomes. (**C**) After entering the tumor microenvironment by attaching to TAM, the nanoparticles are carried around the tumor cells and work. (**D**) Cell membranes are also essential carriers for drug delivery, and nanoparticles are transported through the cell membrane of TAM to exert inhibitory effects on tumors. Abbreviations.

found that lymphocyte function-associated antigen-1 (LFA-1) protein expressed on the surface of macrophage-derived EVs can target intercellular adhesion molecule-1 (ICAM-1), which is overexpressed in breast cancer cells, to deliver chemotherapeutic drugs to tumors and destroy tumor cells [177].

Nie et al. developed a responsive exosome nano-bio-couple, which consisted of aCD47 and aSIRPα bound to M1 exosomes via an acid-sensitive benzoate imine bond, and the team found that $Mn^{2+}$ induced repolarization of macrophages to M1-type [178]. Owing to the targeting nature of aCD47, these nano-bio-conjugates can effectively accumulate in tumor tissues and release antibodies by selectively cleaving benzoic acid imine bonds through the acidic tumor microenvironment. Consequently, M1-Exo effectively repolarized tumor-promoting M2-type macrophages into antitumor M1-type macrophages, while aCD47 and aSIRPα significantly enhanced the phagocytosis of macrophages by blocking the "don't eat me" signal, resulting in a vigorous antitumor effect.

Therefore, taking full advantage of macrophage-derived exosomes involved in positive immune responses is pivotal to exosomal antitumor strategies. M1-Exos inherits the low immunogenicity, tumor cell homing, and low toxicity of parental cells [179], which can carry drugs to preferentially accumulate in tumor tissues with very low toxicity to other tissues. M1-exos as a drug carrier not only promotes the release of anti-cancer drugs but also releases Th1-type cytokines to promote inflammation and enhance anti-tumor effects [180]. In conclusion, M1-type macrophages have tumor-targeting and antitumor effects. M1-type macrophages and their derived exosomes have promising tumor suppressive potential and can be utilized as drug carriers.

*3.3.2.2. Combine drug with cell.* The majority of the macrophage-based drug delivery systems use macrophages as indirect carriers of anticancer drugs where they are loaded with drug-containing NPs [181] (Fig. 6C). NPs is loaded in such a way that it reduces the toxicity of the drug to macrophages, thus increasing the drug loading rate [182]. SN38-NPs [174], MSN-NPs [183], RGO-conjugated DOX NPs [184], and Ironic Oxide NPs-loaded macrophages [185] exhibited excellent anti-tumor ability against diverse tumor models in animal [186]. NP/drug-loaded macrophages were more effective compared with than directly drug-loaded macrophages, and the *in*

*vivo* construction of macrophage-loaded Aunr inhibited tumor metastasis and suppressed its recurrence in hormonal mice [187].

Due to the excellent tumor targeting properties of M1 macrophages, M1 macrophages loaded with NPs have been widely used in tumor therapy because of better tumor targeting properties than NPs alone [188]. Li et al. compared the therapeutic effects of loading paclitaxel and SOC-PTX (SOC: *N*-succinyl-N_8-octyl chitosan) on macrophages to find that both reduced tumor volume by 69% and 93%, respectively, after 15 d. Meanwhile, macrophages loaded with SOC-PTX had higher drug loading efficiency.

Macrophages can show improved tumor targeting by surface modifications of enzyme-responsive peptides. By way of example, Gambhir's team developed transgenic macrophages with an ARG1 (M2-type macrophage marker) response, which can detect tumors as small as 50 $mm^3$ by a susceptible blood test. To achieve the therapeutic goal of enhancing tumor growth inhibition, Prof. Jun Wang's team loaded both BLZ-945 and CIS prodrugs on the previously developed tumor acidity-sensitive cluster nanoparticles (SCNs) to form an immunostimulatory nanocarrier (called $^{BLZ-945}$SCNs/Pt) [189]. In acidic TME, $^{BLZ-945}$SCNs/Pt can instantly disintegrate into small-sized NPs and deliver BLZ-945 and CIS prodrug to TAMs and tumor cells, respectively. To accomplish TAM clearance, the released BLZ-945 is preferentially taken up by perivascular TAMs, whereas tiny particles containing CIS prodrug can infiltrate deep into the tumor and release CIS within tumor cells, resulting in the combo of tumor chemotherapy and immunotherapy [190].

*3.3.2.3. Combine drug with membrane.* Macrophage cell membrane-loaded NPS has excellent drug delivery capability [191] (Fig. 6D). Coextrusion of nanoparticles and vesicles from extracted macrophage membranes to complete the coating of macrophage membranes with nanoparticles [192]. Xuan et al. developed macrophage-encapsulated mesoporous silica nanocapsules to deliver DOX to tumors and inhibit their proliferation [191]. Meng et al. found that macrophage-coated $Fe_3O_4$ exhibited the same long blood circulation as erythrocyte-coated $Fe_3O_4$ [193]. Zhang et al. developed macrophage membrane-loaded PTX, that allowed rapid drug release from drug carriers in an acidic TME, which resulted in superior tumor eradication compared to non-pH-sensitive control groups [194].

## 4. Discussion

TME has a complex population of non-tumor stromal cells promote tumor growth, cause tumor immune escape, and affect the response to immunotherapy and patient survival [195]. Macrophages are a major component of leukocyte infiltration and have become leukocytes and mediators of inflammation present in the TME [196]. Significant differences exist in the inflammatory component of TME in cancers of different tissues, making the stages vary widely between different tumors or different parts of the same tumor by coordinating the signaling of this plasticity, resulting in different TAM phenotypes [197]. Macrophages have an essential dual role in the various anti-cancer modalities, including radiotherapy, chemotherapy, anti-angiogenic, hormonal therapy, and immunotherapy with immune checkpoint blockade [16,198]. Besides, macrophages play an important role in tumor immunity, and modulating macrophages against tumors is a promising immunotherapeutic strategy.

TAM is highly abundant in tumors. M1-type macrophages can engulf tumor cells, reshape the tumor microenvironment and promote tumor-killing effects; on the other hand, M2-type macrophages promote tumor proliferation and intra-tumor angiogenesis, providing more nutrients and channels to tumor cells, thus facilitating their invasion and metastasis, and also assisting tumor cells to evade the attack of other immune cells leading to immune escape. Macrophages provide more options for tumor immunotherapy as well as a power that should not be underestimated. Macrophages in the tumor microenvironment are capable of secreting various factors, and reprogramming M2-type into M1-type macrophages would be a higher quality potential cancer treatment modality with important implications compared to depleting macrophages in a broad-brush approach. More research on macrophages will open a new door for tumor treatment, and more therapeutic strategies in combination with macrophages need to be explored in the future in order to deal with various malignancies.

Macrophages in nature can engulf foreign particles, therefore macrophages can act as drug carriers and can directly engulf the drug and then deliver it to the tumor. To further improve the targeting of macrophages to tumors, a macrophage cell membrane coating was developed to improve the uptake of drugs by tumors by using targeting ligands to target macrophage-membrane coating technology, whose application prospect is also increasingly promising.

Despite the recent partial progress in clinical and preclinical studies of macrophages, some technical or methodological problems still remain unsolved. In several preclinical model's macrophage reprogramming associated with nanoparticles has shown good therapeutic potential, but the efficiency, safety and tolerability of nanoparticles in humans need to be carefully evaluated. When loading n nanoparticles TAM-reeducating therapies still have certain developmental challenges, such as how to load NPs onto macrophages or membranes stably and how to obtain durable and sufficient anti-tumor responses. Macrophage-centered therapies are entering the clinical arena, and with both risks and opportunities, it is worthwhile to seek out more insights before proceeding with treatment.

## Author contribution statement

Conceptualization, Y.S., R.S., and H.Y.; Picture drawing and discussion, Y.S., Y.W. and Y.Q.; writing—original draft preparation, Y. S., S.C. and L.F.; writing—review and editing, Y.S., W.P., S.Y., Y.Q. and H.Y.. All authors have read and agreed to the published version of the manuscript.

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## Data availability statement

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

## 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.

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