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Nanotherapeutics for Macrophage Network Modulation in Tumor Microenvironments: Targets and Tools

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Abstract: Macrophage is an important component in the tumor immune microenvironment, which exerts significant influence on tumor development and metastasis. Due to their dual nature of promoting and suppressing inflammation, macrophages can serve as both targets for tumor immunotherapy and tools for treating malignancies. However, the abundant infiltration of tumor-associated macrophages dominated by an immunosuppressive phenotype maintains a pro-tumor microenvironment, and engineering macrophages using nanotechnology to manipulate the tumor immune microenvironment represent a feasible approach for cancer immunotherapy. Additionally, considering the phagocytic and specifically tumor-targeting capabilities of M1 macrophages, macrophages manipulated through cellular engineering and nanotechnology, as well as macrophage-derived exosomes and macrophage membranes, can also become effective tools for cancer treatment. In conclusion, nanotherapeutics targeting macrophages remains immense potential for the development of macrophage-mediated tumor treatment methods and will further enhance our understanding, diagnosis, and treatment of various malignants.

Keywords: engineered macrophages, nanomedicine, cancer therapy, anti-tumor immunity

Introduction

Macrophages, serving as the fundamental component in innate immune responses, are prevalent throughout all tissues, which is capable of clearing pathogens, cellular debris, tumor cells or other external substances through phagocytosis. They play a pivotal role in different biological processes including maintaining homeostasis, inflammatory responses, and wound healing.[1–3] However, the relationship between macrophages and cancers is complex and multifaceted.[4] On the one hand, some macrophages activate tumor immunity by releasing inflammatory cytokines, phagocytosis, and antigen presentation, thereby eliminating malignant cells. On the other hand, macrophages, as an integral part of leukocyte infiltration within tumor tissues, can readily transition into tumor-associated macrophages (TAMs) in the tumor microenvironment (TME), exerting profound effects on cancer progression and distant metastasis.[5] The abundance of TAMs is tightly associated with poor clinical prognosis in various cancers.[6] A deep understanding of the dual role of macrophages in tumors not only provides new targets for cancer immunotherapy but also offers the possibility of modifying macrophages as tools for targeted killing cancer cells and other applications in cancer therapy.

The high plasticity of macrophages has paved the avenue for new methods of cancer treatment, which have shown promising results in basic research and clinical trials.[7,8] TAMs originated from bone marrow-derived or tumor-resident

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precursors have already become the focus of therapeutic interventions.[9,10] Current research focuses on inhibiting macrophage recruitment, depleting TAMs residing in tumor tissues, reprogramming TAMs, and enhancing their phagocytosis.[11] Meanwhile, with the rapid progress of cell engineering, new strategies centered on engineered macrophages have led to various innovative therapeutic methods by enhancing the macrophage's abilities of intrinsic phagocytosis and tumor targeting.[12–14] Engineered adoptive macrophage and macrophage membranes have been designed as therapeutic drugs, living sensors and vehicles of drug delivery for cancer diagnosis and treatment, achieving remarkable results in vitro experiments.

The swift advancement of nanotechnology in biomedical applications has led to the approval of various nanomedicines for routine clinical use.[15] In macrophage-based tumor immunotherapy, novel multifunctional immune nanomedicines, with their unique advantages on nanoscale drug delivery platforms, can more effectively deliver immunomodulators to TAMs, thereby promoting adaptive immune responses to eradicate tumor cells.[16–18] Moreover, macrophages possess a prolonged half-life in the circulating system and specifically binding to tumor tissues for phagocytosis and antigen presentation.[7] Therefore, combining the characteristics of nanomedicine with those of macrophages, we can engineer macrophages to achieve new breakthroughs in improving the effect of tumor treatment in combination with other therapeutics. In conclusion, designing appropriate nanomedicines is crucial for augmenting the effectiveness of macrophage-based cancer treatment approaches.[19]

This article highlights the dual role of macrophages as therapeutic targets and agents in nanotechnology-facilitated tumor treatment. Initially, we discuss the macrophage's properties and roles within the TME. Subsequently, we delve into the potentials of macrophages as therapeutic targets in tumor immunotherapy, encompassing the strategies like inhibiting macrophage recruitment, depleting TAMs, reprogramming TAMs, and enhancing phagocytic capacity, and analyze the role of nanotechnology in these processes. Furthermore, we discuss the applications of engineered macrophages utilizing nanotechnology in drug delivery, cell therapy, phototherapy, tumor bioimaging, and other cancer treatments (Figure 1). The objective of this article is to provide a thorough insight into the status and applications of nanomedicine-engineered macrophages in cancer therapeutics.

Macrophage and Its Role in Cancer Biology

Macrophages, which are treated as the core of innate immune system, are prevalent in various tissues and form the primary component of the mononuclear phagocytic system (MPS).[20] Within the bloodstream, a subset of monocytes with high C-C motif chemokine receptor 2 (CCR2) and Ly6C expression are recruited to certain tissues, where they differentiate into mature macrophages, particularly in response to external invasion, inflammation, crucial for immune surveillance, tissue repair, and homeostasis maintenance.[21–23] Contrary to the traditional view that macrophages merely originate from bone marrow, recent studies have reported that certain tissue-resident macrophages arise from some yolk sac precursors, independent of circulating monocytes.[24] Furthermore, self-renewal of macrophages has been observed in many tissues.[25] Therefore, the origin of macrophages in tissues remains an unresolved question.[26]

Macrophages are classified into two primary types according to their distinct functions: M1, usually activated by pathogens, and M2, activated by anti-inflammatory signals.[27,28] M1 macrophages mount a strong immune response against pathogens and cancer cells upon stimulation by pathogenic substances.[28] Following phagocytosing, they process and present exogenous antigens via the major histocompatibility complex (MHC) while secreting an abundance of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1). This process attracts various kinds of leukocytes to inflammatory sites and generates oxidative and reactive products, thereby enhancing immune response.[28] Conversely, M2 macrophages, activated by cytokines like IL-4, promote the repair of damaged tissues and wound healing by releasing cytokines such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β).[29] They also exert immunosuppressive effects and prevent the excessive proinflammatory effects of M1 macrophages, thus preventing chronic inflammation and immune system self-attack. The M1/M2 balance is vital for immune homeostasis. However, due to the co-presence of numerous proinflammatory and anti-inflammatory signals in the tissue microenvironment,[30] the state of macrophages recruited to specific tissues is highly dynamic. Therefore, rather than focusing solely on the classical M2/M1 macrophage ratio, it is more appropriate to analyze the various subsets of

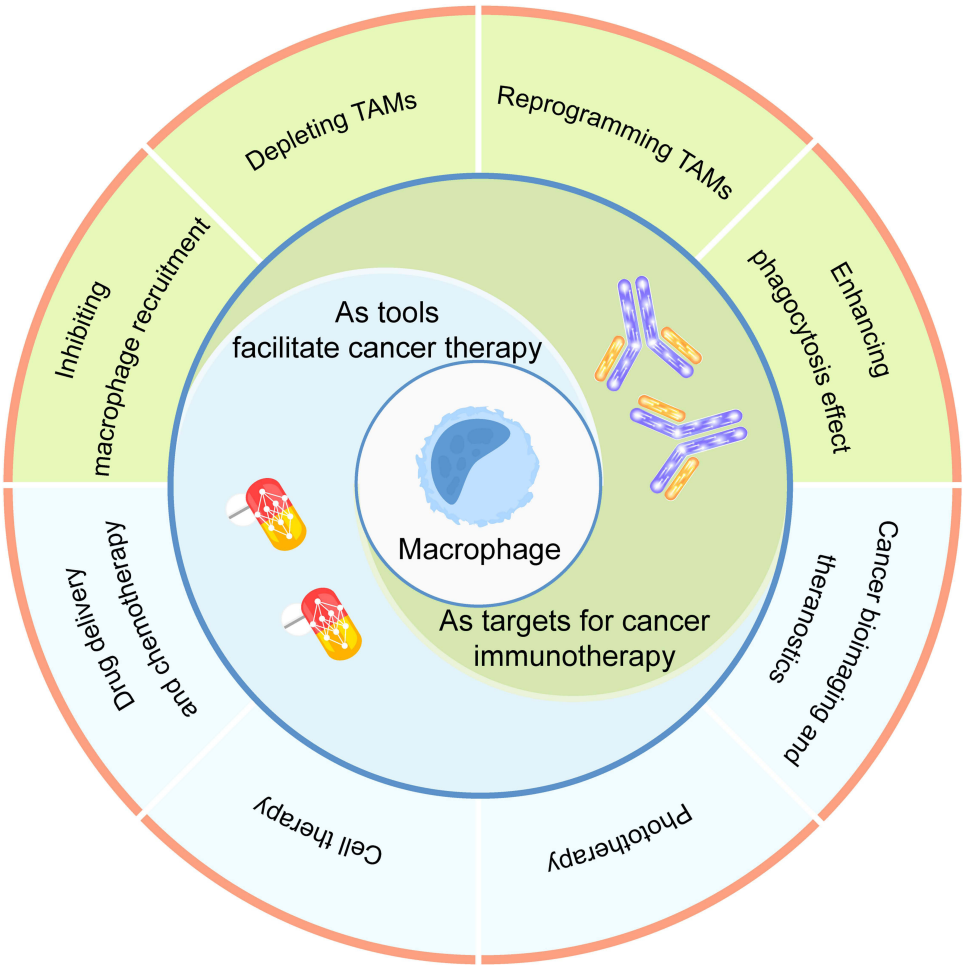

Figure 1 Function of engineered macrophages in cancer therapy as targets and tools. In cancer immunotherapy, macrophages could serve as targets to modulate tumor microenvironment by diminishing the immunosuppressive effect from TAMs. As tools for cancer therapy, engineered macrophages, as well as macrophages-derived exosomes and macrophage cell membrane, could facilitate different aspects in cancer diagnosis and treatment due to the ability of phagocytosis and tumor targeting.

macrophages to understand their roles in specific biological processes after integrating multiple signals in the microenvironment.[31]

Macrophages that resident in the tumor microenvironment (TME) are named as tumor-associated macrophages (TAMs), significantly influencing the progression of cancer. Typically, M1-like TAMs are proinflammatory and facilitate the elimination of tumor cells, whereas a higher prevalence of M2-like TAMs in the TME correlates with more aggressive cancer.[32–35] The complex population of M2-like TAMs can contribute to tumor malignancy from different aspects, including immunosuppressive TME, angiogenesis, intravascular infiltration, invasion, and metastasis (Figure 2).[36–38] Additionally, cytokines produced by TAMs, such as VEGFA and TGF-β, as well as associated receptors, such as VEGFR1, CXCR3, and CCR2, are pivotal in tumor cell survival, growth, and metastasis. TAMs promote the angiogenesis and formation of tumoral lymphatic vessels in the hypoxic and immunosuppressive TME, and the recruitment of TAMs and their interactions with tumor cells are also beneficial for tumor cell's survival and metastasis during the chronical inflammation in the TME.[39,40] Consequently, macrophages exhibit diverse roles in tumor development with both pro- and anti-tumorigenic functions. Their unique characteristics position macrophages as crucial targets and tools in cancer therapy.[41]

The interplay between TAMs with other immune cells further modulates the immune landscape in the TME. Due to the plasticity and dynamic patterns, immune processes could be affected by TAMs in the TME, impacting cancer progression.[42] For instance, Cytotoxic T Lymphocytes (CTLs) and Natural Killer (NK) cells can trigger the

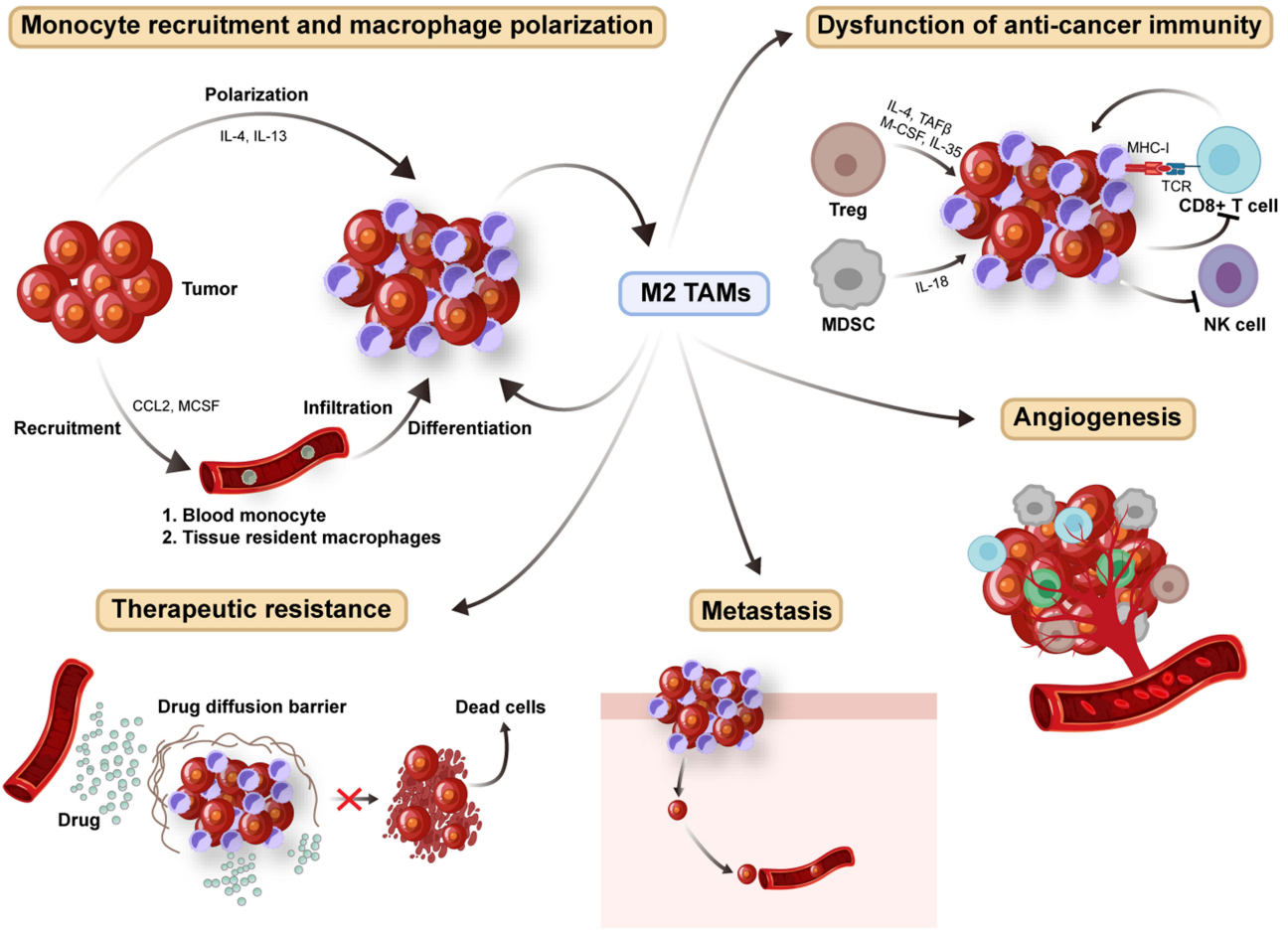

Figure 2 The biological role of M2-like TAMs in TME. During the process of tumor progression, the malignant and stromal cells released specific cytokines or chemokines, like CCL2, to recruit monocytes or tissue-resident macrophages to the tumor tissues, which would further differentiate into M2-like TAMs. The predominant TAMs could establish a pro-tumor microenvironment through the dysfunction of anti-tumor immunity, promotion of angiogenesis and metastasis, and downregulation of therapeutic resistance.

macrophage's polarization to an M1-like phenotype using interferon-γ (IFN-γ), thereby secreting inflammatory cytokines to suppress tumor growth.[42] C-X-C chemokine ligand (CXCL9 and CXCL10) secreted by M1-like macrophages are also able to recruit more Th1 cells, forming a positive feedback loop in tumor immunity.[43] Conversely, the Regulatory T (Treg) cells, or Th2 cells, can prompt macrophages to polarize towards an M2-like phenotype, thereby promoting tumor progression.[44] C-C motif chemokine ligand released by activated M2-like macrophages (CCL17, CCL22, CCL24) can further recruit Th2 cells to the TME, forming a negative feedback loop in tumor immunity.[45] Additionally, the recruited Tregs can activate the PD-L1 receptor on macrophage surfaces, further suppressing the tumor immune response of macrophages.[45] Similar to cellular immunity, the IL-10 and immunoglobin released by B cells can reshape macrophages towards an M2-dominant population.[46,47] M2-like macrophages can also cause the decreased the antigen-presenting function of Dendritic Cells (DCs).[48] Given their prevalence, high plasticity and dynamism in the TME, macrophages can serve as global targets for regulating immunity in the TME and modulating the tumor immune landscape.[49]

Nanomedicine Enhances Anti-Tumor Immunity by Modulating Tumor-Associated Macrophages

The M2-like TAMs are able to suppress the antitumor immunity and exhibit a various tumor-supporting features, including tumor development, angiogenesis, tumor metastasis and therapeutic resistance, which could lead to poor prognosis. In

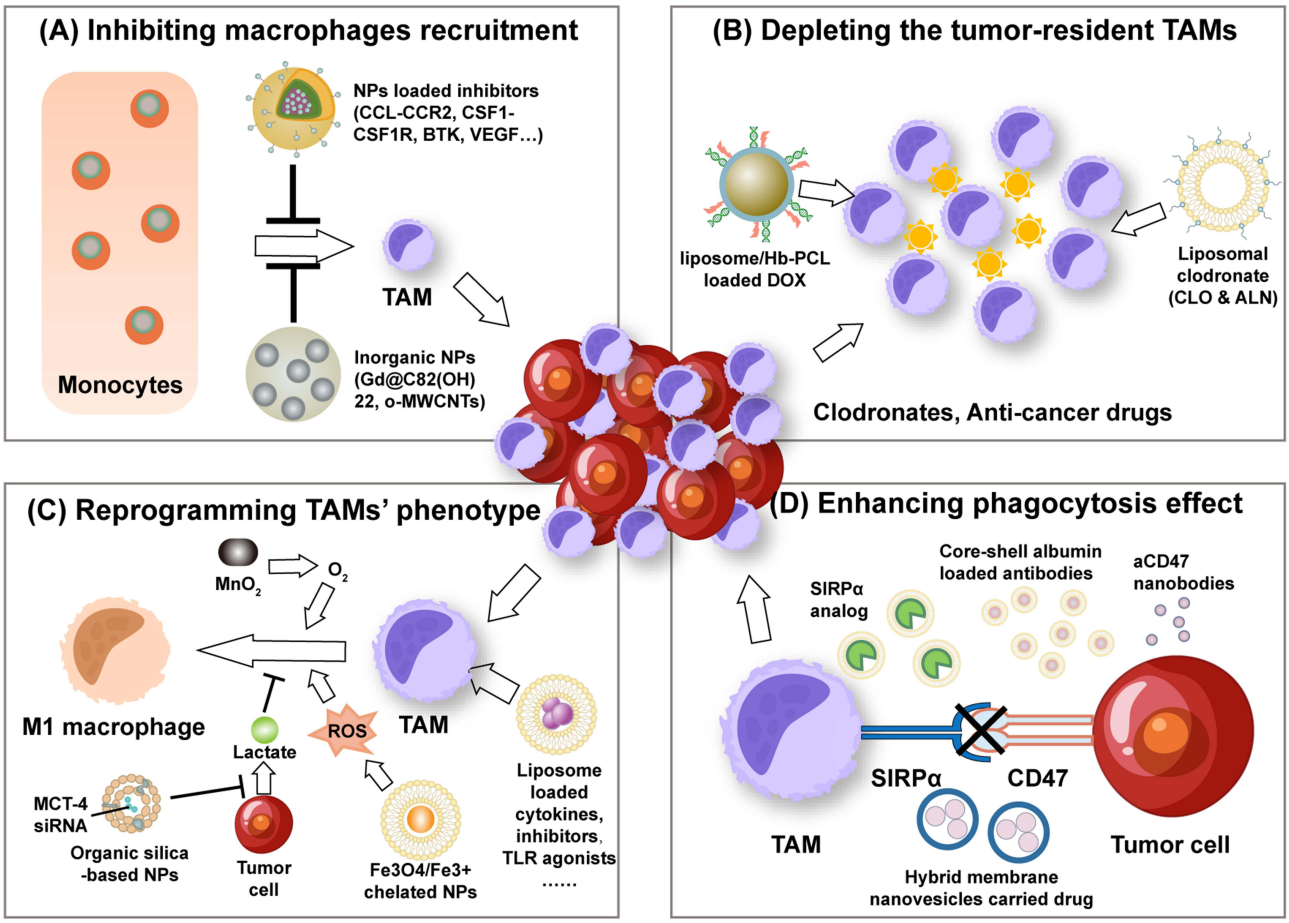

Figure 3 TAMs-based strategies in cancer immunotherapy. The TAM-targeting therapeutic methods aiming at reshaping anti-cancer immunity could be assessed in the following ways: (**A**) The recruitment of macrophages/monocytes could be inhibited through (1) chemokine inhibitors and (2) inorganic NPs by modulating the spatial and physical conditions in TME; (**B**) The tumor-resident TAMs could be depleted by chemical agents inducing apoptosis or other anti-cancer drugs with macrophage-targeting NPs; (**C**) Reprogramming TAM towards proinflammatory phenotype could be done through (1) macrophage-targeting NPs loading drugs regulating inflammatory signaling pathways in macrophages and (2) NPs capable of relieving the anaerobic and hypoxia environment in TME; (**D**) Blocking the CD47-SIRPα interactions between TAMs and tumor cells could restore phagocytosis effect of macrophages through nano antibodies and nanovesicles with larger capacity.

addition, TAMs also present a fully accumulated and auspicious target in the TME for cancer immunotherapy.[50] Considering the immunosuppressive TME caused by the infiltration of M2-like TAMs, the key concept of cancer immunotherapy targeting macrophages is reducing the influence of TAMs and activating cancer immunology. To achieve this, current therapeutic approaches can be divided into two primary strategies: One is to limit the presence of M2-like TAMs, like inhibition of macrophage recruitment to tumor sites and depletion of tumor-resident TAMs. The other is to transform the anti-immune macrophages into pro-immune ones by reprogramming the phenotype of macrophages or enhancing their phagocytosis effects (Figure 3).[51] Recently, various nanoplatforms have been fabricated to target the macrophages and exhibit remarkable therapeutic efficacy and excellent application potential in cancer immunotherapy. The examples of the applications for TAM-based cancer immunotherapy are summarized in Table 1.

Design and Modification of Nanoparticles for Specific Targeting and Uptake by TAM

In general, a rational design of nanoparticles (NPs) should be able to tackle the following challenges in targeting TAMs specifically. Initially, the nanoscale of NPs must be optimized to prevent invading capillaries or engulfment by reticuloendothelial system. Second, the biosafety, bioavailability, and pharmacokinetic profiles of nanoplatforms are significantly influenced by the NP's morphology and surface charge, which in turn affects cellular internalization processes and efficiency. Third, while the enhanced permeability and retention (EPR) effect of tumor vasculature may promote the accumulation of nanocarriers in tumor sites, the intricate TME may impede the uptake of TAMs.

Table 1 Examples of Different TAM-Based Cancer Immunotherapy Strategies Based on Functional Nanomedicine

Strategy	Nanomaterial	Drugs and Agents	Therapeutic Effects	Cancer Type	Reference
Inhibition of external macrophages/monocytes recruitment	SA modified nanocomplexes	IBR	SA targets and blocks myeloid cell recruitment and IBR induces BTK downregulation in TAMs	Sarcoma	[52]
	Cationic polymeric NP	siCCR2	siCCR2 inhibits CCR2 expression in monocytes to block TAMs recruitment	Breast cancer	[53]
Depletion of TAMs	Pt prodrug-conjugating polymeric NP	BLZ-945	BLZ-945 blocks CSF1R to eliminate TAMs	Breast cancer, Colon cancer	[54]
	DSPG/Cholesterol	CLO	CLO blocks mitochondrial adenine translocase to induce TAMs apoptosis	Breast cancer	[55]
	Polysaccharide BSP NP	ALN	TAMs deleted through apoptosis by ALN	Sarcoma	[56]
	Au NP	siVEGF	Eradicate TAMs by siVEGF actively silencing VEGF pathway	Lung cancer	[57]
	Clodronate-cationic nanoliposomes	Gemcitabine and R837	Depletes TAMs by activating APCs and reshaping TME	Breast cancer, Cervical cancer	[58]
	DMPC/DSPE-PEG2000/Cholesterol oleate	siCD115	Inhibit CSF1-CSF1R pathway by siCD115 with α-peptide/M2pep targeting TAMs	Melanoma	[59]
Reprogramming TAM's phenotype	Cholesterol/PEG-DMG	BisCCL2/5i mRNA	Neutralize CCL2 and CCL5 to induce polarization of M1-like macrophages	Liver cancer	[60]
	PEG-PLGA NP	ICG and TiO_2	Activate MAPK and NF-κB pathways by photo-triggered ROS	Breast Cancer	[61]
	PLGA NP	Methotrexate	Block STAT3 and NK-kB pathways to transfer phenotypes of macrophages	Breast Cancer	[62]
	CL4H6-LNPs	STAT3/HIF-1α siRNAs	Silence STAT3 and HIF-1a in TAMs to repolarize M2 macrophages	Renal cell carcinoma	[63]
	Mannosylated liposomes	CHA	CHA activates STAT1 and suppress STAT6 in TAMs to induce M1 transformation	Glioblastoma	[64]
	Polysaccharide NP	R837	Activate M1-TAMs through TLR7 by R837	Breast cancer	[65]
	Liposome modified by PD-L1 antibody and mannose	Rapamycin	Block mTOR pathway to reprogram M2-like TAMs incorporating with anti-PD-L1 effects	Colon cancer	[66]
	Fe_3O_4 NP	N/A	Fe^{3+} activates inflammatory signals of IRF5	Breast cancer	[67]
	3D-printed co-axial scaffold composed of PLGA-sodium alginate	SR-717/ MK-2206	SR-717 activates STING pathway, and MK-2296 inhibits AKT phosphorylation to reprogram TAM	Melanoma; Liver cancer; Breast cancer	[68]
	Liposome	Cabozantinib and IDO-IN-7	IDO-IN-7 inhibits Indoleamine 2,3-dioxygenase and cabozantinib promoted TAM transformation and infiltration of T/B cells	Breast cancer	[69]
	Organo-silica BSA/PEI/PEG	MCT-4 siRNA	Inhibit the lactate efflux between tumor cells by MCT-4 silencing	Melanoma	[70]
	4T1/U87MG based supramolecular membrane vesicle	ICG, R848, 1-methyl-tryptophan	ICG and 1-methyl-tryptophan promote tumor ablation and R848 reprograms TAMs	Breast cancer	[71]
	Fe-based magnetic NPs modified with hyaluronic acid	N/A	Magnetic NPs promote the effect of magnetic hyperthermia by M1-polarization and formation of multinucleated giant cells	Breast cancer	[72]

CD47-SIRPα pathway inhibition	$CaCO_3$ NP	Anti-CD47 antibody	aCD47 bind CD47 to block CD47-SIRPα axis	Melanoma	[73]
	Polymeric NP	Cas9/sgRNA of aCD47 and pIL-12 plasmids	Knockdown the SIRPα and produce IL-12 by CRISPR-Cas9 editing	Melanoma	[74]
	Liposome	SHP2 and CSF1R inhibitors	Dual blocking CD47-SIRPα and CSF1-CSF1R axis to restore proinflammatory functions	Breast cancer	[75]
	DBP metal-organic framework	Imiquimod, anti-CD47 antibody	Reform the phagocytosis ability of macrophages in combination with anti-PD-L1 effects	Colon cancer	[76]
	Mannose-PEG-PAEMA-PDPA	R848 and cGAMP	Repolarize TAMs and downregulate SIRPα expression by STING pathway activation	Melanoma	[77]

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Consequently, modifying NPs with various TAMs-specific targeting ligands can augment cellular targeting and uptake efficiency. Finally, the development of stimulus-responsive NPs that respond to specific cues, either from external or internal environments, can enhance drug accumulation and controlled release at tumor sites.[78]

Upon overcoming the physical and chemical barrier of human body, NPs interact with the outer cell membrane and then be internalized.[79] Endocytosis is the primary process for NP internalization, which involves the invagination of cell membrane and the formation of endocytic vesicles.[80] The endocytosis could be divided into two major classes: pinocytosis and phagocytosis.[81] Pinocytosis, associated with fluid-phase uptake, has been reported in the context of NP internalization by macrophages.[82,83] Phagocytosis, predominantly occurring in specific phagocytic cells like macrophages, DCs, and monocytes, is the process of engulfing larger particles such as bacteria and cellular debris.[84] For NPs in nanoscale, it is hypothesized that phagocytosis often takes place following their aggregation through opsonization,[85,86] which means that those NPs dispersed in physiological fluid are able to adhere certain proteins onto their surface, like albumin,[87,88] and then be recognized by the receptors on the cell membrane, leading to NP internalization subsequently.[89] Moreover, macrophages also possess non-opsonic receptors, including mannose and scavenger receptors, which facilitate interactions with molecular groups on NPs and the following engulfment.[89,90]

The composition and conformation of the molecules on the NP surface affect the phagocytosis mediated by macrophage surface receptor,[91] potentially impacting inflammatory responses or macrophage phenotype shift.[85] For instance, silica NPs of specific sizes (eg, 50 and 100 nm) have been shown to induce inflammation in macrophages through scavenger receptor activation, while other sizes (eg, 10 and 1000 nm) do not.[92] The receptor-mediated phagocytosis is capable of leading to a series of cascade reactions upon cell-NP interplays, including actin filament polymerization, membrane cup-shaped extensions and the internalization of NPs.[93] Apart from the molecules in NPs, the physiological properties of NPs, such as size, shape, surface charge, and functionalization, also influence receptor-mediated phagocytosis in macrophages.[94]

The passive accumulation of NPs around tumors, facilitated by the EPR effect due to the leaky vasculature and dysfunctional lymphatic system in tumor sites, leads to the increased concentration of these NPs around tumors.[95] Yet, this accumulation does not guarantee specific and efficient delivery to the targeted cells, owing to the complex TME. Therefore, the active delivery based on ligand–receptor interactions exhibits superior advantages over passive accumulation, and the incorporation of TAMs-targeting ligands onto the NPs could not only significantly increase drug concentrations inside the TAMs via ligand–receptor interactions but also decrease systemic side effects with higher selectivity.[96] Additionally, the uptake of NPs by TAMs has been viewed as an hurdle in the tumor-targeting nanomedicine because the NPs loaded with drugs are predominantly engulfed by TAMs in tumor sites,[97–99] but the TAMs could be regarded as a target for immunotherapy conversely to reverse the immunosuppression TME. Hence, it is reasonable to develop ideal nanoplatforms for targeted delivery towards M2-like TAMs to regulate the TME, which also holds the promise in synergy of cancer immunotherapy.[11]

In general, the specific TAMs-targeting modifications on the surface of NPs could be classified into the following categories: First, for carbohydrate ligand, mannose receptors (CD206) are overexpressed in M2-like TAMs, and the mannose and *Bletilla Striata* polysaccharide ligand can promote the selective targeting for immune modulators towards TAMs.[61,100,101] Besides, other carbohydrate ligands like dextran and carboxydetran could also be used for drug delivery and TAM imaging.[102,103] Second, for protein and peptide ligand, M2pep, an M2-macrophage binding peptide, and α-peptide, a scavenger receptor B type 1 (SR-B1) targeting peptide, are covalently modified on various NPs due to their properties of targeting TAMs preferentially.[59,104,105] Albumin could also be internalized by TAMs as the source of amino acids through albumin-binding proteins, such as SPARC, and the modification of NPs with albumin and other ligands could lead to the specific targeting of M2-like TAMs and the reprogramming of TAMs.[106] Third, the organic acid ligands, such as sialic acid (SA) and folate (FA), have been utilized for enhanced drug delivery for anti-cancer immunotherapy with the specific binding to the overexpressed receptors, like SA-binding immunoglobulin-type lectins (Siglecs) and FA receptor.[107,108] Finally, the specific molecules on M2-like TAM's surface could also be served as the target for NP.[109] For example, anti-PD-L1/anti-HER2 antibodies and legumain could be designed as ligands or adjuvants for specific TAM-targeting solely or

incorporated with other modifications for nanocarriers, enabling the precise delivery of therapeutic agents for effective TAM elimination.[66,110,111]

Considering the complex TME and different treatment methods, it is reasonable to combine stimuli-responsive groups with therapeutic NPs to trigger effective anti-cancer immune process. In TAM-based immunotherapy, designing NPs in response to either internal microenvironment or external stimuli could facilitate drug delivery and therapeutic effects through the targeted accumulation and timely release of therapeutic agents. Among the internal microenvironment, the acidic TME is the main factor, and the NPs composed of pH-sensitive materials, including O-carboxymethyl-chitosan, modified poly-β aminoesters and ZnO,[100,112,113] are able to achieve the rapid release of carried drugs in tumor sites. Glutathione has also been broadly applied for drug release in the redox-responsive TME. The introduction of disulfide bonds to NPs could be served for specific drug delivery aiming at the glutathione and release in TAMs due to the high redox conditions with the M2-like TAMs.[70,114] As for the external stimuli, the physical stimulus caused by anti-tumor therapies could be utilized for the response of NPs. For example, hyperthermia triggered by external heat, magnetic field or light could promote the drug release.[115] Photo, from another perspective, is also usually used by certain inorganic NPs with optical or electronic properties, including gold or iron relevant NPs.[116] Photodynamic therapy applies photosensitizers to react with oxygen to produce chemically active singlet oxygen and some reactive free radicals in tumor tissues under lights. These products interact with biomolecules, disrupting the structure and function of cells and organelles, thereby selectively killing tumor cells directly or modulating TME and inducing anti-cancer immunity. The photosensitive nanomaterials are capable of depositing drugs in a specifically spatiotemporal manner and promoting the precise targeting of phototherapy while exposed to lights with certain wavelengths.[117]

Inhibition of Macrophages Recruitment

Peripheral monocytes are drawn to tumors by chemokines emanated from tumors, including CCL2 and Colony Stimulating Factor 1 (CSF1), and evolve into different phenotypes with the induction of specific signals in TME. Therefore, specific targeted therapies against these signal molecules have demonstrated the ability to impede the aggregation of TAMs in the TME.[8] In the basic research and clinical studies, various inhibitors, such as CSF1/CSF1R, CCL2/CCR2, and Vascular Endothelial Growth Factor (VEGF), have demonstrated the efficacy in restraining the accumulation of macrophages and promoting cancer development.

The CCL2-CCR2 signaling axis is a primary controller of macrophage recruitment in tumors, which is responsible for the survival, invasion and migration of CCR2+ cancers.[118] CCL2-CCR2 axis is helpful to maintain the homeostasis through its constitutive expression in different cell types in normal condition, while under pathological condition, such as cancers, CCL2-CCR2 axis is able to attract CCR2+ cells, including TAMs, myeloid cells, Tregs and tumor cells, to promote chronical inflammation and cancer extravasation.[119] Targeting this axis to weaken monocyte function and thereby reduce the production of bone marrow-derived TAMs is feasible. Specific therapeutic approaches targeting this axis, including small-molecule inhibitors or antibodies, have demonstrated superior efficacy in preclinical and clinical trials.[118,120] CCR2-siRNA (siCCR2) is also considered a promising targeting reagent for blocking monocyte recruitment. For instance, Shen et al engineered siCCR2-encapsulated cationic poly ethylene glycol-poly lactate NPs that effectively target monocytes in breast cancer treatment, notably suppressing the CCR2 expression in monocytes and the recruitment of bone-marrow derived TAM, thereby ameliorating the immunosuppressive TME and enhancing anti-tumor and anti-metastasis efficacy.[53] In addition, pathological angiogenesis induced by CCL2 has also facilitated TAM's recruitment and impeded drug delivery.[118] To address this, Möckel et al developed a liposome loaded with CCL2 L-RNA aptamer to inhibit the CCL2-CCR2 axis, which further increased blood vessel maturity, reduced TAM's infiltration and improved drug delivery and therapeutic effects of chemotherapy agents.[121]

Additionally, overexpressed Bruton's tyrosine kinase (BTK) in TAMs promotes bone marrow cell recruitment to tumors and tumor growth by polarizing the immunosuppressive M2-like TAM.[122,123] BTK inhibition may consequently represent a strategy to inhibit TAM recruitment to foster anti-tumor immunity.[124] For instance, ibrutinib (IBR) encapsulated in sialic acid-modified nanocomplexes was used as a possible TAM modulator for sarcoma immunotherapy.[52] These nanocomplexes exhibit high loading capacity, extended circulation time, and a compact radius, delivering IBR to tumor

sites. The internalized NPs by TAM release IBR and inhibit the immunosuppressive effects caused by M2 TAM, which are able to impede tumor progression without significant systematic cytotoxicity.

Some inorganic NPs have also been demonstrated to prevent macrophage migration to tumor tissue. $Gd@C_{82}(OH)_{22}$, for instance, constrained macrophage migration through the collagen matrix by suppressing the expression of matrix metalloproteinase-9 to inhibit the breakdown of extracellular matrix.[125] Oxidized multiwalled carbon nanotubes (o-MWCNT) can not only competitively recruit macrophages from other tissues but can also enhance the phagocytosis ability of tumor- resident macrophages, diminishing the number of macrophages and the density of blood vessels surrounding the tumor tissues.[126] Additionally, Chen et al discovered the antitumor effects of hydroxyapatite by inhibiting the accumulation of TAMs. The macrophages treated by hydroxyapatites demonstrated a great tendency to gather around those inorganic NPs with elevated protein level of STXBP6, which can induce the apoptosis of TAMs and the formation of multinucleated giant cells to reduce the presence of monocytes and TAMs in tumor tissues.[127] These inorganic inhibitors can reduce the enrichment of TAMs in the TME by physical and biochemical methods and suppress tumor progression.

Depleting the Tumor-Resident TAMs

Resident TAMs within tumors have a propensity to transition towards an immunosuppressive M2 phenotype, triggering immune evasion mechanisms in various malignancies.[128] Studies have demonstrated that M2 TAMs induce dysfunction in DCs and CTLs while releasing an array of growth factors, cytokines, and proteases that suppress tumor-specific immune responses.[129] Consequently, current research on nanotherapeutic strategies for antitumor treatment focuses on reducing the numbers of M2 TAMs, aiming to reshape the immunosuppressive microenvironment and enhance anti-tumor immunity.

As an important pathway, CSF1-CSF1R axis is responsible for regulating the whole lifetime of macrophages and polarizing TAMs towards an immunosuppressive phenotype.[75] Molecularly targeted inhibitors, such as anti-CSF1R antibodies, BLZ-945, and CSF1R-siRNA, directly suppress CSF1R to inhibit cell growth or survival and significantly eliminate TAMs in the TME, thereby activating CD8+ T-cell-mediated antitumor immune responses.[130,131] For example, Shen et al designed tumor acidity-sensitive dendrimeric NPs spatially target TAMs and tumor cells through hydrophobic interactions and covalently bound platinum prodrugs for cancer chemo-immunotherapy. These NPs are sensitive to the low pH condition around tumors and facilitate the absorption of BLZ-045.[132] Xie et al also created a nanovaccine with bioactivity, loading BLZ-945 and effectively suppressing M2-like TAMs and ultimately reshaping the immunosuppressive TME to enhance immunotherapy outcomes.[133] Li et al developed alginate hydrogels carried with ponatinib-encapsulated NPs to eliminate M2 TAMs.[134] Additionally, the exhaustion of TAMs is also capable of facilitating the binding to PD-1 antibody. Qian et al engineered a liposome NP, functionalized by M2-macrophage binding peptide (M2pep) and α-peptide for targeting both TAMs and tumor cells, to carry anti-CSF1R siRNA (siCD115) and deliver them to tumor cells in melanoma models. The siCD115-loaded NPs not only remarkably reduced the population of TAMs by inhibiting the CSF1-CSF1R pathway but also decreased the PD-L1 expression on M2 TAMs.[135]

Liposomal clodronate analogues have also been formulated as immunogenic nanotherapeutics to target the depletion of M2 macrophages.[136–138] Sousa et al employed liposomes (distearoylphosphatidylglycerol (DSPG) and cholesterol at 2:1 ratio) encapsulating clodronate (CLO), exhibiting high cytotoxicity towards macrophages to significantly eliminate TAMs by inducing the apoptosis through the inhibition of mitochondrial adenine nucleotide transferase.[55] Zhan et al designed a conjugate of bisphosphonate alendronate-dextran (ALN-BSP) that depletes TAMs, thereby reducing blood vessel density around tumors, reactivating surveillance in the immune system, and inhibiting tumor growth in an S1800A tumor-bearing mouse. They prepared poly(lactic-co-glycolic acid) (PLGA) NPs reactive with matrix metalloproteinase-2 (MMP-2) to engulf the ALN-BSP, and resulting from MMP-mediated decomposition, these immune nanomedicines can effectively accumulate and release ALN-BSP at the tumor site to deplete TAM.[56]

The depletion of TAMs can also be synergistically integrated with some anti-cancer drugs to achieve the suppression of cancer cells and augment therapeutic efficacy. Zhao et al designed an NP, which is composed of disulfiram/copper and regorafenib coated with mannosylated albumin, which concurrently targets both drug-resistant tumors and immunosuppressive TAMs, thereby reducing the resistance to therapies in mouse models carrying drug-resistant tumors.[139] Deng

et al used an engineered liposome, which can target TAMs and respond to MMP-2, to load Doxorubicin (DOX) against breast cancer.[107] Similarly, Wang et al designed hemoglobin (Hb) and PCL-composed hollow nanovesicles loaded with chemotherapy drug DOX for TAMs-targeted cancer immunotherapy, achieving the depletion of intra-tumoral M2 macrophages by the combination effects of the affinity of Hb-binding globing to CD163 to target M2 TAMs and the oxygen released by Hb, which also decreased the ratio of M2 macrophages by alleviating tumor hypoxia.[140] The cytotoxicity of chemotherapeutic drugs towards TAMs could also be paralleled with the biological reactive agents. A liposome loaded with sonosensitizer, hematoporphyrin monomethyl ether, and zoledronic acid was generated for TAM depletion. With the implementation of ultra sound and sonotherapy, the integration of the generated reactive oxygen with drug-loaded liposome, which was highly affinitive to TAMs, effectively exhausted M2-like TAMs in the TME to normalize tumor vasculatures, alleviate tumor hypoxia and increase proinflammatory cytokines, which facilitated the reshape of immunosupportive TME and the inhibition of tumors.[141]

Reprogramming the Phenotype of TAMs

The reprogramming the phenotype of TAMs to an antitumor one using immunotherapeutic nanomedicines has been emerging as a widely explored strategy.[142] This reprogramming is associated with modulation of distinct signaling pathways by NPs carrying agents targeting specific molecules. The γ isoform of Phosphatidylinositol 3-kinase (PI3K-γ), which is highly expressed in myeloid cells, regulates macrophage programming.[143] Hybrid nanomicelles were engineered to transport a PI3K-γ inhibitor and CSF1R siRNA to synergistically enhance TAM repolarization and antitumor immune responses.[105] There is also evidence implicating that M1 polarization is associated with the Signal Transducer and Activator of Transcription (STAT) expression.[144] Shobaki et al utilized a pH-sensitive cationic lipid NP loaded with siRNA to silence STAT3 and Hypoxia-Inducible Factor 1α (HIF-1α) in TAMs, achieving M2 repolarization and reversal of the immunosuppression in TME.[63] In addition, an alginate-based hybrid hydrogel, loaded with STAT3 siRNA and lidocaine hydrochloride, was developed for non-small cell lung cancer surgery, which could not only induce the apoptosis of cancer cells and repolarization of TAMs but also be beneficial for pain relief and NK cell activation. This combination effectively inhibited tumor growth and significantly reduced the volume of malignant pleural effusion and postoperative pain.[145] Mechanistic Target Of Rapamycin Kinase (mTOR) signaling plays a pivotal role in M2 macrophage polarization by upregulating p-STAT3 and IL-10 expression.[146] Chen et al employed rapamycin to inhibit the activity and function of mTOR and designed it as a TAM-targeted liposomal nanomedicine to stimulate immune M1 polarization by inhibiting mTOR signaling.[66] Additionally, the Fe-doped carbon dots could also activate anti-tumoral macrophages through IL-10/Arg-1 axis and exhibit promise assisting tumor immunotherapy.[147]

Activating Toll-Like Receptor (TLR)-related pathways in macrophages, through the application of specific agonists such as CpG,[148,149] Imiquimod (R837),[65,67] and Resiquimod (R848),[150,151] have become a standard therapeutic strategy to re-educate TAMs and reform their anti-tumor activity. As an immunomodulator, TLR9-specific unmethylated CpG oligodeoxynucleotides could be internalized by antigen-presenting cells, including macrophages, to release various cytokines for the initiation of cascade immune responses, which is proven to be effective in inhibiting tumor growth and metastasis.[152] A multifunctional biomimetic NP loaded with baicalin and CpG was designed to activate TLR9, repolarizing TAMs towards M1 phenotype with tumoricidal activity. This conversion significantly reversed tumor immunosuppression and simulated specific anti-tumor immunity in melanoma.[104,153] A small lipid NP loaded with CpG enhanced macrophage's phagocytosis and tumor antigen presentation ability by reprogramming the TAM's phenotype, which eradicated most of tumor cells and induced a long-term anti-tumor immunity.[154] A $CaCO_3$ NP loaded with CpG and tumor cell lysates achieved the TAM reprogramming in the acidic TME. The $CaCO_3$ NP neutralized the lactate in the hypoxic TME and the CpG triggered the further immune responses, which both increased the proportion of the M1/M2 macrophages and the infiltration of effective immune cells in the TME.[155]

Additionally, TLR7/8 agonist-loaded nano emulsions could also induce TAM repolarization toward M1 macrophages in different cancer models.[156,157] Zhao et al engineered NPs composed of mannose precursor glycopeptides, R848 and CD40 antibodies. The upregulated MMP-2 under hypoxia transferred the precursor glycopeptides on the NP surface into abundant mannose to bind the mannose receptors on TAM membrane. The precursor glycopeptides' high diffusivity and weak affinity to the perivascular TAMs enabled the accumulation of these NPs in the TME and strong interactions with

tumor-resident TAMs, which promoted the efficiency of R848 to repolarize TAM towards an inflammatory phenotype.[158] The applications of TLR7/8 agonist could also enhance anti-tumor efficacy through the activation of the antigen presenting cells to reprogram the TAM's phenotype to recruit and activate T lymphocytes, transferring the TME from a "cold" to a "hot" immune state.[153] The liposomes loaded with R848 and oxaliplatin were capable of reducing the resistance of oxaliplatin in colorectal tumor by reprogramming the TAM's phenotype and increasing the T cell infiltration to promote the immunogenic cell death (ICD) in the TME.[159] Chen et al utilized a chimeric peptide engineered bioregulator (ChiP-RS) to repolarize TAMs and restore their phagocytosis ability. After internalization by TAMs, the loaded R848 repolarized the TAMs towards an inflammatory phenotype, and the Src homology 2 tyrosine phosphatase 2 (SHP-2) inhibitor SHP099 promoted the phagocytosis ability of macrophages after reprogramming, which would also activate the T cell-mediated anti-tumor immunity.[160] Meanwhile, Zhang et al developed a multifunctional nanoplatforms containing the TLR7/8 agonist motolimod, catalase and PD-L1 siRNA, achieving the repolarization of TAM and maintaining the anti-tumor function of T lymphocytes in the TME by hydrolyzing the excessive reactive oxygen species (ROS) produced by reprogrammed TAMs and decreasing the expression of PD-L1.[161] The application of these nano emulsion also elicited a response against PD-L1 in a TC-1 cervical tumor model with combination, offering a new prospect for clinical anti-PD-L1 therapy.[58]

The cyclic GMP-AMP (cGAMP) synthase (cGAS) and stimulator of interferon genes (STING) pathway is crucial to activate the innate immune responses, and as an important component in innate immunity and TME, macrophages are regarded as an optimal target for cGAS-STING activation to trigger the cascade antitumor immune activities after reprogrammed by STING agonist through the selectively phagocytosis by TAMs, which could be further facilitated by nanotechnologies to improve the specific intakes and amplify the cGAS-STING signals in TAMs.[68,162,163] Liu et al developed responsive NPs containing STING and TLR-4 agonists to repolarize the TAMs into M1-like phenotype and decrease the proportion of Tregs through the increased IFN-β and other proinflammatory cytokines by augmented STING activation, which demonstrated a complete tumor rejection effect and prolonged antitumor memory in either inflamed or noninflamed cancer models.[164] In addition, the STING agonist could be integrated with CCR2 antagonist to establish an immunosupportive TME through the repolarization of tumor-resident TAMs and the inhibition of bone marrow-derived monocyte recruitment synergistically in a co-delivery nano system based on gemcitabine-conjugated polymer.[165] To avoid the off-target effects, a liposome vesicle loaded with STING agonist MSA-2 was engineered for intravenous administration, which exhibited better immune stimulatory capacity than merely drugs with elevated proinflammatory cytokine level in tumor sites and lymph nodes and very limited systematic cytotoxicity.[166] Chen et al also designed a nano system with self-resembled DNA modules through base pairing to achieve the specific uptake by TAMs and programmable activation of cGAS-STING. This system included 4 distinct parts: 1) a selective uptake module with macrophage scavenger receptor; 2) an endosomal escape module for effective release; 3) an ATP-responsive modules for dsDNA dissociation; 4) a STING activation module, which reshaped the immunosuppressive TME with the increased infiltration of M1-like TAMs and CD8+ T cells, and also showed an enhanced antitumor effect in combination with anti-PD-L1 therapies in colorectal cancer and melanoma.[167]

Modulating the microenvironment is also a considerable approach to reprogram the phenotype of TAM. Hypoxia mediates TAM generation and accumulation in solid tumors, thus NPs which can produce oxygen are capable of reversing TAM's phenotype. For instance, Yang et al synthesized hollow MnO_2 NPs that effectively repolarize M2 TAMs by producing oxygen and relief the hypoxia condition within the TME, which can also be paralleled with immune checkpoint blockade (ICB) therapy.[168] A core-satellite nanoplatform composed of different metal ion NPs was developed to deeply penetrate tumors and enhance cancer therapy. The nanoplatform would disintegrate into the TME and then produce oxygen and release TGF-β inhibitors to reprogram TAMs, which would facilitate the ICB therapy and cytotoxic Ag^+ mediated metal-ion therapy.[169] A novel ZnS NP was engineered to consistently provide hydrogen and oxygen in tumor sites with highly effective sonocatalysis, inducing the M2-to-M1 reprogramming and relieving the suppression of CD8+ T cell's function to demonstrate the immunological co-activation capability and anti-tumor effect in deep hypoxic tumors.[170] The alleviated TME with in-situ generated oxygen could also further promote the consumption of chemotherapy agents and apoptosis of tumor cells by photothermal effect, reshaping anti-tumor activity.[171] Concurrently, lactate generated by aerobic glycolysis in the hypoxic TME also engages in the transformation of TAM's phenotype and

dysfunction of CD8+ T cells.[172] Li et al utilized an intelligent organic silica-based nanoplatform to transform anti-MCT-4 siRNA (siMCT-4), hindering lactate efflux from tumors through monocarboxylate transporters MCT-4 silencing, leading to a phenotypic shift of TAM's state and reactivation of CD8+ T cells.[70] A nanoenzyme carrier loading lactate oxidase (LOD) and hypotensor syrosingopine (Syr) was also utilized to restore the anti-tumor immunity. Syr blocked the lactate efflux by inhibiting MCT1/MCT4 functions, and the excessive intracellular lactate was then catalyzed by LOD to produce abundant hydrogen dioxide and ROS, which further increased M1 TAMs in the TME, promoted the release of proinflammatory cytokines and restored the function of cytotoxic T and NK cells.[173] The inhibition of lactate efflux in the TME could be accompanied with phototherapy. A photodynamic regulator CASN was composed of photosensizier Chlorin e6 (Ce6) and MCT-1 inhibitor AZD3965, and the inhibition of MCT-1 reduced the immunosuppressive TME by recruiting CTLs and repolarizing TAMs, which synergized the ICD caused by phototherapy.[174]

ROS is able to mediate the repolarization of TAMs to a proinflammatory phenotype by lipopolysaccharide recognition, serving as a pivotal regulator of macrophage function.[175] Therefore, NPs spontaneously producing ROS, like metal oxides or ions, could re-educate the TAM's phenotype primarily through the disruption of mitochondrial oxidative respiratory chain.[176–178] Fe_3O_4 NPs or Fe^{3+} chelated NPs[15,179,180] could induce phenotypic shifts of TAMs from supporting tumors to against tumors by stimulating TLR inflammatory responses or activating NF-κB signaling, enhancing macrophage-modulated cancer immunotherapy. In addition, the ferroptosis induced by Fe^{3+} NPs could also promote ICD, antigen-presenting ability and proinflammatory effect of immune cells in the TME through released ROS, cytokines and tumor cell lysates, including macrophages.[181,182] Xu et al constructed a nanocoordinator with silica-based imprinting layer coated on the iron oxide core (Sia-IMNPFe). The external magnetic field and tumor-targeting sialic acid on the surface facilitate Sia-IMNPFe's fast accumulation and precise targeting to the tumor cells, and the silica and iron matrix-generated cytokine and ROS promoted the TAM's repolarization towards M1 phenotype after Sia-IMNPFe taken up by tumor-resident TAM, activating their immunotherapeutic efficacy.[177] Apart from metal ions, NPs containing photosensitizers, which can also release ROS under phototherapy, could also repolarize TAMs towards an M1-like phenotype.[183,184] The combined nano system of glutaminase inhibitor C968 and photosensitizer Ce6 reformed antitumor activity from tumor metabolism and immunity: C968 inhibited glutamine metabolism in tumor cells and preserved the abundant ROS generated by phototherapy from exhaustion by glutathione, enhancing the intra-tumoral oxidative stress of the ICD effects. Meanwhile, the blockage of glutamine metabolism and excessive ROS remodeled the TAM's phenotype to proinflammatory one and recruit and activate the CTL in the TME.[185]

The restored antitumor immunity after the repolarization of TAM is beneficial for cancer immunotherapy, thus integrating TAM reprogramming with different immunotherapies could be regarded as an applicable strategy against immune evasion and potential therapeutic resistance in conventional ICB therapies.[69,71,186,187] An engineered milk exosome modified with M2pep and epidermal growth factor receptor (EGFR) antibodies was able to specifically deliver the PD-L1 siRNA to TAMs, repolarize TAMs and reshape the TME, achieving a significant tumor inhibition after systematic administration in EGFR cancer models.[188] Furthermore, a complicated immunosuppressive TME was constructed by tumor cells and various immune cells, including M2-like TAMs, myeloid-derived suppressor cells (MDSCs) and Tregs, which requires a multiple-targeting regulation towards different immunosuppressive cell types for effectively establishing anti-tumor immunity. Lee et al engineered a hyaluronic acid-bilirubin NP encapsuling SC144, an inhibitor blocking IL-6/gp130/STAT3 pathway, to selectively accumulate in tumor cells and MDSCs, which induced the ICD of tumor cells, further increasing the M1/M2 ratio of TAMs, decreasing the proportion of MDSCs and Tregs, and holding a promise to eliminate tumor cells effectively in combination with anti-PD-L1 therapy in ICB-resistant tumors.[189] Yan et al constructed a complex nano system composed of a micelle named BEM and the scavenger receptor A (SR-A) ligand dextran sulfate (DXS), which decomposed in acidic TME and released DXS to repolarize TAMs by inhibiting SR-A on TAMs. The co-loaded MDSC inhibitor, entinostat, and the ICB agent, BMS-1, in BEM inhibited MDSC and blocked the PD-1/PD-L1 pathway separately, leading to rejuvenated immune responses in the TME and providing a possible approach for improving the effect of cancer immunotherapy through a multi-targeting strategy.[190] Additionally, the tumor vaccines loading different immune agents could also manipulate the TME from different perspectives to conquer the immune evasion with a long-term immune memory.[191,192] For instance, a polyoxazoline-mannose (POx-Man)

nanovaccine loaded with peptide-antigens, adjuvants and TGF-β regulators was capable of repolarizing M2-like TAMs, activating CD8+ T cells, and blocking PD-L1 synergistically, which demonstrated a great potential in treating solid tumors.[193]

In addition to immunotherapy, TAM reprogramming could also be combined with other cancer treatments to overcome the therapeutic resistance and improve their treatment effects, including chemotherapy, radiotherapy, phototherapy, and magnetic hyperthermia.[71,72,194–197] Chen et al reported a nanodrug-delivering-drug leveraging 2D stanene-based nanosheets and a small molecule anticancer drug β-Elemene (ELE), which was able to elevate the proportion of M1-like TAMs, CD4+/CD8+ T cells and mature DCs in the TME, cooperating with ELE to improve chemotherapeutic effects against melanoma.[198] A biomimetic nanoimmunoregulator utilized ICD effect caused by phototherapy to promote the PD-L1 inhibition and TAM reprogramming by 2 distinct parts: PM@RM-T7 and PR@RM-M2 (metformin/R837 encapsulated by red blood cell membrane embedded with T7/M2 peptide, carried by biocompatible mesoporous polydopamine). PM@RM-T7 enhanced the ICD effects via the photothermal effects by targeted NIR, impeded immune evasion through the degradation of PD-L1 by metformin, while PR@RM-M2 specifically targeted TAMs via M2pep reprogrammed them into M1-like phenotype and broke the immunosuppressive TME, of which the integration significantly inhibited the growth of primary and metastasis tumor cells.[199] In addition, Liu et al also prompted the strategy to combine the chimeric peptide-engineered TAM repolarization with photosensitizer Ce6 and trigger ICD of tumors through phototherapy, which not only re-educated the TAM reprogramming to activate the CTL-dependent antitumor activity but also released High Mobility Group Box 1 (HMGB1) and exposed calreticulin, providing an approach for metastatic cancer treatment.[200]

Enhancing Phagocytosis Effects

CD47, a ubiquitously expressed transmembrane protein, is highly expressed on naive erythrocytes and most cancer cells.[201] CD47 generally interacts with SIRPα in most of cells to keep the homeostasis, especially to suppress macrophage's phagocytosis. Elevated CD47 expression is closely associated with poor prognosis in solid tumors. As a transmembrane protein expressed in multiple immune cells, SIRPα recognizes CD47 and initiates a protective signal, which may be regulated by super-enhancers,[202] preventing SIRPα-expressing macrophages from engulfing tumor cells with overexpressed CD47. Interference with the CD47-SIRPα axis holds promise in restoring the antitumor function of TAMs.

The deployment of nanoplatforms serving as transportation vehicles can block the "do not eat me" signaling, significantly enhancing the in vivo therapeutic effect of anti-CD47 agents and overcoming biological barriers.[203] A pH-dependent CD47 antibody has been developed to accumulate in acidic TME and targeted tumors specifically with a long-term antitumor memory and unobvious off-target inflammatory responses.[204] Nanobodies (Nbs), owing to their comparative small radius, optimistic affinity, and stability, are considered as innovative drug building blocks superior to traditional antibodies.[205,206] Ma et al identified CD47-specific Nbs utilizing phage display and engineered HuNb1-IgG4, a hybrid protein fused with those Nbs, which enhances tumor cell clearance without erythrocyte agglutination in vitro experiments and demonstrates enough security in the circulating system of cynomolgus monkeys.[207] CD47/SIRPα inhibitors also enhance antitumor responses by potentiating antibody-dependent cellular phagocytosis (ADCP). The nanoplatforms loaded with calcium channel inhibitor (TTA-Q6) and CD47 inhibitor (RRX-001) were sensitive to acidic TME. TTA-Q6 inhibited tumor's consumption of Ca2+ and presented the calreticulin to macrophages and DCs to activate their antitumor immunity, while the decreased CD47 level in tumors by RRX-001 further impeded the potential immune evasion by diminishing the interaction between CD47 and SIRPα and enhancing macrophage's phagocytosis.[208] Chen et al also utilized core-shell albumin NPs responsive to ROS, loaded with anti-CD47 (aCD47) and anti-PD1 (aPD1) complex, initially releasing aCD47 and inhibiting the "do not eat me" signal, followed by aPD1 release to elevate the lymphocytes infiltration surrounding tumors.[209] Moreover, the implementation of paclitaxel (PTX) hydrogel with aCD47 stimulated the antitumor immunity in TME and augment the aCD47-triggered macrophage's phagocytosis of tumor cells, inhibiting the recurrence of glioma with minimal side effects.[210]

As a special method to rejuvenate the proinflammatory and antitumor function of TAM, it is an ideal strategy to integrate the CD47- SIRPα blockage with TAM repolarization for the amplification of TAM's phagocytosis capability.[161] Li et al engineered a polymetric nano system loaded with R848 and 2',3'-cGAMP to achieve the cascade reaction from

TAM's repolarization to enhanced phagocytosis. The co-delivery of R848 and cGAMP activated the TLR and STING-mediated phenotypic transformation of TAMs towards an M1-like one. Furthermore, the activation of STING pathway deregulated the expression of SIRPα through the oxidation metabolism of fatty acids in TAMs, and the further implementation of aCD47 synergized the blockage of CD47-SIRPα axis, which promoted the phagocytosis ability of tumor-resident macrophages, significantly inhibited the lung metastasis and prolonged the survival rate in TNBC with the integration of aPD1.[77] Additionally, ROS generated by phototherapy and the application of SHP099, the inhibitor of SHP-2, could also restore the phagocytosis and antitumor activity of TAMs and promote the CTL infiltration through a TAM-targeting albumin NP.[211]

Exosome, or other extracellular vesicle (EV), has been explored to disrupt the CD47-SIRPα interaction loading different modulating agents.[209] Koh et al developed exosome variants bearing SIRPα analogs to trigger enhanced tumor phagocytosis and stimulate potent antitumor activities of T cells.[212] However, poor cargo encapsulation and targeting capability of exosomes may limit their potential.[213] To address this, hybrid membrane nanovesicles or biomimetic nanovesicles received attention. By combining exosomes or cell membrane vesicles with liposomes, the latter are endowed with biogenesis capabilities, creating hybrid nanovesicles.[214,215] Cheng et al utilized genetically modified exosomes fused with drug-loaded thermosensitive liposomes to generate CD47-overexpressing hybrid nanovesicles, combining photothermal therapy with immunotherapy to achieve antitumor effects.[216] Researchers have also prompted different strategies to modify the EVs for longer circulation time, better biocompatibility and phagocytotic effects of macrophages. Zheng et al created a nanoplatform termed ARMFUL for a multifunctional EV. The hybrid membrane fused by M1 macrophage membrane and liposomes inserted an aCD47-modified coat onto the NP's surface to enhance the macrophage's phagocytosis, while the loaded BLZ945, a CSF-1R inhibitor, was also working against the immunosuppressive polarization of tumor-resident macrophages along with the CD47-SIRPα blockage.[217] Gong et al also engineered a small EV with the 7D12 (an anti-EGFR Nb) and humanized aCD47 modification on its surface, which improved the macrophage's phagocytosis of malignant cells and better targeting ability to EGFR+ tumors.[218] The applications of those engineered exosomes and EVs demonstrate a feasible approach for restore macrophage's phagocytosis in TME and hold a promise in the future clinical practice to facilitate cancer therapy.

Engineered Macrophages Facilitate Cancer Therapy

Considering the pivotal functions of macrophages in the TME, especially the tumor-targeting and cancer cell phagocytic abilities of inflammatory M1 macrophages,[219] researchers have been exploring the utilization of macrophages as tools to facilitate various kinds of cancer therapy.[220] The homing ability of M1 macrophages stems from their cell membrane proteins, enabling their derived exosomes to inherit this trait. The functions of surface markers on macrophage cell membrane and their corresponding receptors or ligands could be classified into the following 3 categories: 1). CD47-SIRPα axis prevents immune clearance of macrophages;[202] 2). The CCR2-CCL2 interaction recruits macrophages and results in inflammation;[118] 3). The selectins or integrins on the macrophage cell membrane promote cell–cell adhesion. For example, α4β1 integrin-vascular cell adhesion molecule-1 (VCAM-1) axis increases the macrophage uptake in VCAM-1+ metastatic cancer, and αMβ2 integrin-intercellular adhesion molecule-1 (ICAM-1) facilitates macrophages' adhesion to endothelium to cross blood–brain barrier (BBB) and migrate towards tumor sites.[221,222] Furthermore, isolating macrophage membranes and applying them as coatings on diverse NPs can further enhance targeting capabilities. The macrophages can be manipulated by cell engineering, gene editing and nanotechnology, and they can serve as both the capture or killer of tumor cells and supporting characters in drug delivery, phototherapy, cancer imaging and other theranostics (Figure 4). Examples of the adoptive engineered macrophages and cell membranes in the applications of cancer treatment are outlined in Table 2.

Drug Delivery

These macrophage-derived drug carriers not only circulate in the bloodstream but also selectively adhere to VCAM-1 present on the cell membrane of cancer cells through α4 and β1 integrins, allowing tumor tissue targeting.[223] Macrophages directly loaded with drugs can be fabricated through incubation with the lived macrophages. For instance, Fu et al utilized RAW 264.7 macrophages to load DOX for treating metastatic 4T1 tumors.[223] However, to enhance the

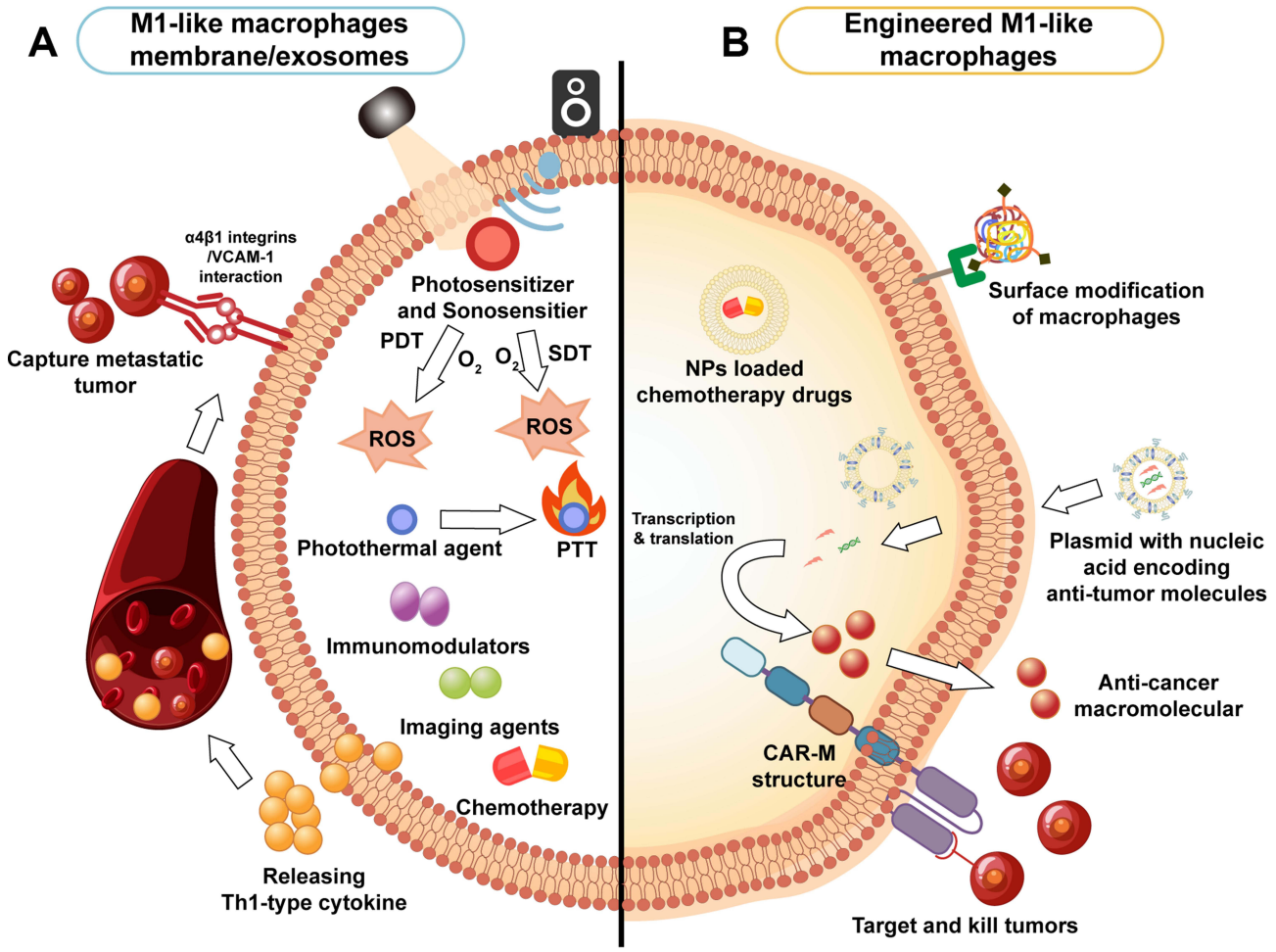

Figure 4 Application of engineered macrophages in different cancer therapy. (**A**) The M1-like macrophages membrane/exosome can (1) carry chemotherapy and immunotherapy drugs; (2) release cytokines facilitating cancer immunotherapy; (3) capture metastatic tumor cells via α4β1 integrins/VCAM-1 interaction; (4) load photosensitive/sonosensitive materials and mediate phototherapy/sonotherapy; (5) load imaging agents and track tumor state in human bodies. (**B**) The M1-like macrophages could be engineered by (1) incubating drugs or NP-loaded drugs; (2) chemical conjugation on membrane for tumor-targeted drug delivery; (3) CAR engineering to target and kill tumors; (4) genetic manipulation to massively produce anti-cancer molecule.

drug loading capability and minimize toxicity to macrophage carriers, most delivery systems adopt an indirect approach, where macrophages are loaded with drug-containing NPs. M1 macrophages loaded with NPs exhibit superior advancement to target tumors compared to NPs alone, which are extensively applied in cancer therapy.[255] Tao and his team utilized bone marrow-derived macrophages to load PTX for the treatment of gliomas.[224] Additionally, these cells can target hypoxic tumor regions and even cross the BBB.[226,256] Injection of NP-containing apoptotic bodies in vivo can also form NP-loaded macrophages. In a study conducted by Zheng et al, they applied apoptotic bodies loading gold-silver nanorods with the modification of CpG (AuNRs) and entered the tumor in the form of AuNR-loaded macrophages through phagocytosis by inflammatory monocytes.[257]

To enhance targeting or confer multifunctionality, three approaches can be used to modify macrophages: 1) incorporation of lipid-ligands, lipid-proteins, or NPs into the cell membrane through incubation; 2) chemical conjugation to the cell membrane surface, such as amine ligand or NP coupling; 3) genetic engineering through transfection with gene plasmids or gene editing techniques.[258–262] For instance, the Gambir team[259] developed genetically modified macrophages capable of detecting tumor cells as small as 50 mm^3. Macrophages can also be engineered to boost their immunological activity through genetic manipulation or chemical conjugation. Ray et al knocked out the SIRPα in macrophages by arginine NPs loaded with gRNA and Cas9 protein to enhance their capabilities of enhanced phagocytosis.[260] In a work completed by Guo et al, the lipopolysaccharide-anchored macrophages loaded with DOX

Table 2 Various Nano Systems Engineered by Macrophages, Macrophage Cell Membrane and Exosomes for Cancer Diagnosis, Therapy, and Theranostics

Applications	Macrophages	Nanomaterials	Cargoes	Cancer Models	Outcomes	Reference
Drug delivery	Raw 264.7 macrophages	N/A	DOX	Ovarian carcinoma cell	(1) Better inhibition of tumor invasion than liposome-DOX (2) No significant affection on macrophage targeting and viability	[223–225]
	Bone-marrow derived macrophages	PLGA/ Pluronic P123 NP loaded drugs	PTX/DOX	Glioma U8 7 tumor cell and mouse model	(1) Better tumor targeting effects and inhibition of tumor development (2) Better treatment than DOX-loaded M1 macrophages (3) Able to cross blood–brain border	[224,226]
	Macrophages	Cooperate with Fe_3O_4 NPs	Oncolytic adenovirus	Prostate tumor mouse models	(1) Targets hypoxic areas of tumor (2) Abolish growth of primary tumors before radio- and chemotherapy (3) Better tumor targeting with magnetic field	[227–229]
	Modified Macrophages	Lipopolysaccharide-anchored	DOX	Mouse orthotopic lung cancer model.	(1) Stimulated microtube formation with tumors (2) Induce secretion of TNF-α in TAMs (3) Enhance anti-tumor effect	[230]
	M1 macrophages exosomes	Modified by aminoethylanisamide-polyethylene glycol (AA-PEG) vector	PTX/DOX	Lung cancer mice model, Nude mice bearing drug-resistant solid tumors	(1) High biological compatibility (2) High loading capability (3) Targets σ receptor in lung cancer cell (4) Enhance anti-tumor effects on metastatic and drug-resistant cancer	[231–233]
	M1-exosomes-mimetics nanovesicles	Fusion by liposome to be a hybrid exosome	DOX	CT26 colon adenocarcinoma cell lines and mouse model	(1) Higher production and drug loading capability (2) Able to polarize M2 to M1 (3) Higher colloidal stability (4) Higher pH-sensitive sustained drug release in vitro	[234–236]
	Raw 264.7 macrophages cell membrane	Coextrusion with mesoporous silica nanocapsule	DOX	4T1 breast cancer mouse model	(1) Better biological compatibility (2) Longer blood circulation time (3) Better targeting to tumors (4) Cancer ablation with chemotherapy	[237]
	IL-4-induced M2 macrophages cell membrane	Coextrusion with polyfluorocarbon NPs	Cabazitaxel	4T1 and MCF-7 mouse models	(1) Intrinsic targeting properties to tumor (2) Better intratumoral penetration (3) Inhibition of tumor development (4) Clearance of cancer stem cells	[238]
	Macrophages cell membrane	Coextrusion with PLGA NPs	Gemcitabine	Mouse model of pancreatic cancer	(1) Immune evasion properties (2) Minimal toxicity (3) Downregulation of PI3K/AKT and MEK/REK pathways	[239]

(*Continued*)

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Table 2 (Continued).

Applications	Macrophages	Nanomaterials	Cargoes	Cancer Models	Outcomes	Reference
Therapy for metastatic cancers and CTC	Raw 264.7 macrophages membrane	DNA tetrahedron dendrimer-liposome	DOX-MPK	4T1 breast cancer mouse model with lung metastasis	(1) High and selective accumulation on lung metastatic sites (2) Decreased metastatic nodes in lung tissue (3) Better biological compatibility and drug uptake	[240]
	Azide-attached macrophages membrane (with anti-EpCAM antibody)	Electrostatic interaction with Fe_3O_4 NPs	N/A	N/A	(1) Good CTCs capture ability in vitro (2) Limited disruption from leucocytes in blood	[241]
	Transformable macrophages (LD-MDS)	N/A	Legumain protease	Lung metastatic tumor	(1) LD-MDS can be transformed into soravtansine-loaded nanovesicles (4) Nanovesicles could be internalized by 4T1 cancer cell	[242]
PTT	Raw 264.7 macrophage membrane	Coextrusion with Fe_3O_4 NPs	N/A	MCF-7 breast cancer	(1) Higher biological compatibility and macrophage uptake (2) Intrinsic targeting to tumors (3) Heat responses under NIR for cancer elimination in vivo	[243]
	Macrophage cell membrane with PD-L1 antibody	Coextrusion with hollow Au nanocage composites	Galunisertib	CT26 colon carcinoma mouse model	(1) Selective intakes by tumor cells (2) Synergism of PTT and immunotherapy (3) Inhibition of primary and metastatic tumor development	[244]
	Macrophage-hepatic cancer cell hybrid membrane	Sonication with CuS NP	Sorafenib	Hepatocellular carcinoma mouse model	(1) Higher biological compatibility (2) Homotypic tumor-targeting ability (3) Higher NIR absorption capacity for PTT ablation (4) Synergetic effects of PTT and chemotherapy	[245]
PDT	Lipopolysaccharide-induced M1 macrophage membrane	Sonication and extrusion with PEGylated bilirubin NP	IND and Ce6	4T1 breast cancer mouse models	(1) Longer blood circulation time (2) Tumor targeting and codelivery of IND and Ce6 (3) Higher production of ROS with NIR (4) Synergism of chemotherapy, anti-tumor immunity and PDT	[246]
	Macrophages membrane	Coextrusion with mesoporous silica nanocapsule and folic acid	DOX, L-menthol and indocyanine green	4T1 breast cancer mouse models	(1) Multitargeting properties and immune evasion properties (2) Higher accumulation and intake by tumor cells in low pH TME (3) Synergism of chemotherapy, PTT and PDT	[247]

	M1 macrophages membrane	Sonication with AIEgen	PTX prodrug	4T1 tumor-bearing BALB/c mice	(1) Fluorescence and photoacoustic imaging of tumors (2) PDT promotes ROS generation and ICD of tumors (3) Oxygen exhaustion by ROS generation facilitates the release of PTX (4) Better tumor targeting and biocompatibility	[248]
SDT	AS1411 aptamer-modified macrophage exosomes	SiO_2 NPs	ICG and catalase	Orthotopic glioblastoma mouse model	(1) Good ability to cross BBB and tumor targeting (2) Alleviate hypoxia in TME by catalase and glutathione (3) Exhaustion of glutathione and generated oxygen facilitate SDT promoting ICD of tumors (4) Good biocompatibility and long circulation time	
Cancer Imaging and synergistic theranostics	Raw 264.7 macrophage membrane	Coextrusion with liposome	N/A	MCF-7 breast cancer	(1) Higher biological compatibility and tumor-targeting ability (2) Immune evasion properties (3) Good performance of fluorescent UCNP and cancer imaging in vivo	[249]
	Raw 264.7 macrophage membrane	Coextrusion with liposome	DOX and quaternary quantum dots	4T1 breast cancer mouse model with lung metastasis	(1) Immune evasion properties (2) Capability of targeting metastatic tumors (3) Fluorescent imaging, tumor targeting and elimination in vivo	[250]
	Macrophages membrane	Sonication with silver nanocluster	N/A	Dalton lymphoma ascites tumor mouse model	(1) Strong fluorescent intensity at tumor site in vivo (2) Cytotoxicity against tumor cells in vitro	[251]
Genetic-engineered macrophages for cell therapy	Macrophages	Mannose-conjugated poly ethylenimine nanocarriers	Genes expressing CAR and IFN-γ	Solid tumor bearing mouse model	(1) Generating CAR-M1 to execute tumor phagocytosis (2) Decrease Tregs to improve the function of CD8+ T cells (3) No significant systematic cytotoxicity	[252]
	RAW264.7 macrophages	Cavity-injectable NP-hydrogel superstructure	Anti-CD133 CAR plasmids (pCARs)	Orthotopic glioblastoma mouse model	(1) NP-hydrogel superstructure creates CAR-M surrounding cavity (2) Prevent recurrence of brain tumors by eradicate tumor stem cells (3) Robust tumoricidal immunity surrounding the postsurgical area (4) No significant systematic cytotoxicity	[253]
	RAW264.7 macrophages	Dendritic-grafted poly(lysine) (DGL)	pDNA coding TRAIL molecule and TAT molecule	4T1 breast cancer cell line and mouse model	(1) Good tumor-homing ability in systemic circulation (2) Long-term anti-tumor efficacy through generating apoptosis-inducing protein (3) Positively charged penetrating domain endows it the ability of deep tumor penetration	[254]

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were found to be effective in stimulating the formation of microtube structures within tumor cells and triggering the release of TNF-α in the surrounding TAMs in a lung cancer mouse model.[230] In addition, the engineered NPs derived from alpha fetoprotein (AFP)-overexpressing macrophages was applied to enhance the immunotherapy in hepatocellular carcinoma. M2pep-conjugated macrophages efficiently transported R848 to TAMs and repolarized them to M1-like phenotype due to the nature tumor tropism of macrophages and M2pep modification, and the AFP-overexpressing engineered macrophages served as antigen-presenting cells to activate the CTL-mediated anti-tumor immunity and maintain an intra-tumoral niche for CD8+T cell differentiation.[263]

In addition to macrophages themselves, exosomes and cell membranes derived from them can also function as delivery vehicles. Exosomes derived from M1-macrophages (M1-exos) retain membrane properties similar to their parent cells, which are also stable, pleiotropic, biocompatible and low immunogenic in vivo, and can be deployed to transport anticancer agents, demonstrating great potential in immunological modulation and cancer therapy.[264,265] Kim et al utilized M1-exos loaded with PTX and demonstrated their efficacy in treating drug-resistant tumors.[231] M1-exos not only deliver drugs but also release proinflammatory Th1 cytokines to enhance antitumor effects.[266] Furthermore, M1-exos can be used as adjuvants for cancer vaccines and modulating the TME, which serves as both targets and tools in cancer immunotherapy.[267] Zhen et al integrated the M1-exos and AS1411 aptamer-conjugated liposomes for better drug-loading capability and system stability. This combined nanoplatform was loaded with perfluorotributylamine and IR780 for alleviating the hypoxia and immunosuppressive TME and repolarizing TAMs in TNBC.[268] In addition, M1-exos genetically modified by sialic-acid-binding Ig-like lectin 10 (Siglec-10) was designed as a gelator. After the X-ray radiation and activated immunogenicity, the loaded efferocytosis inhibitor in the M1-exos promoted a series of immune responses to repolarize the peritoneal macrophages for treating ovarian cancer.[269] Apart from M1-exos, the EV constructed by M1 macrophage-derived membrane could also be treated as an effective drug delivery vessel with high tumor-targeting ability.[270] Yu et al developed a hybrid cell nanovesicles loaded with DOX (DNV) to boost antitumor immunity. The hybrid membrane constituted by M1 macrophage membrane and 4T1 tumor cells not only facilitated the accumulation of DNVs in tumor sites and lymph nodes but also promoted antitumor humoral immunity, especially activating the B cells and repolarizing TAMs towards an M1-like phenotype, further extending the understanding and application of EV in drug delivery and antitumor humoral immunity.[271]

Both macrophages and their derived exosomes or EVs exhibit wonderful tumor targeting capabilities and biocompatibilities. Consequently, applying macrophage membranes as coatings on NPs can significantly improve the efficacy of the NPs' specific aggregation in tumors. Given the limited delivery efficiency of NPs in solid tumors via the elevated permeability and retention effect,[96] macrophage membrane coating holds massive potential in drug delivery. Lu et al created an Fe_3O_4 vortex nanodrug, loaded with DOX and EZH2 siRNA and coated with M1 macrophage cell membrane, which showed a facilitated tumor-targeting capability even without exogenous magnetic fields, enhanced antitumor efficiency, and limited systematic toxicity compared to routine chemotherapy.[272] A nanocomplex based on aPD1 and phosphorus dendrimer named AK128, coated with macrophage membrane, was engineered to facilitate the immunotherapy against orthotopic glioma. The α4 and β1integrins on the macrophage membrane possessed good stability and compatibility for crossing BBB, extending circulation time and accumulating in pathological sites, and the synergistic effects of AK128 and aPD1 restored the antitumor immunity in TME, achieving a promising strategy for glioma immunotherapy.[273] Moreover, the therapeutic agents capable of impairing tumor metabolism could also be delivered to tumors via M1 macrophage membrane-derived nano systems to optimize their antitumor ability,[274] and the macrophage membrane-camouflaged nanoplatforms also play a critical role in precise drug delivery, enhancing therapeutic efficacy and decreasing systematic toxicity for synergistic therapies combining different cancer treatment strategies.[275–277]

Cell Therapy

The advancements in gene editing and synthetic biology have introduced new avenues for cellular therapeutic strategies.[278] In the paradigm of chimeric antigen receptor T-cell (CAR-T) therapy, T cells extracted from patients themselves have demonstrated potent tumoricidal activity through genetic reprogramming.[279] Similarly, genetically modified macrophages have demonstrated tremendous potential in the realm of cancer therapy.

Gill et al successfully created CAR-modified macrophages (CAR-Ms) by genetically engineering of human macrophages using CARs, thereby enhancing their ability to phagocytose tumor cells.[280] The CAR structure usually consists of those elements: an extracellular single-chain antibody fragment, a hinge and transmembrane domain, and intracellular domains for activation and co-stimulatory.[281] For further optimization of CAR-M's composition in alignment with the characteristics and function of macrophages, the intracellular activation and co-stimulatory domains of CAR molecules could be modified by (1) using domains like FcRγ or CD3ξ to elevate the ability of phagocytosis and (2) integrating the inflammatory signaling domains with the original CAR structure.[280,282–284] Such genetic manipulations induced CAR-Ms to exhibit an M1-like phenotype, secreting proinflammatory cytokines that can reprogram TAMs and stimulate an anti-cancer condition in the TME. Vale and his team genetically modified mouse macrophages by coupling specific CARs to their surfaces, screening various intracellular and extracellular domains.[285] In xenograft tumor models, CAR-Ms demonstrated precise and potent phagocytosis of cancer cells, leading to improved outcomes of survival.[280]

Many researchers have also engineered CAR-Ms in different ways. Zhang et al constructed CAR-iMacs, which are capable of selectively engulfing tumors in a manner dependent on antigen recognition.[135] They further incorporated CARs into induced pluripotent stem cells (iPSCs) via lentiviral transduction and developed a bone marrow cell differentiation protocol to achieve massive production of engineered macrophages.[286] Kang et al utilized macrophage-targeted mannose-conjugated poly ethylenimine nanocarriers targeted to macrophages to deliver genes encoding CAR and IFN-γ in vivo, producing CAR-M1 capable of executing tumor phagocytosis. The CAR-M1 could also assisted the function of CD8+ T cell by reducing Tregs abundance in TME.[252] Furthermore, Chen's group integrated macrophage-targeted CAR NPs (pCAR-NPs) with CD47 antibodies and incorporated them into a hydrogel to treat glioblastoma and prevent recurrence by injection. The pCAR-NPs induced the polarization towards M1 phenotype and increased the secretion of TNF-α and IL-1β by M1 macrophages without significant toxicity in the mouse model.[253] These studies demonstrate the broad prospects of genetically engineered macrophages in cancer treatment and the potential of nanocomplexes to encounter the challenges of CAR-M, including facilitating the manufacture, enhancing the therapeutic effects and decreasing the risk in production and treatment.

Other genetically modified macrophages also excel in phagocytosing antigen-coated particles and cancer cells. Unlike CAR engineering methods, these cells can stably transduce at tumor sites, producing anti-immunosuppressive and immunostimulatory cytokines, providing new avenues for cancer immunotherapy.[287] Jiang et al fused tumor suppressor proteins with penetrable peptide genes and used macrophages as bioreactors to specifically colonize tumor sites and express antitumor macromolecular protein drugs, achieving significant tumor suppression and improving protein drug delivery efficiency.[254]

NPs coated with macrophage cell membrane have shown promise in treating metastatic tumors.[288] Researchers designed a macrophage-like nano system named macrophage-membrane-coated emtansine liposomes that can selectively target lung metastatic sites, achieving efficient drug delivery, superior anti-metastatic effects, and significant inhibition of lung metastasis.[240] Circulating tumor cells (CTCs) migrating through the circulatory system are a critical factor in tumor metastasis. However, their low abundance in the blood and nonspecific binding to leukocytes hinder their effective capture.[241] To address this, researchers designed a nanoplatform utilizing electrostatic interactions to bind macrophage membranes with NPs, which were composed of magnetic composites with positive charge and covered with azide-coupled membrane carrying negative charge. This biomimetic immune magnetosome excels in recognizing EPCAM+ tumor cells. The macrophage membrane coating on its surface also reduces nonspecific adsorption to leukocytes in the blood.[241]

Phototherapy

Phototherapy is a kind of cancer therapy applying external light source, generally near-infrared light (NIR), to trigger heat effect or chemical reactions of materials injected into tumor sites, which can kill tumor cells with high selectivity, optimal efficacy, and limited side effects and toxicity in normal tissues.[78] Given its features, phototherapy is not only utilized in treating primary tumors but also applicable in diminishing metastatic tumors and preventing cancer recurrence or metastasis.[289,290] NPs coated with macrophage cell membranes play a crucial role in adjuvant phototherapy for improved biocompatibility and precise targeting to tumors. In photothermal therapy (PTT), the NP core serves as a photothermal agent, absorbing NIR and producing heat effect, effectively damaging tumor cells and causing their demises. Fe_3O_4 NPs are widely used in PTT due to their remarkable light absorption properties and heat generation capabilities.[291] Recent studies have shown that coating macrophage-derived membrane vesicles on Fe_3O_4 NPs can

enhance the PTT effect on breast cancer.[243] Gold nanoshells (AuNSs) also possess ideal near-infrared absorption capabilities, and their integration with macrophage cell membranes targeting tumors can remarkably enhance the treatment effects of PTT in vivo.[292]

Combined cancer therapy aims to achieve more significant therapeutic effects than single-modality therapy. The concept of combining ICD and tailoring the immunosuppressive TME is applicable in cancer therapy, thus the integration of PTT and immunotherapy has demonstrated synergistic therapeutic effects in treating primary and metastatic cancers due to the effective ICD induced by PTT.[244,293] In this context, researchers have utilized macrophage-derived membrane-coated hollow gold nanocages loaded with galuniserib and functionalized with anti-PD-L1 antibodies to enhance therapeutic efficacy.[244] Additionally, the combination of PTT with chemotherapy has also demonstrated significant efficacy in hepatocellular carcinoma from animal models.[245] CuS NPs were loaded with sorafenib and coated with a hybrid membrane derived from macrophage-hepatoma cells. These NPs were then conjugated with VEGFR antibodies, resulting in the formation of NPs named CuS-SF@MCV. This combination significantly inhibited tumor growth and conferred immune evasion capabilities and tropism for homologous tumor cells.[245] A biomimetic nano system, which consisted of macrophage membrane modified with angiopep-2 loading indocyanine green (ICG) and chemotherapy agent SN-38, was utilized to treat glioma, which demonstrated an elevated ability to overcome BBB, accumulation in tumor sites, and synergistic treatment effectiveness of both PTT and chemotherapy.[294] In addition, NPs could also be internalized or attached to macrophages to be engineered as a macrophage-mediated drug delivery system through hitchhiking cells in vivo.[295] Liu et al engineered an apoptotic body (Ab) loaded with DOX and ICG for treating glioma. The Abs were able to cross the BBB through the hitchhiking effect after uptaken by macrophages, and the synergized chemotherapeutic and photothermal effects significantly prolonged the survival time in the orthotopic glioma mouse model.[296]

Photodynamic therapy (PDT) enhances anti-tumor immunity by delivering photosensitizers to tumor sites and activating them under laser illumination to generate ROS (particularly singlet oxygen), inducing photooxidative damage to tumor cells.[78,297–299] The NPs coated by macrophage cell membrane, or loaded by engineered macrophages, have been applied to PDT with the advantage of better tumor targeting ability. For instance, the engineered macrophages carrying photosensitizers and oxaliplatin prodrug were developed for primary and metastatic tumors. The engineered macrophages were M1-polarized to effectively target both primary and bone metastatic tumors, and the tumors were further killed through the PDT-mediated ICD effect, which brought the promise in combining immunotherapy for better therapeutic effects.[300]

Similar to PTT, the ROS-induced ICD through PDT makes it possible for the combined of PDT, immunotherapy, and chemotherapy, which provides a new synergistic biomimetic approach in augmenting the therapeutic effects and combating different cancers.[246] For instance, NPs coated with polarized M1 macrophage cell membranes, loading DOX, photosensitizer CeG, and IDO1 inhibitor IND, could significantly inhibit primary tumor growth and recurrence through the ROS-induced tumor eradication and ICD triggered by PDT and IDO1 inhibition.[246] Kang et al also designed a nanoplatform camouflaged with macrophage cell membrane, containing aggregation-induced emission luminogen (AIEgen) and a hypoxia-responsive PTX, for tumor imaging and combined therapy, which not only accelerated the exhaustion of oxygen and the release of PTX through PDT but also induced ICD to inhibit the growth of primary and metastatic tumors by the released PTX and generated ROS.[248] A rational design of NP could also allow the combination of PDT and PTT under a single NIR irradiation regardless of the difference in inherent excitation wavelengths of the two types of phototherapy.[293] For instance, NIR-absorbing CuS, in combination with PTX and M1 macrophage membrane coating, can form NPs named as PTX@CuS@MM, achieving triple combination therapy of chemotherapy, PDT, and PTT, effectively destroying and eliminating metastatic breast cancer cells.[301] This integrated treatment approach demonstrates the tremendous potential and promise of nanomedicine in cancer therapy.

Cancer Bioimaging and Other Theranostics

Precise localization prior to cancer treatment is crucial, and tumor imaging is a pivotal approach in achieving this objective.[302] Currently, techniques like magnetic resonance imaging (MRI) and fluorescence imaging are extensively

employed in cancer diagnosis. Materials like upconversion NPs (UCNPs) have garnered attention due to their unique optical properties, good photostability, limited toxicity and deep penetration capabilities in tissues. However, a major challenge faced by these technologies is the lack of tumor-specific targeting and local delivery capabilities of contrast agents in vivo.[249] To overcome these challenges, NPs coated with cell membranes have been extensively explored as biomimetic nano messengers for delivering imaging agents to certain pathologic locations, facilitating local and metastatic tumor bioimaging.[302,303] In an innovative research, macrophage-derived membrane vesicles were used to encapsulate UCNPs, resulting in macrophage cell membrane-coated UCNPs (MMUCNPs). Compared to uncoated UCNPs, MMUCNPs demonstrated superior tumor cell uptake, biocompatibility in vivo, prolonged persistence time, and improved fluorescence intensity in tumors. These results implicate that imaging nanoprobes mimicking macrophages have great potential in optimizing in vivo fluorescence imaging of tumors.[249] Additionally, a microfluidic mixing platform was developed to produce macrophage membrane-derived nanovesicles, with high loading capability of ICG and better tumor targeting ability for tumor imaging in brain and glioma.[304]

Despite radiotherapy and phototherapy, sonodynamic therapy (SDT) is another emerging therapeutic method utilizing external energy to activate antitumor efficacy by producing bioactive species, such as ROS, and it could deeply penetrate into tumor sites by ultrasound with negligible damage to normal tissues and lower cost, which is especially suitable for tumors with significant difficulties in drug delivery and surgical process like glioma. The macrophage membrane coating nano systems enables the targeted transportation of sonosensitizers to tumor sites to overcome the BBB and hypoxic condition in TME with higher biocompatibility and prolonged half-life of circulation. The nanoplatforms encapsulated by macrophage membrane or M1-exos were discovered to be able to release chemical agents after delivered to tumors, like HIF-α siRNA or catalase, to alleviate tumor hypoxia and improve SDT efficiency in glioma.[305,306] Moreover, Shan et al integrated SDT and ICB by developing a biomimetic NP cloaked with macrophage membrane and loaded with both Ce6 (sonosensitizer) and JQ1 (an inhibitor to down-regulate PD-L1 expression). The ROS produced by SDT could not only directly damage malignant cells but also could trigger the immunogenic death of tumors, which served as a cooperation with JQ1 for elevated antitumor immunity to achieve a cascade effect of SDT and immunotherapy.[307]

With the continuous advancement of cell-mimetic nanotechnology, macrophage cell membrane-coated NPs have emerged as multifunctional nanocarriers for therapeutics. They can integrate both diagnosis and treatment into a mere nano system.[308] Recently, notable advancements have been achieved in the development of therapeutic nanoplatforms capable of simultaneously achieving tumor imaging and treatment, which successfully transport therapeutic and imaging agents to certain tumor sites.[309,310] Various nanoplatforms based on macrophage membrane were developed to combine cancer imaging with different treatment strategies, such as chemotherapy and phototherapy.[311–313] Furthermore, utilizing the principles of biomimetic therapeutic nano systems, scientists have also engineered a multifunctional NP resembling macrophages to deliver both therapeutic drugs and imaging agents. The objective is to monitor the status of tumor cells and to prevent lung metastasis in real-time and in vivo.[250]

Conclusion and Perspective

Over the past decades, macrophage-mediated therapies have undergone impressive development for various disease with extensive inflammatory components, including cancer. Macrophages have been strategically employed in cancer therapy, primarily through two approaches: one uses TAMs as immunotherapy targets, and the other utilizes adoptive engineered macrophages and membranes as biological products and drug delivery tools in tumor therapy. Nanotechnology has promoted the development of macrophage-mediated tumor therapy in many aspects, such as macrophage modification, drug delivery assistance, and coordination of multiple therapeutic methods. Despite the considerable progress in basic research, some challenges remain to be addressed for the widespread clinical application of macrophage-based therapies in cancer. The following discusses the challenges and future prospects of macrophage-based cancer therapy.

Despite the promising anti-tumor advantages of macrophage-based strategies documented in various researches, the impact of macrophages on tumors remains controversial, primarily because of the intricacy of the TME, the highly dynamic distribution of TAMs and perhaps the limited understanding of the intrinsic characteristics during the whole life of macrophages. It is still a crucial area of inquiry to clarify the underlying mechanisms of macrophage's diversity, activity and evolution across various tissues including tumors. Further fundamental studies on the molecular and single cell level can elucidate the effects of macrophages on tumors, providing new perspectives for the development of macrophage-directed strategies.[30,314]

In clinical settings, numerous investigations have corroborated the close association between TAMs and resistance to diverse cancer treatment modalities. Specifically, TAMs have been found to contribute to chemotherapy resistance across various types of cancer,[315,316] while the polarization and presence of M2 macrophages may significantly undermine patient's benefits after radiotherapy.[317] Furthermore, TAMs maintain an immunosuppressive environment through impeding the infiltration of cytotoxic T cells, meanwhile sustaining the functionality of MDSCs and Tregs, thereby being intricately related to intrinsic/adaptive resistance to immunotherapy.[318] Therefore, we propose TAM-targeting immunotherapy as a complementary approach rather than an independent treatment. On the one hand, macrophage-mediated tumor immunotherapy alone is insufficient to eliminate tumors. On the other hand, rectifying the dysfunction of TAMs to reconstruct the TME can offer a combined effect to overcome treatment resistance, especially through the amplification of ICD effect. This approach requires meticulous design of combination therapies tailored to their characteristics and the dynamics of the TME to achieve synergistic effects and minimize severe side effects.[319–323]

The high off-target effect caused by non-specific macrophages poses a major obstacle for macrophage-targeted immunotherapy. While reprogramming inducers can repolarize TAMs in the TME towards a proinflammatory population to promote inflammatory responses, these agents may also induce M1 macrophage infiltration in normal tissues, leading to undesired excessive autoimmune responses. Macrophages expressing specific receptors are present in other normal tissues, and some M2 macrophage phenotypic markers are also shared with dendritic cells or other cells in the immune system, complicating the precisely targeting of TAMs for nanodrugs. Moreover, the complex immune microenvironment and the extracellular matrix in tumor tissues affect the transportation of nanodrugs within tumors and the approachability of TAMs.[324] The rational design of nano systems to precisely target and regulate TAMs with high efficacy for cancer immunotherapy is paramount, which requires more consideration of nanomaterial properties and the molecular mechanisms for drugs targeting TAMs to improve pharmacokinetics, enhance delivery stability and accuracy, achieve effective accumulation around tumors, and minimize systemic toxicity.[325–327]

The use of engineered macrophages in therapeutic applications has shown considerable promise for clinical applications,[42] yet two major challenges remain to be overcome for clinical translation: the establishment of large-scale production with stringent quality control and potential biosafety concerns during production and clinical use. To enable widespread clinical use, it is imperative to prompt techniques for large-scale production of macrophages, while maintaining quality control for human macrophages remains a big challenge. The absence of standardized protocols for macrophage selection, extraction and purification can result in inconsistent batch-to-batch outcomes, necessitating the development of reliable detection techniques to assess macrophage characteristics.[328–331] In addition, a long-term conservation of engineered macrophage's or macrophages cell membrane's biological activity, along with reduced toxicity of loaded drugs to macrophage transporter and the maintenance of M1-like phenotype, is a big concern while designing the macrophage-engineered therapeutic agents.[331] The properties of macrophage membranes also bring safety concerns. The presence of immune-related molecules, like MHCs, on macrophage membranes can easily lead to immune rejection and safety issues. Therefore, macrophages should be autologously derived from each patient and genetically modified to exclude side effects by editing genes related to immune responses.[221,332] From another perspective, during the preparation of engineered macrophage membranes, the membranes are prone to damage, potentially leading to loss of membrane protein functions and strong immune responses from damaged membrane markers. The development of optimized protocols for macrophage cell membrane coating is a critical procedure towards the clinical application of those biomimetic nano systems.[333] Consequently, future developments in these nano systems will focus on enhancing their ability to target tumor cells with prolonged circulation time, better cellular interactions, smoother drug release, and limited systematic cytotoxicity in vivo, and addressing those mentioned limitations is very essential before they can be successfully integrated into clinical practice.[221,261]

Following the successful implementation of CAR-T therapy in clinical settings, CAR-engineered macrophage therapy also holds significant anticipation for clinical translation. Despite promising results demonstrated by CAR-M therapy in recent years, the generation of modified therapeutic macrophages remains a challenging task. CAR-Ms exhibit remarkable phagocytic activity and tumor killing ability in vitro, but they often have comparative limited effects on tumor progression in vivo. Intravenous injection of CAR-Ms at limited cell doses often results in limited infiltration of macrophages into tumor sites due to organ sequestration, such as in the liver, kidney, and lung, indicating their limited ability of expansion and potential off-target cytotoxicity in vivo.[252,280,334] Additionally, CAR-M's inhibitory effect on

metastatic tumors is not satisfactory. Ongoing research efforts are being directed towards ameliorating the composition and structure of CAR molecules to bolster their mechanical strength and anti-tumor ability.[335] There is evidence suggesting macrophages derived from iPSC enable large-scale production of therapeutic cells. Since pluripotent stem cells are commonly amenable to genetic modifications, optimizing the core molecules of CAR-M effects by gene editing can facilitate the advancement of innovative therapies.[336,337] In addition, monocytes, macrophage's precursor, are being considered in some projects instead of using macrophages directly in CAR engineering.[338] Considering the synergy of innate and adaptive anti-tumor immunity, it is reasonable to develop CAR-Ms in conjugation with CAR-Ts. Macrophages can primarily reduce the toxicity of cytokines released by CAR-Ts, including IL-6, and exhibited the ability to undermine the possibility of cytokine storms.[339] Meanwhile, CAR-T cells produce IFN-γ and demonstrate their potent ability to transmit co-stimulatory signals and activate macrophages, laying the foundation for a potential combination of engineered cell therapy in the future.[340] Moreover, the potential of integrating CAR-M with conventional therapies, like radiotherapy, chemotherapy, or other targeted drugs, is also worth exploring. Finally, there are some clinical and preclinical trials about CAR-M in recent years (Table 3). Most of them are in the early stages, and the consequences of some trails starting earlier are not ideal. Therefore, there is still significant progress required for the clinical application of CAR-Ms. With advancements in tumor immunology and CAR technology, the clinical landscape will witness the development of next-generation CAR-M therapies with more sophisticated design, construction, and evaluation.

Generally, there are a variety of promising outcomes from macrophage-based cancer therapies in basic research, but only a few of these have been approved for clinical applications. To overcome the obstacles in the clinical practice of macrophage-based cancer treatment, more considerations are required. To a large extent, the translation of a technique from laboratory to clinical settings, and even commercialization, relies on its feasibility for large-scale treatment, clinical application to production, along with a clear understanding of underlying mechanisms and robust evidence of clinical

Table 3 Overview of Current Clinical Studies Related to CAR-Macrophages

Product Names	NCT Number	Study Type	Macrophage Sources	Tumor Type	Molecular Targets	Location	Initial Year	Status
MCY-M11	NCT03608618	Clinical Trial (Phase I)	Peripheral blood mononuclear cells (PBMC)	Refractory/relapsed ovarian cancer and peritoneal mesothelioma	Mesothelin	United States	2018	Terminated
CT-0508	NCT04660929	Clinical Trail (Phase I)	Autologous monocyte-derived macrophages	HER2 overexpressing solid tumors	HER2	United States	2021	Active, not recruiting
CT-0525	NCT06254807	Clinical Trail (Phase I)	Autologous monocyte-derived macrophages	HER2 overexpressing solid tumors	HER2	United States	2024	Recruiting
MT-101	NCT05138458	Clinical Trial (Phase I/II)	mRNA-engineered myeloid cells	Refractory/ relapsed peripheral T-cell lymphoma	CD5	United States	2021	Suspended
MT-302	NCT05969041	Clinical Trial (Phase I)	mRNA-engineered myeloid cells	Advanced/metastatic epithelial tumor	TROP2	Australia	2023	Recruiting
Human anti-HER2 CAR-M	NCT06224738	Clinical Trail (Early phase I)	Autologous monocyte-derived macrophages	HER2 positive advanced gastric cancer	HER2	China	2024	Not yet recruiting
N/A	NCT05007379	Cohort Study	N/A	Against organoids from breast cancer patients	N/A	France	2021	N/A
CT-1119	N/A	Pre-clinical study	Primary human macrophages	Mesothelin positive solid tumor	HER2	United States	N/A	Pre-clinical
CAR-iMAC	N/A	Pre-clinical study	Human iPSC-derived macrophages	Hepatocellular carcinoma	EGFRvIII, GPC3	China	N/A	Pre-clinical

safety and efficacy to obtain regulatory approval. Meanwhile, nanomaterials have demonstrated their ability to deliver therapeutic agents, thereby enhancing the outcomes of macrophage-based therapies. Given the unique capability of nanomaterials to translate the signals of disease and the surrounding microenvironment into the changes of functional properties like sizes and conformation, the combination of nanoplatforms with the innovative technologies will be greatly likely to promote more intelligent, safe and effective macrophage-based cancer therapies.

Abbreviations

Ab, apoptotic body; ADCP, antibody-dependent cellular phagocytosis; AFP, alpha fetoprotein; AIEgen, aggregation-induced emission luminogen; ALN, alendronate; ALN-BSP, bisphosphonate alendronate-dextran; AuNRs, gold-silver nanorods; AuNS, Gold nanoshell; BBB, blood–brain barrier; BTK, bruton's tyrosine kinase; CAR-T, chimeric antigen receptor T-cell; CAR-M, chimeric antigen receptor-modified macrophages; CCL, C-C motif chemokine ligand; CCR, C-C motif chemokine receptor; Ce6, chlorin e6; cGAMP, cyclic GMP-AMP; cGAS, cyclic GMP-AMP synthase; ChiP-RS, chimeric peptide engineered bioregulator; CLO, clodronate; CSF, Colony Stimulating Factor; CTC, circulating tumor cell; CTL, cytotoxic T Lymphocyte; CXCL, C-X-C chemokine ligand; DC, Dendritic cell; DNV, nanovesicles loaded with DOX; DOX, doxorubicin; DSPG, distearoylphosphatidylglycerol; DXS, dextran sulfate; EGFR, epidermal growth factor receptor; ELE, Elemene; EPR, enhanced permeability and retention; EV, extracellular vesicle; Hb, hemoglobin; HIF-1α, hypoxia-inducible factor 1α; HMGB1, High Mobility Group Box 1; IBR, ibrutinib; ICAM-1, intercellular adhesion molecule-1; ICB, immune checkpoint blockade; ICD, immunogenic cell death; ICG, indocyanine green; IL, interleukin; IND, indoximod; IFN-γ, interferon-γ; iPSC, induced pluripotent stem cell; LOD, lactate oxidase; M1-exos, M1-macrophages derived exosome; M2pep, M2-macrophage binding peptide; MDSC, myeloid-derived suppressor cell; MEL, macrophage-membrane-coated emtansine liposomes; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MMUCNPs, membrane-coated UCNP; MPS, mononuclear phagocytic system; MRI, magnetic resonance imaging; mTOR, mechanistic target of rapamycin kinase; Nb, nanobody; NIR, near-infrared light; NK, natural killer; NP, nanoparticle; o-MWCNT, oxidized multiwalled carbon nanotubes; pCAR, plasmid CAR; PDT, photodynamic therapy; PEG, poly ethylene glycol; PI3K-γ, γ isoform of Phosphatidylinositol 3-kinase; PLA, poly lactate; PLGA, poly (lactic-co-glycolic acid); POx-Man, polyoxazoline-mannose; PTX, paclitaxel; PTT, photothermal therapy; R848, resiquimod; R837, imiquimod; ROS, reactive oxygen species; SA, sialic acid; SDT, sonodynamic therapy; SHP-2, Src homology 2 tyrosine phosphatase 2; siRNA, short inference RNA; siCCR2, CCR2-siRNA; siCD115, CD115-siRNA; siMCT4, anti-MCT-4 siRNA; Siglec, sialic-acid-binding Ig-like lectin; SR-A, scavenger receptor A; STAT, Signal Transducer and Activator of Transcription; STING, stimulator of interferon genes; Syr, syrosingopine; TAM, tumor-associated macrophages; TGF-β, transforming growth factor-β; TME, tumor microenvironment; TLR, toll-like receptor; Treg, regulatory T cell; UNNP, upconversion nanoparticle; VCAM-1, vascular cell adhesion molecule-1; VEGF, Vascular Endothelial Growth Factor.

Consent for Publication

Informed consent for publication was received from all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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