Nanoscale

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Nanoscale*, 2020, **12**, 413

Tumor immune microenvironment modulation-based drug delivery strategies for cancer immunotherapy

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Received 19th September 2019,
Accepted 25th November 2019

DOI: 10.1039/c9nr08086d

rsc.li/nanoscale

The past years have witnessed promising clinical feedback for anti-cancer immunotherapies, which have become one of the hot research topics; however, they are limited by poor delivery kinetics, narrow patient response profiles, and systemic side effects. To the best of our knowledge, the development of cancer is highly associated with the immune system, especially the tumor immune microenvironment (TIME). Based on the comprehensive understanding of the complexity and diversity of TIME, drug delivery strategies focused on the modulation of TIME can be of great significance for directing and improving cancer immunotherapy. This review highlights the TIME modulation in cancer immunotherapy and summarizes the versatile TIME modulation-based cancer immunotherapeutic strategies, medicative principles and accessory biotechniques for further clinical transformation. Remarkably, the recent advances of cancer immunotherapeutic drug delivery systems and future prospects of TIME modulation-based drug delivery systems for much more controlled and precise cancer immunotherapy will be emphatically discussed.

Introduction

Cancer is one of the major diseases threatening public health worldwide although some advanced early diagnosis and clinical treatments have significantly increased the number of cancer survivors. Tumor-promoting inflammation and the suppression of antitumor immunity are gradually being realized as the impetus of cancer genesis and progression.[1] Thus, cancer immunotherapy is now developing as the fourth most important cancer therapy modality after surgery, radiotherapy and chemotherapy for precise and efficient cancer treatment.[2] Different from conventional cancer treatment strategies to directly suppress the malignant growth of tumor cells, cancer immunotherapy intends to actively or passively impact the immune system for attacking and finally eliminating targeting cancer cells through natural innate or adaptive mechanisms.[3] Several strategies and techniques for cancer

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immunotherapy have already emerged and gradually become mature, mainly involving the following aspects: (1) applications of immunomodulatory molecules or engineered immune cells, typically some cytokines or chemokines and modified immune cells (such as CAR-T cells).[4,5] These exogenous factors and cells can be equipped with the ability to participate in and control the immune environment to achieve immunotherapy. (2) Stimulations from immune drugs (such as antigen and adjuvant-derived cancer vaccines) to reactivate self-regulation of the immune system.[6] Cancer immunotherapy aims to manage and operate the body's own immune system to target tumor sites and eradicate cancer cells without large physical trauma and normal tissue destruction. Besides, clinical trials for systematic diseases or metastatic cancers have also been developed, proving the attractive potential of immunotherapy.[7]

Despite the many remarkable advantages accompanied with satisfactory therapeutic efficacy achieved, there still exist clinical failures and obstacles in cancer immunotherapy. For example, the delivery kinetics is limited and thus, countless patients with different tumor types have experienced minimal or even no clinical success.[8] Therefore, the comprehensive understanding of diversity, variety and complexity of the tumor immune microenvironment (TIME) and the relationship between its regulatory mechanism and treatment modality is of great significance. Compared to the general tumor microenvironment (TME)-responsive tumor targeting therapy, it is supposed that profound TIME-modulatory strategies focusing more on the immune conditions within the patient's tumor are able to enhance the therapeutic effect of cancer immunotherapy to a greater extent. The ultimate purpose of tumor immunotherapy directed at TIME modulation is to deliberately achieve optimized immune attack or defence towards cancerous sites based on delivering traditional immunotherapeutic agents, improving the bioavailability of immune drugs and reducing various side effects in immunotherapy, thus overcoming the dilemma of clinical cancer treatment tolerance caused by immunosuppression and immune escape in the TIME. A variety of biomaterial-derived drug delivery systems have shown unprecedented potency in TIME control and tumor immunotherapy due to their excellent physiochemical and biological characteristics. With the assistance of biomaterial supports, pharmaceuticals can be readily targeted to the TIME and gain protection by carrier materials for beneficial immune regulation.[9] Moreover, diverse drug delivery systems with tunable physiochemical properties (*e.g.* size, shape, and surface performance) or multiple functions can also be exquisitely designed and constructed to promote inhibitory or stimulatory actions towards the immune system and even generate synergistic effects for combined cancer immunotherapy.[10,11] The last few years have witnessed a variety of efficient and multifunctional TIME modulation-based drug delivery systems for immunotherapy based on different administration methods, and subsequently developed with distinct therapeutic trial achievements.[12]

This review will briefly introduce the TIME first to show the importance of the TIME towards cancer immunotherapy. In the past decades, a series of promising target sites in TIME and relevant immune regulation mechanisms have been discovered and explored, establishing a solid foundation for rationality and feasibility of cancer immunotherapy. The second section will summarize the versatile TIME modulation-based cancer immunotherapeutic strategies, medicative principles and accessory biotechniques subsequently designed or invented together with higher specificity and lower biotoxicity for further clinical transformation. Finally, the recent advances of cancer immunotherapeutic drug delivery systems will be categorized into mainly nanoscale and microscale carriers with some macroscale systems mentioned. Finally, the prospects and future concern of TIME modulation-based drug delivery systems for much more controlled and precise cancer immunotherapy will be highlighted and discussed (Fig. 1).

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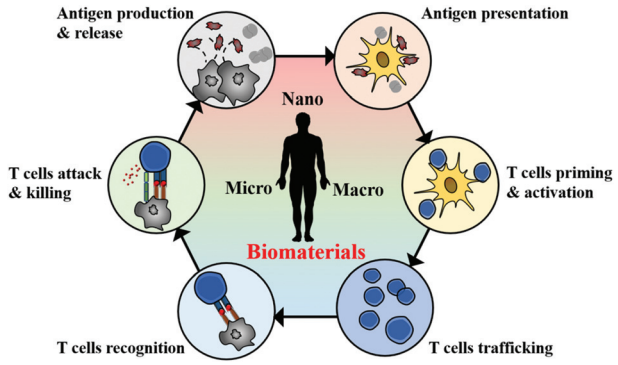

Fig. 1 Overview of the biomaterials for TIME modulation-based immunotherapy and the cycle of cancer and immunity.

Tumor immune microenvironment

As a major scientific breakthrough over the years, tumor immunotherapy has become the most promising cancer treatment.[13] However, clinical studies have shown that a large number of patients are not sensitive to immunotherapy, which has been proved to be related to the heterogeneity of the TME.[14] In the process of tumor development, the TME interacting with tumor cells can lead to the immune tolerance of tumors, thus affecting the clinical effect of immunotherapy and becoming the focus of cancer research.[15] Besides tumor cells, the TME consists of immune cells, cancer-associated fibroblasts (CAFs), extracellular matrix (ECM) and signaling molecules, which can be roughly divided into nonimmune components and immune components. The immune components are mainly based on different types of immune cells and constitute the TIME.[16] In this section, the typical immune cells existing in the TIME, the classification of TIME and the functions and significance of TIME modulation are discussed.

Typical cellular components of TIME

In the TIME, the immune cells infiltrate and secrete inflammatory cytokines, forming the highly heterogeneous inflammatory microenvironment. The components of immune cells are complex and diverse, including T lymphocytes and B lymphocytes from the adaptive immune system, as well as macrophages, natural killer (NK) cells and dendritic cells (DCs) belonging to the innate immune system.

T lymphocytes. T cells play a pivotal role in the immune response as a crucial type of lymphocyte developed in the thymus gland with various immune-associated functions. The primed CD8+ T cells with the cardinal interactions among DCs, NK cells and CD4+ T cells can be activated to form effector cytotoxic T lymphocytes (CTLs), which can release granules or induct Fas ligand (FasL)-mediated apoptosis to kill cancer cells with the presence of major histocompatibility complex (MHC) class I molecules.[17] However, by the regulatory cells recruitment, such as regulatory T cells (Tregs), and the production of molecules such as interleukin (IL)-10 and transforming growth factor-β (TGF-β) to suppress antitumor T cell responses, tumors can escape detection, and thus lead to an immunosuppressive microenvironment and destroy the T cell responses.[18–20] Remarkably, as a subset of CD4+ T lymphocytes, Tregs with the expression of IL-2 receptor (CD25), cytotoxic T lymphocyte antigen-4 (CTLA-4), and forkhead Box P3 (Foxp3), can lead to immunosuppression by inhibiting the proliferation and differentiation of T cells, blocking antigen presentation and even directly mediating the death of targeted cells.[21–24] By enhancing co-inhibitory molecules or immune checkpoints on T cells, such as CTLA-4 and programmed cell death-1 (PD-1), T-cell response modulation can even be beneficial to tumor growth.[25–28] Recent research focused on blocking T cell exhaustion, enhancing the specific immune responses of T cells, reversing these changes and preventing naive CD4+ T cells from being recruited to tumor sites and transformed into induced Tregs (iTregs).[29–31]

Macrophages. Macrophages infiltrate inflamed tissues and are developed from bone marrow mononuclear precursor, which move to various tissues and are activated by stimulation signals into different subsets with different functions.[32,33] Remarkably, macrophages recruited by local tumors, which are often referred to tumor-associated macrophages (TAMs) and provide functionalities similar to M2 macrophages, can contribute to the malignant progression of tumors.[34] TAMs can secrete factors such as basic fibroblast growth factor (bFGF), vascular endothelial growth factor A (VEGF-A), urokinase-type plasminogen activator (uPA) and adrenomedullin (ADM), benefiting tumor angiogenesis, invasion and metastasis.[35,36] The interaction between TAMs and tumor cells form a vicious cycle, accelerating tumor metastasis.[37] Increasing clinical studies have confirmed that the poor prognosis in cancer patients may be associated with TAM infiltration.[38–40] However, in view of the anti-tumor immune function of M1 macrophages and the plasticity of macrophages, reversing the transformation of TAM from M2 to M1 phenotype has great potential for enhancing tumor immunotherapy.[41,42] In addition, blocking the recruitment of TAMs in tumors can also be expected to become a new target for future tumor treatment.

Other cells. With their fantastic as ability antigen presenting cells, DCs have been recognized as a key factor in antitumor immunity.[43–45] DCs can sample the microenvironment to provide antigens and co-stimulatory signals for the adaptive immune system.[46] However, DCs possess large defects, which may even contribute to tumor immune suppression, although they have good potential to promote antitumor responses.[47,48] As cytotoxic immune cells, NK cells with a complex pattern of receptors kill a broad range of cancer cells, together with the release of cytotoxic perforin and granzymes.[49–53] Unfortunately, tumor cells can also downregulate NK cells, activate receptors and shed NK cell activating ligands (NKARLs) to develop immune evasion, which are also associated with tumor metastasis.[54] Myeloid-derived suppressor cells (MDSCs) are a group of cells with immunosuppressive functions, including myeloid progenitor cells and immature myeloid cells, which can inhibit T cell responses.[55] A variety of

cytokines produced by tumor cells can induce proliferation and mediate the immunosuppressive effects of MDSCs, such as selective cyclooxygenase-2 (COX2), IL-6, granulocyte macrophage colony stimulating factor (GM-CSF), and VEGF.[56–61] Studies have also found that MDSCs can secrete IL-1β and tumor necrosis factor-α (TNF-α) to promote tumor cell proliferation by activating the mammalian target of the rapamycin (mTOR) signaling pathway.[62,63] Mast cells (MCs), as immune cells derived from bone marrow hematopoietic progenitor cells, are widely distributed in the human body.[64–66] MCs under pathological conditions release a variety of growth factors such as fibroblast growth factor-2 (FGF-2), VEGF and TGF-β to promote tumor angiogenesis, affecting tumor invasion and metastasis.[67] Studies have confirmed that tumor cells expressing stem cell factor (SCF) can recruit MCs to the primary tumor site and promote the development of early stage tumor by releasing regulatory factors such as matrix metalloproteinase 9 (MMP9) and VEGF.[68] Remarkably, MCs can also interact with MDSCs to enhance the immunosuppression of MDSCs and synergistically release cytokines such as IL-6, IL-13, TNF-α and macrophage inflammatory protein 1α (MIP-1α).[69,70] In addition, the cells in TIME possess cell–cell interactions with not only tumor cells but also cells such as CAFs found around the tumor sites, which can promote the growth and invasiveness of tumor cells by various mechanisms.[71]

Classification of TIME

Thus far, with the development of immunotherapy, a lot of work has been focused on the measurement of TIME and a large amount of information collected, making the classification of TIME possible.[72–76] Overall, the TIME can be broadly classified into three types based on the immune infiltrate composition and the inflammatory response[77,78] (Fig. 2).

Infiltrated–excluded TIMEs (I–E TIME). I–E TIMEs refer to the TIMEs with a large number of immune cells but lack of CTLs infiltrating into the core site of the tumor.[79,80] CTLs are mainly localized along the margin of tumor cells or stuck in fibrotic nests, expressing less activation markers GZMB (GRZB) IFNG.[81] Meanwhile, Ly6Clo F4/80 TAMs can be observed along the tumor margins and be deemed to have an effect on preventing CTL from infiltrating into the core site of the tumor.[82] Tumors with I–E TIMEs are considered to be in a state of immunological ignorance with poor immunogenicity, which is immunologically 'cold' tumors, suggesting by the lack expression of activation-marker and exclusion of CTL infiltration.[83] Thus far, I–E TIMEs have been frequently found in various epithelial cancers, such as melanoma, pancreatic ductal adenocarcinoma, and colorectal carcinoma.[84,85]

Infiltrated–inflamed TIME (I–I TIME). Oppositely, immunologically 'hot' tumors with high infiltration of CTLs are referred to as infiltrated–inflamed TIMEs.[86] The tumor cells express the immune-dampening PD-1 ligand PD-L1, while the infiltrated CTLs express PD-1.[87] For example, patients with microsatellite instability-high (MSI-H), a subset of colorectal cancer (CRC), have prominently higher responses to immune

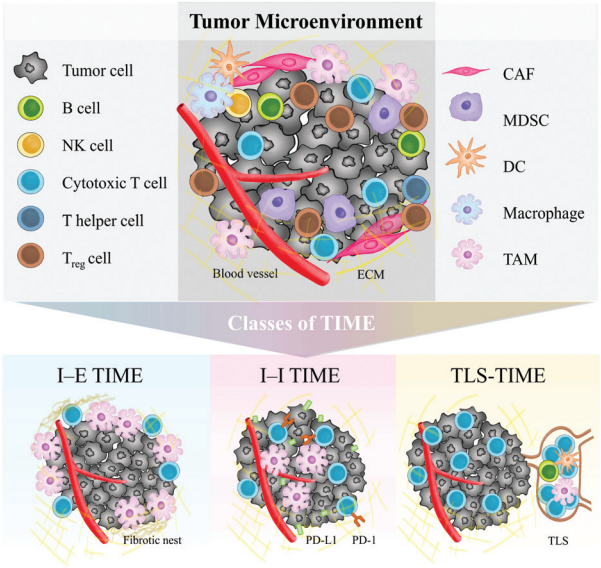

Fig. 2 Tumor microenvironment (TME) and the classes of tumor immune microenvironment (TIME) including infiltrated-excluded TIME (I–E TIME), infiltrated-inflamed TIME (I–I TIME) and TIME with tertiary lymphoid structures (TLS-TIME).

checkpoint blockers (ICBs) than those with microsatellite instability low (MSI-L) or microsatellite stable (MSS) since the tumors of MSI-H possess nonsynonymous single-nucleotide polymorphisms in a higher rate, resulting in an increase in the number of tumor-infiltrating PD-1+ CTLs and neoepitopes.[77]

TIME with tertiary lymphoid structures (TLS-TIME). As a subclass of I–I TIMEs, TLS-TIMEs can be characterized by tertiary lymphoid structures (TLSs) as significant histological evidence.[88] The cellular composition of lymphoid aggregates in TLS-TIMEs is similar to that in lymph nodes (LNs). TLSs in TLS-TIMEs contain lymphocytes including conventional T cells, Treg cells, B cells and DCs, and tend to a positive prognosis most of the time.[89,90] TLSs are mostly observed at the margin or stroma of invasive tumors, and are considered as sites for immune activation.[91] The TLS-TIMEs usually form with the efforts of enhanced inflammation, such as treatment with autologous tumor vaccines.

Functions and significance of TIME modulation

The TIME classification represents the immune composition and status in the tumor. Thus, determining which anti-tumor immunodeficiency is dominant in each patient can play a key role in clinical cancer treatment. The in-depth study of the TIME development and the relationship between TIME and tumors, monitoring the characteristic changes in the TIME and identifying specific relevant indicators in TIME modulation can benefit the early detection of tumors, the choice of treatment strategies and even prognosis analysis for patients.[77,92] Moreover, the classifications of TIME can enhance the understanding of how mutation load, oncogenes, and different tumor types affect the establishment and maintenance of specific immune compositions. Obviously, using

the same strategy for all cancer patients will be inefficient, expensive and wasteful. For example, targeting a local immunosuppressive pathway such as the B7 homolog 1 (B7-H1)/PD-1 pathway as a monotherapy in a patient with a cancer that lacks immune infiltration may be meaningless. Further investigation of TIME can help to develop new immune targets and give appropriate medication strategies for patient with specific TIME types, even resetting TIME, from the initial highly inhibitory TIME to a highly active site of inflammation, or normalized the immunization in the tumor site, thereby effectively treating cancer.

At the same time, increasing studies indicate that the current studies of inferring the state of T cells or macrophages with only one or two proteins will likely miss important information.[93] For a better guiding significance with TIME in cancer treatment, it is necessary to conduct more in-depth and comprehensive monitoring of the dynamic changes of each component in the TIME and a thorough investigation of the interaction between the TIME component and other tumor-associated components. At the same time, due to the importance of TIME components and immune biomarkers in determining prognosis and response to treatment, TIME and immune scores should be included in the part of clinical assessment, which may bring significant breakthroughs in cancer treatment.[94]

Drug or drug delivery systems participating in TIME modulation

Immunotherapy drugs for TIME modulation

Immunotherapy has established new paradigms for the management and treatment of diseases, leading to lots of breakthroughs in clinic, especially for cancer treatment. The key of immunotherapy is to take advantage of the immune microenvironment to eliminate diseased cells or protect healthy cells through numerous coordinated pathways, resulting in enhanced or normalized immune responses, thus curing the disease and rebuilding tissues.[95] Cancer immunotherapy is a form of emerging cancer treatment that takes advantage of the immune system to prevent and eliminate cancer. Different types of cancer immunotherapy, including targeted antibodies, cancer vaccines, adoptive cell transfer (ACT), tumor-infecting viruses, checkpoint inhibitors, cytokines, and adjuvants, focus on the different parts of TIME, following the same goal to eliminate cancer.[96–98] Immunomodulators are molecules acting on a pathway to regulate the activity of the immune system. The immunomodulators can be broadly classified into four categories: checkpoint inhibitors, cytokines, agonists, and adjuvants. The role of checkpoint inhibitors is to block immune checkpoints, referred to the "braking" of the immune system, which are often manipulated by tumors to suppress the immune response and protect tumor tissues.[99] Thus, checkpoint inhibitors can unleash new immune responses and enhance existing responses to promote the elimination of cancer cells. For example, the PD-1/PD-L1 immunological checkpoint pathway can shut down T cells that target cancer, while a checkpoint inhibitor blocking the PD-1/PD-L1 pathway can reflash T cells to eliminate cancer cells. The checkpoint inhibitors are probably the most widely known and most successful immunomodulators ever developed.[100–106] Targeted antibodies are a form of cancer immunotherapy that can destroy cancer cell activity and regulate the TIME to target and eliminate cancer cells.[107] Once antibodies bind to cancer cells, they destroy pathways that are important for tumor cells, such as those that allow tumor cells to grow uncontrollably. These antibodies can also regulate related immune cells in the TIME to eliminate cancer cells. Targeting antibodies can be divided into three types: monoclonal antibodies (mAbs), antibody–drug conjugates (ADCs), and bispecific antibodies.[107–110] The first bispecific antibody, binatumomab, was approved by the FDA in 2014 for a subgroup of leukemia patients. Blinatumomab is known as the bispecific T cell conjugate (BiTE) because it is designed to bind cancer cells as well as T cells, which can make T cells move close to cancer cells and subsequently eliminate cancer cells.[111] Cancer vaccines can enhance the recognition of tumor cells by relevant immune cells at the TIME, and thus increase the elimination of tumor cells.[112,113] The cancer vaccines developed thus far can be divided into preventive cancer vaccines, therapeutic cancer vaccines and personalized neoantigen vaccines. Preventive vaccines play an important role in reducing the risk of infection. For example, cervical cancer and head and neck cancer can be caused by human papillomavirus (HPV), while liver cancer can be caused by the hepatitis B virus or HBV. Several vaccines have been developed to prevent HBV and HPV infection, and thus prevent related cancers.[114–119] The therapeutic cancer vaccine, sipuleucel-T vaccine, was developed and approved by the FDA in 2010 for the treatment of patients with advanced prostate cancer.[117] Meanwhile, adoptive cell therapy (or cell immunotherapy) is become a promising treatment that eliminates cancer by increasing the amount or enhancing the anti-cancer ability of natural immune cells.[120,121] Adoptive cell therapies are primarily involved in tumor-infiltrating lymphocyte (TIL) therapy, engineered T cell receptor (TCR) therapy, CAR-T cell therapy, and NK cell therapy.[122–130] Moreover, oncolytic virus therapy is an immunotherapy that uses a virus to infect and destroy cancer cells.[131] The FDA approved the first oncolytic virus immunotherapy to treat melanoma in 2015.[132] The various cancer immunotherapies and related drugs for various cancer types can be found in Table 1.

Despite these advances, immunotherapy used in clinic is still limited to a small number of diseases with off-target toxicity, unpredictable efficacy and lack of durability.[133] These challenges make improving the existing immunotherapy by gene editing, cell manufacturing, and materials engineering necessary.[134] Among them, a specific drug delivery system combined with proper designed materials and biotechniques can be one of most effective and economical options to improve the effectiveness of cancer immunotherapy with promising potential for further clinical transformation.[135]

Table 1 . Treatment options and targets under evaluation in clinical trials for immunotherapy treatment[101–117,128–132]

Immunotherapy treatment types		Treatment options	Targets/composition	Approved for	Targets under evaluation in clinical trials
Immunomodulators	Checkpoint inhibitors	Atezolizumab (Tecentriq®)	PD-1/PD-L1 pathway	Bladder cancer and lung cancer	• CD40
		Avelumab (Bavencio®)	PD-1/PD-L1 pathway	Bladder cancer and Merkel cell carcinoma, a type of skin cancer	• CD47
		Cemiplimab (Libtayo®)	PD-1/PD-L1 pathway	Cutaneous squamous cell carcinoma, a type of skin cancer	• CD73 or A2AR
		Durvalumab (ImfinziTM)	PD-1/PD-L1 pathway	Bladder cancer and lung cancer	• CD137
		Ipilimumab (Yervoy®)	CTLA-4 pathway	Melanoma	• CSF1/CSF1R
		Nivolumab (Opdivo®)	PD-1/PD-L1 pathway	Bladder cancer, colorectal cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, lymphoma, and melanoma	• CTLA-4
		Pembrolizumab (Keytruda®)	PD-1/PD-L1 pathway	Bladder cancer, cervical cancer, colorectal cancer, esophageal cancer, head and neck cancer, liver cancer, lung cancer, lymphoma, melanoma, and stomach cancer	• CXCR4
	Cytokines	Aldesleukin (Proleukin®)	IL-2/IL-2R pathway	Kidney cancer and melanoma	• GITR
		Interferon (IFN) alpha-2a	IFNAR1/2 pathway	Leukemia and sarcoma	• ICOS
		IFN alpha-2b (Intron A®)	IFNAR1/2 pathway	Leukemia, lymphoma, melanoma, and sarcoma	• IDO
		Peginterferon Alfa-2b (Sylatron®/PEG-Intron®)	IFNAR1 pathway	Melanoma	• IL-2/IL-2R
	Agonists and adjuvants	Poly ICLC (Hiltonol®/ Imiquimod)	TLR7 pathway	Squamous cell carcinoma	• LAG3
					• OX40
					• PD-1/PD-L1
					• STAT3
					• STING
					• Toll-like receptors (TLRs)
Targeted antibodies	Monoclonal antibodies	Alemtuzumab (Campath®)	CD52 pathway	Leukemia	• Angiopoietin
		Bevacizumab (Avastin®)	VEGF/VEGFR pathway	Brain cancer, cervical cancer, colorectal cancer, kidney cancer, lung cancer, and ovarian cancer	• BCMA
		Cetuximab (Erbitux®)	EGFR pathway	Colorectal cancer, and head and neck cancer	• CD19
		Daratumumab (Darzalex®)	CD38 pathway	Multiple myeloma	• CD20
		Denosumab (Xgeva®)	RANKL pathway	Sarcoma	• CD22
		Dinutuximab (Unituxin®)	GD2 pathway	Pediatric neuroblastoma	• CD25 (also known as IL2-R)
		Elotuzumab (Empliciti®)	SLAMF7 pathway	Multiple myeloma	• CD30
		Necitumumab (Portrazza®)	EGFR pathway	Lung cancer	• CD33
		Obinutuzumab (Gazyva®)	CD20 pathway	Leukemia and lymphoma	• CD37
		Ofatumumab (Arzerra®)	CD20 pathway	Leukemia	• CD38
		Olaratumab (Lartruvo®)	PDGFRα pathway	Sarcoma	• CD52
		Panitumumab (Vectibix®)	EGFR pathway	Colorectal cancer	• CD56
		Pertuzumab (Perjeta®)	HER2 pathway	Breast cancer	• CD123 (also known as IL-3R)
		Ramucirumab (Cyramza®)	VEGF/VEGFR2 pathway	Colorectal cancer, esophageal cancer, liver cancer, lung cancer, and stomach cancer	• cMET
		Rituximab (Rituxan®)	CD20 pathway	Leukemia and lymphoma	• DLL/notch
		Trastuzumab (Herceptin®)	HER2 pathway	Breast cancer, esophageal cancer, and stomach cancer	• EGFR

Table 1 *(Contd.)*

Immunotherapy treatment types		Treatment options	Targets/composition	Approved for	Targets under evaluation in clinical trials
	Antibody–drug conjugates	Brentuximab vedotin (Adcetris®)	CD30 pathway	Lymphoma	• EpCAM
		Gemtuzumab ozogamicin (MyloTarg®)	CD33 pathway	Leukemia	• FGF/FGF-R
		Ibritumomab tiuxetan (Zevalin®)	CD20 pathway	Lymphoma	• GD2
		Inotuzumab ozogamicin (Besponsa®)	CD22 pathway	Leukemia	• HER2
		Moxetumomab pasudotox (Lumoxiti®)	CD22 pathway	Leukemia	• Mesothelin
		Polatuzumab vedotin (POLIVYTM)	CD79b pathway;	Lymphoma	• Nectin-4
		Trastuzumab emtansine (Kadcyla®)	HER2 pathway	Breast cancer	• PDGFRα
	Bispecific antibodies	Blinatumomab (Blincyto®)	CD19 on tumor cells as well as CD3 on T cells	Leukemia	• RANKL
					• SLAMF7
					• TROP2
					• VEGF/VEGF-R
Cancer vaccines	Preventive	Cervarix®	HPV types 16 and 18	Prevent the development of HPV-related anal, cervical, head and neck, penile, vulvar, and vaginal cancers	• 5T4
		Gardasil®	HPV types 16, 18, 6, and 1	Prevent the development of HPV-related anal, cervical, head and neck, penile, vulvar, and vaginal cancers	• CEA
		Gardasil-9®	HPV types 16, 18, 31, 33, 45, 52, and 58	Prevent the development of HPV-related anal, cervical, head and neck, penile, vulvar, and vaginal cancers	• Cytomegalovirus (CMV)-related antigens
		Hepatitis B (HBV) vaccine (HEPLISAV-B®)	Hepatitis B virus	Prevent the development of HBV-related liver cancer	• Folate-related proteins
	Therapeutic	Bacillus Calmette-Guérin (BCG)	Weakened bacteria	Early-stage bladder cancer	• EGFR
		Sipuleucel-T (Provenge®)	Patients' own stimulated dendritic cells	Prostate cancer	• HER2
					• Human Papilloma Virus (HPV)-related antigens
					• MAGE antigens
					• Mesothelin
					• MUC-1
					• NY-ESO-1
					• P53
					• PAP and PSA
					• Personalized neoantigens
					• Ras
					• Survivin
					• Telomerase
					• Tumor-associated antigens
					• WT1

Table 1 *(Contd.)*

Immunotherapy treatment types		Treatment options	Targets/composition	Approved for	Targets under evaluation in clinical trials
Adoptive cell therapy	CAR T cell therapy	Axicabtagene ciloleucel (Yescarta®)	CD19	Lymphoma	• BCMA
		Tisagenlecleucel (Kymriah®)	CD19	Leukemia and lymphoma	• CD19 • CD22 • CD30 • CD33 • CD56 • CD123 (also known as IL-3R) • CEA • Epstein–Barr Virus (EBV)-related antigens • EGFR • GD2 • GPC3 • HER2 • Human Papilloma Virus (HPV)-related antigens • MAGE antigens • Mesothelin • MUC-1 • NY-ESO-1 • PSCA • PSMA • ROR1 • WT1
Oncolytic virus therapy		T-VEC (Imlygic®)	Modified herpes simplex virus (HSV) that infects tumor cells and promotes their destruction.	Melanoma	• Adenovirus • Herpes simplex virus • Maraba virus • Measles • Newcastle virus • Picornavirus • Reovirus • Vaccinia virus • Vesicular stomatitis virus

Drug delivery systems for TIME modulation

A variety of drug delivery platforms have been developed to take advantage of the characteristics and overcome the deficiencies of immunotherapeutic drugs, including nanoparticles (NPs), implants, biomaterial- and cell-based platforms, for better therapeutic effect. Drug delivery vehicles can help to solve the problem of drug delivery and off-target side effects in various immunotherapies, expanding immunomodulation, integrating the synergy of different molecules, and helping with homing and manipulating immune cells.

Different drug delivery strategies can be used with different cancer immunotherapy strategies for the optimal therapeutic effect.[136] For immunomodulators, biomaterial scaffolds can load cytokines, antigens and adjuvants to recruit and subsequently program specific cells. For porous biomaterial scaffolds, a good balance between pore size suitable for drug loading and cell interaction, release kinetics of immunomodulators, and degradability of biomaterial scaffolds is important. Among the numerous drug delivery platforms, nanomaterials improve the stability, pharmacokinetics, and tumor accumulation of checkpoint inhibitors, potentially leading to an enhanced anti-tumor effect with reduced systemic side effects. Meanwhile, delivery systems with different nanomaterials can also be beneficial to the therapeutic effect of traditional chemotherapy, radiation therapy and even combination therapies besides checkpoint block therapy. In the case of cancer vaccines, the drug accumulation in LNs can be enhanced in the presence of nanomaterials, which can also improve CTL and humoral responses by delivering them to DCs with controlled release. For nanomaterials as vehicles, their composition, size and even surface properties are important. With ideal nanomaterials, cancer vaccines will exhibit excellent biocompatibility with proper stability, optimal accumulation and retention in LN, as well as effective DC uptake. For adoptive cell therapy, biological materials are often used to accelerate cell proliferation and improve cell viability to minimize treatment time and save cost, while maintaining or even enhancing T cell functionality. Meanwhile, the same cancer immunotherapy strategy can be performed with different drug delivery strategies, leading to different therapeutic effects. For example, designing nanoparticles to directly target cancer surface receptors can improve the retention of nanoparticles in tumors, while local delivery using injectable materials or implantable scaffolds can achieve higher drug accumulation.[137]

Different routes of administration also affect the ultimate therapeutic efficacy, which require consideration of not only the TIME in the tumor, but also the actual operability and convertibility. Even in the same delivery strategy, the type of material, the size of the drug carrier, and the surface physicochemical characteristics (surface structure, charged charge, *etc.*) can have effects on the delivery of the drugs.

Overall, nanoscale materials are expected to improve the mechanisms by which immunomodulatory payloads are targeted and infiltrated into specific tissues. Microscale materials can promote the transport mediated by artificial antigen presenting cells. Meanwhile, macroscale materials tend to form an artificial microenvironment that promotes the infiltration of cells and immunotherapeutic drugs to exert therapeutic effects. Moreover, the same material may show different immunomodulatory effects at different sizes. For example, polycaprolactone (PCL), a types of synthetic polyester, can be naturally degraded *via* ester bond hydrolysis under physiological conditions.[138] PCL with nanoporous features has been proved to increase the *in vivo* inflammation in fiber capsules.[139] Study also shown that PCL with a small nanoparticle size can lead to the increased expression of IL-10 and IL-12 in macrophages, while larger PCL particles do not.[138] Meanwhile, poly(lactic-*co*-glycolic acid) (PLGA) is a biodegradable polymer with mechanical strength and biocompatibility is widely used as a drug delivery material.[140] However, the by-products of PLGA degradation (lactic acid and glycolic acid) reduce the pH of surrounding tissues and cause pro-inflammatory effects. PLGA microparticles have been proven to up-regulate TNF-α and IL-lβ in macrophages, indicating a pro-inflammatory state, while PLGA nanoparticles do not induce any of these effects.[141] Furthermore, the molecular weight of a material also affects its immune response of materials. For example, DCs treated with low molecular weight (MW) PLGA nanoparticles would be in an immunosuppressive phenotype, presumably caused by the release of immunosuppressive lactic acid.[142] Hyaluronic acid (HA) is a particulate coating material widely utilized in cancer treatment due to its capability to target CDs. HA possesses immunomodulatory effects, which largely depend on the MW. At high MW (>1000 kDa), HA has an anti-inflammatory effect, whereas at a low MW (<10 kDa), HA can be pro-inflammatory.[143] Remarkably, at the time of injury, HA with high MW is broken down to HA with low MW, which tends to activate the innate immune response. Meanwhile, the same material with different concentrations sometimes lead to different immune responses. For example, carbon nanotubes (CNTs), as allotropes of carbon, possess anti-inflammatory effects, but in some cases lead to pro-inflammatory effects.[144] Macrophages treated with low concentrations of graphene oxide NPs showed the increased expression of IL-6, CCL3, CCL4 and CCL5. However, at high concentrations, the same NPs were found to produce cytotoxicity.[145]

For the materials used in drug delivery systems, various researches have focused on how they improve the biodistribution (*e.g.*, cycle time, tissue homing and tissue penetration), sustainability (*e.g.*, degradation properties and stability of materials), and efficacy (*e.g.*, their interaction with TIME and their synergy with cancer immunotherapeutic drugs) of drugs. The main materials currently used in preclinical studies, especially those that are intrinsically activated or inhibited by the immune system, have been initially investigated to better function in drug delivery systems.[137] In the next part, a few latest advanced biomaterials-based TIME-modulation immunotherapeutic systems will be profiled and summarized.

Drug delivery platforms for TIME modulation-based cancer immunotherapy

The implementation of personalized strategies for delivering immune-related drugs including specific molecules or cells strongly depends on the elaborate design of supporting systems together with the development and appropriate applications of proper techniques. Biomaterials-based drug delivery platforms with the capacity of efficient loading, targeted delivery and successful release of drugs have achieved increasingly outstanding success in the preclinical period of TIME modulation-based cancer immunotherapy.[146] Since a myriad of complicated biomolecular, cellular and physical processes are broadly experienced during tumorigenesis and its further development, drug loading systems ranging from nanoscale and microscale to macroscale exhibit unique own characteristics. For example, nanoscale biomaterials have the capability of size-dependent passive targeting towards tumor tissues and promoting the permeation of loading immunomodulators, and with further surface modification and shape transformation, nanoscale particles can be endowed with specific responsibility suitable for TIME command. Also, microscale biomaterials are at a similar scale to influence or even serve as artificial antigen-presenting cells to facilitate self-immunity, macroscale biomaterials can be made into somatic cells, which can straightforwardly produce various shapes or formations, constructing biomimetic matrices locally or even *in situ* to govern the sophisticated tumor sites.[147]

More importantly, biomaterials-based pharmaceutical agent delivery systems are easily tunable in the aspects involving components, shapes, elasticity, surface charges and chemical groups, inner structures, *etc.* for mastering TIME modulation. Over the recent few years, increasing superb immunotherapy formations have been reported from certain responsive to dual sensitive systems, from individual treating strategies to combination immunotherapies, and from separate treatment to versatile theranostic integration. Also, many different administration routes have been proposed for more convenient, accurate and friendly cancer immunotherapy. In this part, some typical drug carrying techniques and methods applied in TIME modulation-based cancer immunotherapy will be itemized and introduced, including their research progress, superiorities and remaining challenges.

Nanocarrier strategies for immunotherapy drug delivery

The prosperous development of nanotechnology offers more possibilities and opportunities for nanomedicine in cancer immunotherapy. The conventional drug nanocarriers used in practical drug delivery hugely depend on nanoscale biomaterials, which are materials at the scale from 1 to about 200 nm, and can be broadly applied in cancer diagnosis and therapy.[148] These materials with good biocompatibility and low cytotoxicity can prolong the drug blood retention and circulation time, protect payloads against rapid metabolization, selectively

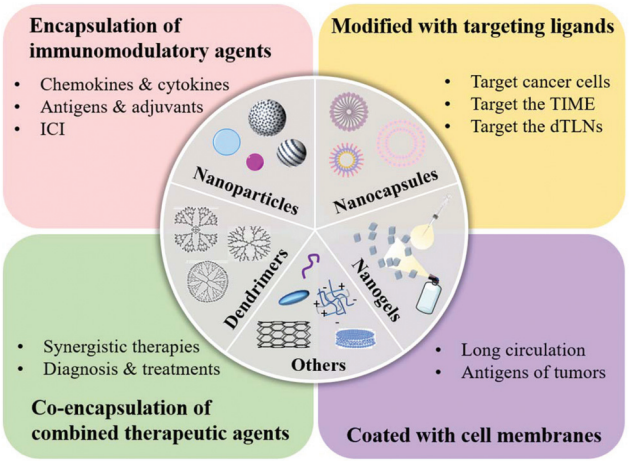

Fig. 3 Nanomaterial-based platforms and strategies for cancer immunotherapies.

target tumor sites and promote their specific penetration and distribution.[149–152] Moreover, nanomaterials are easily armed with tailored physiochemical properties and desirable features based on their own components and structures,[153] functional groups, size and shape, and chemical bonds or surface modification,[154] enriching the applications in the field of tumor theranostics.[155,156] Therefore, this set of materials accounts for the largest part in the field of immune biomaterials research. Nevertheless, some rigid challenges and obstacles still exist, which need to be settled. For instance, immune-related toxicities may emerge due to the lack of specificity in immunomodulatory agents such as checkpoint inhibitors in which the nanocarriers play a role as a guide and guard. However, nanocarriers sometimes have negative functions either underlying off-target effects generating nano toxicity or intrinsic characteristics activating the self-immune response and subsequent attack.[157] In this context, a series of specific nanomaterial-derived treatment strategies have been developed for efficient immunotherapy and their preclinical success encouragingly drives the clinical transformation of immune nanomedicine. This section will be divided into several parts based on the types of nanocarriers and list some of the innovative works with their design principles and advancements made in the design of nanomaterials for cancer immunotherapy (Fig. 3).

Nanoparticles/nanogels. NPs are one of the most common nano modalities widely investigated.[158] In this part, the NPs mainly refer to organic particles. According to the formation and structure of NPs, two main pillars of NPs, namely organic NPs (*e.g.* polymeric NPs and cationic lipid assemblies) and nanogels (*e.g.* synthetic polymers and natural biomacromolecules[159]), have attracted great interest to be explored for the abovementioned different strategies for better applications in cancer immunotherapy.[160]

Conventional immunostimulatory or immunosuppressive therapies are dependent on the efficient delivery and effective function of exogenous antigens and adjuvants or antibodies. The applications of nanovaccines are one of the primary

branches. Increasing attention is focused on the positive co-delivery of antigens and adjuvants and improvement in sufficient immune response with the assistance of the NP systems. Linhua Zhang *et al.* fabricated novel lipid-polymer hybrid nanoparticles from PCL-PEG-PCL polymers and cationic lipid DOTAP with DSPE-PEG-mannose loading both OVA and TLR 7/8 and TLR 4 dual agonists.[161] Multifunctional nano cancer vaccines can promote remarkable DCs targeting and maturity, and benefit the trafficking to secondary lymphoid organs, inducing more antigen-specific CD8+ T cells.

The delivery or stimulation of immune checkpoint inhibitors for prompting ICB therapy based on NPs also plays an important role in cancer immunotherapy. Ni Zhang *et al.* constructed PEG and peptide surface-modified PLGA NPs loading anti PD-1 antibody (aPD-1), iron oxide and perfluoropentane (PFP) for combined photothermal immunotherapy. The PTT-induced immunogenicity and aPD-1-supported immune checkpoint blockade synergistically increased the tumor-specific immune response *via* CD8+ T cell infiltration and T cells immune reinvigoration in TIME.[162]

As mentioned above, TIME modulations hugely rely on immune cells. Due to DC maturation, T cell activation and TAM repolarization, MDSC modulation may become an alternative for cancer immunotherapy. Zhe Wang synthesized a type of c-RGD-decorated conjugated polymer for combined photothermal immunotherapy.[163] PTT-induced TAAs release enhanced T cell activation and cytokine secretion and triggered the proinflammatory polarization of TAMs for more efficient antitumor immunity.

Besides the previous classical spherical NPs, numerous other unique nano shapes have received certain attention to be used under these TIME modulation strategies, including nanostructures containing nanocages, nanoclusters, nanocrystals, nanocubes, nanodiscs, nanorings, nanorods, nanowires and nanoworms since size and shape specificity can reveal distinctive functions or effects. For example, one synergetic multifunctional nanocomposite was developed with multiple components added to the nanocarriers by Qiujun Qiu and coworkers.[164] Sialic acid-stearic acid conjugate modified nanocomposites were designed to selectively deliver the irreversible Bruton's tyrosine kinase (BTK) inhibitor Ibrutinib to TAMs. Huu Thuy Trang Duong and coworkers, in a different way, fabricated pH-sensitive copolymeric nanocubes for co-delivering the chemotherapeutic drug DOX and antigen OVA for chemoimmunotherapy.[165] Kuai Rui and coworkers developed nanodiscs imitating high-density lipoprotein for efficiently carrying both antigen peptides and adjuvants.[166] Together with aPD-1 and anti-CTLA-4(aCD47) therapy, the nanodiscs can give rise to more exhaustive tumor elimination.

Encouragingly, some bioactive molecules themselves are able to self-assemble into immunomodulatory agents, participating in the immune activation in TIME. With the assembly of multi-components, the nanostructures can act as both therapeutic vehicles and treatment drugs. Yuchuan Yuan and coworkers reported a type of carrier-free nanocrystal aggregate from indomethacin, a COX-2 inhibitor, and PTX by forceful intermolecular interactions strengthening the combined chemoimmunotherapy.[167] Qian Chen and coworkers directly generated ROS-induced protein nanocomplexes for the controlled release of aCD47 and aPD-1, which could reverse the immunosuppressive circumstances by specific TME stimulation.[168] Jinrong Peng and coworkers developed photo-chemo-immune tri-modality therapy by assembling drugs, dyes and peptides together for optimum tumor suppression.[169] Another nanocage was designed by Wenjun Shan and coworkers *via* the hepatitis B core protein (HBc) with OVA antigen conjugated on the surface.[170] The engineered OVA-HBc nanocages loaded with the chemotherapy agent PTX realized enhanced combination cancer therapy.

Additionally, the exploration of the relationship among size effects, properties and antitumor functions of nanomaterials has gradually aroused wider interest. Thus, a comprehensive study will be helpful for providing future guidelines to design TIME-targeted cancer immunotherapy systems; however, there are still not enough many related studies. In-depth rod-shape scale effect research was reported by Xiupeng Wang and coworkers.[171] The hydroxyapatite nanorods coupled with antigens with lengths ranging from 100 nm to 10 μm were all investigated, presenting marked antitumor immune responses on account of the different modes. The shorter length proved to enhance the cellular uptake of antigens by APCs, DC maturation and lymph node target activating T cells, and the longer length was shown to prolong antigen retention and DC accumulation and antigen presentation to prime the T-cell immunity. Eventually, the nanorods with a length of 500 nm possessed the optimal immune response for antitumor treatment.

Nanogels, as hydrophilic nanocarriers, exhibit high biocompatibility and flexibility, and thus have become one of the most significant nanovehicles for drug delivery. They can be made from natural biomaterials such as polysaccharides, peptides, and nucleic acids and synthetic polymers such as PEG or PNIPAM and their composites.

Ce Wang *et al.* fabricated amphiphilic galactosyl dextran-retinal (GDR) nanogels with hydrazone bond-based pH-sensitivity and galactosylation-based DC-targetability.[172] The GDR nanogels could provoke retinoic acid receptor (RAR) signaling to accelerate DC maturation and antigen release and then promote MHC I antigen presentation to activate antitumor immunity. The pH-triggered lysosome rupture directly upregulated the intracellular ROS level, facilitating antigen cross presentation. Therefore, the self-adjuvanted multifunctional immunotherapeutic carriers delayed tumor development, showing favorable tumor treating efficacy. Dandan Li and partners utilized cationic dextran to construct vaccine nanogels.[173] The disulfide bonds are conjugated in the gel network to elicit the redox-responsive release of the entrapped antigen OVA and adjuvant. The antigen-induced tumor-specific immunity and prolonged survival in mice.

A type of pH-degradable polymeric nanogel was developed by Lutz Nuhn *et al.* with the intention to passively diffuse the TLR 7/8 agonist imidazoquinoline toward lymph node activat-

ing superior antibody and T-cell immune response.[174] The research showed that the novel nanogels provide a potential platform for small-molecule TLR agonist delivery. Another successful trial was carried out by Xudong Zhang and co-workers, who selected PNIPAM nanogels to co-deliver autophagy inhibitors (chloroquine) and DOX, limiting breast cancer to a great extent.[175]

Furthermore, Qian Chen *et al.* recently described a brand new sprayed bioresponsive gel for postoperative treatments.[176] aCD47 antibodies were loaded in the inorganic calcium carbonate ($CaCO_3$) NPs and then fully encapsulated in the fibrin gels, which can be fast formed during synchronous spraying and mixing of fibrinogen with aCD47@$CaCO_3$ NPs or thrombin. The host innate and adaptive immune systems could be actively aroused for overall postsurgical cancer therapy.

Countless novel strategies and biomaterials have emerged for improving TIME-modulatory cancer immunotherapy. Table 2 briefly summarizes and lists the latest advanced NP systems derived from different biomaterials and based on personalized therapeutic strategies.

Liposomes/micelles. Nanocapsules refer to core–shell structural particles self-assembled from amphiphilic biomaterials, in which lipid-derived vesicular particles are representatives. Spherical lipid monolayer vesicles are named micelles and the bilayer ones are well known as liposomes. As nanoscale particles, liposomes/micelles also encounter many biological obstacles during *in vivo* circulation and some of them such as immunogenicity, inflammatory or allergy responses, phagocytosis and blood clearance can even have adverse immune effects, hindering vesicular functionalization. However, their major merits have been validated, for instance, their amphiphilic regions enable the transport of high payloads of hydrophobic or hydrophilic drugs, protect agents inside from harsh environments and directly or indirectly join in immunomodulation, and their structures are biomimetically similar to cell membranes, thus considerable works based on liposomes and micelles in cancer immunotherapy are still emerging.[177]

Han Young Kim and co-coworkers prepared a class of liposomes embedded with lipid adjuvants for immunotherapy and coated with a photosensitizer (KillerRed, KR)-embedded cancer cell membrane (CCM) for synergistic photodynamic therapy.[178] The CCM with higher affinity to homotypic cancer cells caused the lipocomplex to targeting tumors, inducing stronger immunoregulation. In the tumor-bearing mice model, the functionalized liposomes successfully prohibited the tumor development and lung metastasis in the infant period. Another folate acid(FA)-modified matrix, metalloprotease-2-responsive DOX-loaded liposome, was synthesized by Caifeng Deng *et al.*, which could achieve the dual target of cancer cells and M2-tumor associated macrophages (M2-TAMs), resulting in immunogenic cell death (ICD).[179] With the CpG combined therapy, this liposomal tumor vaccine could significantly maturate the DCs and activate the systematic T cells immune response.

Other innovative liposomes aim to modulate the TIME using indirect approaches, but not acting as immune members straightway. Boyang Zhou with workmates constructed a new immune cell-recruiting liposome, which could enrich the immunocytes infiltration in the tumor site by antigen fragment generations and heat shock protein 70 exposure.[180] FA-decorated $NaHCO_3$-encapsulated liposomal systems will break out when CO_2 generates under the acidic TME to provide enough tumor antigens. The sufficient assembly of activated immune cells in the tumor could provide anti-PD-1 therapy with more effective antitumor outcomes. Similarly, Chao Liang *et al.* proposed a liposomal delivery strategy of internal radioisotope therapy (RIT) to reach the auxiliary purpose of improving second-wave cancer therapies including ICB immunotherapy.[181] One of the nanosystems showed that the designed iodine-131-labeled albumin-encapsulated liposomes have the capability to elevate the tumor-specific uptake of anti-PD-L1 therapeutic agents through enhanced tumor vasculature permeability and finally yield excellent synergistic treating effects. Also, Yanzuo Chen, under analogical tactics, chose to promote NPs vascular penetration to increase the local dose of cytotoxic drugs in the immunosuppressive TME for optimized cancer immunotherapy.[182]

The architecture of the liposomes mimicking cell membranes inspired Xue Liu and other researchers to design engineered cell-membrane-derived nanovesicles displaying full-length mAbs as arrows selectively targeting TAMs.[183] As biocompatible nanoplatforms, nanovesicles transport cargos including cytotoxic agents, immunomodulators, and others for the goal of surveilling and regulating the TIME. The applications of co-delivering both immune drugs and other chemotherapeutic or gene drugs or photosensitive or imaging agents will make combined cancer therapy be realized to further facilitate immunotherapy. The immunotherapeutic strategy depending on antibody-dependent cell-mediated cytotoxicity based on this nanovesicle has been evaluated, showing outstanding thorough tumor eradication.

Nanovesicles can be also made from amphiphilic materials containing polymers and protein. Zhuoya Wan with group members developed a polymeric prodrug delivery micelle with pendent indoximod, an indoleamine 2,3-dioxygenase (IDO) inhibitor, to burst immune suppression and the cargo of DOX to generate ICD.[184] The dual functions realized, DOX-induced ICD and indoximod clearance, gave rise to an increase in the intra-tumoral infiltration of CD8+ T cells, less immunosuppressive Tregs and more IFN-c-secretion. The breast cancer model verified that the DOX/POEG-*b*-PVBIND micelles remarkably improved the overall antitumor immunity. Alternatively, Fangyuan Zhou[185] utilized a polymeric nanovehicle co-delivering the oxaliplatin (OXA) prodrug and PEGylated photosensitizer together with CD47 blockade. ICD and CD47 blockade corporately brake the primary and abscopal tumors progression, prevent tumor metastasis and recurrence, which guarantee chemoimmunotherapy as a promising candidate for cancer therapy.

Dendrimers. Dendrimers are highly regular polymers endowed with reduplicative branched structures and plentiful cavities. They can be accurately controlled in volume, size,

Table 2 The latest advanced NP systems derived from different biomaterials and based on personalized therapeutic strategies

Types of biomaterials	Delivery nanocarriers	TIME immunomodulators	Key properties of nanoscale systems	Immunomodulatory strategies	Ref.
Natural biomolecules	Phospholipids	Melittin peptide with α-helical peptide (DWFKA-FYDKVAEKFKEAF-NH2)	Targets liver sinusoidal endothelial cells (LSECs); core–shell structures with the size of 20 nm	As an APC; cytotoxicity producing TAAs; activate LSECs avoiding immunologic tolerance	186
	DSPE-PEG(2000)-DBCO solid lipid	siRNAs against EGFR and PD-L1	A cyclic peptide iRGD (CCRGDKGPDC)-conjugated for targeting; combined radiation therapy and immunotherapy	Low-dose radiation improving cellular uptake; downregulation of PD-L1 and EGFR; T cells activation	187
	Lipid(cholesterol engaged)	Oxaliplatin(OxPt) and dihydroartemesinin (DHA)	OxPt in the core and DHA in the shell by cholesterol-DHA conjugate; with average diameters of 73.8–103.4 nm	Induce ICD and generate ROS for further promoting ICD; antigen presenting and T cells immune response; aPD-L1 synergistic supplementary therapy	188
	Mannosylated lactoferrin	Shikonin and JQ1	Dual-targeting to both cancer cells and TAMs; with a diameter of ~150 nm	Repress glucose metabolism; repolarize TAMs; promote DCs maturation and CD8+ T cell infiltration and Treg suppression; PD-L1 immune checkpoint blockades	189
	OVA with PEI	OVA and CpG ODNs	OVA NPs are antigens and carriers of CpG	Cancer vaccine; inspire immune response and IFN-γ production	190
	Modified γ-cyclodextrin	DOX and surface layer proteins (as natural antigen and adjuvants)	Cancer cell membranes coating; with a diameter of ~200 nm	Induce ICD producing TAAs; lymphocytes proliferation and activation, and cytokine secretion	191
	β-Cyclodextrin	Resiquimod (R848)	With a size of ~30 nm	Promote the polarization of TAMs to M1 phenotype	192
	HA and poly(AAm-*co*-AN)-PEG	Bovine lactoferricin	pH and thermal dual-sensitive; combined immunotherapy and microwave thermotherapy; with the diameter of 52.9 ± 1.31 nm	Induce ICD and tumor-specific immune responses based on damage-associated molecular patterns (DAMPs)	193
Synthetic polymers	PLGA	Imiquimod (R837) and catalase	With an enzyme in the inner core and an agonist within the shell; with the diameter of ~100 nm	Enhance radiotherapy by tumor hypoxia; postradiotherapy-generated TAAs-stimulated ICD; adjuvant-induced antitumor immunity	194
	PLGA	—	Glioma cells and human breast cancer cells membrane coating; with the size from 100 to 300 nm	Inhibit cancer cell-stromal cell interactions; to draining lymph nodes inducing an immune response	195
	DOTAP and soy lecithin	Sorafenib (SF) or TAM re-polarization agents IMD-0354	Mannose-modified targeting; pH-responsive *O*-carboxymethyl-chitosan (CMCS) coating; combined chemoimmunotherapy; with the size from 115 to 135 nm	Tumor vascular blockage and hypoxia construction; M2-type TAM repolarization and recruitment	196
	DOTAP and MPEG- poly (lactic acid) (PLA)	Chemokine (C–C motif) ligand 19 (CCL19) plasmid	Folic acid modified targeting; with the DLS size of 108 nm	Higher CCL19 expression in cancer cells after transfection; enhance DCs maturation, cytotoxic T lymphocytes activation and the macrophages polarization	197
	DOTAP and PEG-PLGA	siRNA and aPD1	Reduce lactate production and reverse acidic tumor microenvironment; combined gene and immunotherapy	Increase CD8+ T and NK cells infiltration in tumor site; PD-1 immune checkpoint blockades	198
	RGD-PEG-*b*-PGA-*g*-(TETA-DTC-PHis) block copolymers	Resiquimod (R848)	With copper chelation to antiangiogenesis; with the diameter of ~200 nm	Induce the maturation and activation of human plasmacytoid dendritic CAL-1 cells	199
	mPEG-PLGA-PLL triblock copolymers	Superparamagnetic iron oxide (SPIO) NPs and CpG ODNs	Photoacoustic (PA)/magnetic resonance (MR) dual-modal imaging and magnetic-selective combined photothermal immunotherapy; around 261.1 nm in size	PTT destroy the primary tumors release TAAs; CpG ODNs as adjuvants to improve vaccine immunity	200
	Triblock copolymers	DOX, 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a (HPPH)	PDT for ROS generation; combined photodynamic immunotherapy	Induce ICD producing TAAs; DC maturation and recruitment; increase CD8+ T cells in tumor tissues	201
	Nitrilotriacetic acid-related polymers, hemagglutinin (H1-NB)	OVA	Influenza virus-mimetic structure; with the similar diameters of 100–200 nm	OVA antigen delivery to DCs; DC maturation and T cells activation	202

Table 2 *(Contd.)*

Types of biomaterials	Delivery nanocarriers	TIME immunomodulators	Key properties of nanoscale systems	Immunomodulatory strategies	Ref.
Inorganic substrates	Mesoporous silica NPs	Glucose oxidase (GOx)	Cancer cell membranes coating; combined starvation therapy to release TAAs	TAA-induced DCs maturation; increase CD4+ and CD8+ T cells in tumor tissues	203
	NaYF4:Yb/Er@NaYF4:Nd upconversion NPs and DSPE-PEG-maleimide	Indocyanine green (ICG), rose bengal (RB), anti-CTLA-4	Combined phototherapy and immunotherapy; with the average diameter of 41 nm	Tumor-derived protein antigens produced by PTT and captured by DSPE-PEG-maleimide; the tumor antigen uptake and presentation by APCs	204
	Gold NPs	Resiquimod (R848)	With a size of ~5 nm	Transported to the tumor-draining lymph nodes; cultivate tumor-specific cytotoxic T-cell response	205
	Fe_3O_4 NPs with polymeric shells	Oxaliplatin (IV) prodrug	α-Enolase targeting peptide modified tumor targeting; immunogenic chemotherapy; magnetic resonance imaging(MRI)-guided; with an average hydrodynamic diameter of 24 nm	Prompt ICD by DNA lesions and ROS generation; DAMPs-based immune response	206
	PEGylated pure iron NPs (Fe NPs)	Anti-CTLA4 PLGA NPs and imiquimod (R837)	With a hydrodynamic size of ~100 nm	Magnetic hyperthermia (MHT) therapy for produce TAAs; DCs maturity and T cells activation; CTLA-4 immune checkpoint blockades	207

chemical functional groups, multivalent surfaces and molecular weight at the molecular level. The cavities naturally built in the dendritic architecture allow dendrimers to physically entrap or chemically conjugate pharmaceutical payloads (*e.g.*, genes, vaccines and antibodies) for immunotherapy with high efficacy. The well-defined repeating construction is beneficial to not only exponentially amplify immunogens for human vaccines and simultanesouly improve the immunogenicity of small antigenic substances, but also remarkably enhance the immune-targeting intensity.[208]

The naked poly(amidoamine) (PAMAM) as the paradigm, is a representative of the dendrimer family owning intrinsic immunomodulatory capability, which can be positively applies in tumor immunotherapy.[209,210] Pirouz Daftarian and coworkers further modified the fifth generation (G5)-PAMAM dendrimers with MHC II-targeting peptides on the surface to construct DNA nanovaccines.[211] The DNA–peptide–dendrimer complexes significantly improved the APC targeting, immunogenicity and transfection efficiency of naked plasmid DNA, making them more suitable for application in immunotherapy.

Kuo-Ching Sheng *et al.* synthesized an innovative immune promoter based on mannosylated dendrimer ovalbumin (MDO) augmenting the binding avidity to DCs.[212] The immunogenicity of MDO induced DC maturation in the lymph node, potentiated the antigen cross presentation and subsequently initiated the T cell immune response, which makes the mannosylated dendrimer a potential cancer vaccine delivery platform. Carlo Pifferi and workmates designed glycosylated cyclopeptide dendric scaffolds grafted with Tn and TF antigen analogues to serve as tumor-associated carbohydrate antigens (TACA)-based antitumor vaccines.[213] The nanocarriers can be recognized as cancer-related antigens to perform active immunological availability.

Inorganic nanoplatforms. The inorganic TIME-modulation nanosystems can be mainly classified into metal NPs, mesoporous silica NPs and carbon-based nanostructures. Inorganic nanomaterials generally have their own structural morphologies with intrinsic properties broadening their performances in biological and nanomedical applications. In addition to their role as constituents for drug delivery, different inorganic nanostructures are also likely to be photosensitizers, photothermal conversion agents, magnetic response sensors, and contrast agents, providing much more possibility to achieve synergistic immunotherapy or theranostic applications with the combination of photodynamic therapy, photothermal therapy, photoacoustic imaging, *etc.*

Iron-based NPs and gold NPs are two representative metal NPs. The magnetic response (magnetic targeting and imaging) of iron NPs enriches the practice of cancer immunotherapy. Xiaoli Liu and coworkers synthesized a ferrimagnetic nanoring, which will preclude tumor metastasis immunologically initiated by appropriate magnetic hyperthermia.[214] Another instance is the magnetic nanoclusters armed with aPD-1 prepared by Weidong Nie and coworkers.[215] The synergistic therapy was implemented through superparamagnetism magnetically recruiting activated T cells and MRI guidance-based

anti-PD-1 immune blockade. Gold NPs, as a TIME-modulation nanocarrier, have more obvious size and shape effects impacting the immunomodulatory capacity. Besides, they enable photoacoustics, optical imaging and photothermal therapy to be realized. Gold NPs are certainly pluripotent platforms for advanced cancer immunotherapy, and many effective trials have already been published. For instance, Rakeshchandra R. Meka *et al.* reported mannose-mimicking shikimoyl ligand (SL) conjugated gold NPs loading melanoma antigen (MART1) encoded DNA.[216] The DNA transfection of DCs for genetic immunization will induce an anti-melanoma immune response for immunotherapy.

Carbon-based nanostructures include graphene or graphene oxide nanosheets, carbon nanotubes, and carbon dots. Mengmeng Yan and coworkers engineered graphene oxide-based nanosheets with both IDO and PD-L1 inhibiters.[217] The multi-combined therapy of PTT, IDO inhibition and PD-L1 blockade powerfully achieved antitumor effects *via* evoking multiple pathways. Also, antigen-loaded aluminum oxyhydroxide-modified graphene oxide nanosheets were constructed by Xiaoli Wang and coworkers as a cancer vaccine holding both antigens and adjuvants.[218]

Other novel inorganic nanoplatforms are still being innovated worldwide. For example, Linnan Yang and coworkers developed a novel nanoplatform with layered double hydroxides loading miR155 for TAMs repolarization to modulate TIME.[219] Hanh Thuy Nguyen and coworkers established core–shell nanocomposites equipped with black phosphorus for photoimmunotherapy combined with additional photosensitizers or imaging agents, which enable the further perfection of diagnosis and treatment integration.[220] Prashant Sharma and coworkers creatively built nanoscale and microscale combined vehicles. Cancer antigens could be loaded in the poly(L-lactide) microfibers together with the growth of ZnO nanowires for promoting tumor-specific immune attack.[221]

Other drug delivery systems in nanomedicine. Some biomimetic or biological derivative NPs, such as virus-like NPs, virus-derived or cell-derived NPs open the door for nano immunotherapy. On the one hand, these pseudo-biological particles can imitate natural organisms to camouflage and maintain themselves for prolonged and stable circulation; on the other hand, their own side effects and immunogenicity should also be considered for better security. The engineered red blood cells (RBCs) are one of the most mature and popular selections. Eliran Moshe Reuven *et al.* generated engineered αGal knockout RBCs for *N*-glycolylneuraminic acid (Neu5Gc) TACA target, which presented a remarkable anti-Neu5Gc IgG immune response against Neu5Gc-positive tumors.[222]

Over the years, many TIME-modulation-related cells, such as immune cells (*e.g.* macrophages and DCs)[223] and direct cancer cells,[184,192] have been artificially reprogrammed or used membranes as carriers and stimulating antigens, developing another approach for specific individual immunotherapy.

Moreover, many organic–inorganic hybrid composites such as metal–organic frameworks (MOFs) or multiple combinations have been gradually emerged in enhanced and multifunctional cancer immunotherapy. Aiming to further provoke enhanced tumor necrosis, increasing combined therapeutic strategies together with some other synergistic treating agents have been developed and observed. One of the hybrid composites derived from both DCs and murine mammary carcinoma tumor (4T1) cells, fused cytomembranes and porphyrin-based Zr-MOFs, was designed by Wenlong Liu and coworkers.[224] The external coating from DCs and tumor cell fused cytomembranes maintained cancer antigens and immunological co-stimulatory molecules, which could target the tumor sites and stimulate TIME modulation. The inner MOFs acted as photosensitizers for PDT to produce ROS, inducing ICD, DCs maturation and T cell immunity. The unique system enlightens the future cancer treatment design for total elimination of both primary and distant metastasis tumors.

Microcarrier strategies for immunotherapy drug delivery

Microscale biomaterials open another new avenue for cancer immunotherapy.[225] Acting as a type of potential artificial antigen presenting cell (aAPC), microscale carriers have a mimetic size of pathogens and abilities to be engineered with pathogen-like features to promote the activities of immune cells, especially the expansion of T cells population for strongly enhancing the immunotherapeutic results. As is known, the property of particle size greatly influences the behaviour of drug delivery systems *in vivo*. Indeed, it is still controversial among some researches about the optimum particulate size range that can both activate high-efficiency and durable immune responses and avoid size effect-originating side effects in biosafety. In addition, the active binding to living cells may challenge the circulation stability and specific biodistribution, which also need some extra attention. Thus far, multifarious types of microcapsules manufacturing methods and techniques have been implemented providing more chances for optimizing the micro immunotherapeutic strategies.

Herein, in this section, several novel types of corresponding published works will be surveyed and summarized about the preparation, mechanisms and treatment effects of microscale systems used for immunotherapy (Fig. 4).

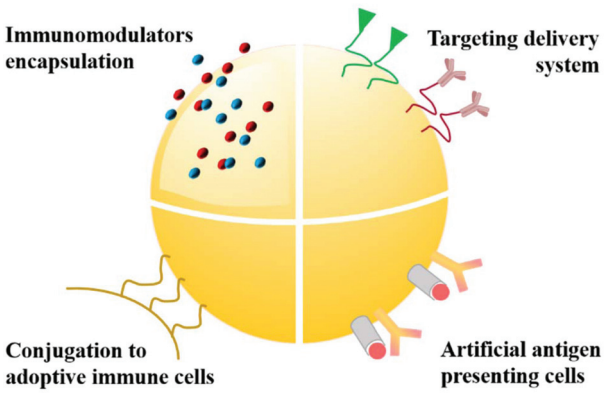

Fig. 4 Microscale material-based strategies for cancer immunotherapy.

Microparticles. Particle size effects can have a great influence on the immunotherapeutic efficiency, but the practical *in vivo* immune response is also impacted by systematic elements, including the types, delivery modes and administration routes of immunomodulators. Microparticles (MPs) as major drugs delivery systems can be made from a large source of biocompatible and biodegradable natural or synthetic polymers.

PLGA-based polymeric MPs also have potential to activate or exacerbate the immune response for tumor eradication. A. K. Kosmides *et al.* developed a PLGA-based aAPC.[226] The aAPC-based tumor antigen-specific immune activation combined with aPD-1 mAb checkpoint inhibitors stimulated sufficient IFN-γ secretion for suppressing tumor cells. Natural polysaccharides such as chitosan, alginate, heparin and dextran have been applied in TIME immunoregulation. Rebekah Watkins-Schulz and colleagues described a type of biodegradable acetylated dextran (Ace-DEX) MP for STING-targeted immunotherapy.[227] The MPs facilitated overcoming the bottleneck of pathogen-associated molecular pattern-associated intracellular delivery. NK cells and CD8+ T cells accumulate for early anti-tumor immunity and successful trials have been carried out in the model of triple negative breast cancer. Also, Fatemeh S. Majedi and coworkers employed microfluidics approaches to prepare alginate-heparin (Alg-Hep) MPs for the controlled release of IL-2 to improve the growth of effector T cells in TIME, which is a new idea for TIME modulation.[228]

Inorganic MPs play a significant role in immunotherapeutic drug delivery also. Tarek R. Fadel and coworkers proposed a carbon nanotube-polymer micro-composite with a high surface area for addressing the issue of T cell proliferation.[229] A large number of cytotoxic T cells is a favorable driving factor for valid cancer immunotherapy. Mesoporous silicon MPs were another choice explored by Motao Zhu and coworkers.[230] B16 melanoma derived-tyrosinase related protein 2 (TRP2) peptide as antigens and TLR agonists as adjuvants were co-encapsulated inside the same MPs, constituting a cancer vaccine against melanoma. Lien Lybaert and coworkers generated a personalized immune-modulating tumor vaccination by entrapping cancer cell lysate within porous $CaCO_3$ MPs with TLR agonists binding on the surface.[231] All these novel MPs were proven to undergo efficient tumor-specific immune responses.

Microcapsules. The similar size of microscale carriers and individual cells indicates a feasible way to engineer mammalian cells into desirable microcarriers. Living cells such as RBCs, platelets, leukocytes and stem cells have been evaluated as immunomodulatory agent delivery systems. In 2017, Wang Chao and coworkers anchored anti-PD-L1 on the surface of platelets.[232] The results showed that the recurrence and metastasis of post-surgical cancer were prevented with high efficacy. Subsequently, Quanyin Hu and coworkers further conjugated exterior anti-PD-1-decorated platelets to the haematopoietic stem cells (HSCs) with the intrinsic ability to enhance anti-leukaemia efficacy.[233] The pioneering HSC-platelet-aPD-1 microcapsules migrated to the bone marrow to home HSCs and release aPD-1, locally generating prominent synergistic myeloid leukaemia curative effects.

Layer-by-layer (LbL) assembly microcapsules are usually produced by sequential deposition of compounds onto a template and then decomposition or direct deposition onto template particles, including inorganic $CaCO_3$ or SiO_2, polystyrene polymers and even living cells. Xiaoli Wang and coworkers constructed the microcapsules with tumor cells as templates.[234] Epigallocatechin-3-gallate (EGCG), an active polyphenol in green tea, and Al(III) were selected as the ligand and ion, respectively. The EGCG-Al(III) coordination outer layer significantly prompted the internalization of MPs by DCs, which will enhance the effects of cancer vaccines.

Other microscale carriers for immunotherapy. The shape and structures of microscale immunomodulatory systems can be dramatically engineered to obtain specific properties or personalized applications. The studies by Garapaty and Champion indicated that the tunable physical properties of microscale rods and ellipsoids could tailor macrophage activities in comparation with MPs.[235]

Recently, microfibers, which are typically made by electrospinning with high processability, have been developed. Using the PLA fibers reported by Hyun Mu Shin and partners as an example,[236] the designed protein G-immobilized cytokine-loaded PLA fibers appeared to be injectable into tumor sites for durably reinvigorating T cell activity, which gives an optional solution to address the current issues confronted in cytokine-based immunotherapy. There are many other types of microscale carriers still being exploited.

Some macroscale carrier strategies for immunotherapy drug delivery

Macroscale carrier biomaterials are generally regarded as materials with a 3D scale greater than 1 mm^3. Compared to nano and micro biomaterials, these biocompatible bulk delivery vehicles display biomimetic performances analogous to organism tissues. Which can be applied more suitably to surrounding physiological environments and they can even possibly act as synthetic immune tissues (*e.g.*, artificial LNs) for immune cell expansion. In addition, it is easier for macroscale materials to localize at the interesting lesion space and realize spatiotemporally controlled administration mechanisms, alleviating the occurrence of systematic toxicity and realizing immunotherapy *in situ*. Also, their macroscale counterparts are also candidates as imperative substrates, where a larger amount of immunocytes can be encapsulated inside for proliferation, growth and activation, offering an alternative for the localized co-delivery of both immune cells and immunomodulatory agents.[237] However, there also exist some leftover issues for practical clinical uses concerned with the adjustment of moderate stiffness and brittleness, shape and volume sensitivity, viscoelasticity-dependent move and flow or *in situ* orientation, which demand more endeavours to be addressed. In this section, we introduce some design strategies consisting of biomaterial components, comprehensive properties, delivery and immunomodulation mechanisms of

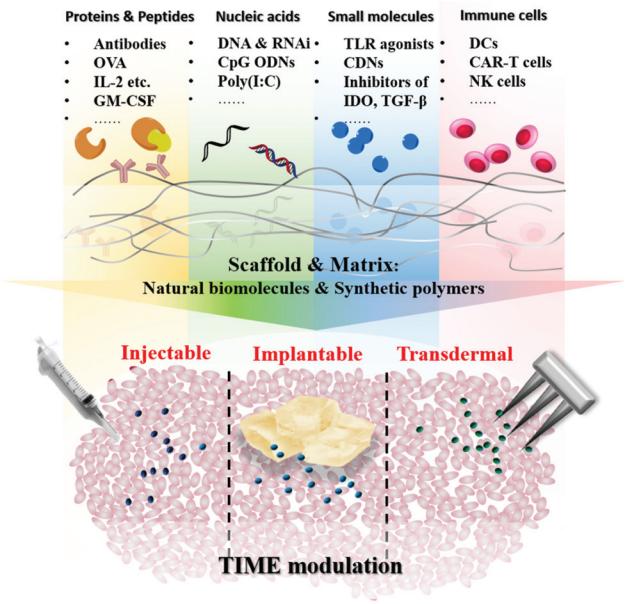

Fig. 5 Macroscale material-based carriers and strategies for cancer immunotherapies.

updated macroscale equipment applied in cancer immunotherapy (Fig. 5).

Porous scaffolds and hydrogels. Porous scaffolds and hydrogels are two types of fundamental biomimetic matrices as macroscale drug delivery tools. Many natural or synthetic, and organic or inorganic biocompatible materials have been corroborated as potential scaffolds and hydrogel biomaterials with immunotherapeutic value in favor of bioactive agent loading and immune cell infiltration, for example, a vast majority of crude biomacromolecules involving polysaccharides (*e.g.*, alginate,[238] chitosan,[239] HA,[240,241] and cyclodextrin[242]), peptides and proteins (*e.g.*, polypeptides,[243,244] fibrin,[245] and collagen[246]) and nucleic acids,[247] and synthetic polymers containing for example poly(vinyl alcohol)(PVA),[248] PEG,[249,250] PLGA and poly(lactic-*co*-glycolide)(PLG),[251] and some inorganic materials such as mesoporous silica.

In the past few years, besides the strategies of assembling antigens of DNA, peptides and protein with various adjuvants as cancer vaccines or inhibitors delivery as ICB therapy or other chemical agents co-encapsulation for combined therapy, immune cells, especially the most extensively applied CAR-T cells, cytotoxic T cells and DCs, have been managed to be loaded in scaffolds or hydrogels used for expansion and delivery for action.

Hathaichanok Phuengkham *et al.* attempted to design an implantable porous matrix *via* collagen and HA cross-linkages to carry gemcitabine (GEM) as a myeloid-derived suppressor cell (MDSC)-depleting agent, successfully suppressing postsurgical breast tumor recurrence and lung metastasis at the surgical site in 4T1 mouse models.[252] Another injectable poly(L-valine) hydrogel prepared by Huijuan Song *et al.* was investigated as a cancer vaccine for the co-delivery of antigens and TLR 3 agonists.[253] This self-assembly polypeptide hydrogel provoked DCs and evoked cytotoxic T cells invasion to destroy the melanoma. Chao Wang *et al.* formed an ROS-inspired hydrogel using PVA as the polymeric matrix with an ROS-labile linker.[254] The hydrogels could be constructed *in situ* at the tumor site and locally released GEM and anti-PD-L1 through ROS-stimulated biodegradation of the hydrogels.[254] Further, Xinyu Ye *et al.* reported combined HA-Pluronic F-127 hydrogels.[255] The thermosensitive hydrogels contained surgically removed tumor cell membrane-coated black phosphorus quantum dots with GM-CSF and lipopolysaccharide (LPS). Together with anti-PD-1 therapy, the hydrogels as promising cancer vaccines enabled combined photothermal therapy and immunotherapy.

As a pioneering cell cultivating promoter, a biomimetic APC system based on mesoporous silica microrod-supported fluid lipid bilayers was developed by Alexander S Cheung *et al.*, which revealed high primary T cell *ex vivo* expansion, nearly the same as the xenograft lymphoma model.[256] The primary mouse and human T cells had greater polyclonal proliferation under sufficient anti-CD3, anti-CD28, and IL-2 and more efficient cytotoxic T-cell subpopulations increase after a single stimulation compared to commercial products or monocyte-derived DCs. Additionally, Pengxiang Yang *et al.* generated a novel peptide nanofibrous hydrogel holding tumor antigens, aPD-1 antibodies, and DCs.[257] This nodule could heavily amplify the antitumor immune response from many aspects for optimal immunotherapy.

Microneedle patches. The entire skin serves as the first line of defense in the natural immune system for human bodies and is one of the most active organs for immunomodulation, providing immunocytes and immunomodulators with an appropriate habitat.[258] Hence, transdermal immunomodulatory drug delivery becomes one of the feasible administration methods with the advantages of less trauma, easier manoeuvrability and friendly patient compliance. Microneedle (MN) patches, in the last several years, have attracted wide attention as a drug delivery platform. Many different types of MN patches contain coated MN, dissolvable MN, degradable MN, and some intelligent bioresponsive MN patches, which can incorporate various drugs for local or systemic delivery and immunomodulation.[259] Thus, MN patches are developing as optional tools for cancer immunotherapy, in particular for superficial cancer such as malignant melanoma.

Zhen Gu and coworkers designed a series of biocompatible HA-derived microneedle patches applied for transdermally delivering immunomodulators. In 2016, Chao Wang *et al.* generated MN patches made from HA coupled with pH-responsive dextran NPs.[260] The immune checkpoint inhibitors aPD1 and GOx were embedded inside the MNs. The acidic TME aggravated by the alteration from glucose to gluconic acid will degrade the NPs to release aPD1. As a potential administration strategy for synergistic therapy, similar vehicles were subsequently decorated with the IDO inhibitor, 1-methyl-DL-tryptophan (1-MT), by Yanqi Ye *et al.* to load immunotherapeutic aPD1.[261] In the B16F10 melanoma animal model, the T cells

immunity was enhanced vigorously, relieving the immunosuppression in the TIME. In 2017, Yanqi Ye *et al.* prepared HA-based devices with B16F10 whole tumor lysate mixed with melanin and GM-CSF as adjuvants.[262] The intradermal MN patches could sharply promote melanin-mediated spatiotemporal photo-responsive immunotherapy *via* both *in situ* heat damage and recruited T cell aggressivity. Besides, increasingly more efforts are being place in the preclinical studies and clinical transformations of other MNs systems for more serious tumors.

Others. Other macroscale carriers such as cryogels[263,264] and 3D-printed networks[265,266] can also possibly provide structural and biochemical supporting matrices for surrounding molecules and cells as ECM analogue scaffolds, which are now confirmed as valuable drug delivery or cell culture systems in the realm of TIME-modulation oncology medicine.

Conclusions and prospects

TIME modulation-based cancer immunotherapy has exhibited exciting therapeutic potential in the cancer therapy. In this review, we introduced some representative immunocytes and factors in TIME and their importance towards TIME modulation. We surveyed and outlined several different TIME modulation-based cancer immunotherapeutic strategies for guiding the innovation and design of biomaterial-derived immunostimulatory systems. Also, we focused on a few latest achievements for TIME regulation and highlighted their advancements and promising potentials in cancer immunotherapy. Considering the data obtained from both preclinical studies and clinical trials, cancer immunotherapy deserves certain attention in the struggle against cancer. Thus far, dozens of immunotherapies, including cancer vaccines, immune checkpoint inhibitors and engineered cells, have earned the approval of the FDA.

Biomaterials and biotechnology from the nanoscale to macroscale significantly break the restriction in immunotherapy. As drug delivery robots, natural and synthetic biomaterials delivery systems will require the transport, protection, delivery, release and actions of the immunomodulatory payloads. The properties of biomaterial devices such as components, size, shape, charge and surface decoration can be controlled to improve prolonged stability, efficient delivery, desirable pharmacokinetics, specific biodistribution, sensitive response and little systemic adverse effects of immunomodulators. Furthermore, smart and multifunctional mono and further combinatorial strategies have arisen one by one based on biomaterials. Besides the combination of various subsets of TIME modulation regimens such as ICB therapy, ACT therapy and cancer vaccines, synergistic cancer therapies and theranostic integrations also intend to create more manifold opportunities for successfully and precisely arousing defence mechanisms in immunosuppressive TIME.

Despite the significant strides of immunotherapy, accumulating evidence still suggest many underlying flaws and risks of cancer immunotherapy. Among them, the most serious challenge is its limited clinical efficacy, which mainly manifests as follows. Firstly, for cancers, there are no dramatically effective immunotherapeutic guidelines for solid tumors due to both the poor accessibility to tumor sites and the immunosuppression of TIME. Secondly, for immunotherapies, the modest patient response rate and the potential toxic effects are still two major barriers for their clinical applications. For example, the contribution of cancer vaccines may be restricted by host immunosuppression, exhaustion of activated T cells and incoordination of the expansion between immune cells and tumor cells. As another example, excessive combination immunotherapy may cause negative effects and extra ineffective costs. Finally, for patients, immunotherapy responses and results vary with every patient because of the individual heterogeneity, only a minority of whom enjoy satisfactory outcomes. In conclusion, more contributions are urgently needed to overcome the clinical transformations of cancer immunotherapy.

For cancer immunotherapy nowadays, some practical drawbacks require further improvements and some potentials demand better developments for addressing the obstacles in clinical cancer immunotherapy as follows:

(1) The conversion of immunosuppressive cold TIME into immunocompetent hot TIME is the essence of cancer immunotherapy. According, the comprehensive grasp of complex networks in the TIME and tumor heterogeneity including genetic, phenotypic, epigenetic, and transcriptomic diversity establishes a solid foundation. The distinctions of tumors contain not only individual specificities but each developing stage during cancerization. The identification and collection of periodical immunotherapeutic biomarkers and related pathways can be standardized into protocols for instructing the use of immunomodulatory medicines, boosting targeted cancer immunotherapy.

(2) The precise optimal doses, administration routes and sequences, and schedules of mono or combined immunotherapy should be fully studied for minimum side effects and maximum therapeutic outcomes to accommodate the personalized heterogeneity of patients. The quick and accurate sense of timing is pivotal for the immune response, which should be investigated in more detail. Besides, the intensity of cancer immunotherapy, especially combined immunotherapy should be carefully harnessed in the aspect of both treatment and cytotoxicity to achieve higher therapeutic efficacy in different cancer patients.

(3) Biomaterials are applied for immunomodulatory agent delivery and partial immunomodulation. The determination of material components and properties, *in vivo* behaviours and fate, intracellular functions or interactions with cells, and intrinsic and systematic immunogenicity is a requisite for the design of superior systems and options. Thus far, there is scarce knowledge on how the cascade of responses and fluctuation processes followed by the former one or two factors change. The interplay between biomaterials and organisms still remains a mystery.

(4) Cancer immunotherapy usually presents excellent preclinical outcomes but fails to be successfully applied in clinic. One of the most influential reasons may be the heterogeneity between *in vitro* cells and animal models, animals and cancer patients. Thus, more elaborate *in vivo* models are extraordinarily required for establishing more vivid TIME for basic research.

(5) Finally, clinical transformation of immunotherapy cannot be separated from multidisciplinary cooperation. The advanced techniques and apparatus including high-throughput genomic and proteomic technologies, gene sequencing chips, protein microarrays combined with computer science for big data analysis and library collection should be entirely integrated into the realm of immune theranostic evolvement.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We sincerely acknowledge the funding from National Science and Technology Major Project of the Ministry of Science and Technology of China (2018ZX10301402), Key International (Regional) Joint Research Program of China (5181001045), Guangdong Innovative and Entrepreneurial Research Team Program (2013S086 and 2016ZT06S029), and the Science and Technology Planning Project of Shenzhen (JCYJ20170307141438157).

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