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INVITED REVIEW PAPER

Emerging strategies for biomaterial-assisted cancer immunotherapy

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Abstract−Among many treatment options to prevent cancer progression, cancer immunotherapy has become a powerful clinical strategy due to its favorable clinical outcomes. The number of clinical trials in immune checkpoint blockade (ICB) therapy and chimeric antigen receptor (CAR)-T cell therapy has been remarkably increasing in recent years. However, the currently available options for these treatments pose significant challenges related to immune-related adverse effects and limited therapeutic efficacy. Excellent delivery technologies by leveraging biomaterials to mitigate these limitations could potentially advance current cancer immunotherapies for a wide range of applications. In this review, we analyze various strategies of biomaterial-assisted cancer immunotherapy for localized, targeted, and combined treatments and then summarize the promises and challenges for integrating biomaterial-based delivery technologies into cancer immunotherapy.

Keywords: Cancer Immunotherapy, Biomaterials, Localized Delivery, Immuno-engineering, Combination Therapy

INTRODUCTION

Recent developments in cancer immunotherapy have demonstrated its remarkable clinical benefits for various types of cancers by awakening the patient's own immune system to kill tumor cells; thus it has become a promising clinical strategy for treating cancer [1-3]. Compared to conventional treatments, such as chemotherapy and radiotherapy, cancer immunotherapy can target cancer cells more specifically by modulating the functions of specific immune cells while reducing unwanted adverse effects of cancer treatment [4-6].

Over the past several years, a variety of cancer immunotherapies, including immune checkpoint blockade (ICB) therapies [7-9], chimeric antigen receptor (CAR)-T cell therapies [10-12], and cancer vaccines [13,14], have been developed to enhance tumor-specific immune responses and also exhibited favorable clinical outcomes for various cancers [15]. Among them, ICB therapies, which target regulatory pathways of programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1) [16,17] or cytotoxic T lymphocyte antigen 4 (CTLA-4) [18] to augment T-cell mediated anti-tumor responses, have been approved for clinical use in treating advanced melanoma, renal carcinoma, non-small lung cancer, Hodgkin's lymphoma, and many other cancers [19-21]. Furthermore, CAR-T cell therapies that employ genetically engineered patient's T cells have achieved outstanding progress particularly in treating hematologic malignancies, such as B cell acute lymphoblastic leukemia [22,23]. In addition, cancer vaccine strategies involve stimulating the tumor antigen presentation process of antigen presenting cells (APCs), such as dendritic cells (DCs), to activate and expand tumor-specific T cells for effective killing of cancer cells [13].

Despite these significant advances in cancer immunotherapies, the current treatment options pose major clinical challenges, mainly related to safety and efficacy [14,24,25]. The key challenges include the risk of severe systemic autoimmune responses, non-specific inflammation, cytokine release syndrome, and vascular leak syndrome, which lead to potentially life-threating toxicity to patients [26,27]. Furthermore, only a small fraction of patients have exhibited durable clinical outcomes in response to immunotherapies, which indicates that low objective response rates remain a great challenge [26].

Biomaterial-based delivery system, such as nanoparticles, scaffolds, hydrogels, and cell-based platforms, has emerged as a promising approach to mitigate these adverse effects and limited efficacy, which allows for the administration of immunomodulatory agents in a safer and more controlled manner [28,29]. Various biomaterials, including polymers, proteins, lipids, and carbohydrates, have been utilized to develop efficient delivery platforms for cancer immunotherapy, which can provide a means of not only improving the controlled delivery of drugs but also eliciting an effective anti-tumor immune response [30-33].

In this review, we provide an overview of recent developments in biomaterial-assisted cancer immunotherapy that aim to enhance the therapeutic efficacy while reducing the adverse effects. This review mainly focuses on several main targets of cancer immunotherapies, applications of localized and targeted immunotherapy, and combined immunotherapy with other therapeutic strategies. Both emerging trends and perspective of recent advances in this field are discussed.

MAIN TARGETS FOR MODULATING THE IMMUNE SYSTEM

The main role of the immune system is to protect the body from a wide variety of diseases by recognizing and responding to invading pathogens, including uncontrolled cancer cells [6,34]. Generally, a number of essential steps are required for eliciting effective

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anti-tumor immunity [35-38]. First, cancer cells must be recognized by the specific immune cell types, including DCs, which are responsible for uptake and presentation of tumor antigens, leading to priming antigen-specific T cell immune responses. The activated T cells then migrate to tumor tissues and kill malignant tumors. However, challenges in these steps, including insufficient DC activation and antigen-presentation and immune evasion in the tumor microenvironment consisting of overexpressed immune-inhibitory ligands and receptors that prevent the function of T cells, remain a great stumbling block for cancer immunotherapy [17,39-42]. Therefore, the following immunotherapy approaches have been typically proposed to improve the efficiency of anti-tumor immunity by modulating potential targets in the immune system.

1. Cancer Vaccines

The development of an effective cancer vaccine involves generating a potent antigen-specific immune response by introducing tumor-associated antigens and adjuvants to DCs and subsequently activating T cells to attack cancer cells (Fig. 1(a)) [43,44]. DCs are considered as key regulators of T cell and B cell immunity due to their superior ability to take up, process, and present antigens [45, 46]. Basically, tumor antigens can be uptaken and processed by immature DCs, resulting in the induction of DC maturation for subsequent $CD8^+$ or $CD4^+$ T cell priming. Therefore, many attempts have been made to manipulate DCs to achieve effective immunity against cancers [47,48]. DC vaccines are generally derived from the patient's own DCs that are engineered to express tumor-associated antigens and further activated *ex vivo* [49,50]. One of examples of therapeutic DC vaccine is sipuleucel-T, which was approved for the treatment of prostate cancer [51,52]. Although the DC vaccine strategy generates potent activated DCs with high specificity and safety profiles, the complexity and high cost associated with labor-intensive purification procedures of personalized treatment remain obstacles for the clinical translation [53]. Furthermore, after infusing engineered DCs back to patients, a rapid decline in viability and function of infused DCs hampers successful homing of DCs to lymph nodes where T cell and B cell immunities can be induced. To address these limitations, many studies have focused on developing novel delivery platforms to achieve high expression of target antigens on DCs, including *in vivo* direct DC targeting strategy, and improve the delivery efficacy of DCs to lymph node [54-56].

2. Engineering Immune Cells

The CAR-T cell approach involves genetically modifying a patient's T cells *ex vivo* and then readministering the engineered T cells back to the same patient to specifically recognize the target antigen on tumor cells and subsequently induce tumor cell death (Fig. 1(b)) [57]. CAR-T therapy has gained considerable attention due to its clinical successes in the treatment of B cell acute lymphoblastic leukemia and non- Hodgkin's lymphoma [58,59]. Moreover, the activity of CAR-T cells can be retained for more than a decade

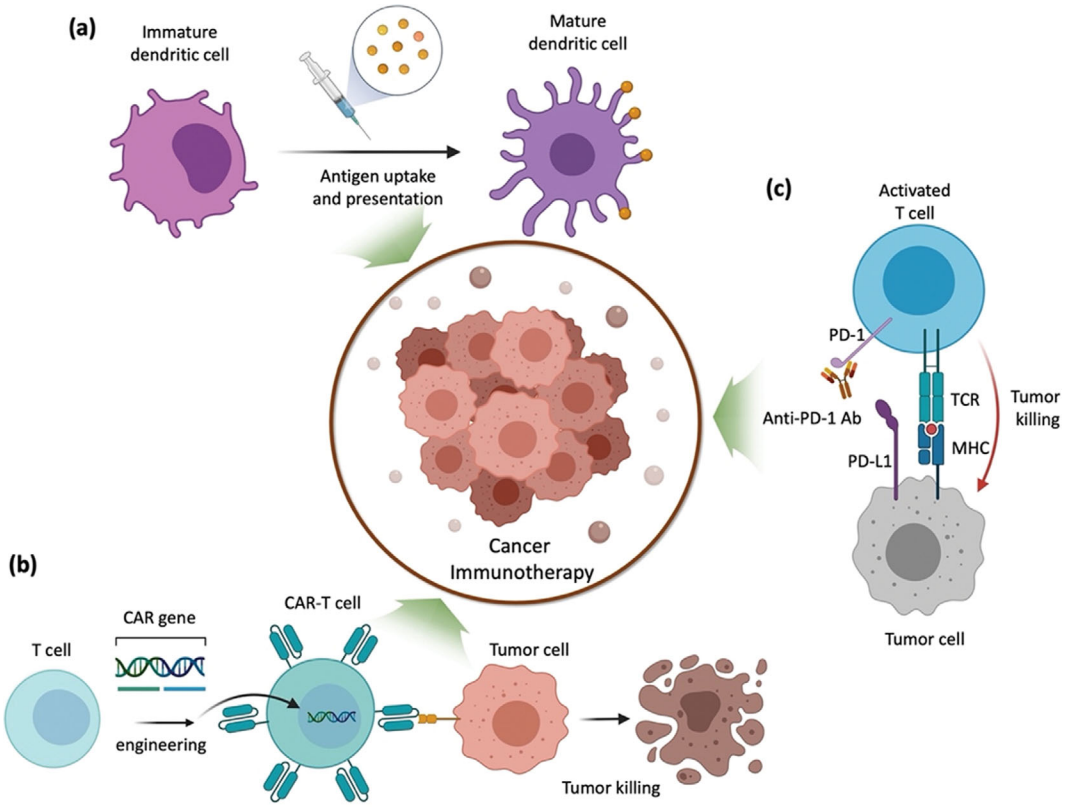

Fig. 1. Main targets for modulating the immune system in cancer immunotherapy. (a) Cancer vaccines enable the fine control of antigen uptake and presentation to DCs for subsequent T cell priming. (b) CAR-T cell engineering approach for expanding tumor-specific T cells *ex vivo* and infusing back to patients. (c) ICB therapy for the inhibition of negative regulatory pathways that can restore T cell activity to exert tumor killing.

after injection, allowing for a one-time treatment [10,60]. The great success of CD19-targeted CAR-T cell therapies in clinical use has stimulated many studies to develop various CAR-T therapy platforms for many other applications [61]. However, adverse effects of CAR-T therapy, such as cytokine release syndrome and neurotoxicity, and its limited therapeutic outcomes in solid tumors remain to be addressed [62]. Therefore, novel delivery technologies by leveraging biomaterials to overcome these limitations could potentially advance current CAR-T cell therapy for a wide range of applications.

3. Immune Checkpoint Blockade

Immune checkpoints, such as PD1/PD-L1 and CTLA-4, play a critical role as negative regulators of T cell function to maintain a balanced immune response, thus minimizing the risk of immune attack to healthy tissues [63]. PD-L1 is a transmembrane protein that downregulates immune response through binding to PD-1 generally expressed on T cells [64]. In the tumor microenvironment, PD-L1 is markedly upregulated on cancer cells, resulting in the suppression of effector T cells [39]. Therefore, the blockade of PD-L1/PD-1 interaction using monoclonal antibodies (Abs) can restore T cell activity to exert tumor killing (Fig. 1(c)). Among many efforts to explore effective cancer immunotherapies, ICB strategies have been the most comprehensively studied due to their remarkable clinical benefits. Furthermore, a number of anti-PD-1 drugs (pembrolizumab, nivolumab) [65-67], anti-PD-L1 drugs (atezolizumab, avelumab, durvalumab) [21,68,69], and anti-CTLA-4 drug (ipilimumab) [26] have been approved by the U.S Food and Drug Administration (FDA) for various types of cancers. Nevertheless, there are still major limitations in ICB therapy, resulting from low objective response rates and severe side effects such as autoimmune disorders [27]. Taking the brakes off the immune system with systemic injection of immune checkpoint inhibitors (ICIs) can potentially cause severe immune-related adverse effects in numerous organs [70]. Thus, the improvement of current ICB therapy demands the innovative design of biomaterial-assisted delivery platforms that can mitigate these limitations.

LOCALIZED CANCER IMMUNOTHERAPY

A controlled and sustainable delivery of immunomodulatory drugs to the site of interest is most desirable to mitigate immune-related toxicities while increasing the local drug concentration,

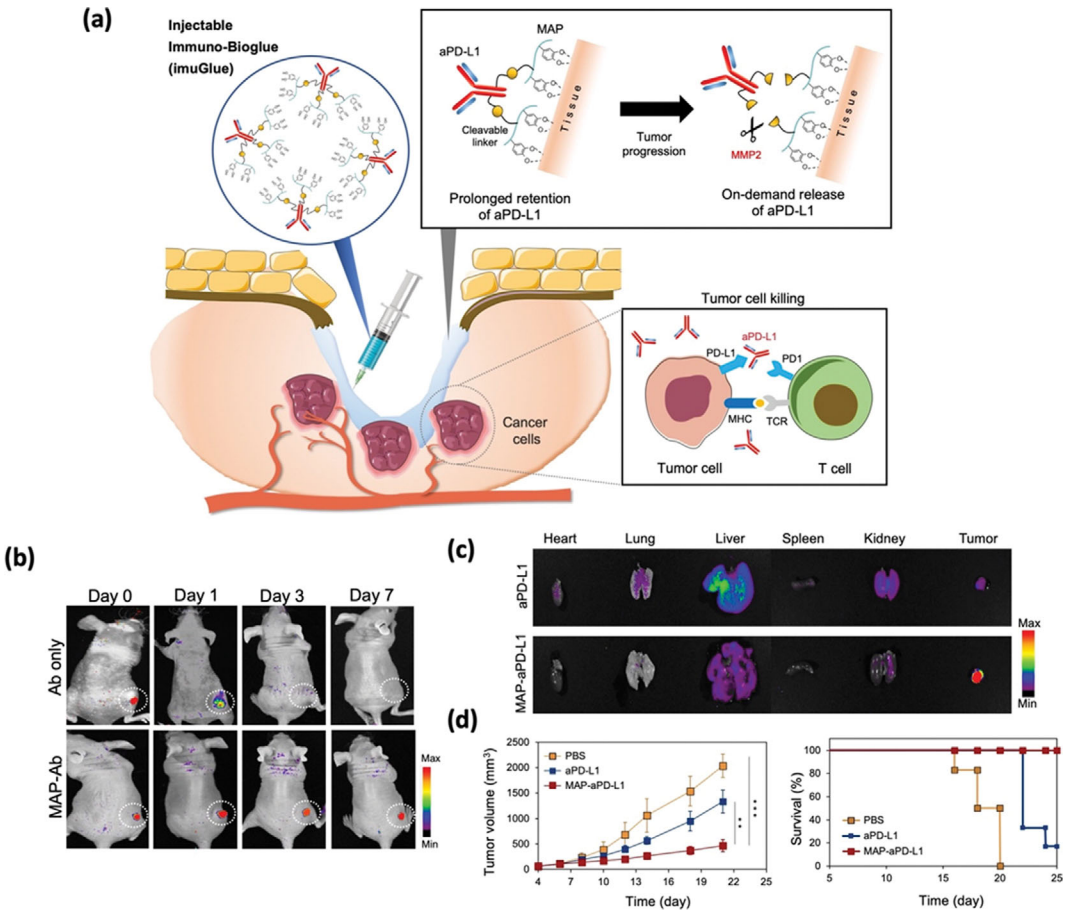

Fig. 2. The localized delivery of immunotherapeutic payloads by imuGlue. (a) Schematic illustration of the imuGlue delivery platform used for cancer immunotherapy. (b) *In vivo* fluorescence imaging of the mice at the indicated time points after the subcutaneous injection of free Abs and MAP conjugated Abs (MAP-Ab). (c) *Ex vivo* fluorescence imaging of anti-PD-L1 Abs in different organs of mice at 24 h after intratumoral injection of free aPD-L1 and MAP-aPD-L1. (d) Average tumor growth and survival curves of the different treatment groups as indicated. Reproduced with permission [76].

which allows for the administration of lower drug doses compared to those used systemically [71-73]. In a recent study, circulating exosomes expressing PD-L1 and/or PD-L1-positive variants secreted by cancer cells have been recognized as the mechanism of therapeutic resistance to anti-PD-1/PD-L1 therapy by functioning as decoys to disable systemically injected anti-PD-L1 Abs, which is possibly counteracting anti-tumor immunity [74,75]. Therefore, localized ICB immunotherapy has emerged as a promising approach capable of not only minimizing immune-related adverse effects but also improving therapeutic efficacy.

Inspired by the intrinsic underwater adhesion properties of marine mussels, Joo et al. developed a bioresponsive immuno-bioadhesive platform for the localized delivery of ICIs, named "imuGlue" (Fig. 2) [76]. Mussel adhesive proteins (MAPs), known as proteinaceous glues secreted by mussels to stably adhere to diverse wet surfaces [77-79], were conjugated to anti-PD-L1 Abs *via* a tumor microenvironment-responsive cleavable linker, allowing for stable retention of anti-PD-L1 Abs at the site of treatment and their controlled release in response to tumor growth. Thus, by leveraging the unique traits of bioengineered MAPs [80-82], imuGlue could significantly enhance anti-tumor efficacy by eliciting a robust T cell-mediated immune response mainly at the tumor site while reducing unwanted immune activation at non-tumor sites by preventing the rapid diffusion of anti-PD-L1 Abs into the systemic circulation. The results demonstrated that significant activation of $CD4^+$ and $CD8^+$ T cells was observed in non-tumor sites, such as lymph nodes of mice treated with free anti-PD-L1, whereas no remarkable immune activation was exhibited in the imuGlue treatment group, suggesting imuGlue treatment had no effect on activation at non-tumor sites but could selectively activate tumor infiltrating $CD8^+$ T cells in tumor microenvironment. Furthermore, the versatility of the imuGlue platform could also expand its utility for the localized delivery of many other types of ICIs and therapeutics.

The Gu group developed a microneedle (MN) patch for locally sustained delivery of ICIs against skin cancer (Fig. 3) [83]. A self-degradable MN patch was made of biodegradable hyaluronic acid that incorporated pH-sensitive dextran nanoparticles pre-loaded with anti-PD-1 Abs, which could achieve sustained and controlled delivery of anti-PD-1 Abs at the tumor sites. The study showed that a single treatment of MN patch loaded with anti-PD-1 Abs could induce a robust immune response against B16F10 mouse melanoma compared to the treatment of free anti-PD-1 Abs. Additionally, a significantly increased survival rate (~40%) was observed in MN patch-treated mice group within 40 days. In addition, the MN patch could be utilized for co-delivery of anti-PD-1 Abs and other ICIs including anti-CTLA-4 or an inhibitor of immune suppressive enzyme, such as 1-methyl-DL-tryptophan (1-MT) [84],

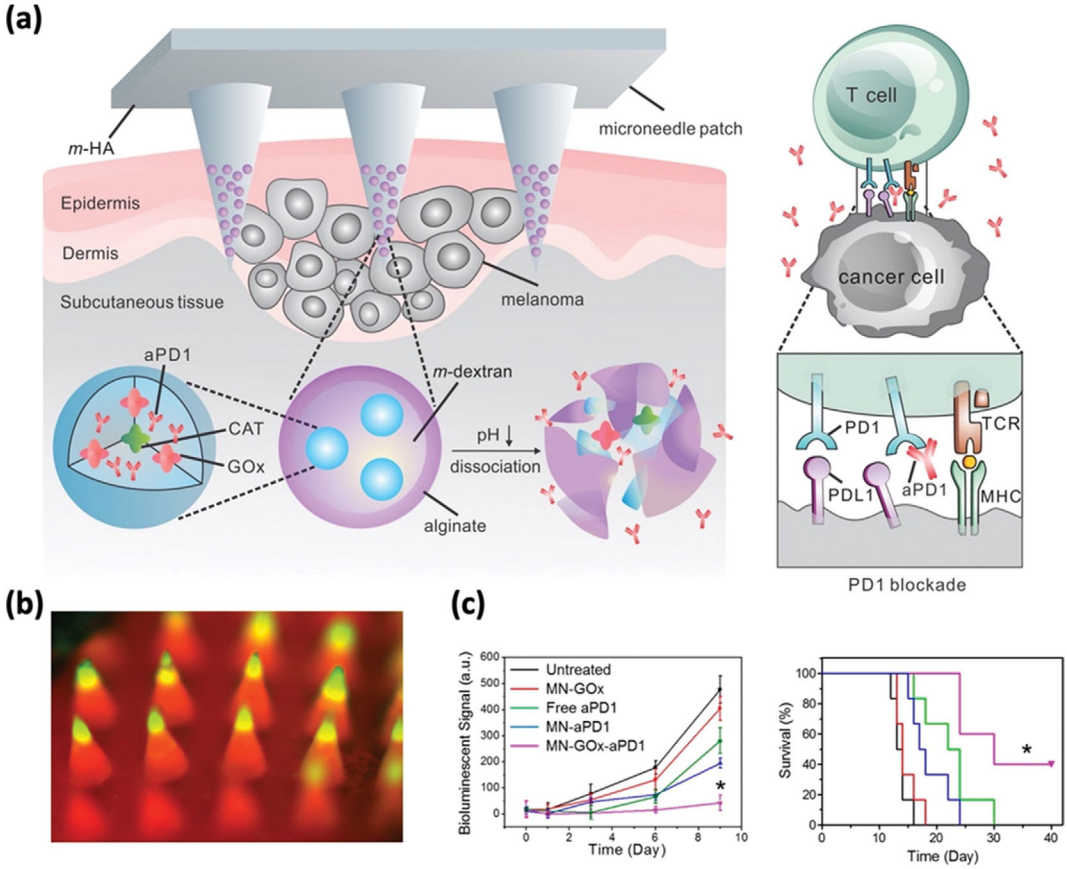

Fig. 3. The MN patch-assisted delivery of anti-PD-1 for skin cancer treatment. (a) Schematic of the anti-PD-L1 delivered by an MN patch loaded with physiologically self-dissociated NPs. (b) Fluorescence imaging of a representative MN patch. (c) The tumor growth and survival curves after treatments as indicated. Reproduced with permission [83].

demonstrating a remarkable synergistic effect after the combination delivery of other ICIs and immunomodulatory agent [85].

Furthermore, a commercially available light mineral oil mixture, Montanide ISA-51, has been widely used in preclinical and clinical studies for cancer immunotherapy [86-88]. The study by the Melief group showed that the local injection of anti-CTLA-4 Abs through a slow-release delivery formulation of Montanide ISA-51 close to the tumor site could potently induce tumor-specific $CD8^+$ T cell responses to eradicate tumors while decreasing the risk of treatment-induced side effects, suggesting that a remarkably lower dose (~8-fold) of anti-CTLA-4 Abs was equally effective to induce tumor killing compared to that of systemic delivery [89].

As a novel approach of personalized cancer vaccine, Kuai et al. designed synthetic high-density lipoprotein (sHDL)-mimicking nanodiscs coupled with antigen (Ag) peptides and adjuvants of 5′-C-phosphate-G-3′ (CpG) motif, a potent Toll-like receptor-9 agonist (Fig. 4) [90]. The results showed that the nanodisc could efficiently co-deliver Ag and CpG for draining lymph nodes, promoting strong and durable Ag presentation by DCs and subsequently eliciting robust Ag-specific $CD8^+$ cytotoxic T cell responses that significantly inhibited tumor growth. Moreover, using murine MC-38 colon carcinoma and B16F10 melanoma models, they found that the nanodisc vaccination strategy combined with anti-PD-1 and anti-CTLA-4 therapy could eradicate established tumors, suggesting a general and effective means for personalized cancer immunotherapy. Additionally, Chen and co-workers synthesized nanocomplexes by conjugating molecular vaccine into albumin-binding vaccines (AlbiVax), which were capable of self-assembling *in vivo* from AlbiVax and endogenous albumin for efficient vaccine delivery to lymph nodes and potent cancer immunotherapy [91].

For an effective post-surgical cancer treatment, Chen et al. engineered an *in situ* formed immunotherapeutic bioresponsive gel that could possibly control both local tumor recurrence after surgery and development of distant tumors (Fig. 5) [92]. This approach involves encapsulating anti-CD47 Abs-loaded nanoparticles in the fibrin gel formed by the interaction of fibrinogen and thrombin, allowing the polarization of tumor-associated macrophages to the M1-like phenotype. Furthermore, the released anti-CD47 Abs could block the "don't eat me" signal in cancer cells [93], thereby enhancing the phagocytosis of cancer cells by macrophages. These results indicate that the localized treatment of the immunotherapeutic fibrin glue could awaken the host innate and adaptive immune systems to inhibit post-surgical tumor recurrence. In addition to these strategies, many other biomaterial platforms have been widely explored for the development of localized cancer immunotherapy [94-100].

TARGETED CANCER IMMUNOTHERAPY

Although localized delivery using various biomaterial delivery

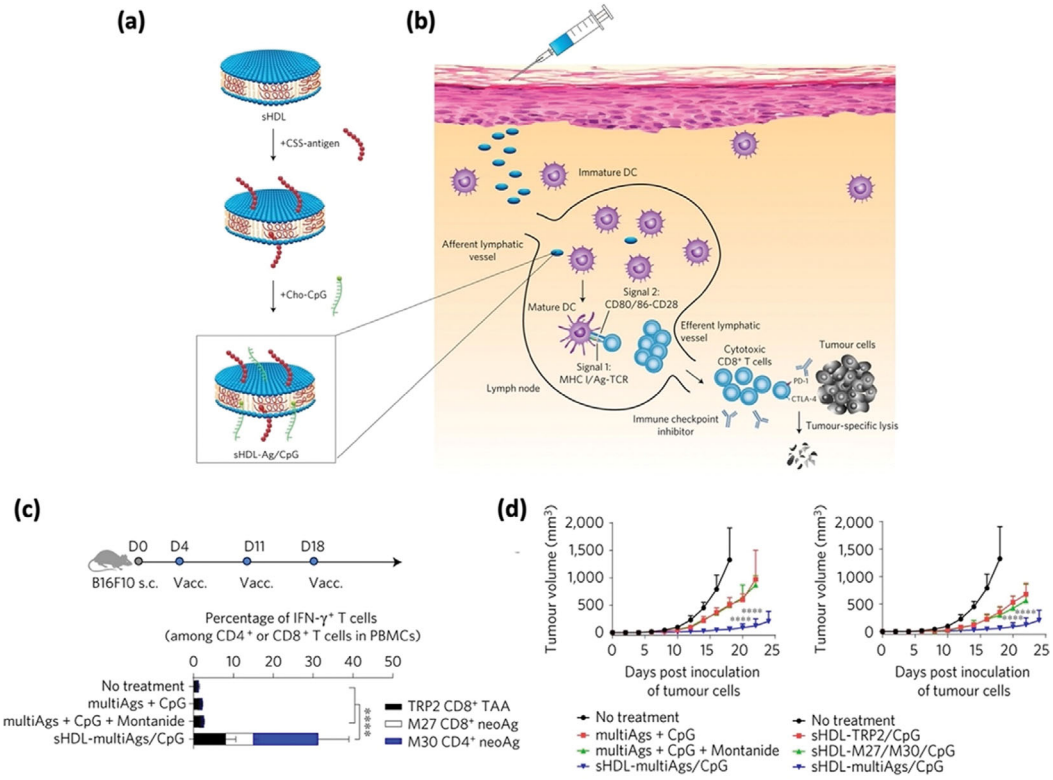

Fig. 4. Design of sHDL nanodisc platform for personalized cancer vaccines. (a) sHDL nanodiscs, composed of phospholipids and apolipoprotein-1 mimetic peptides (22A), are used for co-delivery of antigen (Ag) peptides and adjuvants (CpG) to dendritic cells. (b) Mechanism of anti-tumor immune responses for sHDL nanodiscs. (c) Schematic illustration of localized immunotherapy using the B16F10 murine melanoma model and the percentage of IFN-γ^+ $CD8\alpha^+$ or $CD4^+$ T cells in peripheral blood measured by intracellular cytokine staining. (d) The average B16F10 tumor growth curves of different treatment groups. Reproduced with permission [90].

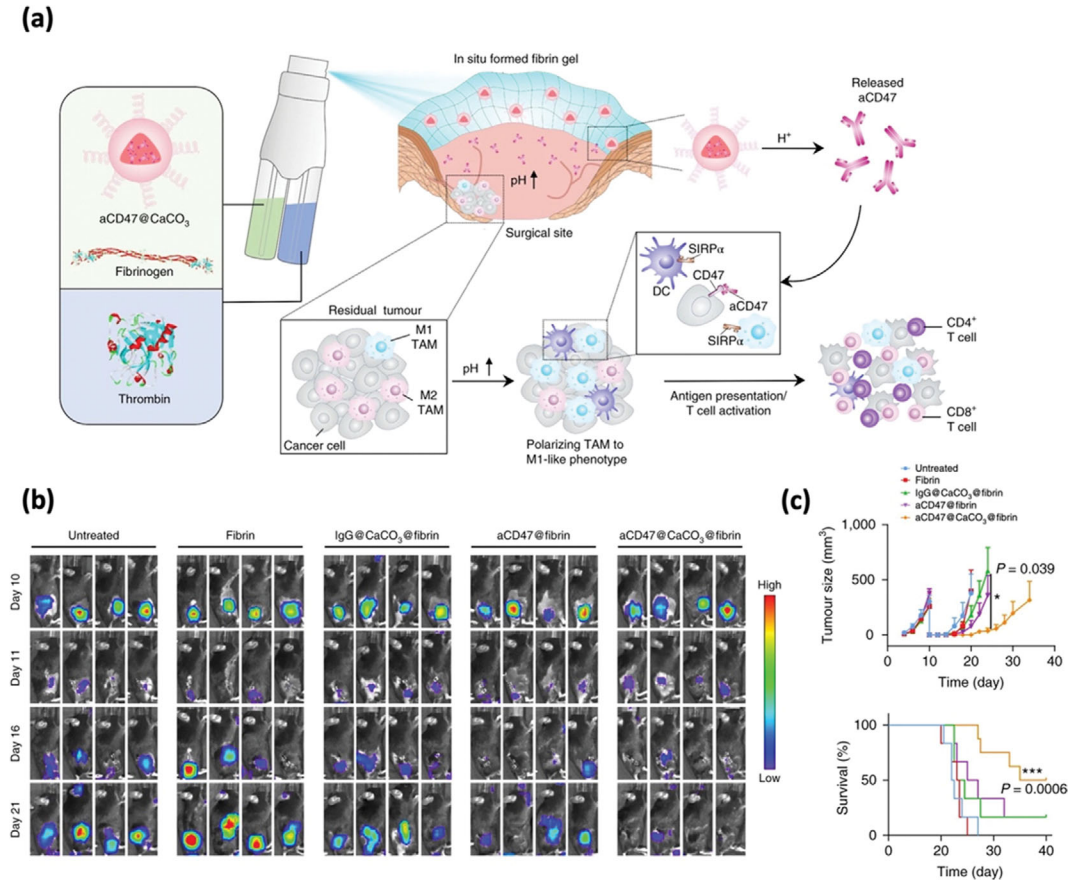

Fig. 5. ***In situ*** **forming immunotherapeutic fibrin gel. (a) Schematic showing** ***the in situ*** **sprayed bioresponsive fibrin gel containing aCD47@$CaCO_3$ nanoparticles within the post-surgery tumor bed. (b)** ***In vivo*** **bioluminescence imaging of B16F10 tumors after removal of the primary tumor. Four representative mice per treatment group are shown. Images associated with day 10 were taken before surgery. (c) Tumor growth kinetics and survival corresponding to the tumor size of mice after different treatments as indicated. Reproduced with permission [92].**

platforms enables higher accumulation and prolonged retention of immunomodulatory drugs in tumors, it may not be feasible when tumor sites are not easily accessible, and/or the multiple sites of distant metastatic tumors exist. Therefore, extensive efforts have been devoted to exploring a variety of targeted immunotherapy strategies that allow for the effective delivery of immunomodulatory payloads directly to desired cell types or tumor microenvironments [101]. Novel biomaterial-assisted delivery systems, including nanomaterials [102-107], scaffolds [32,108-112], and cell-based platforms [113-116], have been utilized to achieve optimal humoral and cellular immune responses for targeted cancer immunotherapy.

Among them, cell-based platforms have recently emerged as a versatile drug carrier for the delivery of immunotherapeutic drugs. For example, Wang et al. utilized the intrinsic properties of platelets, which could quickly migrate to the site of vascular injury and also can recognize and interact with circulating tumor cells, for use as a preventative treatment for post-surgical recurrence (Fig. 6) [117]. This approach shows that conjugating anti-PD-L1 Abs to the surface of platelets could significantly enhance the delivery of anti-PD-L1 Abs to the tumor resection site, where residual tumors may survive after surgery. Using triple-negative breast carcinoma and melanoma models, the strategy used *in situ* activation of platelets demonstrated that anti-PD-L1 conjugated to platelets could effectively release anti-PD-L1 Abs on platelet activation at the tumor site and furthermore significantly reduce the risk of post-surgical tumor recurrence and metastasis.

In a following work, Hu et al. proposed the haematopoietic stem cell (HSC)-based platform by conjugating platelets decorated with anti-PD-1 Abs as a potent therapeutic modality that improves treatment outcomes in acute myeloid leukemia [114]. After intravenous injection into mice bearing leukemia cells, the HSC-platelet-anti-PD-1 conjugate could migrate to the bone marrow and locally release anti-PD-1 Abs, resulting in significantly increasing the number of activated T cells and the anti-leukemia therapeutic efficacy. Furthermore, Zhang et al. utilized HEK 293T cells stably expressing PD-1 receptors to generate cell membrane-derived nanovesicles presenting PD-1 receptors on their membrane, which enhanced anti-tumor responses possibly due to increased $CD8^+$ T cell infiltration into the tumor.

Therapeutic cell engineering with functional biomaterials for enhancement of cell-based therapies has also been proposed [118, 119]. Infusion of *ex vivo*-expanded tumor-specific T lymphocytes has shown promising results for cancer immunotherapy, but the rapid decline in viability and function of transplanted cells remain

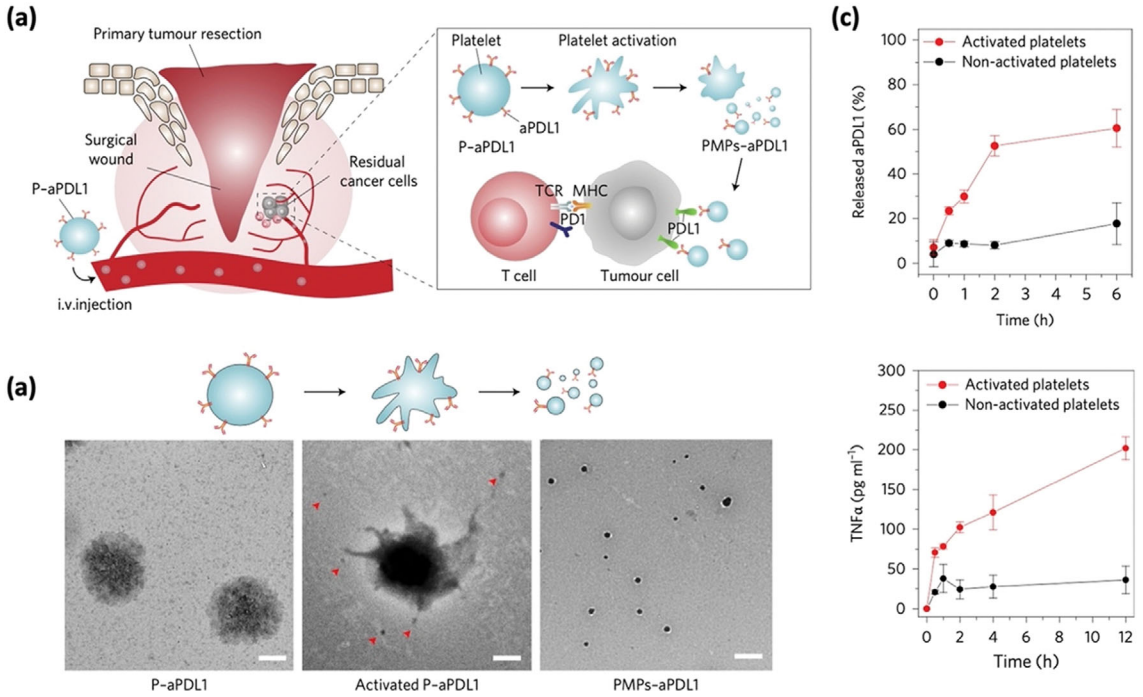

Fig. 6. Platelets with checkpoint inhibitors for post-surgical cancer immunotherapy. (a) Schematic of the delivery of aPDL1 to the primary-tumor resection site by platelets. (b) TEM images of anti-PD-L1 conjugated platelets (P-aPDL1) before (left) and after (middle and right) activation. Anti-PD-L1 is effectively released on platelet activation by platelet-derived microparticles. (c) Percentage of aPDL1 released from non-activated and activated platelets at different time points and amount of TNFα released from non-activated and activated platelets at different time points. Reproduced with permission [117].

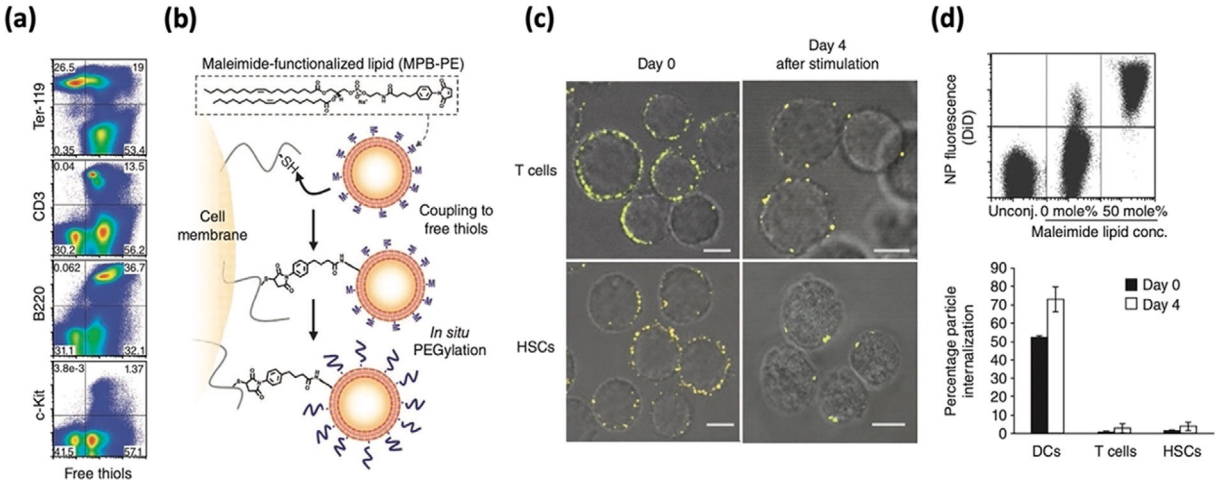

Fig. 7. Stable conjugation of nanoparticles (NPs) to the surfaces of T cells and HSCs via cell-surface thiols. (a) Flow cytometry analysis of cell surface thiols on mouse splenocytes detected by fluorophore-conjugated maleimide co-staining with lineage-specific surface markers for erythrocytes (Ter-119), T cells (CD3), B cells (B220) and hematopoietic stem cells (c-Kit). (b) Schematic of maleimide-based conjugation to cell surface thiols. (c) Confocal microscopy images of $CD8^+$ effector T cells and lineage-Sca-1^+c-Kit^+ HSCs immediately after conjugation with fluorescent-labeled multilamellar lipid nanoparticles (left) and after 4-d in vitro expansion (right). (d) Flow cytometry analysis of $CD8^+$ T cells after incubation with fluorescent-labeled multilamellar lipid nanoparticles synthesized with or without maleimide-headgroup lipids and quantification of nanoparticle internalization. Reprinted with permission [122].

a major limitation. Although cytokines, such as interleukin-15 (IL-15) and IL-2, or other drugs are often concurrently administered to boost immune reconstitution after cell transfer; these reagents need to be maintained at high concentration, which causes dose-limiting toxicity [120,121]. To circumvent these concerns, the Irvine group suggested a novel approach that involves conjugating cytokine-loaded nanoparticles onto the surface of T cells to maintain the survival and activity of the transplanted T cells (Fig. 7)

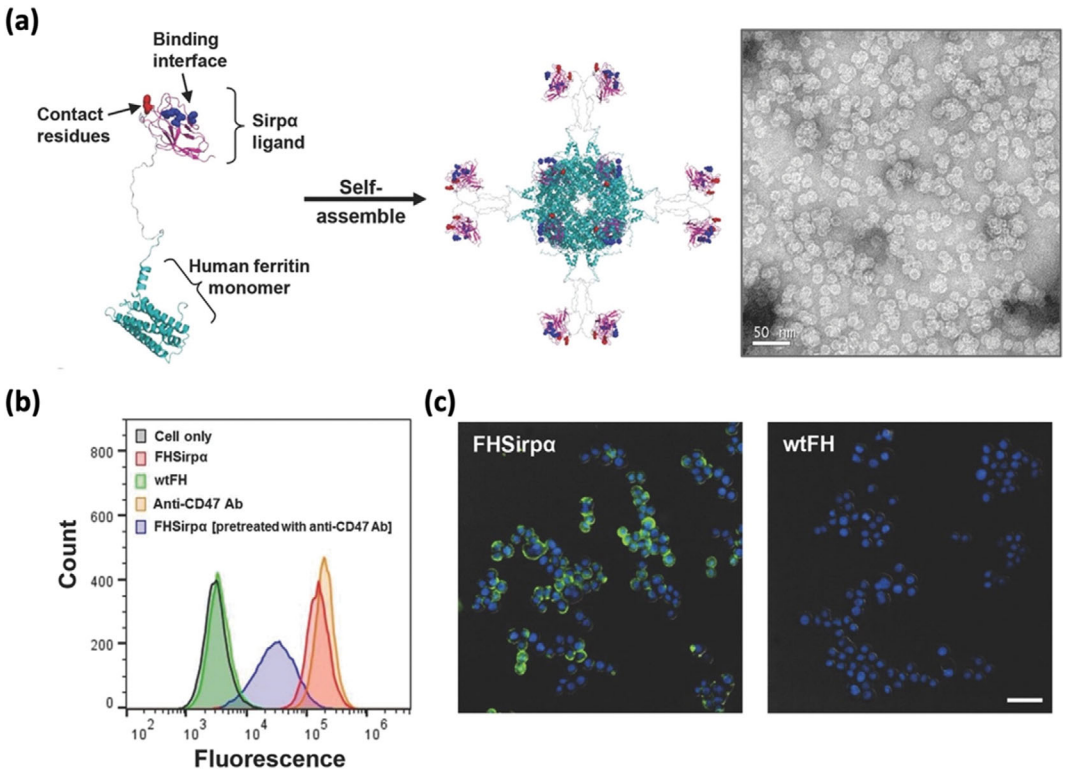

Fig. 8. Design, generation, and characterization of FHSirpa as a CD47 antagonist. (a) 3D model of the Sirpα ligand-fused ferritin subunit and self-assembled FHSirpα, generated using Modellar (v 9.2) simulation software. (b) Representative flow cytometry histograms of CD47-positive HT29 cells incubated with 4×10^{-9} m FHSirpα and wtFH. The specificity of FHSirpα binding to CD47 on the surface of HT29 cells was evaluated by preblocking cells with anti-CD47 antibodies. (c) Representative fluorescence images of HT29 cells treated with 4×10^{-9} m FHSirpα and wtFH showing efficient cell binding of the high-affinity antagonist, FHSirpα. Nuclei were counterstained with Hoechst (blue). Reproduced with permission [125].

[122]. This approach provides sustained pseudoautocrine stimulation to donor cells, eliciting significant enhancement in tumor elimination. Similarly, nanocapsule-functionalized T cells were employed as active targeting of chemotherapy to disseminated tumors, suggesting that tissue-homing lymphocytes can serve as targeting agents for nanoparticle delivery [123].

Blockade of the CD47-Sirpα (signal regulatory protein α) interaction between tumor cells and phagocytic cells is generally considered to increase tumor cell phagocytosis, which is emerging as a novel potent immunotherapy target [93,124]. Lee et al. designed human ferritin-based self-assembling nanocages containing a Sirpa variant (FHSirpa) that is capable of binding and antagonizing CD47 (Fig. 8) [125]. The results indicated that the nanocage could not only efficiently present ligands that enhanced the phagocytosis of cancer cells, but also co-deliver drugs to kill tumors, resulting in potent inhibition of tumor growth and complete eradication of tumors through remarkably enhanced tumor-specific T cell responses in draining lymph nodes spleen and further $CD8^+$ T cell infiltration into the tumor sites.

For stimulating an effective adaptive response against cancer, it is crucial for nanovaccine carrying tumor-specific antigens to be delivered to DCs *in vivo* [126]. Thus, a variety of nanoparticle delivery systems, including liposomes [127], polymeric nanoparticles [128,129], inorganic nanoparticles [130,131], and virus-like particles [132,133] have been utilized as vaccine carriers and further manipulated to deliver into lymphoid organs where many DCs are mainly present. Kranz et al. developed RNA-lipoplex (RNA-LPX) nanoparticles composed of lipid complexes containing RNA that encodes tumor antigens [134]. Based on the optimized ratios of lipid:RNA, the study suggested that the RNA-LPX could be directed to the spleen and various lymphoid tissues and subsequently induce strong effector and memory T cell response.

Despite the great promise of *in vivo* direct DC targeting strategies, the low number of DCs at the site where a tumor antigen is administered generally results in a small pool available to prime the tumor antigen-specific immunity, significantly limiting vaccine efficacy. Several studies have suggested promising approaches to address these concerns by employing biomaterial, creating an infection-mimicking microenvironment by appropriately presenting key elements of infection, such as inflammatory cytokines and danger signals, to attract host DCs and further stimulate DC activation and trafficking. For example, Liu et al. proposed a two-step hybrid strategy by using a biomaterial scaffold capable of modulating DCs *in situ* to enhance antigen uptake and presentation for effective cancer vaccine (Fig. 9) [135]. The first step involves creating a microenvironment where host DCs can be recruited and allowed to proliferate and activated *in situ* by using chemoattractant-releasing injectable thermosensitive hydrogels, clearly demon-

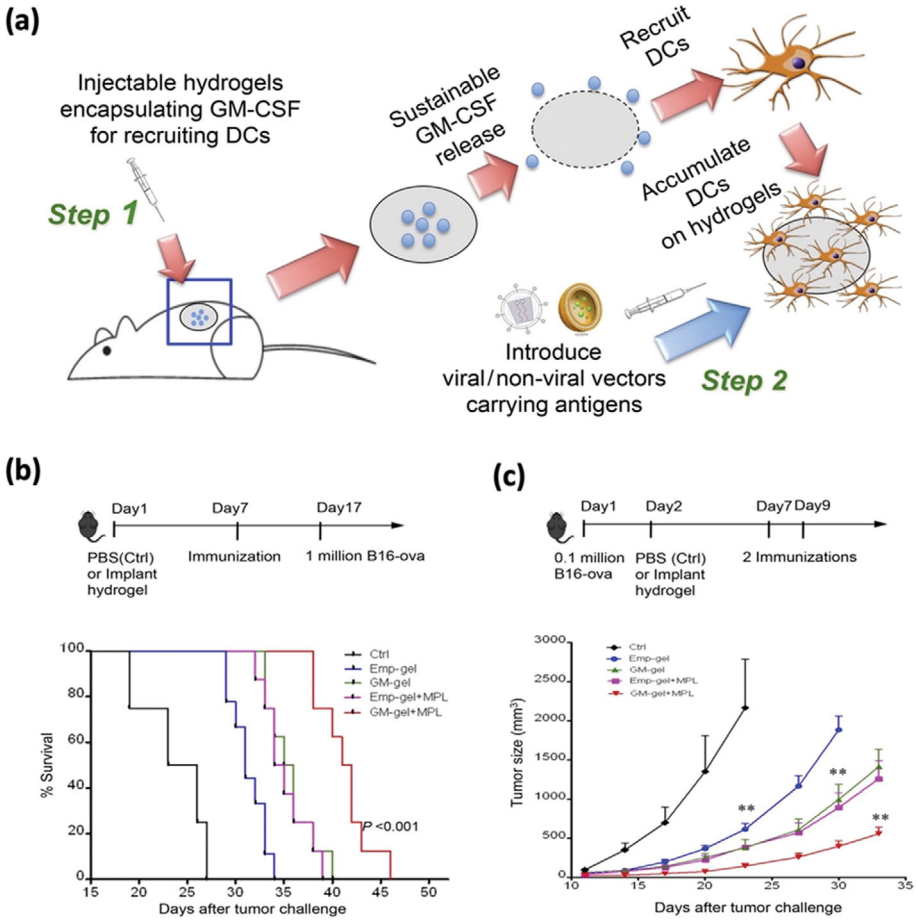

Fig. 9. *In situ* modulation of DCs for cancer vaccines. (a) Schematic illustration of the two-step hybrid strategy for an effective cancer vaccine. (b) Schematic diagram showing the immunization and tumor challenge procedure in the prophylactic model. Kaplan-Meier survival plot of mice treated with PBS (Ctrl), empty hydrogel scaffolds (Emp-gel), GM-CSF hydrogel scaffolds (GM-gel), followed by immunization with DC-LV-OVA only or with adjuvant MPL (Emp-gel+MPL, GM-gel+MPL; n=10). (c) Schematic diagram showing tumor inoculation on day 1 and hydrogel implantation 1 day later, followed by two immunizations in the therapeutic model. Tumor growth was plotted as mean±SEM (n=8) as a function of days after B16-OVA tumor challenge (indicates P<0.01). Reproduced with permission [135].**

strating that a significant number of DCs and macrophages could be successfully recruited *in vivo* through the sustained release of granulocyte-macrophage colony-stimulating factor (GM-CSF) from the injected hydrogels. As the second step, viral or non-viral vectors carrying antigens were then injected to the recruited host DCs around the hydrogels, which could significantly enhance the efficacy of antigen uptake and presentation to DCs, resulting in generating a high level of tumor-specific immunity.

Besides targeting DCs, nanobiomaterials have been engineered to deliver immunomodulatory drugs directly to the tumor microenvironment that is profoundly immunosuppressive, resulting in promoting tumor growth and metastasis. Thus, the modulation of the tumor microenvironment with cytokines and inhibitory molecules can potentially enhance anti-cancer immune responses. Park et al. developed nanoscale liposomal polymeric gels (nano-lipogels) to co-deliver hydrophobic transforming growth factor-β (TGF-β) inhibitor and hydrophilic cytokine IL-2 to the tumor microenvironment [136]. The nano-lipogels significantly delayed tumor growth, increased survival rate, and enhanced the activity of natural killer cells and $CD8^+$ T cells infiltration.

COMBINED CANCER IMMUNOTHERAPY

Combined cancer immunotherapy with other therapeutic strategies, such as radiation, chemotherapy, and phototherapy, has been widely considered to mitigate many concerns arising from the poor therapeutic efficacy of single treatment and has shown synergistically enhanced anti-tumor therapeutic effects [137]. Especially, phototherapies, including photothermal therapy (PTT) and photodynamic therapy (PDT), are emerging as a noninvasive and novel therapeutic technique due to their improved selectivity and low systemic toxicities [138,139]. The Liu group proposed combination anti-CTLA-4 ICB therapy with PTT with single-walled carbon nanotubes (SWNTs), suggesting that debris released from cancer cells upon PTT of primary tumors could possibly act as the tumor-associated antigen to elicit robust anti-tumor immunity (Fig. 10) [140]. Furthermore, this combined strategy of SWNT-based PTT was able to greatly increase the efficacy of anti-CTLA-4 blockade

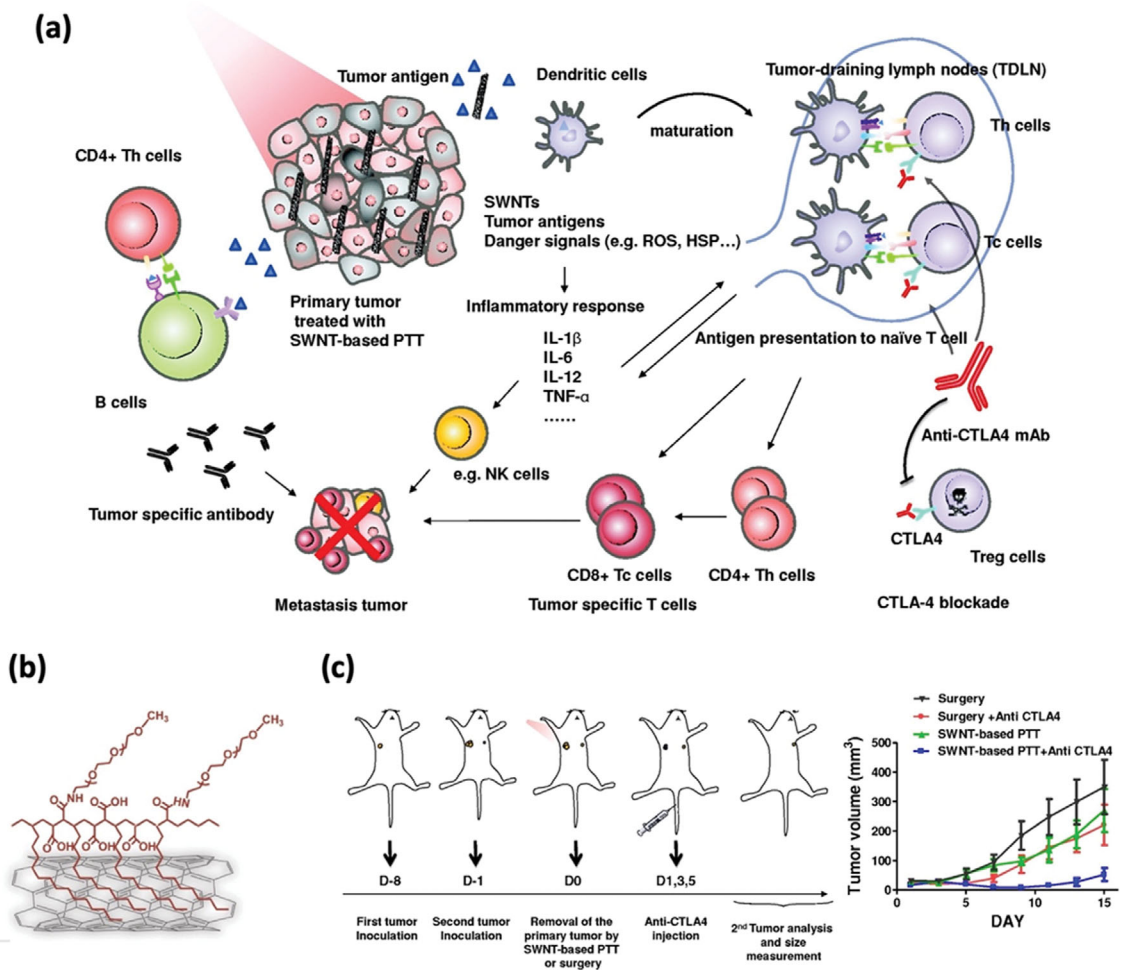

Fig. 10. Combined cancer immunotherapy with photothermal therapy. (a) Mechanism of anti-tumor immune responses induced by SWNT-based PTT combined with CTLA4 blockade therapy. (b) Design of PEGylated SWNTs. (c) Schematic illustration of SWNT-based PTT and anti-CTLA-4 combination therapy. (d) Tumor-growth curves of different groups of mice after various treatments indicated. Reproduced with permission [140].

by inhibiting the growth of distant established tumors.

Another study suggested that PTT could promote tumor infiltration and anti-tumor activity of CAR-T cells. Typically, CAR-T therapies show relatively low therapeutic efficacy in solid tumors due to the desmoplastic structure of tumors and inefficient infiltration of CAR-T cells into the tumor. Thus, the development of novel approaches to promote the infiltration of CAR-T cells into tumors has become an urgent need. Chen et al. developed the combined therapy strategy of intratumoral injection of poly(lactic-co-glycolic) acid (PLGA) nanoparticles loaded with indocyanine green as a photothermal agent and the subsequent intravenous administration of CAR-T cells, leading to the obvious enhancement of anti-tumor efficacy by increasing the CAR-T cell infiltration into tumors destructed by PTT [141].

In addition to PTT, PDT has been widely used for cancer treatment by employing photosensitizers to generate reactive oxygen species (ROS). Xu et al. designed upconversion nanoparticles loaded with a photosensitizer and Toll-like-receptor agonist, imiquimod, which could induce effective photodynamic destruction of tumors via near-infrared (NIR) irradiation [142]. Moreover, PDT combined with anti-CTLA-4 ICB therapy showed excellent efficacy in eliminating tumors exposed to the NIR laser, resulting in stimulating strong anti-tumor immune responses to inhibit the growth of distant tumors [143].

CONCLUSIONS AND PERSPECTIVES

To date, remarkable advances have been made in the development of biomaterials capable of modulating the immune system for use in various cancer immunotherapies. Evidently, biomaterial-assisted delivery technologies show great promise for improving the therapeutic potency of ICB therapy, cancer vaccine, and CAR-T cell therapy and also reducing their immune-related adverse effects. In this review, we introduced many specific examples of novel delivery systems that could improve localized, targeted, and combined cancer immunotherapy by leveraging the engineered properties of biomaterials. However, significant obstacles still exist to be widely used in clinical settings, which includes biomaterial-induced toxicity and immunogenicity, high cost, and feasibility of scale-up manufacturing. Therefore, advanced biomaterials pos-

sessing biocompatibility, biodegradability, low toxicity, high stability, and facile fabrication should be broadly explored for developing improved biomaterial-assisted cancer immunotherapies.

Future work should investigate smart bioresponsive biomaterials that are able to respond selectively to desired biological signals. Based on the understanding of various biologically responsive mechanisms, several physiological parameters resulting from pathological conditions are proposed as attractive targets for on-demand drug delivery at target tissue sites, which would possibly reduce off-target effects. The physiological triggers include pH, redox potential, enzymes, temperature, glucose, ionic strength, and hypoxia, which are closely relevant to disease conditions. The bioresponsive design also includes the implementation of externally triggered signals, such as light, ultrasound, microbubbles, and mechanical cues for remotely controlled immunotherapy. Another emerging design approach involves engineering biomimetic or bio-inspired systems by mimicking the natural structure and functions. For example, the utility of superior underwater adhesiveness of mussel proteins, incorporation of the efficient cell penetration capability of viruses, and response mechanism of granules in pancreatic β cells can be applied to design innovative bioresponsive biomaterials.

In addition, further studies regarding the physiochemical properties of biomaterials, such as size, shape, charge, chemical functionality, and hydrophobicity, can potentially provide a means to design new delivery technologies by understanding their influence on the activation of specific immune pathways. Furthermore, fundamental investigations on the interactions between biomaterials and immune cells should be made to develop new technologies for actively manipulating immune responses.

Overall, this review highlights recent advances in the engineering of biomaterials capable of enhancing cancer immunotherapy. Although biomaterial-assisted immunotherapy strategies described here are still in a proof-of-concept stage, they will prove essential in contributing to new paradigms for broadly applicable cancer immunotherapy.

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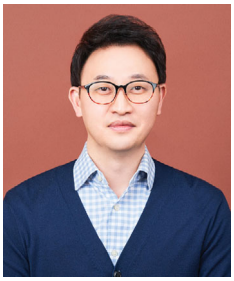

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