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Biomaterials

Improving Cancer Immunotherapy Outcomes Using Biomaterials

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Immunotherapy has made great strides in improving clinical outcomes in cancer treatment. However, few patients exhibit adequate response rates for key outcome measures and desired long-term responses, and they often suffer systemic side effects due to the dynamic nature of the immune system. This has motivated a search for alternative strategies to improve unsatisfactory immunotherapeutic outcomes. In recent years, biomaterial-assisted immunotherapy has shown promise in cancer treatment with improved therapeutic efficacy and reduced side effects. These biomaterials have illuminated fundamental mechanisms underlying the immunoediting process, while greatly improving the efficacy of chimeric antigen receptor (CAR) T-cell therapy, cancer vaccine therapy, and immune checkpoint blockade therapy. This Minireview discusses recent advances in engineered biomaterials that address limitations associated with conventional cancer immunotherapies.

1. Introduction

Cancer immunotherapy is a promising approach that activates a patient's immune system to combat cancer.[1] Unlike traditional chemotherapy or radiotherapy, cancer immunotherapy utilizes activated immune cells to recognize and attack specific tumor cells, which may ameliorate the severe side effects associated with those traditional methods. More importantly, immunotherapy can have abscopal effects that inhibit and eradicate metastatic tumors, a leading cause of cancer mortality worldwide.[2] Currently, cancer immunotherapy includes three major strategies: adoptive cell therapy (e.g., chimeric antigen receptor (CAR) T-cell therapy, T-cell receptor-engineered (TCR) T-cell therapy, and chimeric antigen receptor-natural killer cell (CAR-NK) therapy), immune checkpoint blockade therapy, and cancer vaccine therapy (Figure 1).

For cell-mediated immunity to control tumor growth, cancer immunotherapy requires a series of steps to stimulate an anticancer immune response in patients, a process known as the cancer-immunity cycle.[3] Removal of tumors cannot rely entirely on the immune system due to immune tolerance and immunosuppression in the tumor microenvironment. For instance, regulatory T cells (Treg) may suppress the antitumor efficacy of T cells via anti-cytotoxic-T-lymphocyte antigen 4 (CTLA-4). T cells can also express programmed cell death protein-1 (PD-1) and programmed cell death ligand-1, which dampen the antitumor immune response.[4] Moreover, the immunosuppressive tumor microenvironment, derived from immune-suppressed cells or cytokines, tends to restrain T cell infiltration into tumor sites, impeding cytotoxic efficacy.[5] Taken collectively, disruption of one or more steps of the cancer-immune cycle may result in inefficacious immunotherapy. Encouragingly, materials science has contributed significantly to enhancing cancer immunotherapy. To date, myriad materials have been designed to improve anti-tumor immunotherapy by amplifying the effect of adoptive cell therapy, prolonging antigen action time through controlled release of antigen, lymph node targeting, etc. (Figure 2). In this minireview, we highlight rationally designed biomaterials that possess powerful synergies with immunotherapies. Several commonly used inorganic materials, such as silica, carbon, and metal, are also covered because they can be used as immunoregulators in disease prevention and treatment.

2. Materials for Improving Cancer Immunotherapy Outcomes

2.1. Biomolecule-based materials

Biomolecule-based materials have been employed as immunomodulators, vaccine carriers, and targeting vehicles in tumor and immune cells to improve immunotherapy.[6] These materials include nucleic acids, peptides, proteins, and carbohydrates. For instance, CpG oligodeoxynucleotides (CpG, short single-stranded synthetic DNA molecules) and cGAMP (cyclic dinucleotide) have been adopted as immunostimulators for immunotherapy studies. Immune checkpoint blockade antibodies have been approved for clinical use as specific tumor treatments. Significantly, biomolecule-derived nanoparticles can enhance adoptive cell therapy. For example, using a reversible chemical linker, Tang et al. anchored T cells to protein nanogels loaded with interleukin-15 super-agonist complexes. The conjugated nanogels responded to the surface reduction of T cells in a tumor microenvironment with high-levels of antigens, leading to minimal toxicity compared to the free cytokines. This strategy significantly improved the efficacy of T-cell therapy in mouse models.[6c] Moreover,

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biomolecules can assemble into nanoparticles for therapeutic delivery.[7] Recently, Zhu et al. designed intertwining DNA-RNA nanocapsules (iDR-NCs) through self-assembly from CpG and short hairpin RNA for delivery of tumor-specific peptide neoantigens to antigen-presenting cells in lymph nodes for cancer immunotherapy.[8] These DNA/RNA/peptide-based nanovaccines augmented the response of neoantigen-specific peripheral $CD8^+$ T cells more than 8-fold relative to CpG controls. Consequently, these nanovaccines effectively prevented the growth of neoantigen-specific colorectal tumors. In a subsequent study, exogenous vaccine molecules and endogenous albumin were assembled in vivo for vaccine delivery to lymph nodes, resulting in improved cancer immunotherapy.[9] The endogenous nanocarrier-based strategy may be more efficacious for personalized cancer treatment with fewer side effects. Moreover, adjuvant molecules can assemble into nanoparticles with other therapeutic products for synergistic enhancement of immunotherapy through tumor-related antigen release upon ablation. For example, Pan et al. mixed antigen ovalbumin (OVA) and a theranostic agent, indocyanine green (ICG), to form nanovaccines featuring a high antigen-loading efficiency (80.8 %) and intense near-infrared absorption.[10] By following these nanovaccines with an 808-nm laser, it is possible to track and stimulate dendritic cells and to provide imaging-guided photothermal-immunotherapy of tumors with improved efficacy. Personalized cancer vaccines use patient-specific neoantigens as vaccine targets and potentiate personalized oncotherapy by eliciting tumor-specific immune responses. However, the physicochemical variability of neoantigens can present challenges to manufacturing personalized cancer vaccines and sometimes fails to induce effective T-cell responses. To overcome this challenge, Lynn et al. developed a versatile vaccine platform to co-deliver peptide-based tumor antigen with adjuvants in self-assembled nanoparticles. This assembly, enabled by charge-modified peptide-TLR-7/8a conjugates, enhances neoantigen-specific T-cell responses, suggesting that biomaterials can be chemically programmed to enhance the cross-presentation of neoantigens by antigen-presenting cells and to promote T cell immunity.[6d]

Biomolecules such as immune checkpoint inhibitors have been investigated in clinical trials for cancer immunotherapy. However, their limited beneficial effects need to be improved. Combining multiple immune checkpoint inhibitors with other therapeutic molecules has proven effective in improving immunotherapy, but this approach may generate more severe side effects than single-component treatments. Although nanocarriers are effective for delivering immunomodulators to specific sites, delivery efficiency and release control of loaded molecules need further optimization.

2.2. Polymer-based materials

Polymers are one of the most used multifunctional materials in biomedicine. They have been adopted to deliver various therapeutics via micellar structures or polymer-drug conjugates, and some polymers show special photochemical characteristics that are useful for cancer theranostic applications. Various types of polymer-based materials such as poly(lactic-co-glycolic) acid (PLGA), chitosan, and polyethyleneimine, have been employed as adjuvants or as neoantigen carriers for antitumor immunity augmentation.[11] Polymer-based materials can simultaneously deliver agents with different hydrophilic and hydrophobic properties to enhance conventional therapies such as chemotherapy, photodynamic therapy (PDT), radiotherapy, and gene editing, highlighting their potential to induce immunogenic cell death and antitumor immunity.[12] For instance, Feng et al. reported the use of a light-activatable prodrug of oxaliplatin, a photosensitizer pheophorbide A combined with an indoleamine 2,3-dioxygenase1 (IDO-1) inhibitor to efficiently elicit an immune response and to promote intratumor infiltration of cytotoxic T lymphocytes.[12c] ICG-loaded PLGA nanospheres can enhance efficacy of CAR T-cell therapy by modulating the tumor microenvironment.[12d] In addition, polymeric nanoparticles can target specific immune cells to modulate immunity.[13] Tumor-associated macrophages (TAMs) can be modulated by immunostimulatory polymeric nanoparticles introduced by different routes. For example, Shae et al. designed a pH-responsive polymer-based nanoparticle to deliver cGAMP and stimulate interferon gene (STING) signaling in the tumor microenvironment and in sentinel lymph nodes.[14] They found that as-designed STING nano-

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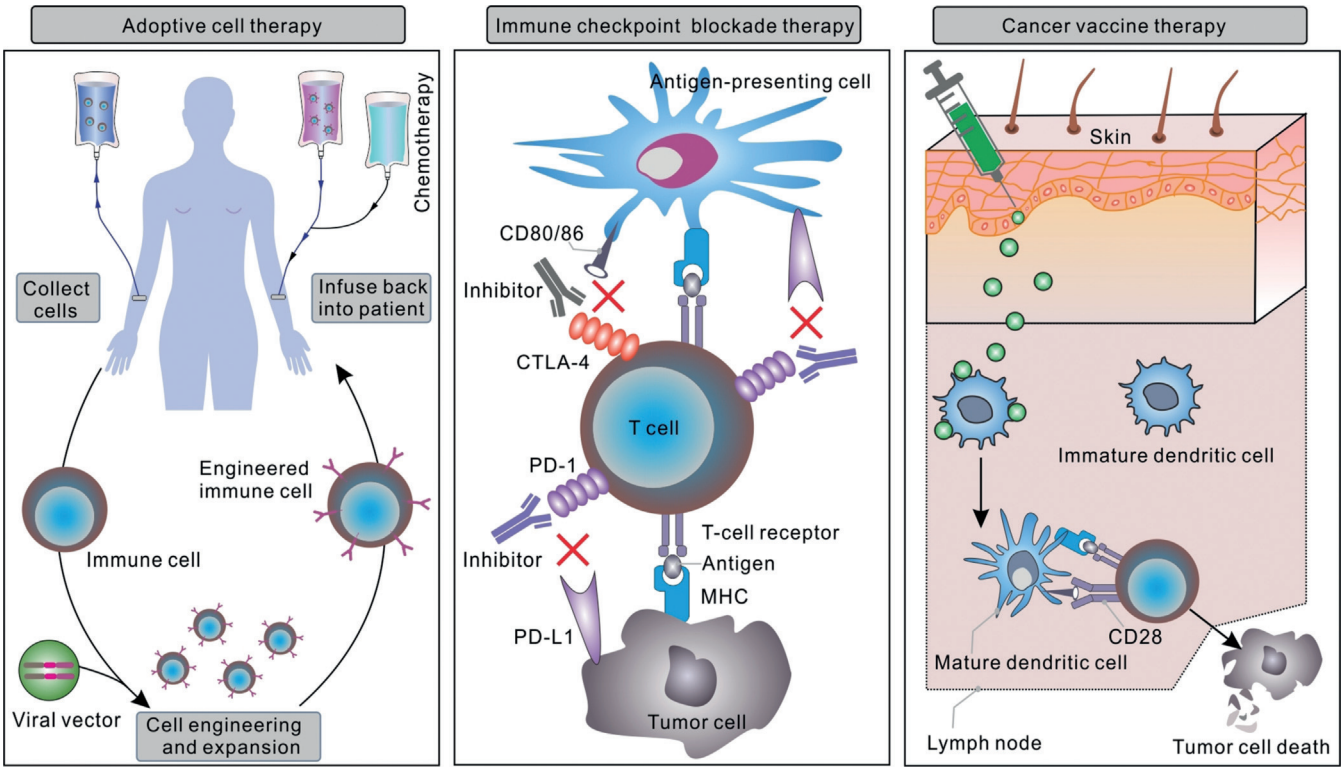

Figure 1. An overview of current strategies for cancer immunotherapy. Adoptive cell therapy works by engineering and proliferating immune cells ex vivo and infusing them back into patients, in whom chemotherapy has been used to lower white blood cell counts. Immune checkpoint blockade therapy employs inhibitors such as CTLA-4 and PD-1 antibodies to block the immune checkpoint and to enhance immune therapy by acting on regular and effector T cells, respectively. The neoantigen vaccine method uses cancer-specific neoepitopes as vaccine targets and shows promise for personalized oncotherapy by initiating tumor-specific immune responses. MHC: major histocompatibility complex. These diagrams are not to scale.

particles potently inhibited B16F10 tumor growth by stimulating an immunogenic, T-cell-inflamed tumor microenvironment (Figure 3). Importantly, polymers can be engineered to respond to tumor-microenvironmental elements by conjugation with functional groups or loading with exogenous moieties (Table 1).[15] Other polymer-based materials have also been used to improve immunotherapy. For instance, using in vivo antigen capture, multiple immune reagents can be delivered, and phototherapy can be integrated with gene therapy.[16] As an added benefit, cryopreservation of immune cell-modified polymer materials is feasible for long-term storage and for maintaining viability and functionality.[17]

Table 1: Representative examples of immunotherapy mediated by polymers responsive to tumor microenvironments.

Response	Functcional group	Major component	Refs.
pH	Tertiary amines	PDPA[b]	[14]
	CDM[a]	PEG-CDM-PDEA[c]	[15a,b]
Caspase	Asp-Glu-Val-Asp peptide	PpIX-1-methyl-tryptophan	[15c]
MMP-9[d]	PLGLWADR peptide	PEG-hyaluronic acid	[15d]
Glutathione	Disulfide bond	Mitoxantrone-celastrol	[15e,f]
H_2O_2	Catalase	PLGA	[15g]

[a] CDM: 2-propionic-3-methylmalaic anhydride. [b] PDPA: poly(ethylene glycol)-block-poly(diisopropanol amino ethyl methacrylate-co-hydroxyethyl methacrylate). [c] PDEA, poly(2-(diethylamino) ethyl methacrylate. [d] MMP-9, matrix metalloproteinase 9.

Polymers can be formulated into μm-size particles and macro-sized devices for drug delivery and disease monitoring.[18] Wang et al. used polymeric needle patches to transdermally deliver immune checkpoint blockers and immunomodulators to enhance immunotherapeutic efficacy, showing potent inhibition of B16F10 cell growth and significant enhancement in survival of tumor-bearing mice.[19] Moreover, functionalized polymeric needle patches may improve therapeutic outcomes by controllable release of stimulators and local induction of immunogenic cell death. For instance, melanin-modified needle patches could stimulate antitumor immunity by heating under near-infrared light irradiation.[20] A charge-invertible polymer-decorated patch could quickly insert into the skin to sustain antigen release over several days.[21] In addition, microneedle arrays have been used to proliferate tumor-specific T cells in vivo.[22]

Polymer immunogenicity is related to physicochemical properties such as molecule weight, surface charge, and chemical stability. Thus, it is highly desirable to fully understand the relationship between physicochemical properties and the antigenicity of a given polymer. Another concern about polymeric materials for immunotherapy is insufficient specificity in targeting tumor sites and T cells, which results in unsatisfactory therapeutic outcomes.

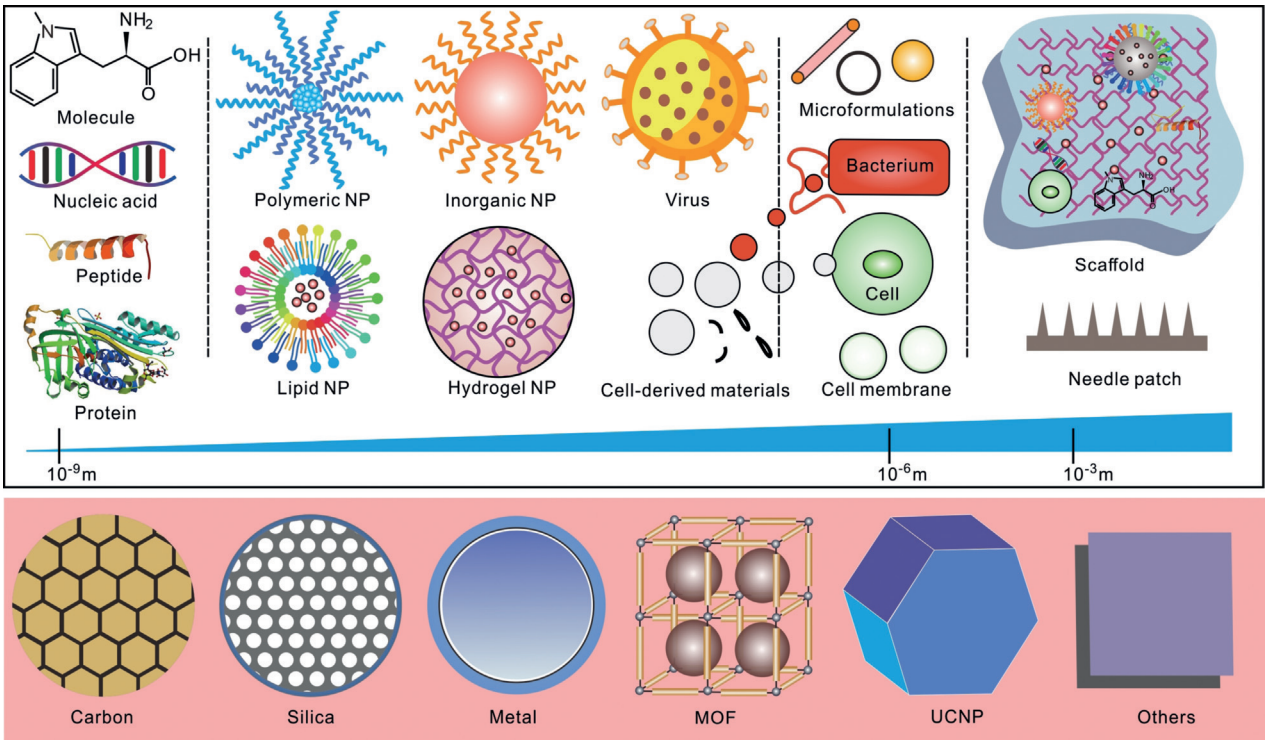

Figure 2. Biocompatible materials to improve cancer immunotherapy. Organic molecules of several nanometers (e.g., indoximod) and biomolecules such as nucleic acids, peptides, and proteins (e.g., ovalbumin) could be used as immunomodulators to elicit anti-tumor immunity. Alternatively, they could be encapsulated in formulations or assembled into nanoparticles for delivery. Sizes of nanoparticles (NPs), including polymeric, lipid, hydrogel, inorganic NPs, viruses, and cell- or bacterial-derived vesicles, range from tens to hundreds of nanometers. These NPs can deliver immunomodulators or therapeutics to trigger anti-tumor immunity. Microsized cells, such as CAR T-cells, show promise in suppressing tumors. Bacteria can also influence host immunity, and other microformulations are commonly used for ex vivo immunity augmentation. Large scaffolds and needle patches are capable of delivering therapeutics to tumors locally. Carbon, silica, metal, and upconversion nanoparticle-based inorganic NPs, metal-organic frameworks, and other formulations are also suitable candidates for cancer immunotherapy.

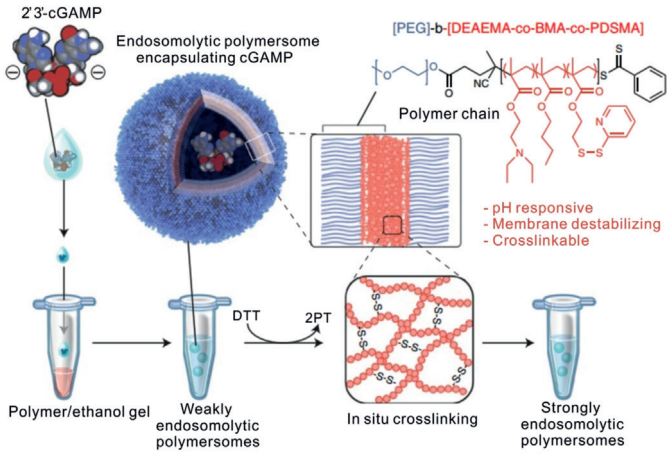

Figure 3. (a) Scheme showing STING nanoparticle fabrication and structural details. Adapted with permission from Ref. [14]. Copyright 2019, Nature Publishing Group.

2.3. Lipid-based materials

Liposomes or lipid-based vesicles are considered one of the most versatile, flexible carriers for drug delivery. They have proven more efficient than synthetic polymers for site-specific drug targeting and delivery due to their high biocompatibility, ready biodegradability, excellent drug loading capacity, and rapid absorption. Moreover, together with other formulations, lipids are often used to reduce cytotoxicity, increase hydrophilicity, and ultimately boost bioavailability of aqueous-soluble drugs. From an immunotherapy perspective, enhanced drug solubility in lipid nanoparticles offers unique possibilities for controlled drug delivery and targeting via different routes of administration.[23] For instance, high-density lipoprotein nanodiscs constructed from phospholipids and peptides could enable simultaneous delivery of antigens and adjuvants or drugs, to elicit host antitumor immunological responses.[24] Hollow lipid nanoparticles can encapsulate high-dose modulators for combined immunotherapies. For example, Yue et al. fabricated a liposome nanoplatform (HMME/R837@Lip) co-loaded with sonosensitizers (hematoporphyrin monomethyl ether: HMME) and immune adjuvant (imiquimod R837) for sonodynamic therapy and antitumor immunity stimulation (Figure 4).[25] When combined with checkpoint blockade, HMME/R837@Lip inhibited tumor growth and metastases in 4T1 and CT26 tumor models with high efficacy. High-dose injection of immunostimulatory agents may elicit acute systemic toxicity while generating antitumor immunity. Experimental data show that drugs incorporated in lipid-based materials can increase bioavailability with minimal side effects because of protection from degradation, rapid delivery into tumors, and suppressed systemic exposure due to enhanced permeability

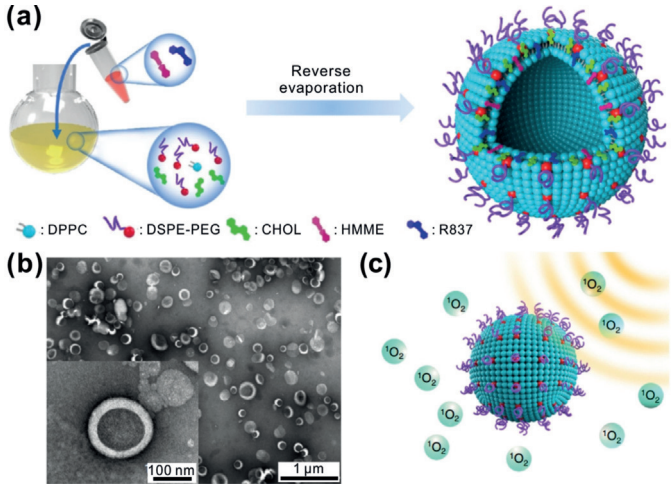

Figure 4. (a) Synthesis of the HMME/R837@Lip. (b) Transmission electron microscopy imaging of HMME/R837@Lip. (c) Scheme of ultrasound-triggered singlet oxygen ($^1O_2$) production enabled by HMME/R837@Lip. Adapted with permission from Ref. [25]. Copyright 2019, Nature Publishing Group.

and retention.[26] The effect of cell therapies usually fades with declining T-cell viability and function. Using adjuvant drugs may alleviate this deficiency, but with severe toxicity. Drug caches on T-cell surfaces could stimulate T cells while decreasing associated toxicity. This was exemplified in the work of Irvine and co-workers,[23g] who conjugated nanosized liposomes to T-cell surfaces using thiol-maleimide chemistry. In their design, drug-loaded liposome particles sustained T-cell stimulation continuously, resulting in robust proliferation of T cells and improved therapeutic efficacy in mouse models. Liposomes have also been used to improve therapeutic outcomes of a malaria vaccine. Huang et al. proved that insertion of recombinant Plasmodium falciparum Pfs25, a transmission-blocking vaccine, into bilayers of nanosized liposomes leads to durable antibody responses.[23f] This functional modality, enabled by spontaneous nanoliposome antigen particleization, has the potential to develop into powerful nanovaccines by conjugating multiple recombinant polypeptides.

Although lipids are widely studied clinically for antitumor therapies, many challenges need to be addressed before use in immunotherapy: i) organic solvents or high temperatures used during synthesis may denature macromolecules and heat-sensitive substances; ii) lipid carbon chain lengths are commonly inhomogenous; iii) electronegativity of lipids reduces adjuvant-loading capacity; iv) lipids lack tumor-targeting ability; and v) lipids manifest poor storage stability.

2.4. Cell-based materials

In addition to CAR T-cell immunotherapy, other immune cells[27] and cell-derived materials, such as microvesicles, exosomes, and membranes, have been used to improve immunotherapy. Apart from their intrinsic functions, cell-derived vesicles can be developed with exogenous abilities by chemical modification and bioengineering.[28] For example, Wang et al. demonstrated that engineered platelets can drastically inhibit tumor recurrence and metastasis after surgical removal of the primary tumor.[29] The authors decorated platelets with PD-L1 antibodies through maleimide-based chemical ligation. With the migration and accumulation of these functional platelets at the site of a wound, PD-L1-blocking antibodies were administered to target circulating tumor cells in the bloodstream. Their approach effectively inhibited cancer recurrence and metastatic spread in postsurgical melanoma and breast carcinoma mouse models.

Cell-derived membranes and vesicles exhibit cell-like targeting abilities.[30] Deng et al. devised a natural killer (NK) cell membrane, coated with mPEG-PLGA nanoparticles and photosensitizer 4,4′,4″,4‴-(porphine-5,10,15,20-tetrayl) tetrakis (benzoic acid), for PDT-enhanced immunotherapy. Antitumor immunity of this formulation, due to the tumor-targeting ability of the NK cell membranes, enhanced polarization of pro-inflammatory M1 macrophages, resulting in selective accumulation of NK nanoparticles in the tumor, which mitigated primary tumor growth and metastatic tumor formation abscopally.[31] Tumor cell-derived vesicles or membrane coatings can function not only as carriers for immunomodulator delivery but also as intrinsic tumor-associated antigens for immune activation.[32]

Although CAR-T-based immunotherapy has proven useful in treating malignancies in clinical trials, applying this therapy across all cell types presents several challenges. This technology is time-consuming and costly and few patients present positive outcomes. There is a strong demand for developing more effective and versatile CAR T-cell therapies. Despite advances in recent years, the promise of cancer cell-derived materials for immunotherapy remains elusive. Side effects of cell vesicles, such as potential carcinogenesis, need to be systematically investigated in animal models.

2.5. Bacteria and viruses

Many bacteria have the ability to target, and in some cases, even destroy tumors, and resulting cellular debris can serve as a natural adjuvant to trigger antitumor immunity.[33] Bacterial cytoplasmic membranes may be employed to target tumors or used as adjuvants for enhanced immunotherapy.[34] Growing evidence suggests that the microbiome can influence diverse human diseases, including cancer.[35] Modulating the gut microbiome may impact outcomes of cancer immunotherapy, especially for immune checkpoint blockade-based therapies.[36] It is also important to understand the complex interactions between the microbiome and host immunity, which will profoundly influence the future of immunotherapy.[37]

Viruses are exquisite nanoscale biomaterials that have been engineered as highly promising platforms for a host of applications, including cancer therapy. Compared to synthetic nanoparticles, viruses are more easily functionalizable with excellent reproducibility, and their subunits can be spatially

arranged with high precision.[38] Immunotherapeutic benefits of viruses have attracted considerable attention over the past decade because viruses can amplify host immune responses, release tumor-associated antigens, and disrupt immune tolerance.[39] Oncolytic viruses have been used to improve patient outcomes in immune checkpoint blockade by preferentially infecting and killing cancer cells.[40] Viral peptides can reinvigorate virus-specific memory T-cells and innate and adaptive immunity to inhibit tumor growth.[41] Viruses have also been modified as carriers for vaccine delivery.[42] In clinical trials, oncolytic virus-based combination immunotherapies have shown promise for treatment of many types of cancers.[43] However, the biggest challenge remains the need to completely understand mechanisms by which bacteria selectively target and destroy malignant cells without harming normal, healthy tissues.

To fully realize the potential of bacteria and viruses in immunotherapy, a thorough understanding of their behavior in the tumor microenvironment is needed. We also need to better understand advantages and disadvantages of various administration routes (oral, intratumoral, or intravenous). By exploring these and biodistribution patterns, we can optimize doses to maximize efficacy and minimize side effects.

2.6. Carbon-based materials

Carbon-based materials such as nanotubes, graphene oxide, quantum dots, and nanodiamonds, have found widespread applications as drug delivery vehicles for immunotherapy. A battery of immunomodulators has been delivered using carbon-based nanomaterials to enhance immune responses.[44] For example, Zhang et al. reported that delivery of immunostimulatory CpG oligonucleotides using nanodiamonds enhanced cytokine secretion.[44a] Yu et al. decorated nanosized graphene oxide (GO) particles with tumor integrin αvβ6-targeting peptide (HK) and photosensitizer HPPH for PDT-enhanced immunotherapy.[44c] The fabricated GO-(HPPH)-PEG-HK nanoprobes accumulated in tumors after systemic administration. Upon 671-nm laser irradiation, necrotic tumor cells preferentially activated dendritic cells and promoted infiltration of cytotoxic $CD8^+$ T lymphocytes into tumors, thereby preventing tumor growth and lung metastasis. Likewise, polyethylene glycol-passivated graphene oxide nanosheets (nGO-PEGs) are capable of stimulated significant cytokine responses in peritoneal macrophages, as evidenced by atomic molecular dynamics simulations and experimental detection.[45] Although in vivo experiments are needed to measure the effects of laser stimulation on immune responses, this work demonstrates that biomaterial interfaces and surface functionalities are indispensable in the development of novel nanomaterials for safe and effective biomedical applications.

2.7. Silica-based materials

Silicon dioxide and its polymeric derivatives (silica) are a family of materials with distinct advantages for therapeutic applications, including mild processing conditions, excellent biocompatibility, high loading capacity, and readily modifiable surface functions. Moreover, silica-based materials can be made completely biodegradable while leaving behind their biological payloads for enhanced therapeutic efficacy. For these reasons, silica-based materials have shown great potential as drug carriers. Many types of silica formulations, such as porous silica nanoparticles,[23a,46] hollow mesoporous silica nanospheres,[47] mesoporous organosilica hollow spheres,[48] and mesoporous silica microrods,[49] have been designed and synthesized for tumor immunotherapy (Figure 5 a–e).[50] It has recently been reported that mesoporous, silica-based nanomaterials (MSNs) display intrinsic adjuvanticity for improved immunotherapy.[51] Although the intrinsic adjuvanticity of MSNs is related to their structures and physicochemical properties, further studies are needed to comprehend the means by which they stimulate immune cells. Various types of adjuvants, antigens, and therapeutics have been loaded onto porous silica nanospheres or nanorods to form vaccines for cancer immunotherapy. For instance, mesoporous silica, loaded with glucose oxidase and then encapsulated with cancer cell membranes, was employed to promote tumor starvation. By blocking tumor energy supply by oxidizing intracellular glucose, Xie et al. demonstrated that tumor starvation therapy can increase the efficiency of immune checkpoint blockade in cancer.[52] Microscale mesoporous silica microrods have also been used as a convenient delivery system for immunotherapy.[53] Cheung et al. showed that interleukin-2-functionalized mesoporous silica microrods promote greater expansion of therapeutic ex vivo T-cells, compared with commercial expansion beads.[54] Alternately, Kim et al. developed an injectable, pore-forming, scaffold-

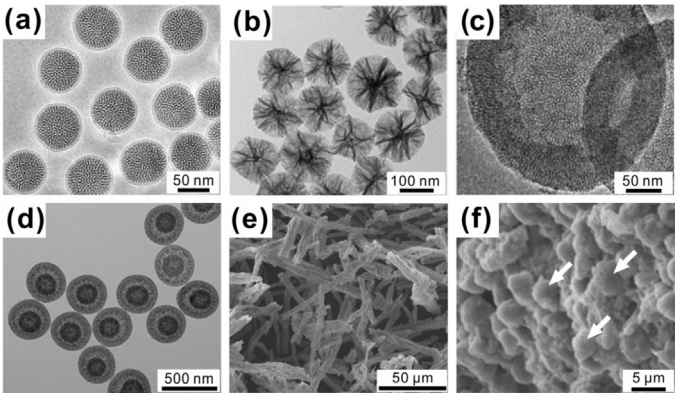

Figure 5. Various types of silica-based materials used for tumor immunotherapy. (a–d) Transmission electron microscopy imaging of mesoporous silica NPs, featuring a lipid shell layer, a large pore size, a hollow-core structure, and a mesoporous organosilica core–shell structure, respectively. (e) Scanning electron microscopy imaging of mesoporous silica microrods. (f) Scanning electron microscopy imaging of recruited cells on assembled silica rod scaffolds isolated from the mouse tumor. White arrows indicate representative cells. (a) Adapted with permission from Ref. [23a]. Copyright 2017, Nature Publishing Group. (b) Adapted with permission from Ref. [46]. Copyright 2019, American Chemical Society. (c) Adapted with permission from Ref. [47]. Copyright 2016, Wiley-VCH. (d) Adapted with permission from Ref. [48]. Copyright 2017, Wiley-VCH. (e,f) Adapted with permission from Ref. [49]. Copyright 2015, Nature Publishing Group.

based vaccine platform to program host immunity (Figure 5e,f). Their design mimicked an immune-tissue-like 3D cellular microenvironment that supported generation of effective humoral (both Th1 and Th2) and cellular immune responses through sustained release of inflammatory signals and adjuvants from the vaccine platform.[49]

2.8. Metal-based materials

Metal-based materials have recently been a focus of biomedical research. In light of their controllable size, shape, and surface functionalities, metal-based materials are ideally suited for medical diagnosis and therapeutics. Among metal-based materials utilized in immunotherapy, the most commonly adopted strategy involves delivery of immunomodulators, including adjuvants, cytokines, neoantigens, and checkpoint inhibitors.[55] Another approach is the induction of neoantigen release by local ablation of tumors through therapeutic delivery or external stimulation.[56] Metallic materials can be used for tumor imaging in different manners, and some of them can even reverse hostile therapy-resistant tumor microenvironments.[57] For example, manganese dioxide can catalyze the oxidation of intratumor H_2O_2 to O_2 to alleviate tumor hypoxia. This situation may reduce the effectiveness of PDT and chemotherapy, as well as facilitating tumor metastasis. To this end, manganese dioxide nanoparticles have been combined with PD-L1 antibody to improve PDT/chemotherapy.[57a] The combined approach triggered a robust antitumor response and inhibited abscopal tumor growth.

In another report, Nam et al. used doxorubicin-coupled spiky gold nanoparticles to treat tumor metastasis in CT26 and TC-1 mouse models under 808-nm laser irradiation.[58] They demonstrated that combined PTT/chemotherapy activated local and abscopal antitumor immunity. Intriguingly, metallic particles also display intrinsic immunotherapeutic properties. For instance, Zanganeh et al. discovered that ferumoxytol, an FDA-approved iron supplement, delays early mammary growth and inhibits lung cancer metastasis in liver and lung by inducing pro-inflammatory macrophage polarization in tumor tissues.[59] Another study by Li et al. investigated the effect of superparamagnetic iron oxide nanoparticles on tumor treatment.[60] The researchers found that surface conjugation of magnetic nanoparticles with hyaluronic acid led to synergistic tumor inhibition and enhanced tumoricidal activity of macrophages in terms of targeting, generation of bioactive substances, resistance to immunosuppression by tumors, and polarization of M2 macrophages. This study shows that nanomaterial-engineered cells can be successfully employed for immune system activation and tumor extirpation.

2.9. Metal-organic frameworks

Metal-organic frameworks (MOFs) are a special class of coordination polymers consisting of metal ions or clusters of ions coordinated to organic linkers. Owing to their high surface area, large pore volume, adjustable pore size, and modifiable physicochemical properties, MOFs show promise in selective adsorption and separation, gas storage, catalysis, and biomedicine. By leveraging different metal building blocks and organic linkers or by loading appropriate therapeutics, nanosized MOFs have been applied to tumor theranostics.[61] The past few years have seen substantial research progress in MOF-based phototherapeutics in cancer immunotherapy and delivery of adjuvants for enhanced immune responses.[62] Besides PDT, radiotherapy has also been used to augment immunogenic cell death for cancer therapy.[63] For example, the Lin group used MOF nanosheets made from a 5,15-di(*p*-benzoato)porphyrin organic linker and hafnium for combined X-ray radiotherapy-radiodynamic therapy.[64] Upon loading with indoleamine 2,3-dioxygenase inhibitor, DBP-hafnium MOFs almost completely inhibited tumors in murine breast and colorectal cancer metastasis models under X-ray irradiation (Figure 6). These findings are exciting because they provide an excellent demonstration of how supplementing radiotherapy-radiodynamic therapy with checkpoint blockade immunotherapy can promote local and systemic tumor inhibition.

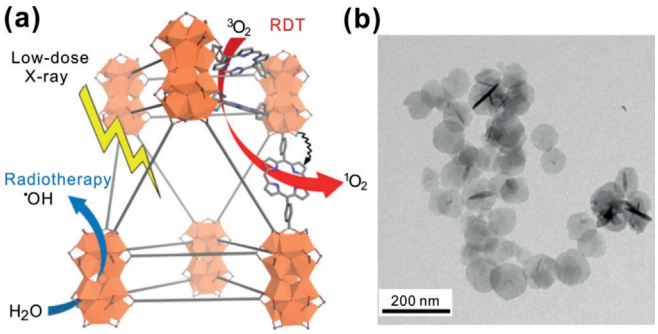

Figure 6. (a) Schematic illustration of X-ray-induced radiotherapy-radiodynamic therapy with metal-organic-framework nanoparticles. (b) Transmission electron microscopy imaging of the nanoparticles. Adapted with permission from Ref. [64]. Copyright 2018, Nature Publishing Group.

2.10. Upconversion nanocrystals

Lanthanide-doped upconversion nanocrystals (UCNPs) exhibit large anti-Stokes shifts, narrow emission spectra, and long excited-state lifetimes, and their nanoscale properties can be tailored for biomedical applications.[65] In recent years, they have also been applied to cancer immunotherapy.[66] Xiang et al. were the first to use UCNPs as nanocarriers to deliver antigens and to track dendritic cells in vivo using upconversion luminescence imaging.[67] When coupled with photothermal agents, photosensitizer-loaded UCNPs could induce immunogenic cell death through combined PDT/PTT under near-infrared laser illumination.[68] For example, Yan et al. demonstrated that simultaneous PDT/PTT, utilizing photosensitizer-loaded upconversion-polymer hybrid nanostructures (PDA@UCNP-PEG/Ce6), enhanced immunogenic cell death and antitumor immunity.[68b] When supplemented with PD-1 antibodies, this dual-mode phototherapy inhibited tumor recurrence and metastasis while extending survival in

tumor-bearing mice. In principle, the loading capacity for therapeutics and antigens enabled by surface anchoring is usually inadequate, which may result in poor therapeutic efficacy. Ding et al. validated improved photodynamic immunotherapy using mesoporous, silica-coated UCNPs featuring large pores for high-dose loading of photosensitizers and antigens.[69] Lanthanide-based nanocrystals that exhibit downshifting luminescence in the near-infrared-II spectrum (1000–1700 nm) may also have broad utility for in vivo imaging in immunotherapy.[70]

Despite enticing prospects of inorganic materials for immunotherapy, one major concern is their biological safety. Although many studies have reported their biocompatibility in mouse models, their long-term safety requires comprehensive evaluation. More effort is required to understand their biodistribution, excretion pathways, metabolism, degradation, and stability in animal models. There are no studies that consider the interactions between inorganic materials and the immune microenvironment. Further studies are also required to evaluate the impacts of inorganic materials on immune organs, such as spleen and lymphoid tissues.

2.11. Hydrogels

Hydrogels are three-dimensional networks of crosslinked polymeric materials, ranging in size from nanoscale to macroscale. Hydrogels can serve as drug carriers to deliver therapeutics, such as immunomodulators, to boost antitumor immunity.[71] Nanoscale and microscale materials can be encapsulated or assembled into larger hydrogel matrices to boost efficacy of immunotherapies.[72] For instance, stimulatory molecules and engineered immune cells could be delivered by gel implants to treat locally inoperable or incompletely resected tumors.[73] Surgical resection cannot completely remove small malignant lesions residing in tissues surrounding tumors. This problem can lead to tumor recrudescence and metastasis. Enhancing antitumor immunity in patients after surgery using biomaterials may avoid these negative outcomes.[74] Chen et al. demonstrated an interesting strategy that utilized an immunotherapeutic gel for postsurgical cancer control (Figure 7).[75] The therapeutic gel was made by mixing two solutions: a fibrinogen solution containing anti-CD47 antibody-loaded $CaCO_3$ nanoparticles and a thrombin solution. These two solutions were crosslinked to hydrogels and sprayed on a tumor surgical bed. The biodegradable $CaCO_3$ nanoparticles were able to polarize tumor-associated macrophages into M1-like phenotypes by scavenging H^+ ions in surgical wounds. Release of anti-CD47 antibodies increased macrophage-mediated cancer cell phagocytosis by blocking "don't eat me" signals expressed on cancer cell surfaces. Consequently, the fibrin gel activated the innate and adaptive immune system to suppress tumor recurrence and metastasis. Integration of in situ hydrogels with immunogenic cell death-inducible therapeutics also holds the potential for improved immunotherapeutic outcomes.[76] The hydrogel can provide extra biophysical cues, such as controllable stiffness, to simulate T cell expansion ex vivo.[77]

Although hydrogels have gained much attention for their potential in conventional cancer therapies, their application in immunotherapy is still in its infancy. More effort must be devoted to time-dependent release of adjuvants in a controlled manner. Chronic inflammatory reactions may emerge upon continuous degradation of hydrogel scaffolds. Hydrogels introduced at tumor sites generally have to persist at application sites for a sufficient period in order to function, which could potentiate damage to normal organ function.

2.12. Other materials

Many other types of materials also show potential in tumor immunotherapy. For instance, TPE-DPA-TCyP, an aggregation-induced, emission-based photosensitizer with a twisted molecular structure, induced immunogenic cell death and immunity more effectively than the commonly used photosensitizers, such as chlorin e6, pheophorbide A, and oxaliplatin.[78] Interestingly, NaCl nanoparticles also selectively killed tumor cells and boosted antitumor immunity.[79]

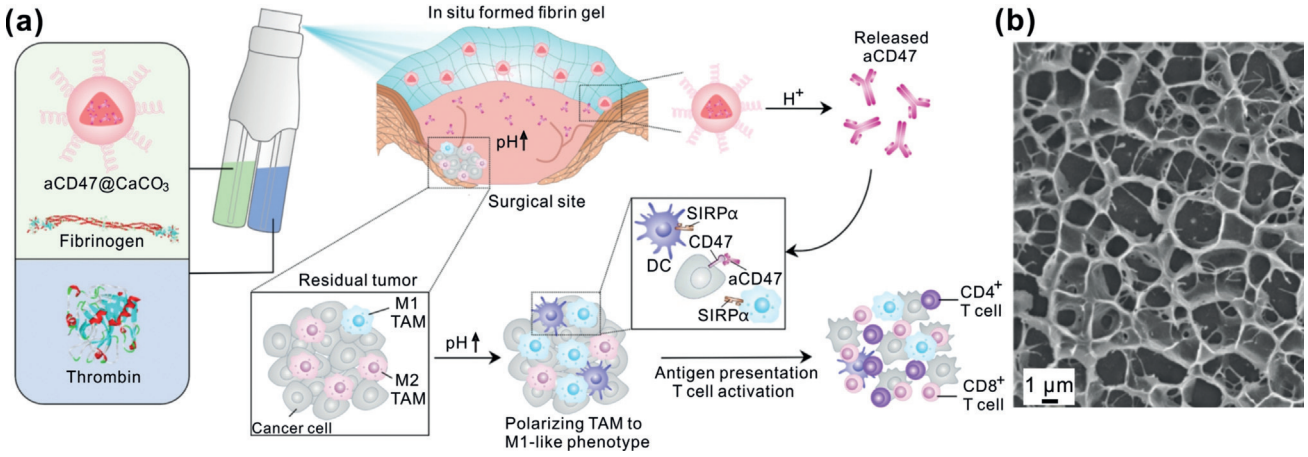

Figure 7. (a) Schematic representation of an in situ sprayed bioresponsive fibrin gel on a postsurgical tumor bed. (b) Cryo-scanning electron micrograph of a fibrin gel loaded with aCD47@$CaCO_3$ nanoparticles. Adapted with permission from Ref. [75]. Copyright 2019, Nature Publishing Group.

In addition, Zn-pyrophosphate (ZnP) nanoparticles, ^{32}P-Labeled $ZnFe(CN)_5NO$ nanosheets, layered double hydroxide, calcium phosphate composites, and Prussian blue are currently in development for cancer immunotherapy.[80]

3. Summary and Outlook

Biomaterials play indispensable roles in cancer immunotherapy, vaccines, CAR T-cell therapy, and checkpoint blockade-related tumor modulation. Many biomaterials have been designed to enhance antitumor immune responses, ranging from small molecules, nanosized organic/inorganic particles, viruses and bacteria, to macroscale particles. These formulations offer different functions and advantages to enhance antitumor immunity, and their use improves therapeutic performance in murine models.

In clinical applications, monomodal therapies are often ineffective at eradicating tumors, due to the complex, immunosuppressive tumor microenvironment. Hybrid therapies offer more effective options for tumor treatment. Novel biomaterials should be exploited in the future for immuno-oncology, in order to target specific tissues or cells, to modulate immunity with improved precision at minimal doses, and to reduce toxicity and side effects. Moreover, processing and quality control of newly designed biomaterials at commercial production scales will require careful development. In addition, understanding the nature and specificity or selectivity of biomaterial-mediated intracellular responses may provide guidance for implementing immunotherapeutic strategies. An effective immuno-positron-emission tomography (immuno-PET) imaging method may allow intratumoral $CD8^+$ T cell-dependent responses to be monitored using less invasive diagnostic procedures.[81] Finally, with the help of surface-engineered biomaterials, we will learn much more about details of tumor microenvironments including acidity, hypoxia, nutrition, reactive oxygen species, and upregulated titers of enzymes. Development of next-generation biomaterials for more potent cancer immunotherapy will require cross-disciplinary partnerships in chemistry, materials, biomedicine, bioengineering, and clinical medicine.

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Conflict of interest

The authors declare no conflict of interest.

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