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Organic/inorganic nanocomposites for cancer immunotherapy

Mingqiang Hao,†[ab] Beibei Chen,†[ab] Xiaoyi Zhao,[ab] Nana Zhao *[ab] and Fu-Jian Xu *[ab]

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Cancer immunotherapy provides an effective way to deal with cancer. Although immunotherapy strategies have shown encouraging therapeutic effects, the inherent limitations of immunotherapy, such as multiple tumor immune evasion methods, low response rate, and systemic toxicity, still hinder its clinical applications. In recent decades, nanomaterials have been considered promising in cancer immunotherapy since they can realize targeted delivery and interact with the immune system to induce or enhance the antitumor immune responses. Among them, organic/inorganic nanocomposites are ideal candidates for cancer immunotherapy since they could combine the advantages of both organic and inorganic components. Multifunctional organic/inorganic nanocomposites could help overcome the shortcomings of current cancer immunotherapy, and realize the combination of immunotherapy and other therapeutic strategies with synergistic antitumor effects. Herein, we review the recent progress of organic/inorganic nanocomposites designed for cancer immunotherapy. The immunotherapy strategies of nanocomposites are summarized from the perspective of achieving immune enhancement. The challenges of nanocomposites in cancer immunotherapy are also discussed.

1. Introduction

Cancer threatens human health and causes leading death worldwide,[1] and has been recognized as incurable for a long time. Immunotherapy provides a promising strategy for cancer treatment.[2] Immunotherapy directly focuses on amplifying anti-tumor immune responses and modulating the tumor immunosuppressive microenvironment.[3] Immunotherapy mainly includes cytokine therapy, tumor vaccines, immune checkpoint blockade (ICB) therapy, chimeric antigen receptor T-cell (CAR-T)

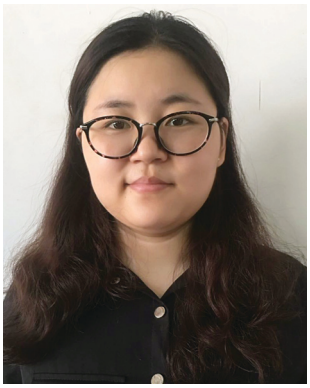
[a] *State Key Laboratory of Chemical Resource Engineering, Beijing University of Chemical Technology, Beijing, 100029, China. E-mail: xufj@mail.buct.edu.cn, zhaonn@mail.buct.edu.cn*

[b] *Key Lab of Biomedical Materials of Natural Macromolecules (Beijing University of Chemical Technology), Ministry of Education, Beijing Laboratory of Biomedical Materials, Beijing Advanced Innovation Center for Soft Matter Science and Engineering, Beijing University of Chemical Technology, Beijing 100029, China*

† Both authors contributed equally to this work.

Mingqiang Hao

Dr Mingqiang Hao received his PhD degree in Medicine from the Chinese Center for Disease Control and Prevention in 2017. He then worked at the Beijing Center for Disease Control and Prevention as a medical researcher for the control of HIV infection. In 2019, he joined Beijing University of Chemical Technology as a postdoctoral researcher. His current research interests focus on the applications of organic/inorganic nanocomposites and novel immune adjuvants in cancer immunotherapy.



Beibei Chen

Beibei Chen received her BS degree from Beijing University of Chemical Technology in 2018. She is currently a master student under the supervision of Prof. Fu-Jian Xu and Prof. Nana Zhao at Beijing University of Chemical Technology. Her research interests focus on the design and synthesis of nanocomposites with special morphologies for cancer immunotherapy.

therapy and so on.[4] The use of bacteria to activate the immune responses and kill tumors is the earliest embryonic form of immunotherapy.[5] However, due to the limited efficacy, it has not received much attention. In the 1980s and 1990s, the US Food and Drug Administration (FDA) approved the treatment of interferon-α (IFN-α, leukemia) and IL-2 (renal cell carcinoma (RCC) and melanoma), respectively, for cancer immunotherapy. In 2004, the US FDA approved imiquimod, IL-12, tumor necrosis factor α (TNF-α) and interferon-γ (IFN-γ). In 2010, the US FDA approved the first therapeutic tumor vaccine, an autologous dendritic cell (DC) vaccine, for the treatment of prostate cancer. In 2011, the high-performance ICB therapy antibody CTAL-4 was approved for the treatment of melanoma. Subsequently, inhibitors related to programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) were approved and significant clinical results were achieved. CAR-T cell adoptive therapy was approved in 2017.[6]

Although cancer immunotherapy has brought dawn to the treatment of tumors, there are still some problems that need to be solved, such as low clinical response rates, immune-related adverse events, atypical clinical reactions, and so on.[3] For cytokine therapy, the use of high doses of cytokines to ensure durable responses in patients might cause serious toxic reactions such as fever, nausea and vomiting, and metabolic acidosis.[7] Tumor vaccines aim to fight against tumors by introducing specific immune responses activated by strong immunogenic tumor antigens. However, several studies have shown that although tumor vaccines could induce tumor-specific T cell responses, they often failed in the control of tumor growth in the clinic.[8] ICB therapy involves the blockade of inhibitory signals to amplify antitumor immune responses and release the brake of the immune system. Although ICB therapy launched a new era in cancer immunotherapy and induced a durable clinical benefit, drug resistance and side effects still limit the use of this therapy.[9,10] T-cell-related cellular immunotherapy produces anti-tumor effects by stimulation *in vitro* or reinfusion of artificially genetically modified T cells into patients. CAR-T cellular immunotherapy such as anti CD19 CAR-T therapy has shown encouraging clinical results among patients with lymphoma. However, this therapy still needs to be strengthened to improve the therapeutic effect on solid tumors.[11,12] The cost of treatment, the complexity of preparation, and the adverse effects of treatment all need to be addressed.[13,14]

On the other hand, nanomaterials have attracted remarkable attention in cancer immunotherapy due to their advantages in targeted delivery, sustained and controlled release of bioactive molecules, facile surface functionalization, high performance in immune response activation, and combination therapy.[15–17] Nanomaterials can enhance the therapeutic effect of immunotherapy in the following aspects. Firstly, targeting the immunosuppressive environment to improve the clinical response rate of immunotherapy. Some nanomaterials can effectively reverse the immunosuppression (such as reeducation of M2 type immunosuppressive macrophages) and then improve the immune response by targeting the tumor immunosuppressive microenvironment.[18,19] Then nanomaterials could activate the immune responses by interacting with immune cells or tumor cells and further promote the therapeutic

Xiaoyi Zhao

Xiaoyi Zhao received her BS from Beijing University of Chemical Technology, China, in 2017. She is currently a PhD student under the supervision of Prof. Fu-Jian Xu and Prof. Nana Zhao at Beijing University of Chemical Technology. Her current research interests focus on the rational design and synthesis of nanocomposites and their related biomedical applications.

Nana Zhao

Prof. Nana Zhao is currently a professor at Beijing University of Chemical Technology. She obtained her PhD degree in physical chemistry from Peking University, China, in 2008 under the supervision of Prof. Limin Qi, and was a postdoctoral scholar with Prof. Eugenia Kumacheva at the University of Toronto, Canada, and Prof. Lutgard De Jonghe at Lawrence Berkeley National Laboratory. She joined Beijing University of Chemical Technology, China, in 2012. She was a recipient of the National Science Fund for Outstanding Young Scholars (NSFC, 2019). Her current research focuses on the design, synthesis, and application of versatile organic/inorganic nanocomposites.

Fu-Jian Xu

Prof. Fu-Jian Xu is the Executive Director of Beijing Laboratory of Biomedical Materials, Beijing University of Chemical Technology. His research interests focus on functional biomacromolecules. He was a recipient of the National Science Fund for Distinguished Young Scholars (NSFC, 2013), Cheung Kong Distinguished Professor (Ministry of Education of China, 2014) and Beijing Outstanding Young Scientist Program (2018).

effect of immunotherapy.[20] In addition, nanomaterials could serve as a targeted delivery system for immunotherapy to increase the enrichment and accumulation of immunotherapy-related drugs or active substances (such as adjuvants, tumor antigens, and checkpoint antibodies) in tumor areas, and further reduce the side effects of immunotherapy.[17] Moreover, some multifunctional nanomaterials could introduce chemotherapy, radiotherapy, thermotherapy and photodynamic therapy. These therapies may lead to the release of tumor antigens and induce immune responses when killing tumor cells to achieve synergistic effectiveness.[10]

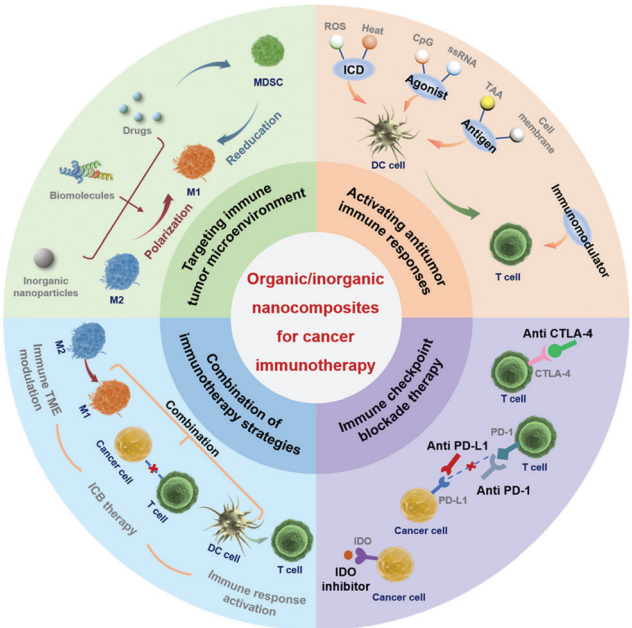


Fig. 1 The application of organic/inorganic nanocomposites in cancer immunotherapy.

Among nanomaterials, polymeric nanomaterials and inorganic nanoparticles with favorable properties show great potential and have been investigated extensively in immunotherapy.[21–23] Organic/inorganic nanocomposites integrate the advantages of organic and inorganic components, and could also produce synergistic effects. In addition, versatile functions could be realized through rational design of the composition, size, and morphology. Therefore, organic/inorganic nanocomposites get a broader application space and development prospects in cancer immunotherapy. Through the design of the composition, size and morphology of nanocomposites to modulate the functions, the immunosuppressive tumor microenvironment (TME) could be adjusted, the anti-tumor immune response could be more strongly activated, and ICB treatment could be enhanced to overcome immune evasion and low response rates in immunotherapy. In addition, the rational design of organic and inorganic components can also enhance the targeting function and responsiveness to the TME to reduce the dosage, thus reducing systemic toxicity. In this review, we will introduce the advantages of nanocomposites and summarize their applications in the following chapters. Detailed information on how nanocomposites settled the challenges in immunotherapy is discussed in the respects of targeting the immunosuppressive TME, activating antitumor immune responses, ICB therapy and combination of immunotherapy strategies (Fig. 1).

2. The advantage of organic/inorganic nanocomposites in immunotherapy

In this review, organic/inorganic nanocomposites refer to nanoparticles integrating organic and inorganic components (Fig. 2),[24] which are promising in a wide range of biological applications.[25–27] Among them, organic components mainly include small molecules, polymers, biomolecules (including polysaccharides), drugs,

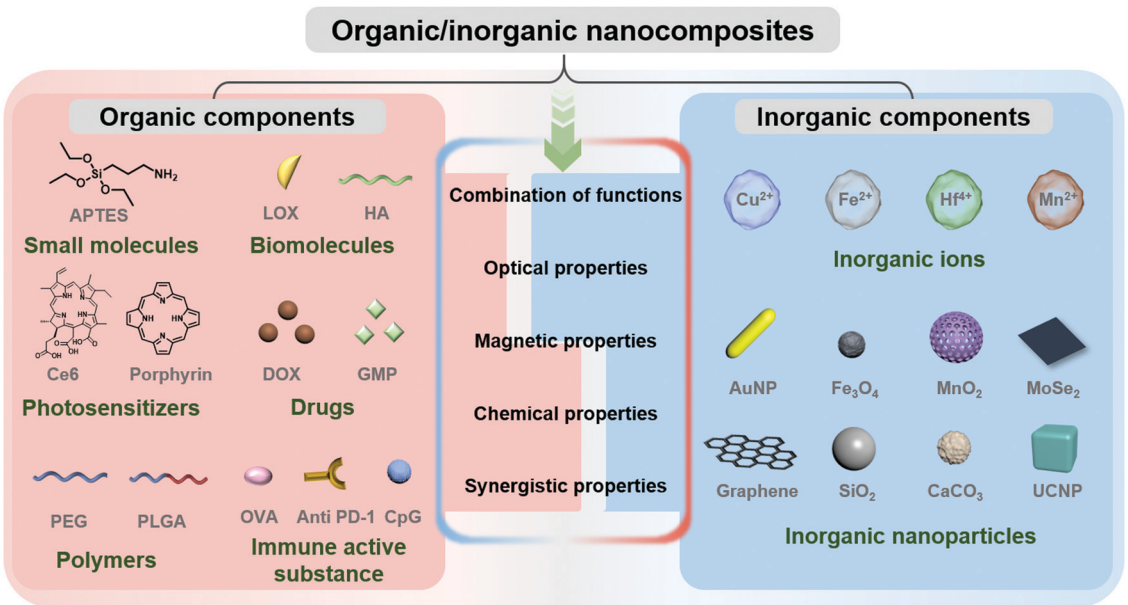


Fig. 2 Complementary compositions of organic and inorganic components of nanocomposites.

photosensitizers, immune active substances, *etc.* Inorganic components mainly refer to inorganic nanoparticles and inorganic ions. The favorable optical, magnetic, and chemical properties of nanocomposites could be utilized in immunotherapy. Organic/inorganic nanocomposites can combine the functions of both organic and inorganic components, which could also produce synergistic effects to promote immunotherapy. Meanwhile, the morphology and size effects of organic/inorganic nanocomposites on the immune system can be investigated. In this part, we mainly introduce the advantages of organic/inorganic nanocomposites for cancer immunotherapy.

2.1. Combination of functions

Organic/inorganic nanocomposites can integrate components with different optical,[28] magnetic,[29] and chemical properties through materials design to achieve dispersibility,[30] targeting,[31,32] and responsiveness.[33,34] For example, synthetic polymers such as poly(ethylene glycol) (PEG)[35,36] or biomolecules[37] can be introduced to increase the dispersibility and circulation time of nanocomposites *in vivo*. In addition to the enhanced permeability and retention (EPR) effect,[38] targeting molecules such as hyaluronic acid (HA),[39] folic acid (FA),[40] and anti PD-1 antibody[41] can also be introduced to improve the targeting of the nanocomposites. It is also feasible to design chemical bonds or inorganic nanoparticles that respond to the TME in nanocomposites to achieve TME-responsiveness. Moreover, immune active substances such as antigens and antibodies could be introduced into nanocomposites to directly enhance the immune responses.

2.2. Optical properties

Regarding optical properties, we mainly focus on the absorption properties which are associated with the activation of immune responses. Through hyperthermia or the generation of reactive oxygen species (ROS),[42] organic/inorganic nanocomposites with strong absorption in the near-infrared (NIR) region can cause immunogenic cell death (ICD).[10] In addition, the mild heating generated by the photothermal properties can reduce the tissue osmotic density between solid tumors and expand tumor blood vessels by destroying tumor cells and the extracellular matrix, thereby enhancing the infiltration of immune cells into tumors.[43]

Moreover, photothermal nanocomposites could result in thermal elastic expansion and generate ultrasonic pressure waves under a pulsed laser, which can be used as contrast agents for photoacoustic (PA) imaging,[44] which could be used to locate the nanocomposites at tumor sites.[45] PA imaging was proved to track the immune responses caused by nanocomposites and may provide guidance for cancer immunotherapy.[46]

2.3. Magnetic properties

Nanocomposites comprising magnetic nanoparticles or ions demonstrate intriguing magnetic properties and related functions.[47] Herein, we mainly focus on magnetic targeting, magnetic hyperthermia and magnetic resonance imaging (MRI) in relation to immunotherapy.

Under a static constant magnetic field, magnetic nanocomposites could be targeted to increase the concentration of the material at the tumor site and enhance the interaction with the immune system.[48] At the same time, the intratumoral retention of reprogrammed macrophages with magnetic nanocomposites could be prolonged.[49] Under an alternating magnetic field, magnetic hyperthermia caused by the high saturation magnetization could damage tumor cells and release tumor-associated antigens.[47]

In addition, MRI could be utilized to monitor the enrichment of nanocomposites in real time and guide anti-tumor therapy.[50–52] Similar to PA imaging, the MRI results can be used to detect the activation of immune responses. In addition, nanocomposites with an MRI function also provide guidance on the treatment time or dose to increase the release of tumor antigens and optimize the treatment effect.[46]

2.4. Chemical properties

Chemical reactions could occur between nanocomposites and H^+, H_2O_2, glutathione (GSH), *etc.*, which exist in the TME.[53] The effect of nanocomposites on immune responses is mainly achieved through the chemical reaction of the nanomaterials with H_2O_2.

Organic/inorganic nanocomposites comprising MnO_2, Fe_3O_4, catalase, lactate oxidase (LOX), *etc.* can trigger the decomposition of H_2O_2 in the TME to H_2O and O_2, thereby alleviating tumor hypoxia.[54] Nanocomposites can also be designed to generate H_2O_2 and improve the oxygen production efficiency.[55] The increase of M2 macrophages in the immune TME is related to hypoxia. Relieving hypoxia can polarize M2 macrophages into M1 macrophages and enhance cancer treatment.[56] On the other hand, some nanocomposites could decompose H_2O_2 by the Fenton reaction to generate $^{\bullet}OH$.[57] This property can be used for chemodynamic therapy (CDT) to cause ICD, or regulate macrophage polarization,[58] both of which could induce T cell penetration into tumor tissue. Nanocomposites can also be designed to degrade in response to H_2O_2, H^+, GSH, *etc.* and release components to stimulate the immune responses.[59]

2.5. Synergistic properties

The organic and inorganic components of nanocomposites may promote each other to produce synergistic properties,[60,61] which promote immune effects by enhanced antigen production or interactions between the material and immune cells.

Nanocomposites can improve tumor hypoxia through the optical, magnetic and chemical properties of the inorganic components. In addition to ICD, nanocomposites with photothermal or magnetic hyperthermia properties can also induce vascular injury to improve tumor oxygenation and vascular perfusion, thereby alleviating tumor hypoxia.[62] Through the design of nanocomposites, H_2O_2 could be catalyzed to O_2, which can enhance the efficiency of photodynamic therapy (PDT) restricted by hypoxia, thus realizing a synergistic effect. The improved ICD caused by PDT could in turn enhance the immune response. Moreover, the heat generated by the inorganic components could promote the release of the organic payload to increase antigen production,[63] thereby improving the anti-tumor immune responses. Nanocomposites can also coordinate

the biological targeting of the organic components with the magnetic targeting of the inorganic components.[64] Magnetic targeting could increase the enrichment of nanocomposites in tumor tissues, while the organic components could promote their binding with T cells. Such synergistic effects could enhance the killing effect of T cells.

2.6. Size and shape effects

The size and shape of nanoparticles will affect the endocytosis, biological distribution, clearance rate and biocompatibility, which will further affect their biomedical applications *in vivo*.[65] The size and shape of nanoparticles are demonstrated to have an effect on cytotoxicity and gene transfection efficiency.[66–69] Moreover, the size, shape, and surface properties of nanoparticles affect the delivery of payloads to tumors or other target organs, which affects the uptake of subsequent antigen-presenting cells (APCs).[70] Therefore, the activation of immune responses may be promoted by designing the size and shape of nanocomposites.

By adjusting the size of nanoparticles, the interaction between nanoparticles and immune cells can be adjusted to promote antigen presentation and immune cell activation.[71–73] When the nanoparticle size is larger than 500 nm, it is more easily absorbed by tissue cells, reducing the interaction between materials and immune cells.[74] When the size is smaller than 10 nm, it will quickly enter the circulatory system and be excluded from the body.[75] Therefore, a size in the range of 10–500 nm may be a suitable range for nanomaterials to interact with the immune system. It is reported that 80 nm gold nanoparticles are moderately endocytosed by DCs, but the content is highest in lysosomes, which is conducive to their degradation and release of antigens. In this regard, maturation of DCs could be maximized and a strong T cell immune response could be induced.[76] In addition, it is found that larger-sized nanoparticles can trigger a strong immune response.[77] This is mainly due to the fact that small-sized nanoparticles (5–15 nm) are easily removed by lymph node follicles, while large-sized nanoparticles (50–100 nm) are easily retained in lymph nodes. The selective retention might induce stronger antigen stimulation to activate the immune responses.

In addition to the size, the shape of nanomaterials will affect the endocytosis efficiency. Nanorods are generally considered to have the highest absorption rate, followed by spherical, cylindrical, and cubic shapes.[78] However, when examining the degree of activation of immune responses by four types of West Nile virus (WNV) protein/Au nanocomposites, it was found that although more rod-shaped nanocomposites were internalized by DCs, the immune response caused by spherical nanocomplexes was stronger. In addition to the endocytosis efficiency, the immune response is also related to inflammatory cytokines induced by different shapes of nanocomposites.[79] The symmetry of nanocomposites also affects the immune responses. It was found that the performance of asymmetric nanocomposites is better than that of symmetric counterparts.[80]

Versatile organic/inorganic nanocomposites offer the possibility to realize a combination of functions, favorable properties, and reasonable design of size and shape. All these factors could be utilized to enhance the immune responses. It is also worth mentioning that combinatorial effects of these factors should also be comprehensively taken into account to evaluate the performance since the interaction of the nanocomposites with the immune system is complicated.[81] We will introduce the various applications of nanocomposites in cancer immunotherapy according to the mechanism of immune responses triggered by nanocomposites.

3. Targeting the immune tumor microenvironment

The occurrence, growth and metastasis of tumors are closely related to the surrounding microenvironment.[82,83] The immunosuppression within the TME evades monitoring of the host immune system, which leads to the failure of immunotherapy.[84,85] The effectiveness of immunotherapy depends largely on whether it can overcome the obstacle of immune escape. Therefore, the regulation of the immunosuppressive TME is of great significance. The immunosuppressive TME is mainly composed of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs) and regulatory T cells (Tregs).[86] MDSCs can directly differentiate into TAMs under hypoxic conditions.[87] TAMs are the main types of inflammatory cells, which are associated with the progression of the disease and are one of the markers of poor prognosis.[88] Macrophages play an important role in innate immunity and acquired immunity. As an important part of innate immunity, they can clear tumor cells and pathogens by phagocytosis, secreting cytokines and other bioactive molecules to modulate the immune TME. Furthermore, the modulated immune microenvironment could promote phagocytosis and presentation of antigens by macrophages, and finally realize the regulation of adaptive immunity.

However, macrophages in the immunosuppressive TME are the main factors that promote tumor progression, and are related to poor clinical prognosis. Based on the inflammatory roles in tumors, TAMs can be divided into pro-inflammatory macrophages (M1) and anti-inflammatory macrophages (M2). M1 macrophages can kill tumor cells and secrete a variety of pro-inflammatory cytokines (IL-γ, TNF-α, and IL-12). As immunomodulatory cells, M2 macrophages can secrete immunosuppressive cytokines (IL-10 and TGF-β), inhibit the activity of DCs and effector T cells, and finally terminate the anti-tumor immune response. Macrophages are susceptible to the immunosuppressive TME; M1 macrophages with killing effects often differentiate into immunosuppressive M2 cells, which will lead to the failure of tumor therapy.[18] However, immunosuppressive M2 can also be reeducated to M1. To date, novel strategies for targeting TAMs have been developed.[19,89] Herein we focus on the application of TAM-targeted organic/inorganic nanocomposites to modulate the immunosuppressive TME for improved cancer immunotherapy.

3.1. Composition and construction of nanocomposites targeting the tumor immune microenvironment

Organic/inorganic nanocomposites could modulate the immunosuppressive TME. In most cases, inorganic components of the

nanocomposites play a major role, such as Fe_3O_4,[49,90–92] MnO_2,[55,93,94] $MoSe_2$,[95,96] and Au.[97] The synthesis of these nanoparticles is relatively simple and the yield is high, which has certain potential for large-scale preparation and promotion to clinical use. They could be synthesized through template,[55,93] one-step reduction,[94] chemical co-precipitation,[49] hydrothermal,[91,92] liquid exfoliation,[95,96] or seed-mediated growth[97] methods. However, the dispersibility of the as-prepared nanoparticles is poor. The combination with organic components, such as chitosan,[95] PEG,[92,93] polyvinyl pyrrolidone (PVP),[96] carboxymethyldextran,[90] and bovine serum albumin (BSA),[97] could improve the stability and biocompatibility. In addition, organic molecules could introduce a targeting function to improve the accumulation of the nanocomposites at the tumor site, such as HA,[49,94] mannose,[94] targeting peptides,[55,92] *etc.* Moreover, other organic components such as chemical drugs,[93,97] photosensitizers,[93] and enzymes[55] can also be included in organic/inorganic nanocomposites. The combination of these organic components and inorganic nanoparticles is mainly realized by electrostatic adsorption,[55,94,95] ligand exchange,[49,90,97] hydrophobic interaction,[96,97] or conjugation through ester[92,97] or amide bonds.[93]

Furthermore, some organic components may play a regulatory role in the immune microenvironment, such as HA,[94] LOX,[55] chemical drug Gem analogue gemcitabine monophosphate (GMP)[98] and so on. They can regulate the polarization of macrophages by regulating the metabolism of lactic acid[55] or directly acting on macrophages[94,98] to achieve the modulation of the immunosuppressive TME. They are combined with inorganic nanomaterials through electrostatic adsorption[55,94] or direct precipitation[98] to realize increased delivery efficiency through active and passive targeting.[55,94,98] Taking advantage of the responsive degradation characteristics of MnO_2[55,94] and calcium phosphate[98] nanoparticles in the TME, the resultant organic/inorganic nanocomposites could achieve efficient and controlled delivery. We believe that other properties of inorganic nanoparticles, including photothermal effects, magnetic targeting, and MRI, can also be used to give nanocomposite nanomaterials more functions with improved anti-tumor effectiveness.

Some organic/inorganic nanocomposites as a whole regulate the immune microenvironment, such as nanoparticles extracted from cuttlefish ink (CINP),[99] and metal complex copper *N*-(2-hydroxy acetophenone)glycinate (CuNG).[100,101] CINP is obtained by direct centrifugal extraction from cuttlefish ink; the main component is melanin, and in addition ~20% polysaccharides and ~1% Cu, Zn and other metals. These two materials can also repolarize macrophages from an immunosuppressed M2 phenotype to an immune-promoted M1 phenotype. We will review the immune effects and mechanisms mediated by organic/inorganic nanocomposites.

3.2. Iron oxide-based nanocomposites

Iron is an essential element of the human body with important physiological functions.[102] Biological macromolecules such as hemoglobin, non-heme enzymes, cytochrome and myoglobin all contain iron. Meanwhile, since it is easy for iron to gain and lose electrons, iron ions can mediate the generation of superoxide anions and hydroxyl radicals. Iron may also have some toxicity to organisms. The Fenton reaction of iron with hydrogen peroxide leads to the formation of ROS and destroys biological macromolecules such as proteins, lipids and DNA.[103]

Iron oxide-based nanocomposites have been approved by the US FDA for the treatment of iron deficiency and are widely used as contrast agents or drug carriers in clinical or preclinical studies.[104,105] In recent years, an FDA-approved iron oxide nanocomposite (ferumoxytol) has been found to inhibit the growth of tumors.[90] Ferumoxytol is composed of an iron oxide nanoparticle core and a carboxymethyldextran coating.

The level of iron in tumor cells is higher than normal cells. Tumor cells are more likely to induce ROS with iron and this leads to tumor cell apoptosis. Then the apoptotic tumor cells can cause persistent polarization of macrophages from an M2 to an M1 phenotype.[106] H. E. Daldrup-Link *et al.* found that ferumoxytol can induce the reeducation of TAM from an M2 to an M1 phenotype and increase lymphocyte infiltration in the tumor.[90] They demonstrated that ferumoxytol can increase cancer cell cytotoxicity by up-regulating the production of macrophage ROS. Dead tumor cells can further promote the activation of macrophages and the production of ROS, maintain the sustained production of TNF-α and nitric oxide (NO), and finally realize continued M1 macrophage polarization.

For the better intracellular internalization of iron oxide-based nanocomposites, X. Z. Zhang *et al.* designed HA modified superparamagnetic iron oxide nanoparticles (HIONs) to artificially reprogram macrophages.[49] The HA coating could enhance the macrophage internalization of iron oxide nanoparticles (IONPs) to increase the intracellular ROS level and inflammatory factors, which could effectively induce tumor cell apoptosis and educate M2 to M1 macrophages. For a better targeted-delivery efficiency, tumor targeted peptides can be used to functionalize nanoparticles. Short peptide CREKA (Cys–Arg–Glu–Lys–Ala) could target fibrin–fibronectin complexes on 4T1 breast tumor cells. H. M. Fan *et al.* designed an elaborate hybrid nanoparticle which could realize ICD of 4T1 cells by magnetothermodynamic (MTD) therapy. In addition, amplified ROS could be generated under an alternating magnetic field, which effectively induced calreticulin (CRT) exposure and macrophage polarization to pro-inflammatory M1 phenotypes.[92] Short peptide CREKA was chosen as a ligand to form nanocomposites to target the tumor more efficiently and could significantly improve tumor inhibition.

Besides ROS, iron also participates in the polarization of M1 macrophages through other pathways such as the interferon regulatory factor 5 (IFR5) signal pathway and NF-κB signal pathway. TNF receptor associated factor 6 (TRAF6) is upstream of IRF5 activation. It has been proved that iron mediates the activation of IRF5 by participating in the ubiquitination of TRAF6. IRF5 further participates in the TLR-MyD88 signal pathway, and finally promotes M1 macrophage polarization by inducing the expression of proinflammatory cytokines (IL-6, IL-12, and TNF-α).[107,108] In addition, the crystallinity of IONPs could also influence the activation of the IFR5 signal pathway. C. Z. Yu *et al.* designed magnetite and hematite IONPs with similar size, morphology, and surface properties to study the

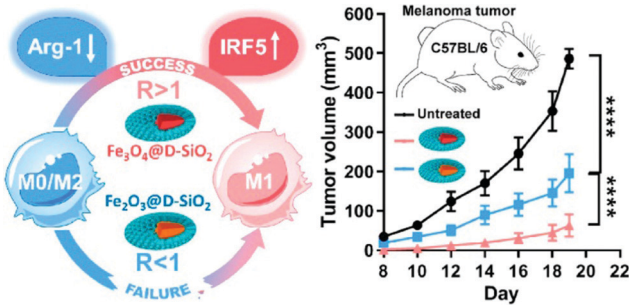


Fig. 3 Mechanism of M1 activation induced by magnetite and hematite INOPs with different crystallinity. Reproduced with permission from ref. 91. Copyright 2019, American Chemical Society.

mechanism of iron oxide-induced macrophage activation (Fig. 3).[91] Compared with hematite IONPs, magnetite IONPs are more effective in M1 polarization and inhibition of tumor growth. Magnetite IONPs specifically rely on the IFR5 signal pathway to achieve M1 polarization and down-regulate M2-related arginase-1.

3.3. Manganese dioxide-based nanocomposites

MnO_2-Based organic/inorganic nanocomposites have been widely used as responsive materials for the acidic TME. Studies have shown that MnO_2 can be degraded by reacting with H^+ or GSH in the TME, and can catalyze the decomposition of H_2O_2 into H_2O and O_2, and thus relieve hypoxia.[109–111] The hypoxic TME can promote the infiltration of Tregs and transform the TAMs into immunosuppressive M2 macrophages.[112,113] Therefore, relieving tumor hypoxia can promote the reversal of the immunosuppressive TME. MnO_2 can be degraded *in vivo* and then excreted through the kidneys with low risk of accumulation *in vivo*, which is a promising material targeting the immunosuppressive TME.

Z. Liu *et al.* designed biodegradable MnO_2/PEG nanocomposites for TME-targeted combination therapy.[93] The nanocomposites were reported to respond to the low acidic TME, produce oxygen to relieve hypoxia, promote the repolarization from M2 to M1, upregulate the secretion of IL-12, and increase the infiltration of cytotoxic T lymphocytes (CTLs) in the tumor.

The macrophage mannose receptor is highly expressed on M2-like macrophages, and mannose-modified nanoparticles can effectively target M2-like macrophages.[94,114] X. Y. Chen *et al.* effectively targeted the high accumulation of TAMs using mannose and HA modified manganese dioxide nanoparticles to relieve hypoxia. In their study, mannose/MnO_2 nanocomposites could target M2 macrophages, which effectively alleviate the hypoxia in the tumor sites. HA can further polarize the anti-inflammatory, pro-tumoral M2 macrophages into pro-inflammatory, anti-tumor M1 macrophages.[94]

In addition to hypoxia, the accumulation of a metabolite, lactic acid, is also a feature of the immunosuppressive TME. It is supposed that lactic acid can promote M2 macrophage polarization by maintaining the expression of hypoxia-inducible factor-1 α (HIF1-α). X. Z. Zhang *et al.* designed red

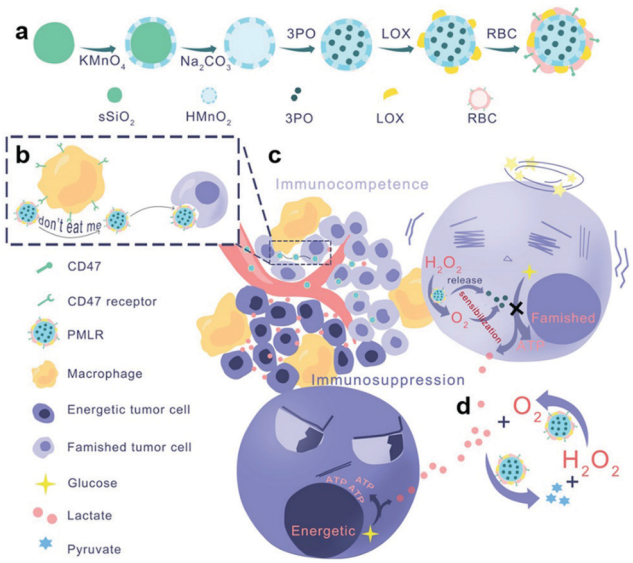


Fig. 4 Schematic illustration of the (a) preparation steps, (b) avoidance of macrophage phagocytosis, (c) intra/extracellular lactic acid exhaustion process and (d) cascade catalysis process of PMLR nanocomposites. Reproduced with permission from ref. 55. Copyright 2019, Wiley-VCH.

blood cell membrane (mRBC)-coated hollow MnO_2 nanoparticles embedded with LOX and a glycolysis inhibitor (denoted as PMLR nanocomposites) (Fig. 4a).[55] The mRBC helps nanocomposites avoid the clearance of macrophage phagocytosis through CD47 (Fig. 4b). In tumor cells, the acidic pH and endogenous H_2O_2 decompose MnO_2 and release LOX to catalyze the oxidation of lactic acid (Fig. 4c and d). The resultant H_2O_2 could then be catalyzed by MnO_2 to produce O_2 and further promote the oxidation of lactic acid by LOX. At the same time, the released glycolysis inhibitor could stop the production of lactic acid by inhibiting glycolysis. The PMLR nanocomposites were found to activate the macrophages by lactic acid exhaustion through the toll-like receptor (TLR) signaling pathway and NF-κB signaling pathway. Hollow MnO_2 nanoparticles could further amplify the lactic acid exhausting function of the nanocomposites by alleviating tumor hypoxia.

3.4. Other material-based nanocomposites

Several studies have reported that thermal effects induced by nanoomposites could modulate the immunosuppressive TME. Nanocomposites that could be applied for photothermal therapy (PTT) can up-regulate the expression of cytokines such as IFN-γ or TNF-α, or down-regulate the expression of CD206 receptor or Arg-1 to mediate the polarization of macrophages to M1 type. PTT mediated by mRBC coated $MoSe_2$ nanocomposites (mRBC/$MoSe_2$) could significantly decrease the mRNA level of Arg1 and CD206, and enhance the mRNA level of TNF-α, suggesting TAM reprogramming from the M2 to the tumoricidal M1 phenotype.[95] In the study, the release of tumor antigens induced by the photothermal effect activated CTLs and up-regulated the secretion of IFN-γ, and thus promoted the transformation of M2 macrophages to M1 macrophages (Fig. 5). In addition, BSA/Au nanocomposites were reported to downregulate the expression of

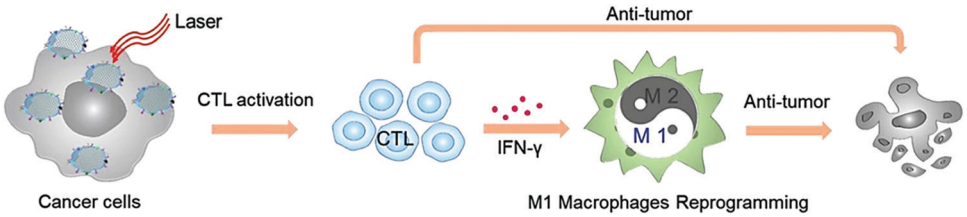


Fig. 5 Schematic illustration of TAM reprogramming to the tumoricidal M1 phenotype mediated by mRBC/$MoSe_2$-mediated PPT to potentiate the antitumor effect. Reproduced with permission from ref. 95. Copyright 2019, Wiley-VCH.

CD206 and legumain after photothermal treatment.[97] The photothermal effect of Au nanorods in the nanocomposites can directly inhibit the polarization of TAMs to M2 macrophages. X. Z. Zhang *et al.* extracted natural melanin nanoparticles from cuttlefish, which can effectively induce the polarization of M1 macrophages by activating the mitogen-activated protein kinase signal pathway.[99] Copper chelate also has the potential to reeducate macrophages from the M2 phenotype to the M1 phenotype. S. K. Choudhuri *et al.* reported that CuNG could reprogram TAMs to the pro-immunogenic phenotype leading to an anti-tumor immune response.[100,101]

TAMs can be differentiated from MDSCs,[87] which also play a negative role in regulating immune activation in the immunosuppressive TME.[115] MDSCs can inhibit the anti-tumor response by interacting with other immune cells, thus promoting tumor growth and immune escape. In the TME, they can differentiate into TAMs, Tregs and other immunosuppressive cells.[87] Therefore, targeting MDSCs can alleviate tumor immunosuppression and improve anti-tumor activity. The common drugs targeting MDSCs are Gemcitabine (Gem), 5-fluorouracil (5-FU), cyclophosphamide and paclitaxel.[115] J. A. Chen *et al.* realized high performance Gem delivery in the TME by formulate GMP into a lipid-coated calcium phosphate (LCP) nanoparticle. The resultant LCP-GMP nanocomposites can significantly mediate the down regulation of p-STAT3 in tumors and then suppress the MDSCs in the TME. They could induce the apoptosis of tumor cells and the transformation from M2 macrophages to M1 macrophages, and further restore $CD8^+$ T-cell-mediated anti-tumor immune responses.[98]

Scavenger receptor type B-1 (SCARB1) is highly expressed on MDSCs. Spherical high-density lipoproteins (HDLs) rich in apolipoprotein A-I (apo A-I) can bind to this receptor with high affinity. At the same time, some studies have proved that apo A-I has anti-tumor effects in a mouse model. C. S. Thaxton *et al.* obtained high density HDL/Au nanocomposites[116] which are similar to natural HDL particles in size, shape, surface charge and surface composition. The HDL/Au nanocomposites could target MDSCs by specifically binding to SCARB-1 receptors. In the metastatic TME, the HDL/Au nanocomposites could increase the inflammation of $CD8^+$ T cells and reduce the ratio of suppressive Tregs.

All-*trans* retinoic acid (ATRA) can promote the differentiation of MDSCs into mature DCs, macrophages and granulocytes to regulate the immunosuppressive TME and enhance the anti-tumor immune response. Z. P. Zhang *et al.* realized chemo-immunotherapy by using biodegradable hollow mesoporous silica nanoparticles (DHMSN) to co-deliver ATRA, doxorubicin (DOX) and IL-2.[117] ATRA could significantly reduce the number of MDSCs in tumors, and the combined effect of ATRA and DOX could increase the number and promote the maturation of DCs. The combined use of IL-2 further enhanced the proliferation of T lymphocytes. The resultant A/D/I-dHMLB nanocomposites could realize effective combination of tumor cell immunogenic death, regulation of the immune microenvironment and promotion of the T lymphocyte response, resulting in a synergistic anti-tumor effect.

4. Activating antitumor immune responses

Activating antitumor immune responses, especially the T cell-mediated immune responses, is one of the effective strategies for cancer immunotherapy.[4,118] Due to the immunosuppressive TME, the body is often unable to successfully initiate anti-tumor immune responses.[119] According to the biological characteristics of the immune response, the establishment of an effective anti-tumor immune response usually requires the release of tumor antigens, activation of the innate immune system, maturation of APCs, the activation and proliferation of tumor-specific T lymphocytes, T cell infiltration in the tumor site and specific recognition of tumor cells. Through these steps, the body can establish effective anti-tumor immune responses and then inhibit the growth of tumors.[120,121]

Traditionally, immune activation is mainly achieved through the use of immune adjuvants and tumor therapeutic vaccines.[122] Traditional biological adjuvants (such as CpG and poly(I:C)) and tumor vaccines (protein vaccines, peptide vaccines, and nucleic acid vaccines) cannot induce effective immune responses due to their low immunogenicity and easy degradation.[123,124] Studies have shown that nanoparticles can stimulate the innate immune responses and activate APCs to promote antigen presentation.[125] Moreover, they could effectively protect antigens and adjuvants from degradation as carriers to enhance targeted delivery to APCs and the antitumor immune responses. In this chapter, the application of organic/inorganic nanocomposites in antitumor immune response activation is discussed through different activating routes.

4.1. Inducing immunogenic cell death

ICD mainly refers to a kind of cell death modality that stimulates an immune response against dead-cell related antigens.

Usually, the identification of ICD is mainly based on the release of damage-associated molecular patterns (DAMPs), such as surface-exposed CRT, passively released high mobility group protein B1 (HMGB1) and secreted adenosine triphosphate (ATP).[126,127] ATP facilitates the recruitment of DCs into the tumor. CTR and HMGB1 stimulate the uptake, processing and presentation of antigens by DCs. Altogether, the anti-tumor immune responses could be finally initiated, resulting in a tumor killing effect.[128] Various therapies for tumors such as chemotherapy, radiotherapy, CDT and PDT have been reported to have the ability to induce ICD.[10] ICD can be induced by cell death signals triggered by non-endoplasmic reticulum (ER) associated targets.[129] Herein, we mainly focus on the organic/inorganic nanocomposites that can activate the immune system by tumor antigens by ICD.

4.1.1. ICD induced by ROS. ROS-based ER stress can elicit ICD with high immunogenicity. PDT is a promising strategy for tumor treatment which has been approved by the FDA for clinical treatment.[130] For PDT, tumors are killed by photoactivating exogenous ROS or singlet oxygen ($^1O_2$) produced by photosensitizers.[131] PDT can induce ICD and tumor antigen release. The most prominent feature of ICD is the release of DAMP signals. The DAMP signals further lead to the activation of APCs and promote the presentation of tumor-associated antigens by ICD, which will promote the immune response.[128,132] Z. F. Liu *et al.* designed tumor integrin $\alpha_v\beta_6$-targeting peptide functionalized graphene oxide (GO) to deliver a photosensitizer, photochlor(2-[1hexyloxyethyl]-2-devinyl pyro pheophorbide-alpha, HPPH), to tumor cells for PDT.[133] ICD induced by PDT was found to significantly stimulate DC maturation, increase the infiltration of CTLs, and finally effectively inhibit the growth and metastasis of the tumor.

The porous nature of nanoscale metal–organic frameworks (nMOFs) facilitates high loading efficiency of photosensitizers and the diffusion of ROS in tumor cells.[134] W. Lin *et al.* designed Hf-porphyrin and chlorin-based nMOFs for improved PDT,[135,136–138] leading to surface CRT expression on tumor cells. The exposed CRT would serve as a signal to activate APCs and induce a tumor specific T cell response. Indoleamine 2,3-dioxygenase (IDO) is an immunoregulatory enzyme highly expressed in tumors that prevents the activation of T cells and promotion of T cell energy and apoptosis. For further enhancement in PDT, they combined PDT with an IDO inhibitor and achieved effective local and distant tumor eradication in colorectal cancer models. Hypoxia is common in tumors and will impair the effect of PDT.[139] In order to overcome tumor hypoxia and enhance cancer immunotherapy induced by PDT, W. Lin *et al.* designed Fe-nMOFs composed of Fe_3O and porphyrin (Fig. 6).[138] When irradiated under hypoxic conditions, the Fe-nMOFs catalyzed the decomposition of intracellular H_2O_2 into O_2, and then O_2 was converted to cytotoxic $^1O_2$ by photoexcited porphyrins. It was proved that Fe-nMOFs could induce higher levels of CRT exposure, indicating a stronger ICD induction ability.

In addition to PDT, ICD can also be induced by ROS produced by CDT. In the presence of Fe^{2+}, H_2O_2 can be decomposed into highly active hydroxyl radicals in a pH-dependent way, which drives the production of tumor-specific ROS. J. L. Shi *et al.* reported that amorphous iron nanoparticle-based composites could induce a Fenton reaction in the TME.[140] Copper-based nanocomposites also possess the ability to induce a Fenton reaction.[141,142] M. Y. Gao *et al.* prepared nanocomposites employing polyethylene glycol modified $Cu_{2-x}Se$ nanoparticles, β-cyclodextrin and chloride e6 (Ce6).[143] Cu^+ and Ce6 can decompose H_2O_2 in tumors and produce a large amount of ROS to induce the production of ICD. The nanocomposites were found to enhance M1 macrophage polarization, effectively kill tumor cells, induce anti-tumor immunity, and inhibit tumor metastasis and recurrence.

4.1.2. ICD induced by hyperthermia. PTT is a promising strategy for local thermal ablation of tumors by converting the energy of incident light into heat. In the clinic, systemic or local hyperthermia can enhance the sensitivity of traditional chemotherapy and radiotherapy. Meanwhile, it has been shown that high temperature can affect the immune response, stimulate the maturation and migration of DCs, enhance antigen presentation and initiate a T cell immune response. The mechanism of the effect of hyperthermia on immune responses is still not clear.[130] Studies have shown that high temperature can up-regulate the expression of heat shock proteins (HSPs).[144] HSPs, especially HSP70, as an endogenous danger signal of the immune system, can activate innate and acquired immune responses. At the same time, HSP70 can also stimulate the maturation of APCs, enhance the expression of major histocompatibility complex (MHC)-I molecules on the surface of tumor cells, and then improve the intensity of immune responses.[145] Z. Zhang *et al.* developed a kind of storage framework composed of graphene oxide-based nanocomposites.[146] After irradiation with an 808 nm laser, the increase of HSP70 expression can stimulate the maturation of DCs. For *in vivo* PTT, DC maturation ($CD86^+CD11c^+$) increased slightly, and Tregs ($CD4^+Foxp3^+$) increased significantly, while CTLs ($CD3^+CD8^+$) decreased significantly. Paclitaxel can effectively block immune escape by eliminating $Foxp3^+$ T cells and promoting the maturation of DCs. When PTT was combined with paclitaxel, a synergistic effect with intensified antitumor immunological efficacy was observed.

The main feature of ICD is the change of DAMP markers, including but not limited to the exposure of CRT, and the release of HMGB1 and ATP. ICD could be confirmed when these three markers could be detected at the same time. In order to clarify the mechanism of ICD caused by PTT, R. Fernandes *et al.* verified the effect of temperature on tumor cell ICD by changing the Prussian blue nanoparticle concentration and laser power (Fig. 7).[147] The results showed that the viability of neuroblastoma cells (Neuro2a cells) decreased when the temperature was higher than 48 °C. The 50.7 °C group and 61.1 °C group exhibited all three markers. Higher temperature (84.3 °C) only showed the exposure of CRT and the release of ATP, so higher temperature may not induce effective ICD. *In vivo* immunotherapy results showed that there was an optimal temperature window of ICD (63.3–66.4 °C). Therefore, a tunable immune response to heat could be realized to maximize the therapeutic effectiveness.

4.1.3. ICD induced by a combination of ROS and hyperthermia. Hyperthermia can induce vascular blood flow in the

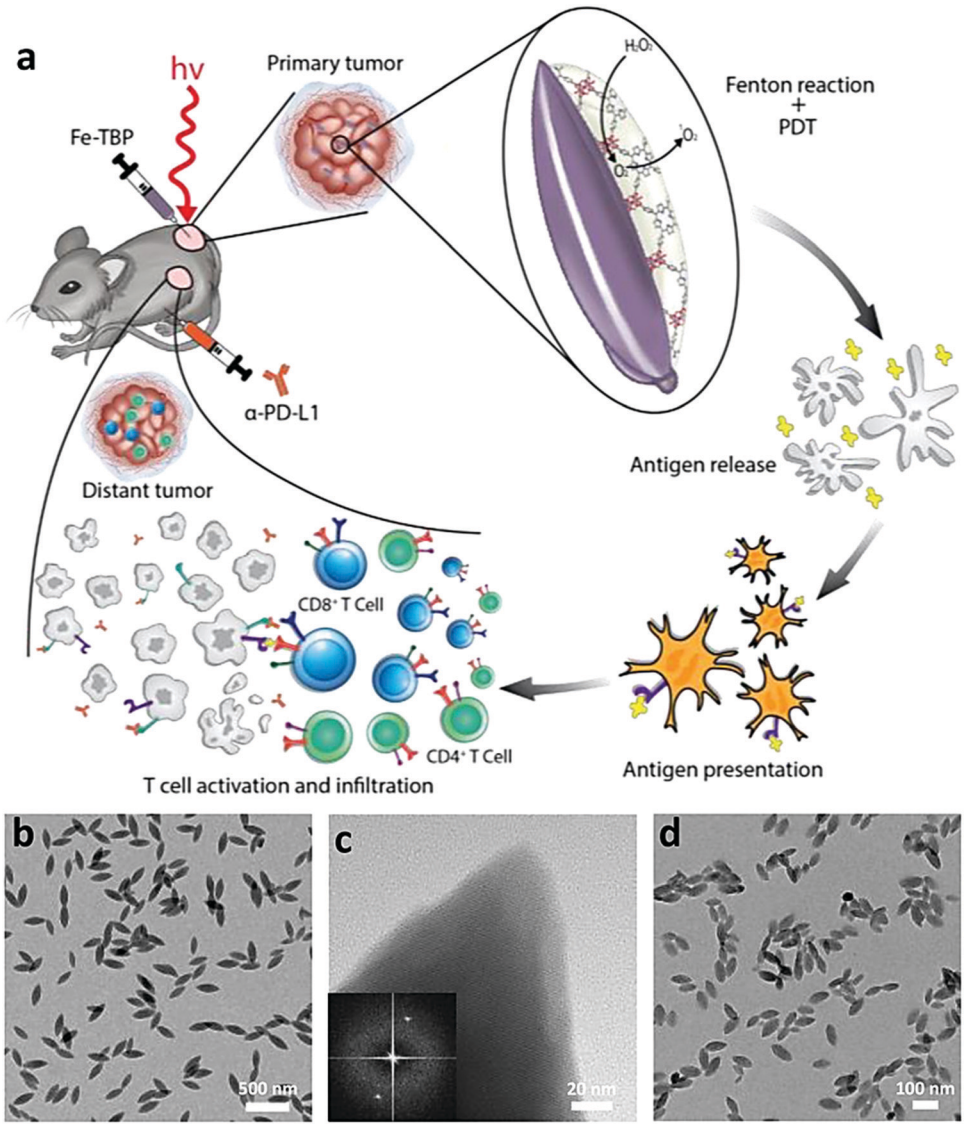


Fig. 6 (a) Schematic illustration of Fe-nMOFs to overcome hypoxia for improved PDT and cancer immunotherapy. Transmission electron microscopy (TEM) images (b and d) and high resolution TEM image (c) of Fe-nMOFs. Inset in (c): fast Fourier transform of Fe-nMOFs. Reproduced with permission from ref. 138. Copyright 2018, American Chemical Society.

tumor site to improve hypoxia and enhance the therapeutic effect of PDT.[148,149] In addition, while a higher PTT treatment temperature cannot successfully induce ICD of tumor cells, PDT can induce efficient ICD through the production of ROS.[147] Therefore, the combination of ROS and hyperthermia could synergistically enhance the antitumor effect. W. F. Dong *et al.* developed a kind of Janus organosilica-iron oxide/Ce6 nanocomposites to induce ICD by PDT and magnetic hyperthermia.[150] They found that PDT and magnetic hyperthermia have a synergistic enhancement effect on the induction of ICD. *In vivo* antitumor experiments showed that the nanocomposites under a laser and an alternating magnetic field partially reduced the number of metastatic foci in the lungs, increased the secretion of TNF-α, IFN-γ and IL-6, and increased intratumoral infiltration of CTLs.

In order to further improve the depth of tissue penetration and therapeutic effect of PDT, J. Lin *et al.* designed PVP/Cu_2MoS_4–Au nanocomposites,[151] which show the enhancement of absorption in the NIR region, and better photothermal conversion efficiency and ROS production. Cu_2MoS_4/Au could also catalyze the decomposition of H_2O_2 into O_2 in the TME, which could significantly improve the hypoxia to improve the therapeutic effect of PDT. Therefore, the PVP/Cu_2MoS_4–Au nanocomposites could release tumor-associated antigens through ICD, activate DCs, promote the secretion of cytokines, induce a strong T cell immune response and prevent tumor metastasis.

4.1.4. ICD induced by an imbalance of osmotic pressure. An imbalance of osmotic pressure in the cells has also been reported to induce ICD.[152] J. Xie *et al.* innovatively synthesized PEGylated sodium chloride nanoparticles (PEG/NaCl) through a microemulsion reaction (Fig. 8a).[152] The degradation of PEG/NaCl nanocomposites can cause an imbalance of osmotic pressure in the cells and the decrease of cell viability (Fig. 8b).

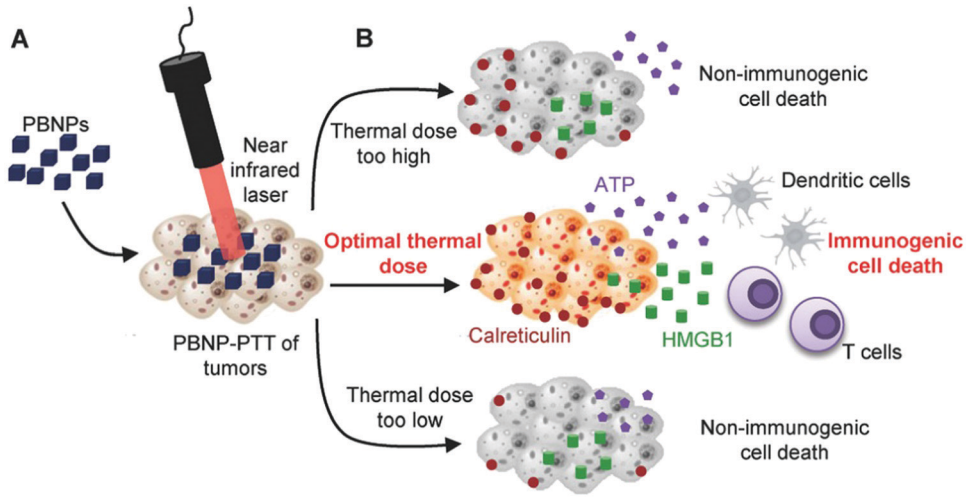


Fig. 7 Optimal thermal window of ICD generated by Prussian blue-based PTT. Reproduced with permission from ref. 147. Copyright 2018, Wiley-VCH.

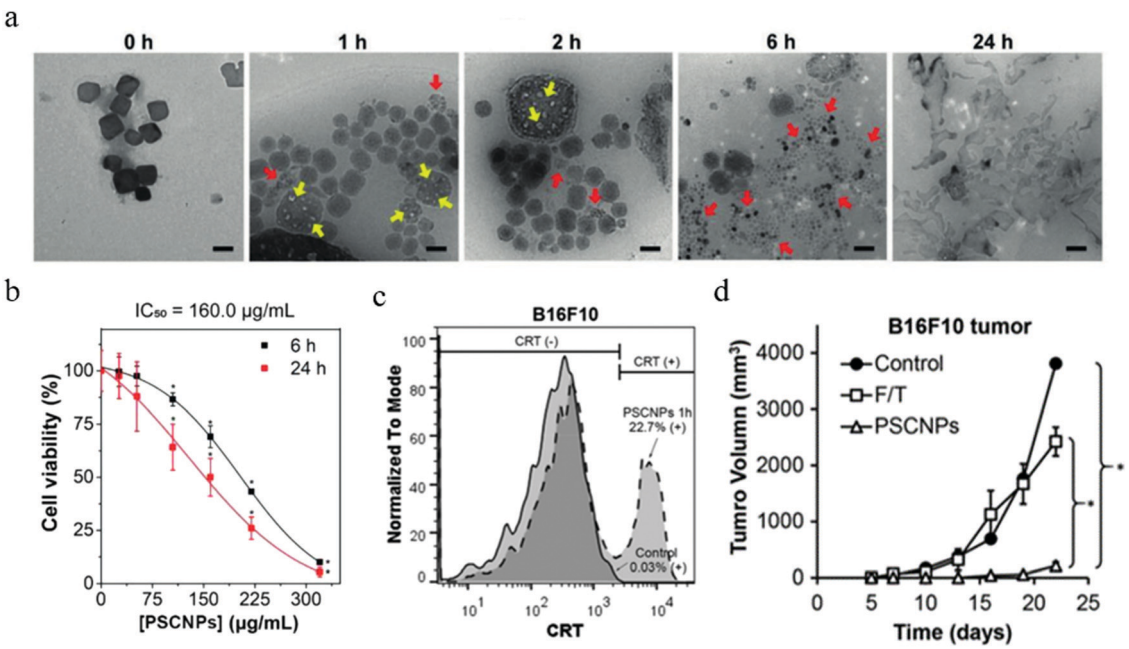


Fig. 8 (a) TEM images of NaCl nanoparticles and their degradation in water over time. (b) Cell viability of PC-3 cells after 6 and 24 h incubation with NaCl nanoparticles at a concentration from 26.3 to 320 μg mL^{-1}. (c) CRT presentation on dying B16F10 cells. (d) *In vivo* tumor growth inhibition of B16F10 tumors. Reproduced with permission from ref. 152. Copyright 2019, Wiley-VCH.

The released cathepsin B induced formation of the NLRP3 inflammatory body, and mediated pyroptosis by the caspase-1 pathway, and finally leads to ICD. The nanocomposite treated tumor cells showed high-efficiency CRT protein exposure and significantly increased ATP and HMGB-1 secretion (Fig. 8c). *In vivo* antitumor results demonstrated significant inhibition of tumor growth in the group of the nanocomposites (Fig. 8d).

4.2. Delivery of Toll-like receptor agonist

TLR is an important part of the mammalian immune system, which plays a role by recognizing pathogen-related molecular patterns (PAMPs), connecting innate immunity and acquired immunity, and TLR serves as one of the earliest determinants of immune activation.[153] TLRs have become important therapeutic targets for the treatment of infectious diseases, cancer and allergies. Many TLR agonists are currently in clinical trials or approved as immune stimulants. TLR3, 4, 7/8 and 9 agonists represent promising immunotherapy for cancer and have been included in the US National Cancer Institute's list of the most promising immunotherapeutic agents for cancer.[154] The maturation of DCs is a prerequisite for initiating an antigen-specific immune response. TLR-mediated DC activation leads to enhanced phagocytosis, up-regulated expression of MHC and costimulatory molecules (CD80, CD86 and CD40), up-regulated expression of CC-chemokine receptor 7 (CCR7), migration to draining lymph nodes, secretion of cytokines and antigen

presentation to lymphocytes. The activation of TLR3, 4, 7/8 and 9 receptors can significantly up-regulate the secretion of type I interferon, which is not only related to antiviral defense, but also enhances the adaptive immune response by promoting cross-presentation of antigens, promoting T cell proliferation, preventing T cell apoptosis, inducing DC maturation and activating NK cells.[155]

CpG oligodeoxynucleotides (CpG ODNs) are a TLR9 agonist that simulates the pathway of innate immunity activated by bacterial DNA.[156] Unmethylated CG dinucleotides can be found in prokaryote DNA with high frequency, but are rare in eukaryotic DNA. When bacterial infection occurs, unmethylated CpG motifs (consisting of a central unmethylated CG dinucleotide plus flanking regions) in bacterial DNA can activate the TLR9 pathway, and initiate a protective immune response against bacteria.[157] CpG ODNs serve as a TLR9 agonist by mimicking the immunostimulatory activity of bacterial DNA. Y. Gao *et al.* constructed nanocomposites by loading CpG ODN agonists onto H3R6 polypeptide conjugated multiwalled carbon nanotubes (MHR-CpG) for immunotherapy of prostate cancer.[158] MHR could efficiently deliver CpG and selectively accumulate in the tumor site and tumor-draining lymph nodes, and could specifically target the TLR9 receptor, increase the proportion of $CD4^+$ and $CD8^+$ T cells in the spleen, and up-regulate the expression of TNF-α and IL-6. The overall tumor inhibition rate of the MHR-CpG nanocomposite group was significantly higher than that of other groups.

PTT can lead to the death of tumor cells and antigen release, while CpG can further promote the maturation of DCs, and promote the presentation of released tumor antigens.[156] N. F. Zheng *et al.* used palladium nanosheets to deliver CpG (PDNCs), achieving the combination of PTT and CpG immunotherapy.[159] CpG combined with PTT can increase the infiltration of $CD8^+$ cells in the tumor, and promote the activation of CTLs and secretion of IFN-γ, and finally induce a strong antitumor immune response, which can significantly control tumor growth and improve the survival rate of mice.

TLR7/8 can recognize single strand RNA and initiate an immune response.[160] D. A. Mitchell *et al.* designed organic/inorganic nanocomposites (RNA/IO) based on mRNA encoding tumor antigen-loaded cationic nanoliposomes and IONPs (Fig. 9).[161] RNA/IO nanocomposites can effectively activate the immune response

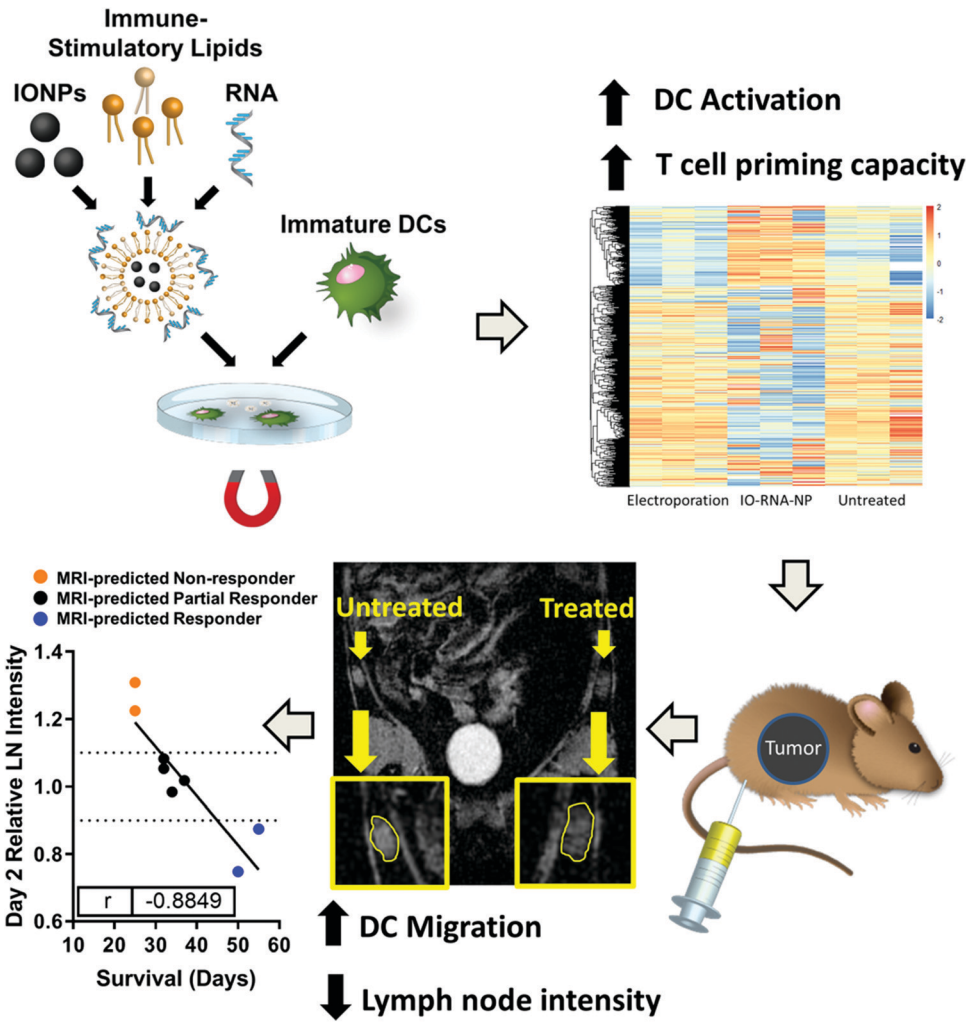


Fig. 9 Schematic illustration of incubation of RNA/IO nanocomposites with DCs in the presence of a magnetic field to stimulate antigen-specific T-cells. Reproduced with permission from ref. 161. Copyright 2019, American Chemical Society.

through the TLR7 pathway. RNA/IO could significantly change the RNA expression profile of DCs and up-regulate the expression of genes related to viral defense including type I interferon production, TLR signaling, the innate immune response, lymphocyte migration (CCL3 and CCL4) and T-cell-activating cytokine IL-12. The introduction of IONPs can not only enhance the RNA transfection of DCs, but also serve as a tracer of DC migration through MRI. They found that the T_2-weighted MRI intensity in the lymph nodes was associated with the transport of DCs and could be used as an early warning indicator of the intensity of the anti-tumor response.

4.3. Delivery of antigens

Antitumor immune responses mainly depend on a T cell-mediated cellular immune response to eliminate tumors.[8] Tumor vaccines were designed to elicit a tumor specific T cell response in the body, and this has been seen as the main strategy for cancer immunotherapy. In the development of tumor vaccines, four key factors determine whether the vaccine works, including tumor antigens, immune adjuvants, delivery vehicles and formulations.[162] Among them, the premise of successful preparation of a tumor vaccine is to select ideal target antigens. The most common antigens used in tumor vaccines are tumor-associated antigens and tumor-specific antigens. Tumor-associated antigens include antigens that are overexpressed in tumor cells or involved in tumor cell differentiation and are not expressed in normal tissues. The common ones are human epidermal growth factor receptor 2 and human telomere reverse transcriptase, mammaglobin-A, prostate-specific antigen, melanoma antigen recognized by T cells and so on. Tumor specific antigens refer to the antigens specifically expressed in tumor cells, which are foreign antigens and not controlled by central tolerance. Both chicken egg ovalbumin (OVA) and tumor cell membranes can be used as antigens to activate immune responses. As the most commonly used model antigen, OVA is easy to obtain and the composition of the antigen is single. For relatively complete cell lines expressing OVA antigen, it can be used to establish tumor models such as the B16-OVA,[163] E.G7-OVA,[164] and LLC-OVA[165] models. The composition of tumor cell membrane antigens is complicated, and contains almost all the antigens needed to activate the immune responses. In addition, the combination with tumor cell membranes could increase the biocompatibility of nanocomposites and endow tumor targeting.[166,167]

When the antigen enters the body, it is first phagocytized, processed and presented through DCs. The entry of antigens into DCs and effective processing and presentation is the first step in initiating an anti-tumor immune response.[168] Nanocarriers have been widely used in the delivery of tumor antigens. They provide protection for tumor antigens and prevent antigens from being degraded by biological enzymes in the circulatory system or tumor tissues.[169] Compared with soluble antigens, nanoparticles are more easily ingested and captured by APCs.[79,170] In addition, better targeting can be achieved by modifying nanoparticles.[171]

Due to the advantages of high accessible surface areas and high payload, mesoporous hollow materials with high radial dendritic pore structure have attracted much attention recently.[172] C. Z. Yu *et al.* report the synthesis of shell number controllable, dendritic mesoporous organosilica hollow spheres.[173] The model antigen OVA and B16F10 tumor cell fragments were used to evaluate their potential in cancer immunotherapy. It was found that the double-shelled nanocomposite induced a stronger anti-tumor immune response than the one-shelled counterparts. J. Lin *et al.* developed large-pore mesoporous-silica-coated upconversion nanoparticles to load OVA or tumor cell fragments and the photosensitizer merocyanine 540 and this acted as a novel strategy for cancer photodynamic immunotherapy.[174] The results showed that the nanocomposites played a synergistic role in stimulating an immune response through PDT. H. A. Santos *et al.* designed thermally oxidized porous silicon nanoparticles encapsulated into acetalated dextran polymeric particles. The particles were then co-extruded together with cancer cell membrane vesicles to formulate the final core–shell nanocomposites.[175] They found that the nanocomposites could significantly promote the expression of CD86 and CD80, which could activate a T cell response toward a Th1 cell mediated response.

IONPs can induce the polarization of macrophages from the M2 phenotype to the M1 phenotype, which has been discussed in the previous chapter.[49,90–92] Aminosilane-coated superparamagnetic IONPs have already been approved by the US FDA and the European Union.[90] A. G. Wu *et al.* used amphiphilic polymer-coated IONPs to react with tumor model antigen OVA by covalent bonding (Fig. 10).[176] IONP-OVA nanocomposites could stimulate bone marrow stromal cells to secrete IFN-γ and TNF-α and activate macrophages. They could further stimulate the maturation of DCs and activate a T cell immune response effectively. This can not only inhibit the growth of B16-OVA tumors, but also prevent the formation of subcutaneous tumors and metastatic tumors. Their studies have proved that IONPs can play the dual role of carriers and immune adjuvants cooperating with antigens to activate the immune responses.

In addition to the effective delivery of antigens, APCs are also very important for the processing and presentation of antigens. APCs such as DCs initiate a specific T-cell immune response through antigen uptake, processing and presentation.[177] Therefore, the antigen presentation efficiency of DCs may also affect the effect of cancer immunotherapy.[178] As the cell component carrying tumor antigens, the tumor cell membrane has been used in the development of tumor vaccines.[167,179] In order to improve the efficiency of DCs in antigen presentation, L. F. Zhang *et al.* prepared a nanoparticle vaccine (BM-Au) by coating AuNPs with bacterial outer membrane vesicles (OMVs) derived from *Escherichia coli*.[180] The data showed that, compared with OMVs, the BM-Au nanocomposites could effectively induce the activation and maturation of DCs in mouse lymph nodes. The tumor cell membrane was also utilized to promote the immune response of the body. Z. P. Zhang *et al.* synthesized gold nanoparticles using B16-F10 cells, and the cells secreted Au nanoparticles (AuNP@B16F10) coated with a tumor cell membrane (tumor antigens) (Fig. 11).[181] Then AuNP@B16F10 is introduced into DCs, and worked as a tumor vaccine through the combination of PTT and immunotherapy. The resultant AuNP@DC_{B16F10} nanocomposites could significantly increase the proportion of $CD3^+CD8^+$ T lymphocytes in distal tumors and promote the secretion of IFN-γ and IL-6, and

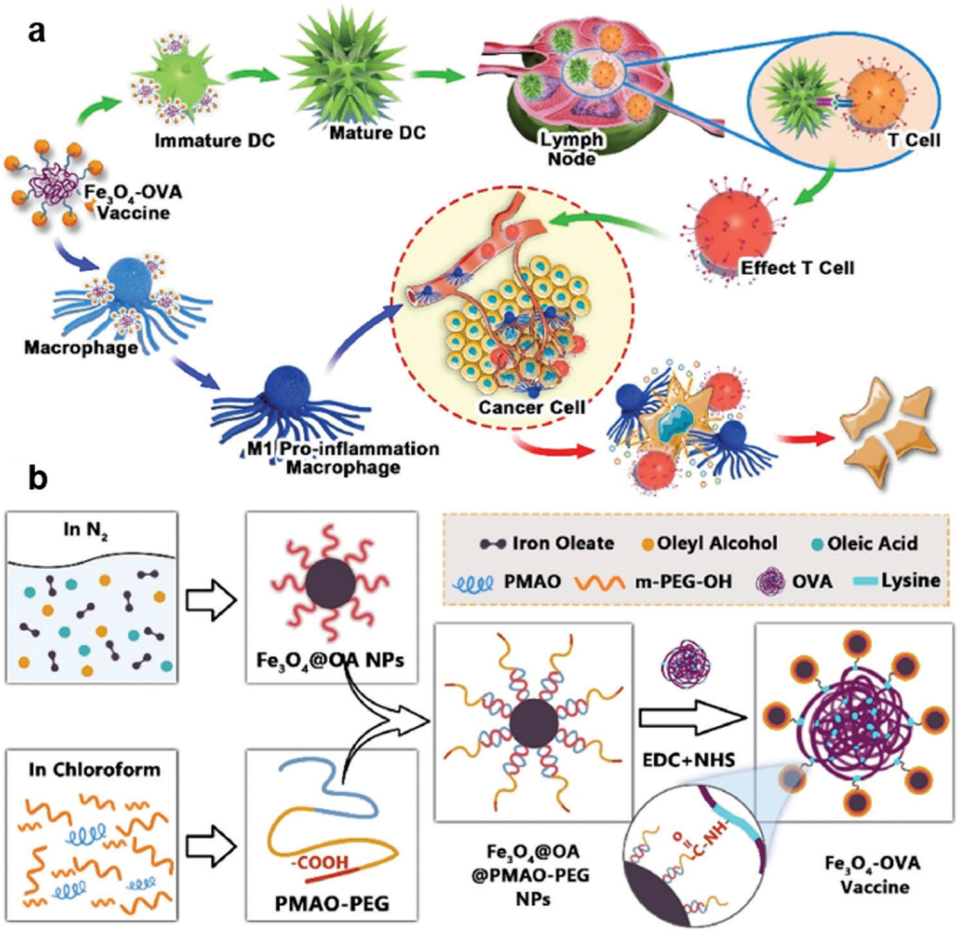


Fig. 10 Schematic illustration of (a) the IONP-OVA vaccine strategy and (b) the synthesis of the IONP-OVA vaccine. Reproduced with permission from ref. 176. Copyright 2019, Elsevier Ltd.

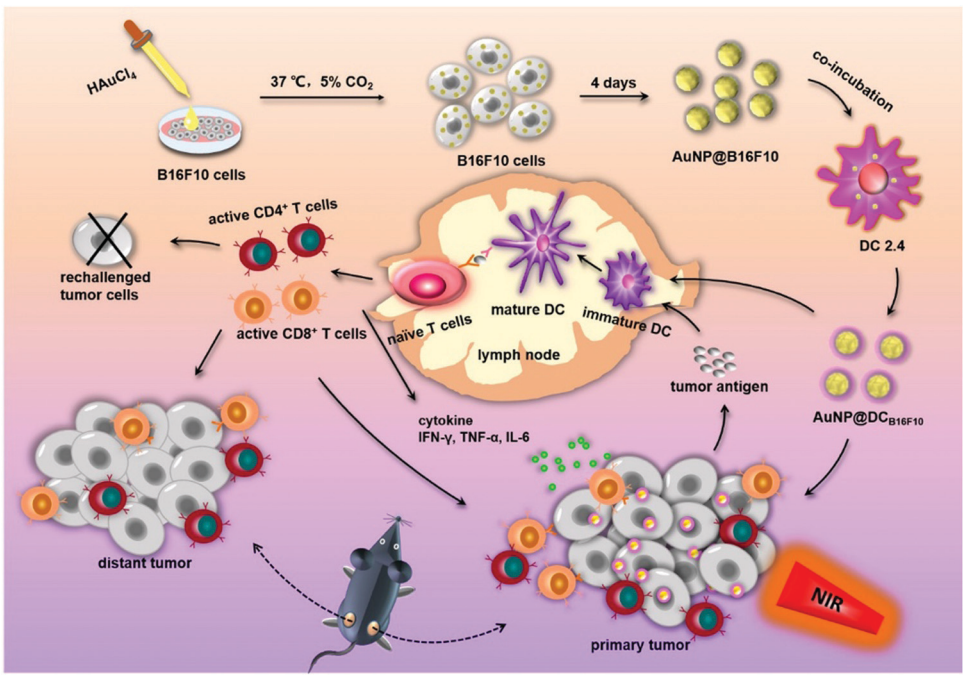


Fig. 11 Schematic preparation of AuNP@DC_{B16F10} and mechanism of the AuNP@DCB16F10-mediated combinational treatment modality. Reproduced with permission from ref. 181. Copyright 2019, American Chemical Society.

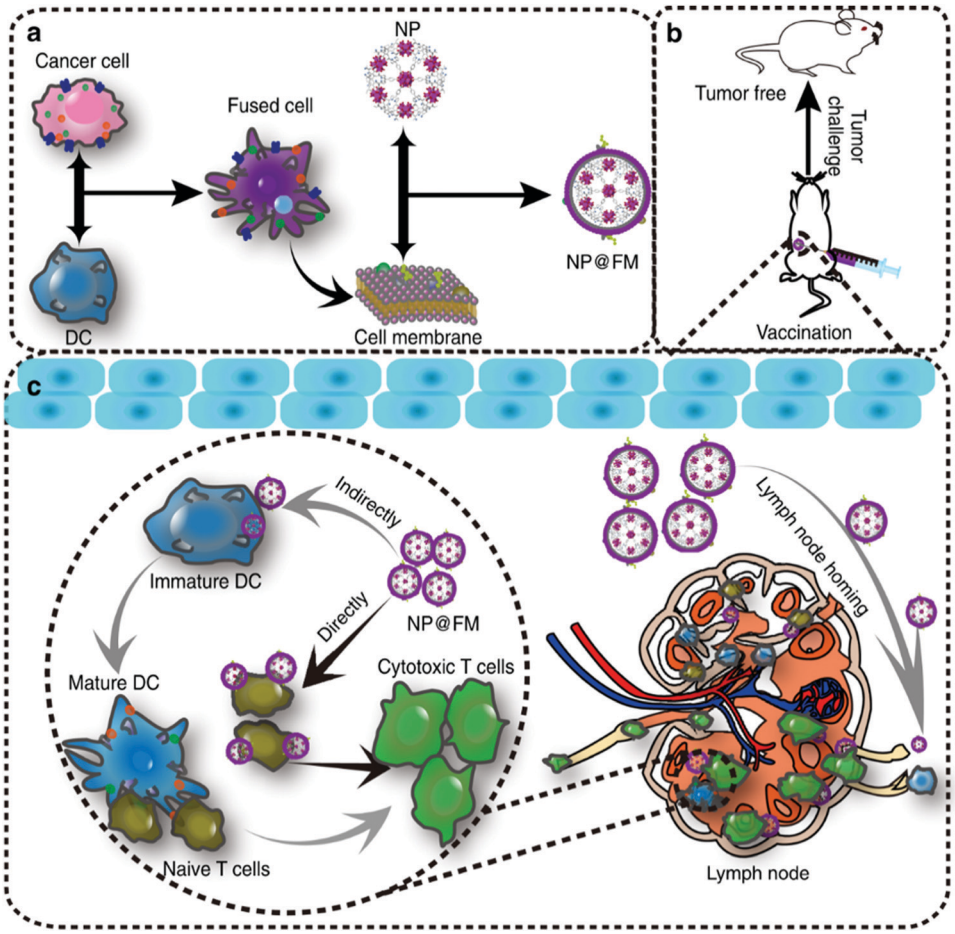


Fig. 12 Schematic illustration of (a) preparation of NP@FM. (b) Vaccination of NP@FM for tumor prevention and (c) mechanisms of MOF@FM inducing immune responses. Reproduced with permission from ref. 182. Copyright 2019, Springer Nature.

TNF-α, among which the immune response was stronger when combined with PTT. X. Z. Zhang *et al.* fused DCs with a tumor cell membrane to share the cytoplasm while having two independent nuclei (Fig. 12).[182] They then used the bio-reprogrammed fusion cell membrane to coat MOF nanoparticles and prepare a tumor vaccine (NP@FM). The vaccine contains both tumor antigens and MHC-1 molecules for antigen presentation. The fused cell membrane has a stronger ability to activate T cells to transform into CTLs, since NP@FM could directly present antigens to T cells and activate T cells. They found that the activation of DCs was mainly through these pathways of cytokine–cytokine receptor interactions, the chemokine signaling pathway, and the TNF signaling pathway. The imaging function of the MOF confirmed that NP@FM nanocomposites could significantly promote the lymphatic migration and homing ability of mature DCs.

4.4. Stimulating T cells

T cells play an important role in cancer immunotherapy. Although T cell activation is generally mediated by APCs *in vivo*, T cell activation can also be achieved by introducing T cell stimulators, *in vitro* antigen stimulation, artificial modification and so on. In the TME, tumors can escape the tumor killing effect of the immune system through a variety of ways. T cells may exist in the form of anergic T cells, exhausted T cells, and senescent T cells.[183] In order to activate T cells for anti-tumor immunity, L. Yin *et al.* used a zeolitic imidazolate framework (ZIF-8) to carry chemotherapeutic drug DOX and immunomodulator Avasimibe for combined chemotherapy and immunotherapy.[184] Avasimibe is an inhibitor of ACAT (a key enzyme of cholesterol esterification in $CD8^+$ T cells), which can enhance its tumor killing effect by changing the metabolism of T cells. The resultant nanocomposites could not only kill tumor cells by DOX, but also improve the tumor killing activity of CTLs, and exert a synergistic antitumor effect of chemotherapy and immunotherapy.

Due to the existence of the immunosuppressive TME, T cells *in vivo* often cannot respond effectively. In order to activate the T cell response and exert its antitumor effect, it is an effective strategy to activate immune cells *in vitro* and then inject them *in vivo*. As early as 60 years ago, adoptive lymphocyte transfer has been used to effectively target tumors in mouse models.[185] The emergence of genetic engineering technology has brought great progress to the activation of T cells *in vitro*.[186] CAR-T therapy is through the introduction of antigen receptor genes into T cells cultured *in vitro*, and then through rapid expansion and activation to obtain a large number of effector T cells,

which can have a powerful anti-tumor effect after being introduced into patients.[187] Because CAR-T depends on the genetic modification and culture of T cells *in vitro*, the process of processing and manufacturing CAR-T is crucial to the success of the treatment strategy.

J. P. Spatz *et al.* prepared an anti CD3 antibody modified quasi-hexagonal array of gold nanoparticles combined with a cross-linked integrin-bound polyethylene glycol (PEG) hydrogel to expand T cells *in vitro*.[188] Then, their group developed a new way to activate and prepare a large number of T cells *in vitro*.[189] They prepared the nanostructured surface composed of quasi-hexagonal ordered gold nanoparticles on the surface of TiO_2 by the block copolymer micellar lithography method. The antibodies of anti CD3 and anti CD28 were used as costimulatory signals of T cell activation, and the surface of TiO_2 was modified with arginine–glycine–aspartic acid (RGD) cell adhesion peptide to promote cell adhesion. The nanocomposites were found to activate primary human $CD4^+$ T cells *in vitro*, which is an effective alternative to the preparation of activated T cells *in vitro*. M. J. Butte *et al.* used superparamagnetic IONPs and alginate to prepare microbeads and modified the surface of microbeads with anti CD3 and anti CD28 antibodies to prepare artificial antigen presenting cells (aAPCs).[190] They confirmed that oscillatory force enhanced engineered aAPCs can provide stronger antigenic signals for T cell activation *in vitro* than traditional dynaband cultures.

The US FDA has approved CAR-T therapy for treatment of acute lymphoblastic leukemia and diffuse large B-cell lymphoma.[185] However, due to the characteristics of the solid immune TME and tumor structure, CAR-T cannot effectively penetrate into the tumor site and have a tumor killing effect. In order to further clear the obstacles, H. Y. Xie *et al.* fabricated PD-1 antibody-coated iron oxide nanoclusters. Then the activated T cells combined with nanoclusters may be successfully recruited to the tumor sites under the guidance of an *in vitro* magnetic field.[191] At the same time, due to the existence of the acidic TME, PD-1 antibodies can undergo targeted release at the tumor site, blocking the inhibition of the function of activated T cells by tumor cells.

4.5. Others

We have previously introduced strategies to activate the immune response by inducing ICD to release antigens, delivery of antigens or agonists, and activating T cells. However, due to the complex interaction between tumor cells and the TME, a single measure may not activate the anti-tumor response effectively *in vivo*.[192] For the antitumor response, the main tumor killing effect is mediated by CTLs. However, the activating of this effective T cell immune response is conducted by functions such as phagocytosis, processing and presentation of antigens by DCs. Mature DCs present antigens to T cells in lymph nodes and activate tumor-specific $CD8^+$ CTLs. DCs play a key role in initiating tumor immunity.[193] Antigens are the premise of activating a specific T cell immune response, but the presentation efficiency of antigens *in vivo* is low, and it is not easy to induce an efficient Th1 immune response. Common TLR agonists include TLR9 agonist (CpG) and TLR3 agonist (Poly I:C), which can effectively promote the Th1 immune response.[194] The use of adjuvants such as TLR receptor agonists can promote the maturation of DCs. The combined use of antigens and TLR agonists can effectively promote the cross presentation of antigens and induce a Th1 immune response to play the role of tumor killing.[195] In recent years, it is found that nanoparticles themselves can play the role of an adjuvant to activate DCs and the adjuvant effect is affected by the size and morphology.[76,170,196,197] In addition, DCs can also be cultured *in vitro* and stimulated by antigens. When these engineered DCs are infused *in vivo*, they will directly activate T cells to exert an anti-tumor immune response.[198]

4.5.1. Co-delivering antigens and TLR agonists. CpG is a TLR9-dependent adjuvant for eliciting a Th1 type T cell response, and ROS can promote APC maturation.[156] C. Z. Yu *et al.* designed PEI-functionalized dendritic mesoporous organosilica nanoparticles to deliver OVA antigen and CpG adjuvants.[199] With the high GSH in the TME and the release of the antigen and adjuvant, CpG bound to intracellular TLR9 receptors and co-activated a OVA-specific immune response. GSH depletion can further lead to elevated ROS levels, and promote the maturation of APCs. J. C. Zhang *et al.* loaded OVA antigen in the synthesis process of a MOF, and realized the co-delivery of OVA and CpG.[200] The resultant nanocomposites could dissociate and promote the lysosome escape of antigens under pH 5.0, and activate the cross presentation of antigens.

Traditionally, aluminum adjuvants have been used as agonists for Th2 type immune responses. They are often used in prophylactic vaccines related to infection prevention and promote antibody production. X. Sun *et al.* transformed an aluminum hydroxide adjuvant from a gel to nanocarriers for the co-delivery of OVA and CpG adjuvants.[201] The resultant nanocomposites could effectively improve the delivery and co-localization of OVA and CpG adjuvants in DCs and macrophages. They could also promote the infiltration of CTLs in tumor tissue, promote the secretion of IFN-γ, and obtain more effective OVA-specific killing efficiency.

The induced immune response is also affected by the size and morphology of nanoparticles.[79] In order to optimize the co-delivery efficiency of antigens and adjuvants, L. Zhan *et al.* used different sizes of spherical Au nanoparticles to deliver OVA antigens and CpG adjuvants respectively.[76] Au nanoparticles of 60 nm showed the strongest effect of antigen presentation while 80 nm nanoparticles have the best CpG delivery ability. Compared with the single component Au nanoparticles, AuNP60/OVA and AuNP80/CpG nanocomposites could significantly promote the homing of OVA and CpG adjuvants to lymphoid tissue and promote the OVA-specific $CD8^+$ T cell response.

Poly(I:C), a TLR-3 agonist, is a negatively charged double-stranded RNA. SIINFEKL is an epitope peptide in OVA antigens that can be efficiently presented by MHC-I. Using the electrostatic interaction between the positive SIINFEKL epitope peptide modified by arginine (SIIN*) and poly(I:C) adjuvant, IPEM-Au nanocomposites were prepared by self-assembly of immune membranes (IPEMs) on Au.[202] The resultant nanocomposites could effectively internalize and activate the TLR signal in primary DCs, and further present SIIN* epitope peptides.

4.5.2. Activating DCs by nanocomposites. DCs are APCs, which play an important role in initiating and regulating innate and acquired immunity. DCs can sense external danger signals, such as foreign proteins, cellular receptors, pathogen associated molecular patterns and DAMPs. These danger signals can activate DCs, and then initiate the specific immune response of antigens and play an anti-tumor effect.[203] In order to further improve the specific immune response of tumor-associated antigens, adjuvants such as TLR agonists are usually needed to further activate DCs.[204,205] In addition to common immune adjuvants, nanoparticles themselves can also induce innate immunity, especially DC activation. The particle size, morphology and symmetry could all influence the activation of DCs. E. G. Bennett *et al.* found that both mesoporous silica nanoparticles (270 nm) and microparticles (2.5 μm) with surface areas above 500 $m^2\ g^{-1}$ could promote the expression of CD86 on the surface of DCs.[197] H. Sawa *et al.* synthesized gold nanoparticles to deliver WNV envelope protein and found that gold nanoparticles could promote the level of WNV-specific antibodies.[79] Meanwhile, the size and shape of nanocomposites may influence the secretion of cytokines by bone-marrow-derived DCs (BMDCs). C. Z. Yu *et al.* synthesized asymmetric silica nanoparticles and found that asymmetric nanostructures could induce higher levels of CD40 and CD86 expression on the surface of DCs and macrophages compared with symmetrical structures.[206] H. Y. Liu *et al.* used glucose modified mesoporous silica nanoparticles to obtain a biodegradable carbon–silica nanocomposite (denoted as CSN).[207] CSN could significantly induce the expression of CD86 and CD80 markers on DCs and promote the maturation of DCs. The cGAS-STING pathway can enhance the secretion of type I IFN and promote the maturation of DCs by sensing the damage of DNA in cells.[208] Studies have shown that Mn^{2+} can promote the activities of cGAS and STING and enhance the ability of the STING pathway to activate innate immunity.[209] Z. Zhang *et al.* prepared nanocomposites employing DOX-loaded amorphous porous manganese phosphate nanoparticles and phospholipids.[210] DOX was observed to lead to DNA damage and then stimulate the STING pathway. Mn^{2+} could further enhance the STING pathway, stimulate the secretion of interferon type 1, and then promote the maturation of DCs.

A DC vaccine has been approved by the US FDA for the treatment of prostate cancer.[211] A DC vaccine refers to the use of patients' own mononuclear cells to induce DC production *in vitro*, and then loading the tumor antigen, and finally obtaining DCs activated by a peptide presenting epitope on the surface. The control of the DC maturation is a key issue in the preparation of a DC vaccine, as immature DCs cannot effectively activate $CD8^+$ T lymphocytes while mature DCs show reduced capability of antigen phagocytosis and cross-presentation.[212] Y. Li *et al.* surface-engineered DCs with polydopamine/Ca^{2+} nanocomposites for control over the DC maturation.[212] Ca^{2+} acted as a physical bridge between the DC surface and polydopamine to maintain cell viability. Polydopamine could effectively prevent DC activation by scavenging ROS. Instead, NIR laser irradiation could remotely activate DC maturation through the photothermal effect of polydopamine (39 °C). Therefore, programmed DC maturation could be achieved *in vitro*, which is beneficial for DCs to play an efficient role in activating T cell immune responses.

5. Immune checkpoint blockade (ICB) therapy

ICB therapy is a widely used anti-tumor immunotherapy which has achieved great clinical success over the past few years. In order to avoid accidental damage to normal cells, when activated, T cells will express certain proteins that have the function of an "immune checkpoint", such as PD-1. Corresponding proteins can be expressed on the surface of normal cells to prevent them from being attacked by T cells. However, tumor cells could overexpress some immunosuppressive proteins, such as PD-L1 or PD-L2, *etc.*, and bind to the corresponding proteins expressed on T cells, tricking T cells and causing immune escape. This combination of tumor cells and T cells can inhibit T cell functions, thereby preventing T cells from effectively killing tumor cells. The role of drugs for ICB therapy is to replace the connection on the surface of tumor cells with corresponding antibodies or inhibitors, so that the matching between tumor cells and T cells could be blocked. Therefore, checkpoint blockade is used to expose the camouflage of tumor cells, so that T cells can restore their functions to attack tumor cells. Currently, checkpoint blockade strategies are commonly used in combination with inhibitors (such as anti PD-L1,[55,93,213–215] anti PD-1,[191,216,217–221] and anti CTLA-4,[222–224]), blocking peptides (such as AUNP12[225]) or plasmids to cut off PD-L1 gene expression in tumor cells,[226] and so on. As mentioned earlier, the application of ICB therapy is still largely limited by low objective response rates, risk of autoimmune disease, and relatively high cost.[227] Therefore, ICB therapy is usually combined with modulation of the immunosuppressive TME or activation of T cells. They work in a synergistic manner to inhibit tumor growth. In this section, we briefly introduce some examples of ICB treatment.

Organic materials are mostly used in ICB therapy. Z. Gu *et al.* employed 1-methyl-DL-tryptophan (1-MT, an IDO inhibitor)-modified HA to load anti PD-1 antibody and then integrated them into a microneedle system to inhibit melanoma growth.[220] Then, the released anti PD-1 could exert PD-1 blockade to effectively induce T cells to attack cancer cells. This synergistic delivery strategy can trigger long-lasting and effective antitumor treatments. In addition, the delivery of anti PD-1 *via* hydrogels proved a good effect of inhibiting tumor angiogenesis. L. Wang *et al.* used an alginate hydrogel to co-deliver two FDA-approved drugs (celecoxib and anti PD-1) for tumor treatment.[221] The combination of chemotherapy and ICB therapy could reduce immunosuppressive Tregs. It also increased the production of anti-vascular chemokines and inhibited tumor angiogenesis.

Organic/inorganic nanocomposites are also employed in ICB therapy. Iron oxide-based nanocomposites show excellent characteristics of a high loading rate and magnetic targeting. They could effectively deliver inhibitors to avoid side effects caused by systemic delivery. H. Y. Xie *et al.* prepared magnetic nanoclusters modified with anti PD-1 (IONP/anti PD-L1, Fig. 13a).[191]

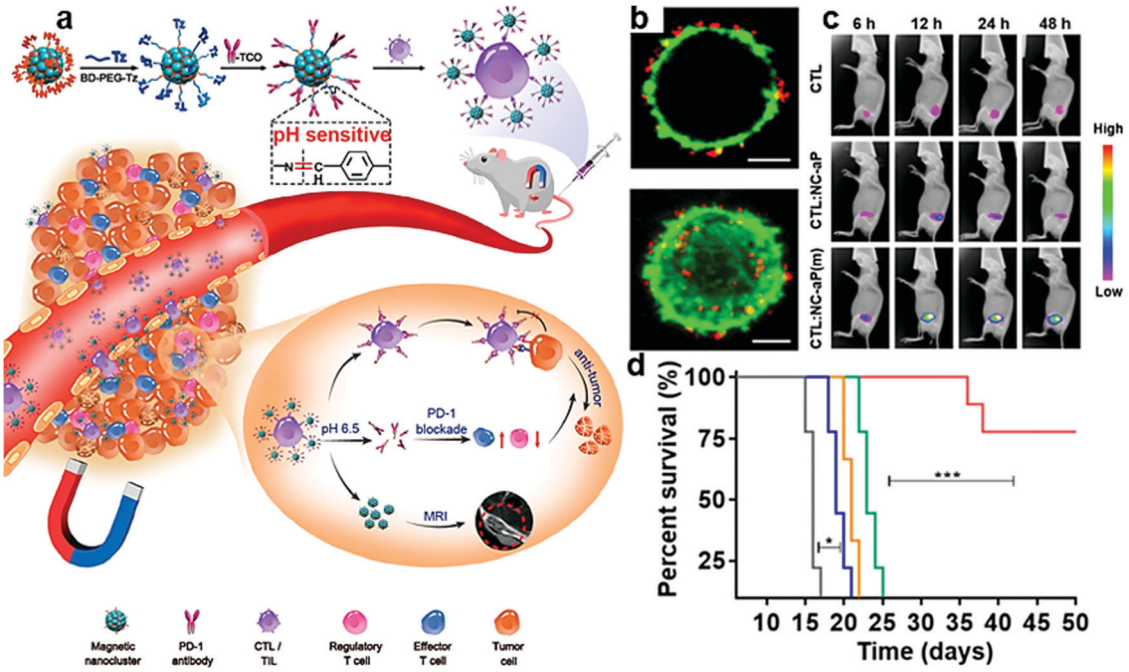


Fig. 13 (a) Schematic illustration of IONP/anti PD-L1 for improved adoptive T cell therapy for solid tumors. (b) Representative confocal and corresponding 3D reconstruction images of T cells (green) and iron oxide-anti PD-L1 (red). (c) Visualization of the tumor-targeting ability. (d) Average survival percentages of mice after different treatments. Reproduced with permission from ref. 191. Copyright 2019, American Chemical Society.

They used anti PD-1 to improve the effect of adoptive cell transfer therapy, which has been widely used in clinical practice. Unlike general medical treatment, it requires extracting T cells from patients, expanding them *in vitro*, and then returning them to patients. Magnetic targeting was utilized to improve the accumulation of nanocomposites and utilization of anti PD-1. Taking advantage of the magnetic properties and combination of anti PD-1 and PD-1, T cells are efficiently transported to the tumor site with MRI guidance (Fig. 13b and c). The therapeutic effect of immune cytotoxicity and checkpoint blockade was significantly improved with prolonged survival time (Fig. 13d).

J. P. Schneck *et al.* developed immunoswitch nanomaterials based on iron-dextran to deliver checkpoint inhibitors.[228] The organic/inorganic nanocomposites can close the immunosuppressive PD-L1 pathway on tumor cells and simultaneously open the co-stimulatory 4-1BB pathway on $CD8^+$ T cells by transmitting anti PD-L1 and anti 4-1BB. T cells are then stimulated by MHC-1 signals on the surface of tumor cells to activate and kill tumor cells. Sequencing analysis of tumor infiltrating T cells showed that enhanced tumor growth inhibition was achieved by altering the T cell receptor sequence and thereby inducing the expansion of the $CD8^+$ T cell population. The design of the nanocomposites could improve the effectiveness of blocking agents and reduce costs, thereby avoiding the complexity of using multiple therapeutic agents. At the same time, further adjustments could be made to optimize the biodistribution, such as designing the shape and size of the nanoparticles to reduce the clearance rate.

Gold-based nanocomposites provide excellent computed tomography (CT) imaging capabilities for ICB therapy. This is of significance since it usually takes two months after treatment to assess whether a patient responds to ICB therapy. R. Popovtzer *et al.* utilized the CT imaging function of gold nanoparticles to integrate visualization of the treatment and shorten the evaluation time.[229] Tumor-bearing mice showed different anti PD-L1 uptake rates, which corresponded to the infiltration of T cells in the tumor site and the tumor suppressing effect. This strategy can reduce the amount of immunotherapy drugs, and can predict the patient's response to ICB treatment, and accelerate personalized treatment.

Compared with organic nanomaterials used for ICB therapy, organic/inorganic nanocomposites may provide more possibilities, such as tumor targeting and visualization. Due to their optical, electrical, and magnetic properties, organic/inorganic nanocomposites used in PTT, PDT, magnetocaloric therapy, *etc.* could be combined with ICB therapy to achieve synergistic effects.

6. Combination of immunotherapy strategies

In addition to the immunotherapy strategies discussed above, the regulation of the immune TME, activation of immune responses, and ICB therapy could be combined to effectively inhibit tumor growth. Modulation of the TME can improve the therapeutic effect on tumors, but its own therapeutic effect is not ideal and needs to be used in combination with other treatments. Activation of immune responses by PTT, PDT and other therapies can effectively kill tumors locally, but they may also cause upregulation of immunosuppressive cells, PD-1, and PD-L1. ICB therapy has been used in clinical practice, but it only works for certain patients. The combination of regulating

the immunosuppressive TME and activating immune responses can enable checkpoint inhibitors to function efficiently. Therefore, the combination of immunotherapy strategies has become the general trend. Versatile organic/inorganic nanocomposites offer more possibilities for combination. In this section, we discuss the combined immunotherapy strategies mediated by organic/inorganic nanocomposites.

6.1. Modulation of the immunosuppressive TME and ICB therapy

By modulation of the TME from an immunosuppressive state to a promoted state, ''cold'' tumors are transformed into ''hot'' tumors that are sensitive to treatments. In this case, if ICB therapy is combined then checkpoint blockade will be greatly improved. PD-1/PD-L1 checkpoint blockade is usually selected as a representative.

ROS is an important signaling messenger that affects the immune TME. By adjusting the level of ROS, the polarization of macrophages can be adjusted to make tumor cells sensitive to other treatments, and then up-regulate the expression of tumor-associated antigens, which can significantly improve the effect of ICB therapy. ROS-responsive nanoparticles could regulate the immune TME by modulating the ROS level to enhance the antitumor immune responses.[218]

In addition to adjusting ROS levels, there are more approaches for organic/inorganic nanocomposites to modulate the immunosuppressive TME. Combined with ICB therapy, the survival time of mice could be significantly improved. Z. Gu *et al.* prepared anti PD-1-loaded $CaCO_3$ nanoparticles and the demethylating agent Zebularine to form a pH/ROS dual-responsive hydrogel (Fig. 14a).[217] The tumor-associated antigen expression and reduction of MDSCs could be enhanced by Zebularine (Fig. 14b–d). Therefore, the immune TME was regulated to make tumor cells more favorable for T cell identification. However, Zebularine can induce increased PD-L1 expression on the surface of tumor cells, so it is necessary to combine with ICB therapy. Anti PD-1 blocks the PD-1/PD-L1 interaction and triggers a strong anti-melanoma immune response. The design of pH/ROS dual-responsiveness of the hydrogel helps the controlled and sustained release of Zebularine and anti PD-1. Compared with Zebularine or anti PD-1 treatment, the Zebularine and anti PD-1 combined treatment showed significant tumor suppression, and the survival time of mice was significantly prolonged. It was also found that locally delivered organic/inorganic nanocomposites can effectively induce a systemic anti-tumor immune response. This strategy, which combines the regulation of the immune TME and ICB therapy, can help suppress tumor growth and prolong the survival time of B16F10 melanoma mice.

Taking advantage of $CaCO_3$ and anti PD-L1 to inhibit tumor growth and recurrence, Z. Gu *et al.* designed a fibrin gel for postoperative cancer immunotherapy.[230] In this study, the removal of H^+ during the degradation of $CaCO_3$ nanoparticles may be responsible for the polarization of M2 macrophages to M1 macrophages. Anti CD47 was loaded into $CaCO_3$ nanoparticles to block the ''don't eat me'' signal expressed by tumor cells through CD47 to improve the recognition and clearance of macrophages and T cells. By systemic injection of anti PD-L1, the regulation of the immunosuppressive TME and ICB therapy were combined, while promoted local antitumor immune responses and systemic suppression of tumor recurrence were realized.

In addition to $CaCO_3$, the design of components of organic/inorganic nanocomposites may bring more functions. For example, if MnO_2 or IONPs could be introduced, MRI or magnetic targeting could be integrated for imaging-guided cancer immunotherapy with high effectiveness.

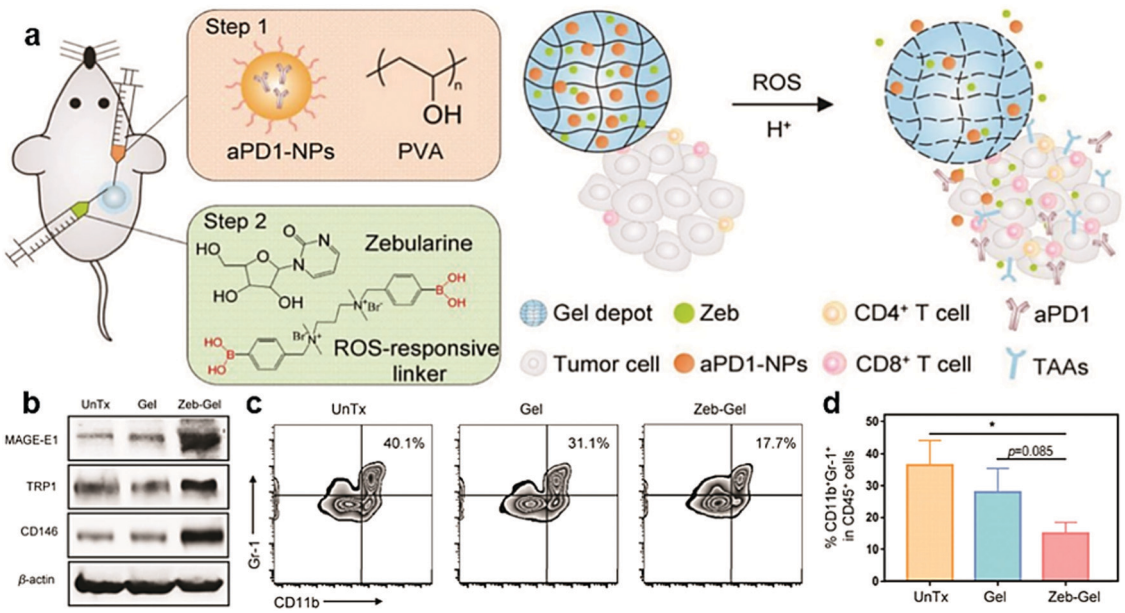


Fig. 14 (a) Schematic illustration of the combination strategy of TME modulation and ICB therapy using ROS/H^+ responsive scaffolds. (b) Tumor-associated antigen expression analyzed by western blotting assay. (c and d) Representative images and the quantitative analysis of MDSCs ($CD11b^+Gr\text{-}1^+$) in $CD45^+$ cells by flow cytometry. Reproduced with permission from ref. 217. Copyright 2019, Wiley-VCH.

6.2. Activation of immune responses and ICB therapy

Among the combined strategies, the combination of immune response activation and ICB therapy is the most widely used. There are various ways to activate immune responses. They could be activated by ICD through some treatments (including PTT,[43,95,214,219,225,231,232] PDT,[137,138,213,233–238] CDT,[235,239] sonodynamic therapy,[213] starvation therapy,[240] magnetic hyperthermia therapy,[222,241] radiation therapy[223,232,242,243]), agonists,[213–215,219,222,223,233,244,245] or antigens,[244,245] *etc.* Many types of checkpoint blockade are used in combination with immunotherapy strategies. Checkpoints PD-L1,[138,213,214,226,233–235,243,245] and IDO,[137,242] which are located on tumor cells, or checkpoints PD-1,[216,219,225,236,244] CTLA-4,[222–224] and CSPG-4,[43] which are located on T cells, can be selected. Some studies directly encapsulate the components used to activate T cells and checkpoint blockade to enter tumor tissue.[137,216,225,242] Other studies choose to first transport materials to activate T cells, and then inject checkpoint inhibitors,[43,138,213–215,219,222–224,233–236,243–245] which can improve the blocking effect more specifically.

6.2.1. ICD and checkpoint inhibitors. PDT, PTT and other treatments can kill tumor cells through ROS or hyperthermia, and generate tumor-related antigens from tumor cell residues, activate the immune system, and produce a local antitumor immune response. However, PD-1/PD-L1 and other similar pathways inhibit the activation of $CD8^+$ T cells. So while ICD causes antitumor immune responses, it will increase the number of immunosuppressive Tregs and up-regulate PD-1 and PD-L1 expression through the increase of IFN-γ,[246,247] so the combined use with checkpoint inhibitors can restore the activity of $CD8^+$ T cells and increase the antitumor effect. Moreover, the activation of immune responses and the use of checkpoint inhibitors can activate a systemic immune response.

PDT is a common tumor treatment method for ICD caused by ROS damage. It can destroy local tumors and minimize normal tissue damage, but it has no effect on suppressing tumor metastasis. The combination with ICB therapy can effectively induce antitumor immune responses.[248] Some therapeutic-related agents, such as photosensitizer porphyrin,[137,138,233–236] can be used as ligands and combined with metal ions to form nMOFs, which are excellent PDT nanoplatforms. PDT inhibits the growth of primary tumors and its combination with ICB therapy can effectively induce a systemic anti-tumor immune response. W. Lin *et al.* prepared Hf-chlorin nMOFs, and used their porous structure to load IDO inhibitors to achieve a combination of PDT and IDO checkpoint blocking to induce regression of treated primary tumors and untreated distal tumors.[137] Massive stressed and dying necrotic tumor cells induced by PDT could be engulfed by the innate immune effector cells. After the tumor derived antigens were presented to T cells, a tumor-specific T cell response could be stimulated. However, IDO expressed by tumor cells can prevent T cells from expanding, inhibiting their activity and even causing T cell apoptosis. Combination with IDO inhibitors can restore T cell activity, increase T cell infiltration into tumors, and effectively kill cancer cells. To alleviate the problem of tumor hypoxia during PDT, Fe-porphyrin nMOFs were prepared to generate $^1O_2$ under stimulation through a Fenton-like reaction.[138] The combination of intraperitoneal injection of anti PD-L1 and PDT can cause systemic antitumor immune responses and induce T cell infiltration into the tumor. C. Yan *et al.* proposed upconversion nanoparticle (UCNP)-porphyrin nMOFs to improve the depth and tissue penetration of PDT (Fig. 15a–c).[234] They used the scaffold structure of the MOF to load the hypoxia-activated drug tirapazamine. Chemotherapy was combined with PDT, and synergistically killed cancer cells to achieve the purpose of more effectively activating immune cells through ICD (Fig. 15d), and then combined with anti PD-L1 to improve the therapeutic effect on hypoxic tumors. W. Lin *et al.* synthesized Cu-porphyrin nMOFs, which cooperate with PDT and CDT to kill cancer cells by ROS,[235] which could cause ICD and promote immune cell activation. After combination with anti PD-1, growth of primary and metastasis tumors could be effectively inhibited. For the combination of ICB therapy with PDT, photosensitizers could also be loaded in the nanocomposites.[237,238] In addition to PDT, sonodynamic therapy could also be utilized to enhance the production of ROS. Y. Chen *et al.* used the ultrasound sensitizer hematoporphyrin monomethyl ether and the adjuvant R837 to prepare nanocomposites.[213] After combining with anti PD-L1, an anti-tumor immune response and long-term immune memory could be realized.

Hyperthermia induced by gold, carbon, and black phosphorus quantum dots with high light-to-heat conversion efficiency shows excellent antitumor efficacy, but at the same time the expression of PD-1/PD-L1 will be up-regulated. The combined use with checkpoint blockers could block the inhibition of T cells by these proteins and has excellent performance in inhibiting tumor metastasis and recurrence. J. You *et al.* encapsulated gold nanoshells and anti PD-1 peptide in poly(lactic-*co*-glycolic acid) to construct a photothermal ablation and ICB treatment strategy for malignant and metastatic tumors.[225] The release of anti PD-1 peptide in the body is controlled by NIR light, which can achieve sustained release of drugs for up to 40 days, solving the problem of frequent clinical administration. This strategy combines a PTT-activated immune response with ICB therapy and shows low systemic toxicity but strong systemic immune responses. L. Mei *et al.* coated black phosphorus quantum dots with cancer cell membranes to form nanovesicles, which were loaded into a hydrogel that contains GM-CSF and LPS, and used them in combination with anti PD-1 (CpG/LPS-P).[219] A good inhibitory effect in the surgical removal of residual tumors and metastatic cancer cells was observed (Fig. 16a and b). After NIR irradiation, GM-CSF and LPS can recruit (Fig. 16c) and activate (Fig. 16d) DCs, enhance antigen presentation, and activate T cells. In addition, injecting anti PD-1 into the tail vein can reinvigorate exhausted $CD8^+$ T cells and induce a strong and durable antitumor immune response (Fig. 16e). This treatment strategy can effectively reduce the metastasis and recurrence of the primary tumor after surgical resection. Unlike conventional PTT, single-walled carbon nanotubes can not only be used for photothermal ablation of tumors, but also stimulate the maturation of DCs. Based on this characteristic, Z. Liu *et al.* selected single-walled carbon nanotubes with high light-to-heat conversion efficiency in combination with anti CTLA-4 to

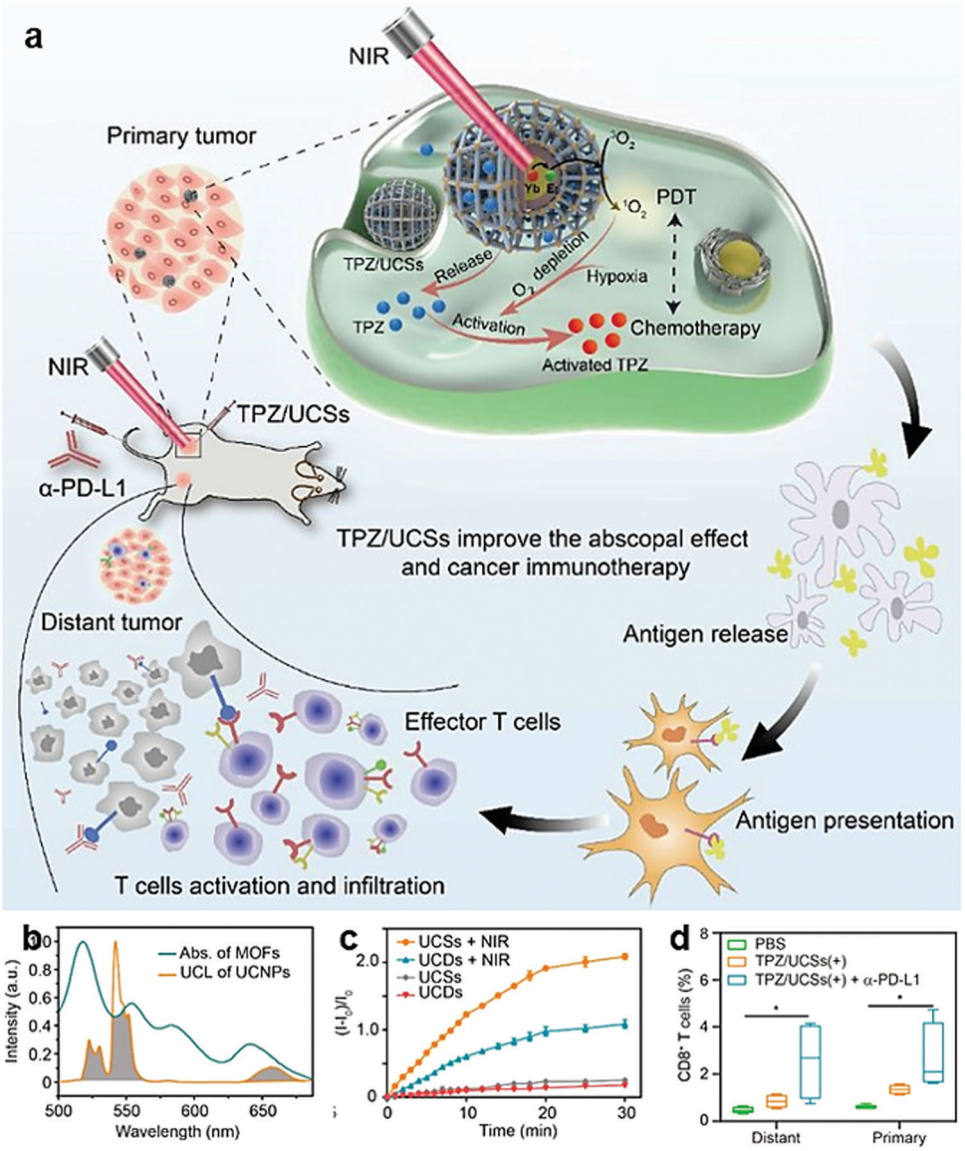


Fig. 15 (a) Schematic illustration of the structure of UCNP-porphyrin nMOFs and their application for tumor treatment through the combination of NIR light-triggered PDT and hypoxia-activated chemotherapy with immunotherapy. (b) Absorption spectrum of the nMOFs. (c) NIR light-induced $^1O_2$ generation by nMOFs determined by SOSG assay. (d) The percentage of tumor-infiltrating $CD8^+$ T cells in total tumor cells. Reproduced with permission from ref. 234. Copyright 2020, American Chemical Society.

perform photothermal ablation of the primary tumor and prevent tumor metastasis.[231] In the absence of light, the nanocomposites only stimulated the maturation of DCs and presented antigens originally present in the tumor cells, which could not provoke an effective immune response or inhibit tumor growth. When PTT was applied, a combination occurred since PTT eliminated the primary tumor and promoted the release of tumor-associated antigens, and then the maturation of DCs increased the activation efficiency of the immune responses. Furthermore, anti CTLA-4 therapy reduced Tregs activity and increased $CD4^+$ T cell and $CD8^+$ T cell infiltration, which improved the effective killing of tumor cells by the immune response. Moreover, magnetic hyperthermia therapy needs to be combined with ICB therapy to trigger a systemic antitumor immune response to treat diffuse metastatic tumors. Z. Liu *et al.* utilized the high magnetocaloric conversion efficiency of Fe_3O_4 to induce ICD caused by magnetic hyperthermia therapy.[222] The combination of local injection of nanocomposites and systematic injection of anti CTLA-4 will lead to systemic therapeutic responses to inhibit tumor metastasis and trigger long-term immune memory to prevent tumor recurrence.

Radiation and starvation treatment can also destroy local tumor growth, and activate immune responses through ICD. After combining with ICB therapy, a systemic anti-tumor immune effect could be achieved. W. Lin *et al.* developed radiotherapy based on HF-porphyrin nMOFs (Fig. 17),[242] which could efficiently absorb X-ray photons for radiotherapy. The combination with ICB therapy will expand the application of

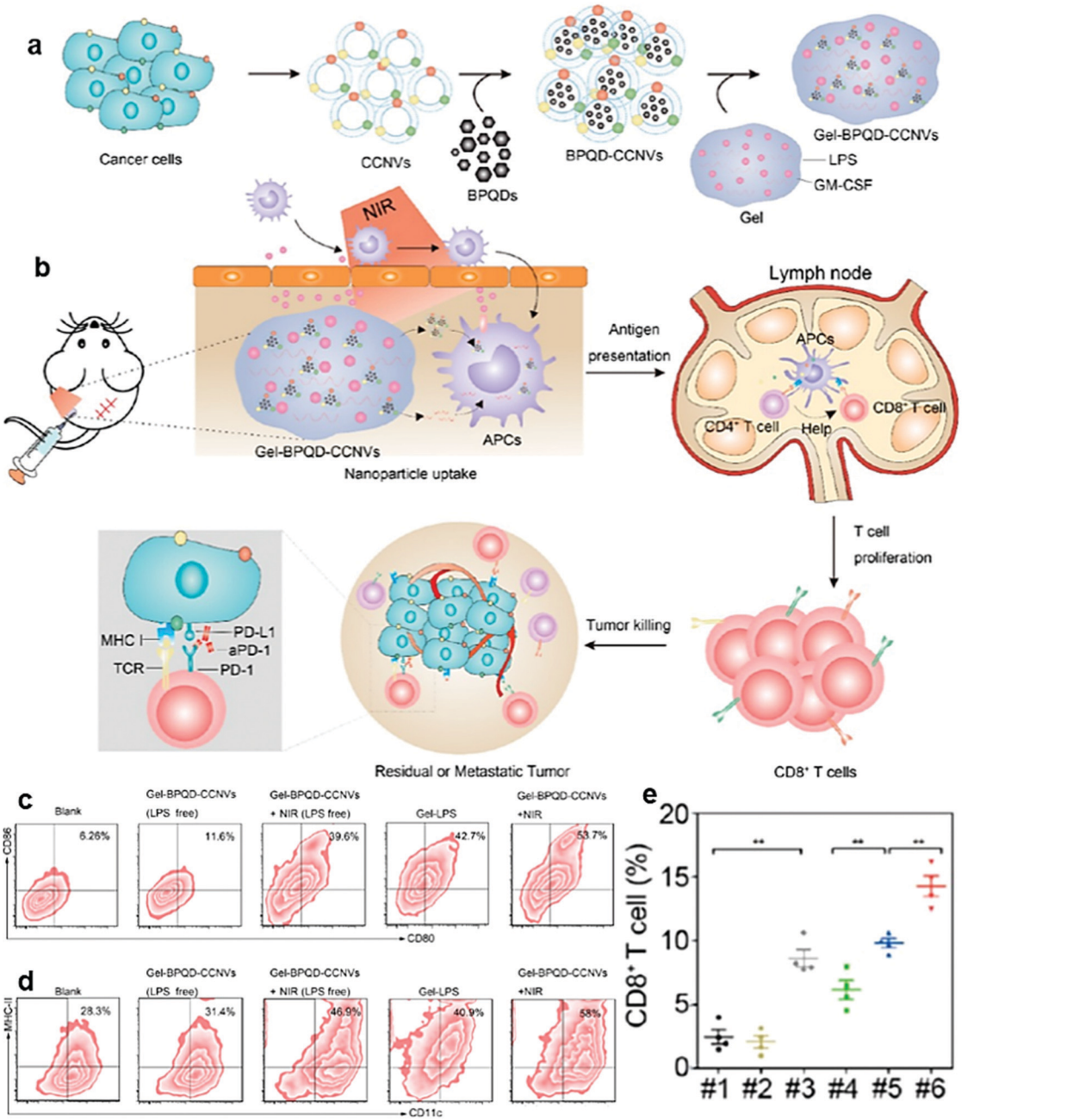


Fig. 16 Schematic illustration of (a) preparation and (b) cancer immunotherapy of CpG/LPS-P. (c and d) Representative flow cytometry plots of (c) mature DCs and (d) $CD11c^+$ $MHC\text{-}II^+$ cells from different treatment groups. (e) Representative ratios of different groups of T cells in residual tumors from different groups. Reproduced with permission from ref. 219. Copyright 2019, American Chemical Society.

radiotherapy with a systemic antitumor immune response. In order to combine with ICB therapy, IDO inhibitors were loaded into nMOF pores and achieved an unprecedented 100% antitumor effect. Compared with traditional therapies, starvation therapy can provide more effective tumor ablation and induce an immune response. W. Liu *et al.* designed glucose oxidase-loaded silica nanoparticles to combine starvation therapy with immunotherapy.[240] Glucose oxidase can convert glucose in tumor tissue to gluconic acid and hydrogen peroxide, cut off the energy supply to tumor cells, and cause apoptosis. After being injected with the nanocomposites and anti PD-1, higher DC maturation and infiltration of $CD4^+$ T and $CD8^+$ T cells were realized. Compared with monotherapy, the combination of starvation therapy and ICB therapy can effectively enhance the blocking effect of anti PD-1, showing great potential for cancer treatment.

6.2.2. ICD and agonists and checkpoint inhibitors. The occurrence of an antitumor immune response is a complex process, which needs specific antigens, effective presentation of antigens, and activation of T cells. ICD can kill tumor cells and release tumor-associated antigens. Agonists can greatly

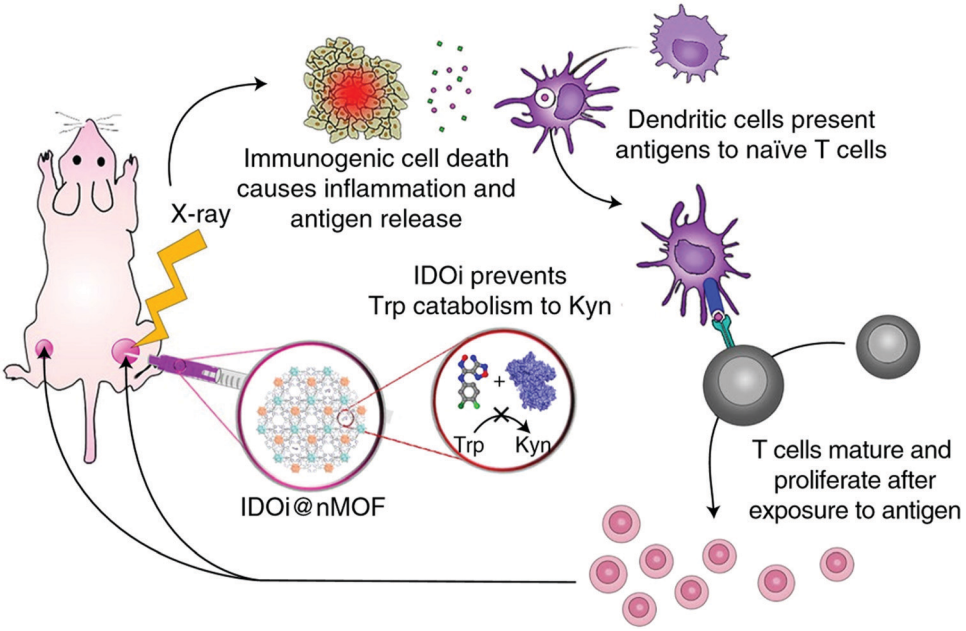


Fig. 17 Hf-porphyrin nMOFs enable synergistic radiotherapy and immunotherapy. Reproduced with permission from ref. 242. Copyright 2018, Springer Nature.

activate DCs to present antigens to T cells. Checkpoint inhibitors will block pathways that inhibit T cell activity and increase the presence of tumor-infiltrating T cells and restore the T cell lethality. The combination of ICD, agonists and checkpoint inhibitors can effectively improve the activation of the antitumor immune response. This complementary therapy can produce systemic immunity against tumors.

When organic nanomaterials are used to realize the combination of ICD, agonists and checkpoint inhibitors, loading of photosensitizers or photothermal agents is usually needed. For example, Z. Liu *et al.* encapsulated the photothermal agent ICG and agonist R837 in poly(lactic-*co*-glycolic) acid to produce a powerful immune response.[249] Then through systemic injection of anti CTLA-4 to combine with ICB therapy, the activated immune response could effectively inhibit tumor metastasis. In contrast, organic/inorganic nanocomposites can cause ICD themselves,[214,222,233,250] making the combination easier. While activating the immune responses, more functions could be achieved, such as increased tissue penetration depth, magnetic targeting, and visualization of treatment. W. Lin *et al.* designed W-porphyrin nMOFs for the combination of PDT with anti PD-L1, and the nMOFs were used to load the agonist CpG (Fig. 18a).[233] Cancer cells killed by PDT could provide tumor-associated antigens, while agonists stimulate DCs to present antigens to increase the T cell activity (Fig. 18b–e). In addition, inhibitors restore the function of T cells. The combination of PDT, agonists and ICB therapy can provide a tumor inhibition rate of ~97%. Z. Liu *et al.* fabricated R837-Ce6/UCNP nanocomposites for a similar combination.[251] Anti CTLA-4 was introduced to combine activated immune responses with ICB therapy. Under NIR irradiation, PDT directly destroyed tumor cells, and R837 stimulated an immune response by triggering DC maturation and cytokine secretion. The combination of immunotherapy strategies could effectively eliminate primary tumors through PDT, inhibit distant tumors, and induce long-term immune memory effects.

In addition to ROS, hyperthermia can also be used in combination with agonists and checkpoint inhibitors to fight tumors. Z. Liu *et al.* prepared Fe_3O_4 nanoparticles as magnetic hyperthermia agents, and through local application of agonist R837 and systemic injection of checkpoint inhibitor anti CTLA-4, long-term systemic therapy is achieved.[222] After magnetic hyperthermia therapy released tumor-associated antigens, a small amount of local injection of R837 could effectively stimulate DCs to rapidly process and present tumor antigens, which in turn stimulated T cells to produce immune responses. However, the Tregs in the distal tumor also increase, and cannot completely inhibit the growth of the distal tumor. After combining with anti CTLA-4, the activity of Tregs was inhibited, and completely inhibition of distant tumors could be achieved. B. Yang *et al.* used FDA approved poly(ethylene glycol)-*block*-poly(lactic-*co*-glycolic acid) copolymer, Fe_3O_4 nanoparticles, and imiquimod (R837) to form nanocomposites.[214] In this work, Fe_3O_4 acts as photothermal, magnetic targeting, and T_2 contrast agents. Under NIR irradiation, tumor-associated antigens could be released to activate immune responses. R837 promotes DC maturation, thereby enhancing the activation and proliferation of antigen-specific lymphocytes. Combined with anti PD-L1, a strong systemic antitumor immune response could be stimulated and promoted by PD-L1 ICB therapy to prevent tumor metastasis.

6.2.3. Antigens and agonists and checkpoint inhibitors. Unlike ICD-induced tumor-associated antigen release, organic/inorganic nanocomposites can carry foreign antigens (such as OVA or cancer cell membranes) to directly stimulate APCs and activate antitumor immune responses. Combined with agonists

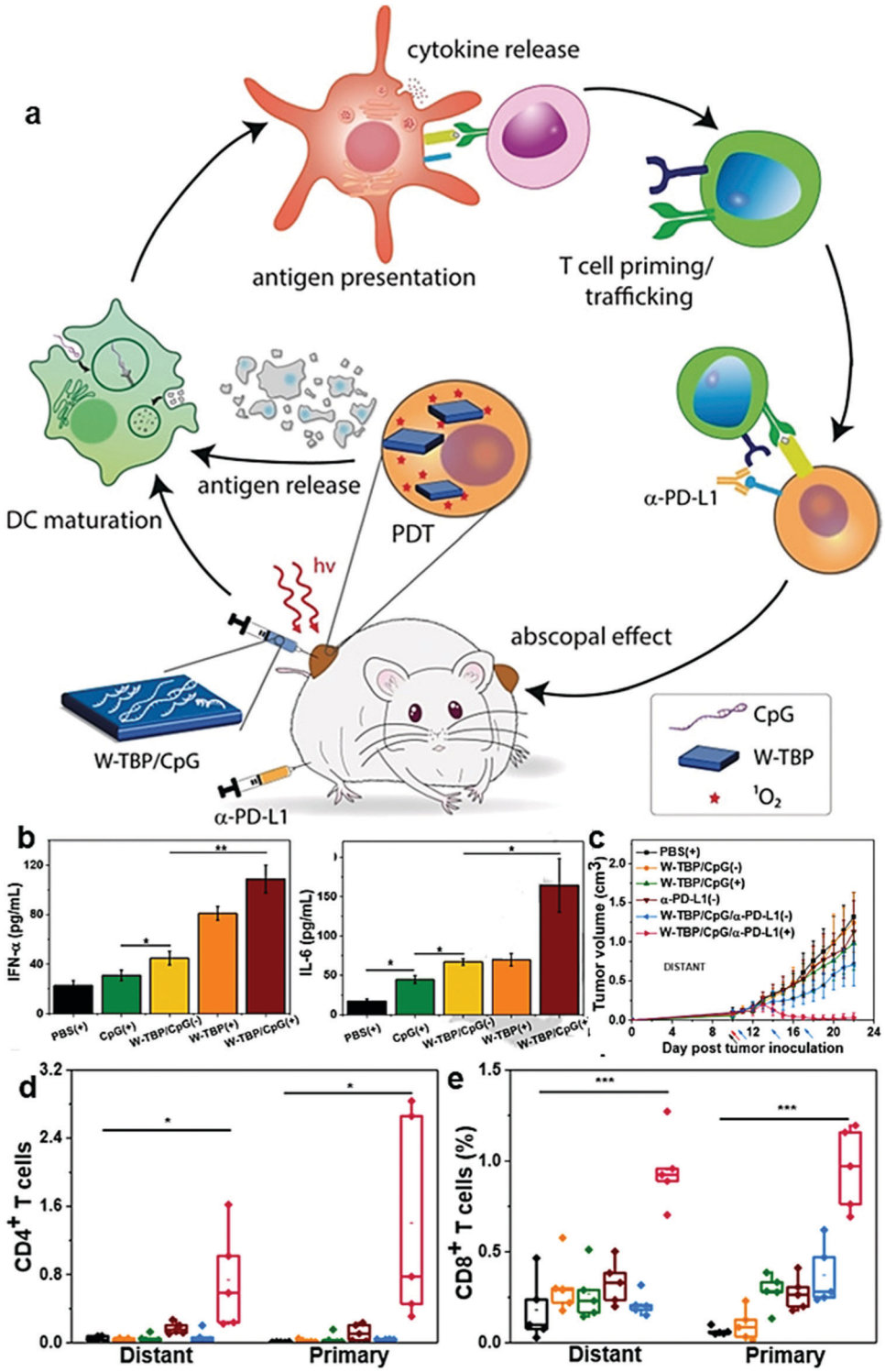


Fig. 18 (a) W-porphyrin/CpG promoted antigen presentation *via* immunogenic PDT to afford systemic antitumor immunity. (b) ELISA of IFN-γ and IL-6 in blood of mice. (c) Growth curves of distant tumors of bilateral TUBO tumor-bearing mice. (d and e) The percentage of tumor-infiltrating $CD4^+$ T cells (d), and $CD8^+$ T cells (e) with respect to the total tumor cells. Reproduced with permission from ref. 233. Copyright 2019, Wiley-VCH.

and ICB therapy, this can help improve the recognition and lethality of T cells to obtain long-term systemic antitumor effects.

The model protein OVA is a commonly used foreign antigen and has broad applications in the design of tumor vaccines. Some metal–organic complexes loaded with OVA and agonists can significantly stimulate the maturation of DCs and present antigens. The synergistic effect with checkpoint inhibitors can improve the therapeutic effect and prolong their survival time.

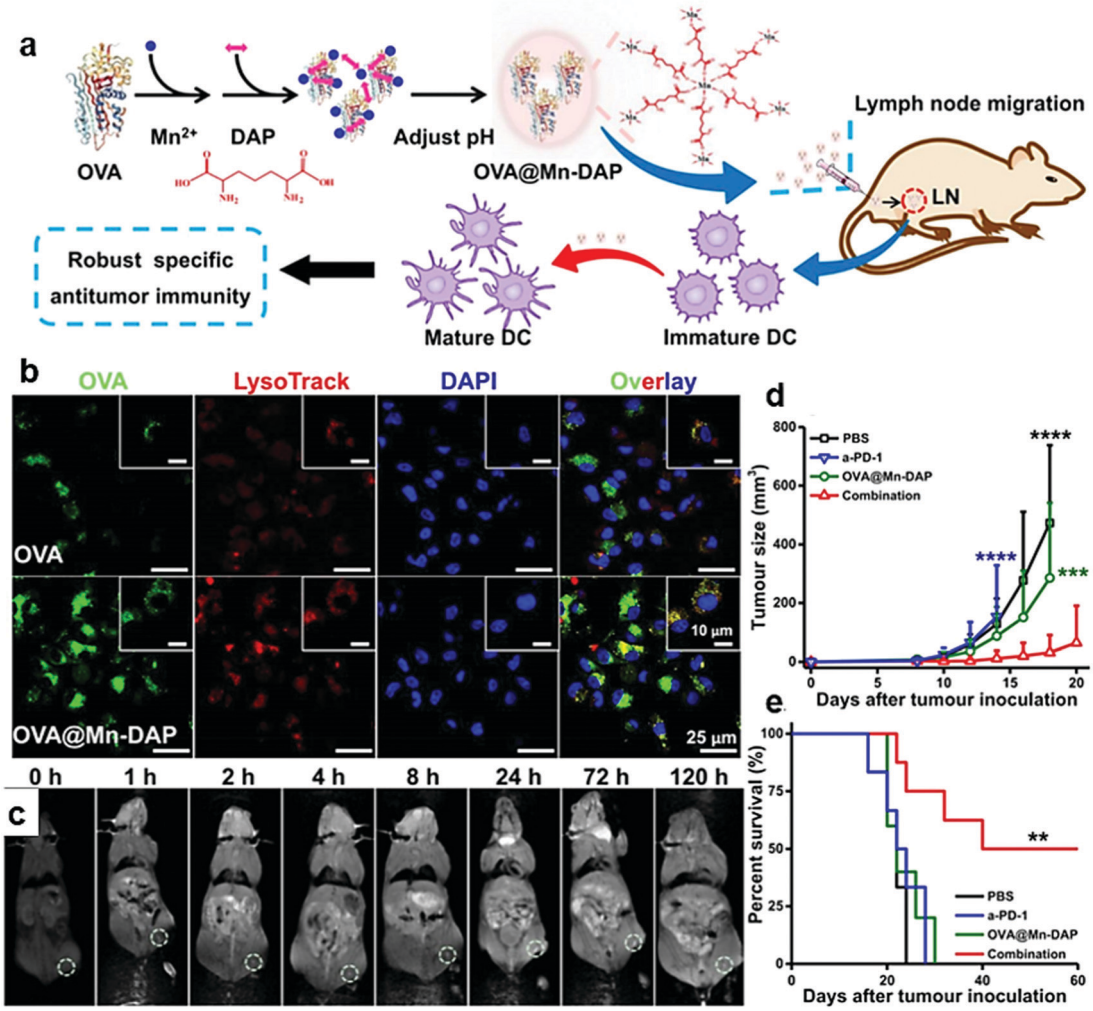


Fig. 19 (a) Schematic illustration of the synthesis and function of OVA-Mn-*meso*-2,6-diaminopimelic acid nanocomposites. (b) Confocal fluorescence images of DCs after incubation with free OVA-cy5.5 or OVA-cy5.5@Mn-DAP for 20 h. (c) *In vivo* T_1-weighted MR images at various time points. (d) Average tumor growth curves for different groups of B16-OVA tumor-bearing mice after different treatments. (e) Survival data of various groups of mice. Reproduced with permission from ref. 244. Copyright 2019, American Chemical Society.

For example, Z. Liu *et al.* constructed a coordination polymer nanoplatform using Mn-*meso*-2,6-diaminopimelic acid, which was used to carry OVA and combined with anti PD-1 to inhibit the tumor growth of B16-OVA tumor-bearing mice (Fig. 19a).[244] In this work, OVA stimulated DC maturation. With the help of agonist *meso*-2,6-diaminopimelic acid, it could effectively enhance the antigen presentation of DCs by promoting the expression of IL-12p40 and TNF-α, and further activate the immune response (Fig. 19b). The presence of Mn^{2+} enabled an MRI function to monitor the *in vivo* delivery of nanocomposites in real time (Fig. 19c). The intravenous injection of anti PD-1 combined ICB therapy with OVA and agonists to obtain better therapeutic effects (Fig. 19d and e). The study also showed that there was an immune memory effect in mice. S. R. Little *et al.* loaded OVA on aluminum-based alginoketal nanoparticles, which encapsulated the IDO inhibitor 1-MT and agonist poly(I:C), and then used anti PD-L1 in combination to demonstrate a good therapeutic effect for melanoma.[252] After the as-prepared nanocomposites were delivered to the tumor site, the level of kynurenine was detected to decrease while the content of INF-α increased, indicating that the activity of IDO was inhibited. After combination with anti PD-L1, the growth of primary and contralateral tumors was significantly inhibited, and the survival rate in one month reached 100%.

Mesoporous silica nanoparticles could easily control the adsorption and release of antigens and adjuvants due to the unique pore structure. J. Kim *et al.* prepared an injectable dual-scale mesoporous silica vaccine which could be loaded with OVA and agonist CpG and combined with anti CTLA-4 for anti-tumor immunotherapy.[253] In this study, mesoporous silica microrods were used to form a three-dimensional macroporous skeleton, which induced DCs to enter the skeleton by releasing DC chemokines. Then mesoporous silica nanoparticles carrying OVA and CpG were internalized by the recruited DCs to activate DCs and stimulate them to present antigens to T cells. This dual-scale mesoporous silica vaccine could activate a large number of

antigen-specific T cells and significantly inhibit melanoma growth. After intraperitoneal injection of anti CTLA-4, the combination of ICB therapy and an antigen-specific vaccine can synergistically enhance the anti-tumor response and further inhibit tumor growth, which demonstrated a higher anti-tumor effect and animal survival rate.

Unlike OVA antigens, cancer cell membrane antigens come from patients, which have more complex surface antigens to mimic clinical conditions and can be metabolized in biological systems without generating by-products. Therefore, for clinical applications, future research may focus on the use of tumor-associated antigens (such as cancer cell membranes or tumor lysates) to achieve personalized cancer therapy. C. Wang *et al.* selected cancer cell membranes to coat Ag nanoparticles and combined with anti PD-L1 to achieve great inhibition of tumor metastasis and recurrence in both B16F10 and 4T1 tumor models.[245] This research directly proved the importance of the combination of tumor-associated antigen-activated immunity and ICB therapy.

6.2.4. Others. There are some other methods to realize the combination of activated immune responses and ICB therapy in addition to those mentioned above, such as combined agonists and checkpoint inhibitors, or combined antigens and checkpoint inhibitors, *etc.* These methods can also enhance the T cell responses to a certain extent, effectively enhance the treatment effects of ICB therapy, reduce adverse reactions, and improve the survival time of mice.

S. Y. Chen *et al.* synthesized Fe_3O_4-fucoidan-dextran nanoparticles, which are coupled with the agonist anti CD3/anti CD28 through dextran. Then anti PD-L1 was integrated to achieve the combined antitumor effect of an agonist and checkpoint inhibitor.[254] By intravenous injection, the magnetic nanocomposites could rejuvenate T cells through agonists. Meanwhile, the nanocomposites could target tumors through magnetic targeting, which could reduce off-target effects to the greatest extent, improve the therapeutic effect and reduce the dosage of nanocomposites. Compared with anti-PD-L1 ICB treatment alone, the combination of the agonist and anti PD-L1 can extend the survival time of mice from 32 to 63 days. This work demonstrates the potential of integrating anti PD-L1 and agonists into a nanocomposite to enhance the therapeutic effect of ICB therapy.

The presentation of foreign antigens by DCs can also cause the activation and infiltration of T cells, which could combine with ICB therapy to promote the activation and proliferation of T cells and reduce tumor recurrence. L. Huang *et al.* skillfully delivered two nucleic acids through liposome-coated calcium phosphate nanoparticles.[255] One nucleic acid encoded the mRNA of melanoma tumor antigen as an antigen, and the other nucleic acid encoded siRNA that blocks the expression of PD-L1 as a checkpoint inhibitor, which combines antigen delivery and ICB therapy to activate the immune system. The nanoparticles are functionally modified with mannose as a targeting ligand and a long-term inhibitory effect on tumor growth and metastasis was observed. After subcutaneous administration, mRNA antigens and siRNA that blocks expression of the PD-L1 immune checkpoint can be introduced into DCs at the same time. Acid-responsive degradation of calcium phosphate in the lysosomal region prompted the internalization of nanocomposites to quickly release the cargo. The mRNA vaccine encoding melanoma antigen stimulated DCs to mature, activated their presentation of antigens to T cells, and triggered a strong antigen-specific T cell response. The co-delivery of PD-L1 siRNA and the mRNA vaccine resulted in the down-regulation of PD-L1, thereby significantly promoting the activation and proliferation of T cells. The enhanced T cell response has an effective inhibitory effect on tumor growth and metastasis. This work provides a reference for the development of mRNA vaccine vectors to enhance the antitumor immune responses.

6.3. Combination of immune TME modulation, immune response activation and ICB therapy

In the last section, we introduced organic/inorganic nanocomposites used for combined activation of the immune system and ICB therapy, which has a significant effect on the effectiveness of immunotherapy to inhibit tumor metastasis and recurrence. However, there are a variety of immunosuppressive cells in the immune TME (such as MDSCs, M2 TAMs, and Tregs), which affect the therapeutic effects. Reversing immunosuppression can enhance the tumor response to various treatments. Therefore, a combination of modulation of the immunosuppressive TME, activation of the immune response, and ICB therapy could further improve the therapeutic effectiveness of immunotherapy. Firstly, modulation of the immunosuppressive TME makes the tumor change to a sensitive state, which is convenient for treatments. Then, more T cells are activated to kill tumor cells. And, finally, the breakthrough in the self-protection of tumor cells by checkpoint inhibitors could avoid immune escape and enable T cells to perform more powerful functions. The combination of these three strategies will improve the efficiency of antitumor immune responses and the therapeutic effect in all aspects.

MnO_2 and Fe_3O_4 nanoparticles exhibit excellent characteristics in the design of nanomaterials combining these three immunotherapy strategies. The fabrication of organic/inorganic nanocomposites based on these two materials can simultaneously modulate the immunosuppressive TME, activate immune responses, and realize ICB therapy. Because MnO_2 nanoparticles can catalyze the decomposition of H_2O_2 in the TME to produce O_2, they could improve hypoxia at the tumor site. MnO_2-based nanocomposites can polarize M2 macrophages to M1 macrophages and improve the immune TME. At the same time, MnO_2 nanoparticles could be easily formed as hollow structures which possess high loading capacity and can be used for drug delivery to activate immune responses. They can be used in combination with checkpoint inhibitors to maximize the effect of immunotherapy. In addition, Mn^{2+} could be utilized for MRI, which is beneficial for tracking the transport and responsive degradation of the nanocomposites in the body, and for visualizing of the treatment process. Fe_3O_4 can regulate macrophage polarization to modulate the immunosuppressive TME. At the same time, Fe_3O_4 nanoparticles possess good magnetothermal and photothermal conversion efficiency, and can activate immune responses through ICD. In combination with checkpoint inhibitors, activated immune responses could be

increased to enhance the antitumor effect. Moreover, Fe_3O_4 possesses unique magnetic properties, which can realize magnetic targeting and MRI at the tumor site.

Z. Liu *et al.* designed hollow MnO_2 nanoparticles to load photosensitizer Ce6 and chemotherapeutic drug DOX, which were modified with PEG to obtain excellent stability and dispersibility. Anti PD-L1 was then integrated to inhibit *in situ* and distal tumor growth.[93] After injection of the nanocomposites, strong Ce6 fluorescence and T_1-weighted MR signals appeared in tumors, indicating the high passive tumor homing of these nanocomposites. Under the acidic microenvironment, MnO_2 nanoparticles degraded to release drugs. In addition, O_2 generated *in situ* could relieve tumor hypoxia, polarize M2 macrophages to M1 macrophages, and improve the immune TME. ICD could be induced by both Ce6-mediated PDT and DOX-mediated chemotherapy, which activated the immune responses to inhibit tumor growth. In order to achieve systemic antitumor immunity, anti PD-L1 was introduced to combine with modulation of the immunosuppressive TME and activation of the immune system. The combination of the three strategies mainly gave $CD4^+$ and $CD8^+$ T cells better tumor cell lethality. X. Zhang *et al.* also used the advantages of MnO_2 and anti PD-L1 to conduct the design of nanocomposites.[55] They used the cavity of hollow MnO_2 nanoparticles to load a glycolysis inhibitor and LOX. In this research, LOX consumes lactic acid, and the resultant H_2O_2 is decomposed into O_2 by MnO_2, which was used in the glycolysis process. The consumption of lactic acid could regulate the phenotype of macrophages, and exhibited excellent regulatory capacity for the immune TME. The use of glycolysis inhibitors impedes glucose metabolism in tumor cells, thereby cutting off the supply

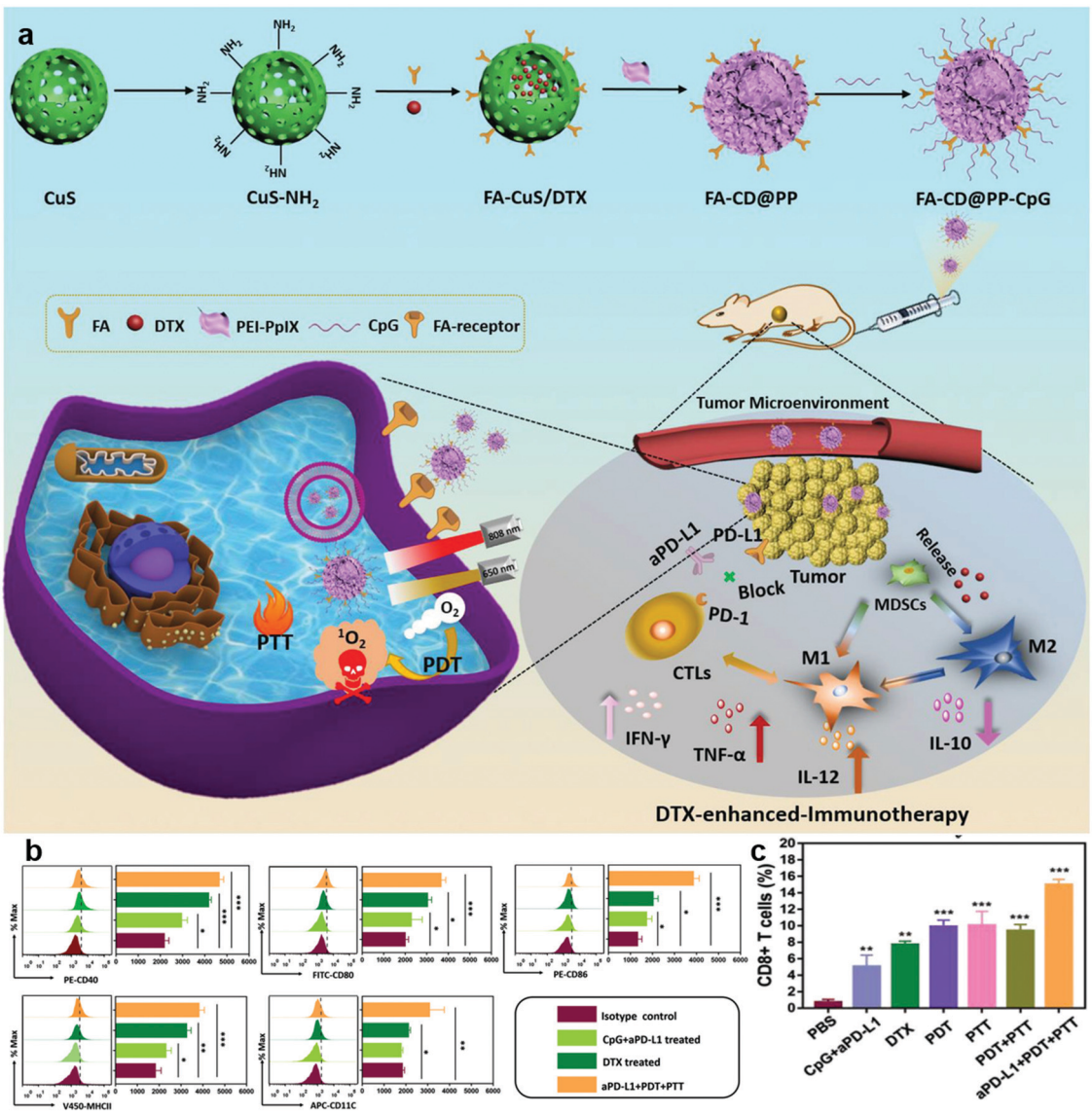


Fig. 20 (a) Rational design and synthesis of CuS-docetaxel/CpG nanocomposites for docetaxel-enhanced immunotherapy. (b) Flow cytometric assay of CD40, CD80, CD86, MHC class II, and CD11c expression from different groups. (c) Proportion of tumor-infiltrating $CD8^+$ T cells. Reproduced with permission from ref. 256. Copyright 2019, Wiley-VCH.

of energy to achieve antitumor therapy and induce ICD, which activated T cell immune responses. After combining with anti PD-L1, the T cell function was enhanced and synergistic tumor suppression effects were realized.

Z. Zhang *et al.* designed organic/inorganic nanocomposites based on Fe_3O_4 that regulated the immune TME, activated the immune system, and blocked checkpoints.[58] They encapsulated Fe_3O_4 nanoparticles in tumor-derived antigen particles, and loaded the agonist CpG on the surface. By applying anti PD-L1 to combine with ICB therapy, the nanocomposites can synergistically regulate the immunosuppressive TME and the host's anti-tumor immunity. The nanocomposites distributed in the TME can regulate ROS through a Fenton reaction, and modulate the infiltrating TAMs to the M1 phenotype. The regulation transformed the "cold" tumor into a "hot" tumor, and induced the infiltration of a large number of CTLs. The tumor inhibition rate reached 83%, and the survival time of the mice was extended to 3 months. This strategy shows that the co-delivery of antigens, agonists, and checkpoint inhibitors, and the regulation of the immune TME are very effective for combination immunotherapy strategies, but more in-depth research is still needed for clinical cancer treatment.

In addition to MnO_2 and Fe_3O_4, the chemotherapeutic drug docetaxel also exhibits excellent immune TME regulation ability, which can be used to design nanocomposites for a combination of immune TME modulation, immune response activation and ICB therapy. C. Dong *et al.* proposed multifunctional CuS-docetaxel/CpG nanocomposites for collaborative phototherapy (including PDT and PTT) and enhanced immunotherapy (Fig. 20a).[256] FA provided a targeting function for the nanocomposites to improve their accumulation at the tumor site. CuS nanoparticles with high photothermal conversion efficiency worked as photothermal agents and carriers. As a photosensitizer, porphyrin participated in the PDT. The resultant ROS hyperthermia from PTT could damage cancer cells to activate the immune responses by ICD. Docetaxel could reduce the proportion of MDSCs and induce MDSC polarization to M1 macrophages, which helped promote the production of inflammatory cytokines for improved immunotherapy (Fig. 20b). The presence of CpG accelerated the maturation of DCs and better presented the antigens to T cells. Combined with anti PD-L1, it is beneficial to block the dysfunction and failure of T cells in the PD-1/PD-L1 pathway, which could enhance T cell infiltration and effectively kill tumor cells (Fig. 20c). Therefore, CuS nanoparticles, porphyrin and CpG activated T cell immune responses by hyperthermia, ROS and DC maturation, respectively. Docetaxel was responsible for immunosuppressive TME regulation. Anti PD-L1 restored the T cell function to improve the tumor lethality. These three ways cleverly combined to regulate the immune responses and enhance the effect of T cells by employing CuS nanoparticles as carriers. This combination of docetaxel, PDT, PTT, CpG, and anti PD-L1 demonstrated a strong antitumor effect and may provide new ways for breast cancer immunotherapy.

7. Conclusions and perspectives

In this review, we mainly summarized the design and application of organic/inorganic nanocomposites in cancer immunotherapy. From the perspective of achieving immune enhancement, nanocomposites play a role in cancer immunotherapy in three strategies: targeting the immunosuppressive TME, activating antitumor immune responses, and ICB therapy. Due to the versatility of nanocomposites, a combination of these immunotherapy strategies could also be realized through rational design of the components.

In general, hypoxia and the acid TME are the main causes of tumor immunosuppression. Therefore, nanomaterials that can improve hypoxia and the acidic pH inside the tumor might be able to alleviate the immunosuppressive TME. Some previous studies targeting the TME may require re-assessment of their impact on the immune microenvironment. At the same time, the combination of drugs targeting the tumor metabolic pathway can interrupt the production of hypoxia and lactic acid, and further modulate the immunosuppressive TME to activate antitumor immunity. Nanocomposites targeting the immune TME could usually polarize immunosuppressive M2 cells to pro-inflammatory M1 cells. When the nanocomposites are administered systemically, it is necessary to pay more attention to the side effects such as their accumulation and abnormal immune activation in non-tumor sites. This further raises higher requirements for the design of nanocomposites targeting the immunosuppressive TME.

The activation of antitumor immune responses is one of the most widely studied strategies mediated by nanocomposites for cancer immunotherapy. ICD can lead to the release of tumor-associated antigens, which in turn leads to the activation of immunity. However, immune activation induced by ICD can up-regulate the expression of cytokines such as IFN-γ, and then up-regulate the expression of PD-L1 on the surface of tumor cells to reduce the intensity of the immune response. Therefore, when ICD is used in tumor therapy, it is best to combine PL-L1 or PD-1 inhibitors to maximize the tumor killing effect of activated CTLs. In research of activating the immune response by delivering antigens, coating the nanoparticles with tumor cell membranes is an ideal strategy to improve the biocompatibility and delivery efficiency. However, due to the low abundance of tumor antigens on the surface of the tumor cell membrane, the intensity of the cellular immune response still needs to be further improved. Therefore, how to improve the abundance of tumor-associated antigens on tumor cell membranes is a problem that needs to be solved in the future. In addition, there is a risk of introducing PD-L1 while delivering tumor cell membranes, so the need for combined ICB therapy still needs to be considered.

When organic/inorganic nanocomposites are used in immunotherapy strategy combinations, most nanocomposites contain checkpoint inhibitors. Currently, more work is focused on the combination of activating immune responses and ICB therapy. The immunotherapy by this combination seems to be sufficient to suppress primary and metastatic tumors. A few studies were reported on combination of immune strategies to modulate the immunosuppressive TME and activate the immune response. Reversal of the immunosuppression can make the tumor cells sensitive to various therapies and may better activate antitumor immune responses. However, in some studies, it is found that if

there are no checkpoint inhibitors, the immunotherapy effect is limited, which may cause tumor recurrence. Therefore, the combination of these three strategies may improve the interaction of T cells and tumor cells more comprehensively, which leads to a longer-term and effective therapeutic effect. From this perspective, organic/inorganic nanocomposites with the virtues of multiple functions, favorable properties, and diverse design strategies may have great potential in cancer immunotherapy.

Abbreviations

1-MT	1-Methyl-DL-tryptophan
$^1O_2$	Singlet oxygen
5-FU	5-Fluorouracil
aAPCs	Artificial antigen presenting cells
APCs	Antigen-presenting cells
apo A-I	Apolipoprotein A-I
ATP	Adenosine triphosphate
ATRA	All-*trans* retinoic acid
AuNP@B16F10	Au nanoparticles secreted by B16-F10 cells
BM-Au	Coated AuNPs with bacterial outer membrane vesicles
BMDCs	Bone-marrow-derived DCs
BSA	Bovine serum albumin
CAR-T	Chimeric antigen receptor T-cell
CCR7	CC-chemokine receptor 7
CDT	Chemodynamic therapy
Ce6	Chloride e6
CINP	Nanoparticles extracted from cuttlefish ink
CpG ODNs	CpG oligodeoxynucleotides
CpG/LPS-P	Hydrogel with GM-CSF/LPS and black phosphorus quantum dots
CREKA	Cys–Arg–Glu–Lys–Ala
CRT	Calreticulin
CSN	Carbon–silica nanocomposite
CT	Computed tomography
CTLs	Cytotoxic T lymphocytes
CuNG	Copper *N*-(2-hydroxy acetophenone)glycinate
DAMPs	Damage-associated molecular patterns
DHMSN	Biodegradable hollow mesoporous silica nanoparticles
DOX	Doxorubicin
EPR	Enhanced permeability and retention
ER	Endoplasmic reticulum
FA	Folic acid
FDA	Food and drug administration
Gem	Gemcitabine
GMP	Gemcitabine monophosphate
GO	Graphene oxide
GSH	Glutathione
HA	Hyaluronic acid
HDL	High-density lipoprotein
HIF1-α	Hypoxia-inducible factor-1 α
HIONs	HA modified superparamagnetic iron oxide nanoparticles
HMGB1	High mobility group protein B1
HPPH	2-[1Hexyloxyethyl]-2-devinyl pyro pheophorbide-alpha
HSPs	Heat shock protein
ICB	Immune checkpoint blockade
ICD	Immunogenic cell death
IDO	Indoleamine 2,3-dioxygenase
IFN-α	Interferon-α
IFN-γ	Interferon-γ
IFR5	Interferon regulatory factor 5
IONP/anti PD-L1	Magnetic nanoclusters modified with anti PD-1
IONPs	Iron oxide nanoparticles
IPEMs	Immune membranes
LCP	Lipid-coated calcium phosphate
LOX	Lactate oxidase
MDSCs	Myeloid-derived suppressor cells
MHC	Major histocompatibility complex
MHR	H3R6 polypeptide conjugated multiwalled carbon nanotubes
mRBC	Red blood cell membrane
mRBC/$MoSe_2$	mRBC coated $MoSe_2$ nanocomposites
MRI	Magnetic resonance imaging
MTD	Magnetothermodynamic
Neuro2a cells	Neuroblastoma cells
NIR	Near-infrared
nMOFs	Nanoscale metal–organic frameworks
NO	Nitric oxide
NP@MF	Fusion cell membrane coated MOF nanoparticles
OMVs	Outer membrane vesicles
OVA	Ovalbumin
PA	Photoacoustic
PAMPs	Pathogen-related molecular pattern
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PDNCs	Palladium nanosheets to deliver CpG
PDT	Photodynamic therapy
PEG	Poly(ethylene glycol)
PEG	Polyethylene glycol
PEG/NaCl	PEGylated sodium chloride nanoparticles
PTT	Photothermal therapy
PVP	Polyvinyl pyrrolidone
RCC	Renal cell carcinoma
RGD	Arginine–glycine–aspartic acid
RNA/IO	Organic/inorganic nanocomposites based on mRNA
ROS	Reactive oxygen species
SCARB1	Scavenger receptor type B-1
SIIN*	SIINFEKL epitope peptide modified by arginine
TAMs	Tumor-associated macrophages
TEM	Transmission electron microscopy
TLR	Toll-like receptor
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor α

TRAF6	TNF receptor associated factor 6
Tregs	Regulatory T cells
UCNP	Upconversion nanoparticles
WNV	West Nile virus
ZIF-8	Zeolitic imidazolate framework

Conflicts of interest

The authors declare no conflict of interest.

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