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REVIEW

Sensitize Tumor Immunotherapy: Immunogenic Cell Death Inducing Nanosystems

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Abstract: Low immunogenicity of tumors poses a challenge in the development of effective tumor immunotherapy. However, emerging evidence suggests that certain therapeutic approaches, such as chemotherapy, radiotherapy, and phototherapy, can induce varying degrees of immunogenic cell death (ICD). This ICD phenomenon leads to the release of tumor antigens and the maturation of dendritic cells (DCs), thereby enhancing tumor immunogenicity and promoting immune responses. However, the use of a single conventional ICD inducer often fails to achieve in situ tumor ablation and establish long-term anti-tumor immune responses. Furthermore, the induction of ICD induction varies among different approaches, and the distribution of the therapeutic agent within the body influences the level of ICD and the occurrence of toxic side effects. To address these challenges and further boost tumor immunity, researchers have explored nanosystems as inducers of ICD in combination with tumor immunotherapy. This review examines the mechanisms of ICD and different induction methods, with a specific focus on the relationship between ICD and tumor immunity. The aim is to explore the research advancements utilizing various nanomaterials to enhance the body's anti-tumor effects by inducing ICD. This paper aims to contribute to the development and clinical application of nanomaterial-based ICD inducers in the field of cancer immunotherapy by providing important theoretical guidance and practical references.

Keywords: tumor immunotherapy, immunogenicity, ICD, DAMPs, nanosystems

Introduction

The advent of malignant tumors poses a considerable threat to human society. Traditional treatments including surgery, radiotherapy and chemotherapy, often exhibit limitations in achieving complete tumor eradication or yield unfavorable prognoses due to tumor cell tolerance and recurrence. Immunotherapy, an emerging field in antineoplastic medicine, has revolutionised cancer treatment. It utilises various approaches, including immune checkpoint inhibitors (ICIs), lymphocyte activating factors, chimeric antigen receptor (CAR)-T cells, other cells, cancer vaccines, lysosomal viruses, and bispecific antibodies. Cancer immunotherapy is a significant milestone in cancer treatment.[1,2] In 2011, the antibody ipilimumab, targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), was approved. Additionally, in 2014, pembrolizumab and nivolumab, both antibodies blocking programmed cell death protein 1 (anti-PD-1) and its ligand 1 (anti-PD-L1), were also approved.[3] However, the low response rate seen in most patients on treatment results in the emergence of immune-related adverse side effects such as cytokine storm, myocarditis and neurotoxicity, which can be fatal due to off-target distribution of ICIs.[4] Hyporesponsiveness to ICIs can be attributed to the "cold tumour" of most tumour patients, including inadequate antigen presentation and an immunosuppressive microenvironment. Therefore, activation to enhance tumour immunogenicity has become a key focus of tumour immunotherapy in this field.[5] Substantial evidence has demonstrated that various tumor immunotherapies, encompassing chemotherapy, radiation therapy, phototherapy, sonic therapy, chemodynamic therapy, ablation treatment, high hydrostatic pressure (HHP), or oncolytic virus (OVs), can elicit Immunogenic cell death (ICD) under specific conditions. This process leads to the release of tumor-associated antigens (TAA) and tumor-specific antigens (TSA), along with the exposure of damage-

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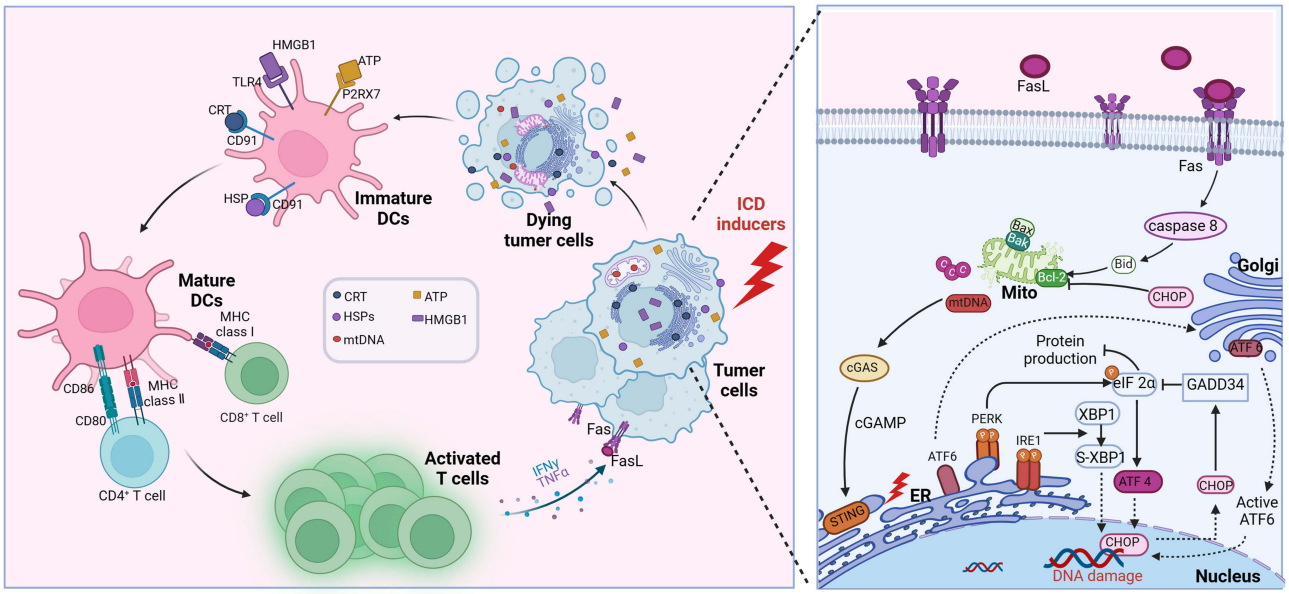

Figure 1 Antitumor immunity elicited by ICD inducers and pathways involved in the endoplasmic reticulum stress response triggered. Created with BioRender.com.

associated molecular patterns (DAMPs) (Figure 1). Upon release, TAA are typically phagocytosed by antigen-presenting cells (APCs), particularly dendritic cells (DCs), and subsequently presented to T cells.[6] Concurrently, DAMPs facilitate DC maturation, activate cytotoxic T lymphocytes (CTLs), and stimulate the secretion of various pro-inflammatory cytokines associated with innate and adaptive immunity, such as IFN-γ, TNF-α, IL-6, and IL-1β. This orchestrated cascade of events ultimately induces a robust immune response. The activation of anti-tumor T cells and the release of cytokines profoundly remodel the tumor microenvironment, converting immunosuppressive "cold" tumors into immunoresponsive "hot" tumors, thereby augmenting the efficacy of immunotherapy.[7–9] However, conventional inducers of ICD are insufficient in achieving in situ tumor ablation and long-term anti-tumor immune responses. Combination strategies have demonstrated synergistic effects, yet the inherent variations in physical and chemical properties of individual drugs result in disparate in vivo delivery outcomes upon systemic administration. In recent years, the emergence of nanodrug delivery systems (NDDS) has exhibited promising potential in enhancing the efficacy of ICD by addressing challenges such as improving drug solubility, facilitating specific targeting of tumor cells, and enabling effective combination therapy.[10,11]

This review comprehensively examines the impact of various inducers of ICD on tumor immunity, serving as a foundational reference for the design of nanoparticles. The subsequent section provides an overview of existing strategies in nanomedicine for the restoration or enhancement of ICD effects. Emphasis is placed on highlighting emerging nanoparticle designs that leverage induced or enhanced ICD technologies, aiming to advance the field of tumor immunotherapy. The primary objective of this review is to inspire and guide researchers in the efficient design of nanosystems that induce ICD, ultimately enhancing immune responses against tumors and facilitating the clinical translation of ICD-based nanosystems.

Immunogenic Cell Death

Formation of Immunogenic Cell Death

In recent years, the concept of ICD has undergone refinement and evolution. It is important to note that not all forms of cell death have the capability to induce an anti-cancer immune response.[12] Specifically, only certain types of cell death possess the ability to induce ICD. Extensive literature supports the requirement of two key factors for inducing ICD: antigenicity and adjuvancy. ICD is a biological process in which cells that have been enhanced antigenically undergo death, releasing or exposing molecules that serve as adjuvants or danger signals for the innate immune system.[13] These

molecules are then recognized by immune cells, leading to the initiation of an immune response. In the absence of reactive antigens (ie, antigenic determinants that are not subject to central or peripheral tolerance), the released signals may trigger inflammation but are unable to participate in adaptive immunity.[13] Furthermore, malignant cells experiencing immunogenic stress and undergoing cell death drive APC maturation by releasing a series of endogenous adjuvant signals known as DAMPs. In the absence of these signals, T cells are typically presented with antigens that result in peripheral tolerance.[14]

ICD triggers the release of DAMPs, such as calreticulin (CRT), high-mobility group box 1 (HMGB1), adenosine triphosphate (ATP), and heat shock proteins (HSPs), from the surface of tumor cells. CRT, a calcium-binding protein primarily found in the endoplasmic reticulum (ER), translocates to the cell membrane under stress conditions.[15] This translocation facilitates the interaction of CRT with ERp57, exposing "eat me" signals and promoting the phagocytosis of dying tumor cells by DCs or their precursors.[16] Furthermore, CRT binds to CD91 on APCs, facilitating antigen presentation and activation of cytotoxic T-lymphocytes.[16–19] During the apoptosis process, ATP is released into the extracellular space, acting as a" find me" signal to attract APCs towards dying tumor cells.[20,21] ATP binding to P2RY2 on DCs activates NLRP3 inflammatory vesicles, leading to the secretion of IL-1β. This pathway promotes DC maturation and enhances their antigen-presenting capabilities.[22] Importantly, studies have highlighted the role of autophagy in regulating ATP release during ICD, particularly by influencing lysosomal ATP stores.[23,24] Manipulating autophagy in autophagy-deficient cells can restore tumor cell immunogenicity by increasing extracellular ATP concentration.[23] Another crucial event during apoptosis is the translocation and release of HMGB1 from the nucleus to the cytoplasm and subsequently outside the cell under stress conditions.[25] Extracellular HMGB1 interacts with pattern recognition receptors (PRR) on myeloid cells, including TLR4 and RAGE, promoting DC maturation and the release of pro-inflammatory factors, thereby eliciting potent immunostimulatory effects.[26,27] The immunogenicity of HMGB1 is influenced by its redox state, with cysteine-dependent reactive oxygen species (ROS) triggering its oxidation and inhibiting its immunostimulatory activity, leading to immune tolerance in dying cells. Additionally, other DAMPs, such as membrane-linked protein 1 (ANXA1), HSP70, and HSP90, attract phagocytes and activate natural killer (NK) cells.[28,29]

Sequentially, the aforementioned chain of events has the potential to induce a significant influx of myeloid and lymphoid cells into the tumor microenvironment (TME), thus converting the tumor from an immunologically 'cold' to a 'hot' phenotype. Nonetheless, various characteristics of the TME can impact its capacity to elicit a robust adaptive immune response, such as immunosuppressive cells, growth factors, and cytokines.[30–32]

Stress-Responsive Pathways Underlying ICD

Intracellularly, the induction of ICD is closely associated with the activation of the ER stress response, also known as the unfolded protein response (UPR)[33](Figure 1). This response involves three pathways: inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6), and protein kinase R (PKR)-like ER kinase (PERK). ICD inducers can be categorized based on their ability to induce ER stress. Type I ICD inducers, such as conventional chemotherapeutic agents (eg, anthracyclines, alkylating agents, platinum drugs) and ionizing radiation, primarily cause cell death by targeting organelles or molecules unrelated to the ER, leading to an indirect induction of ER stress response.[34,35] The expression of ICD markers induced by type I ICD inducers relies on PERK-mediated phosphorylation of eIF2α, cysteine-8-mediated cleavage of BAP31, and the activation of BAX and BAK proteins.[36] CRT is translocated to the plasma membrane via the ER-Golgi pathway in a snap23-dependent manner.[37] In contrast, type II ICD inducers, such as photodynamic therapy, HHP, or OVs, directly target the ER, resulting in intense ER stress, increased levels of ROS, disturbed homeostasis, and cell death.[34,35] The translocation of CRT in response to type II ICD inducers requires the involvement of PERK, BAX, and BAK proteins, while eIF2α phosphorylation and cysteine-8 activation appear to be less crucial.[38] Notably, PERK-mediated UPR responses play a pivotal role in most ICD processes. Ultimately, cells experiencing ER stress undergo mitochondrial apoptosis involving BAX (BCL2-associated X protein) and BAK1 (BCL2 antagonist/killer 1).

Immunogenic Cell Death Inducers

In recent years, various approaches have been extensively documented for the induction of ICD (Figure 2). These methods can induce ICD to different degrees, leading to cellular stress and the generation of DAMPs through diverse signaling pathways.

Chemotherapeutic Agents

Chemotherapeutic agents exert their anticancer effects primarily by inducing oxidative stress and causing cellular damage mediated by ROS.[39] The immunogenicity of chemotherapeutic agents is closely associated with the intensity and duration of the ER stress response they provoke.[28,40,41] Anthracyclines and alkylating agents are recognized as effective inducers of ICD.[42] Anthracyclines like doxorubicin (DOX) and mitoxantrone (MIT) induce ICD through various mechanisms including autophagy, ER stress, and type I interferon (IFN) response. Alkylating agents such as cyclophosphamide can directly impact immune cells and elicit a tumor immune response.[43] Bleomycin, a cytotoxic antibiotic glycopeptide, induces ICD by promoting ROS production, leading to the exposure of chaperone proteins (calreticulin and ERp57), as well as the release of HMGB1 and ATP.[44] Metal complexes such as Ru,[45] Au,[46] Cu,[47] and Ir[48] have been shown to induce ICD through disruption of DNA cross-linking or generation of reactive oxygen species (ROS) similar to oxaliplatin (OXA).[49] Additionally, natural products derived from traditional Chinese medicine, such as shikonin, wogonin, and paclitaxel, have demonstrated the ability to induce ICD by eliciting mitochondrial or ER stress responses.[50–52] This leads to the exposure of CRT and membrane-bound proteins, activation of DCs, and stimulation of pro-inflammatory cytokine release through the release of HMGB1 and adenosine ATP, ultimately resulting in potent

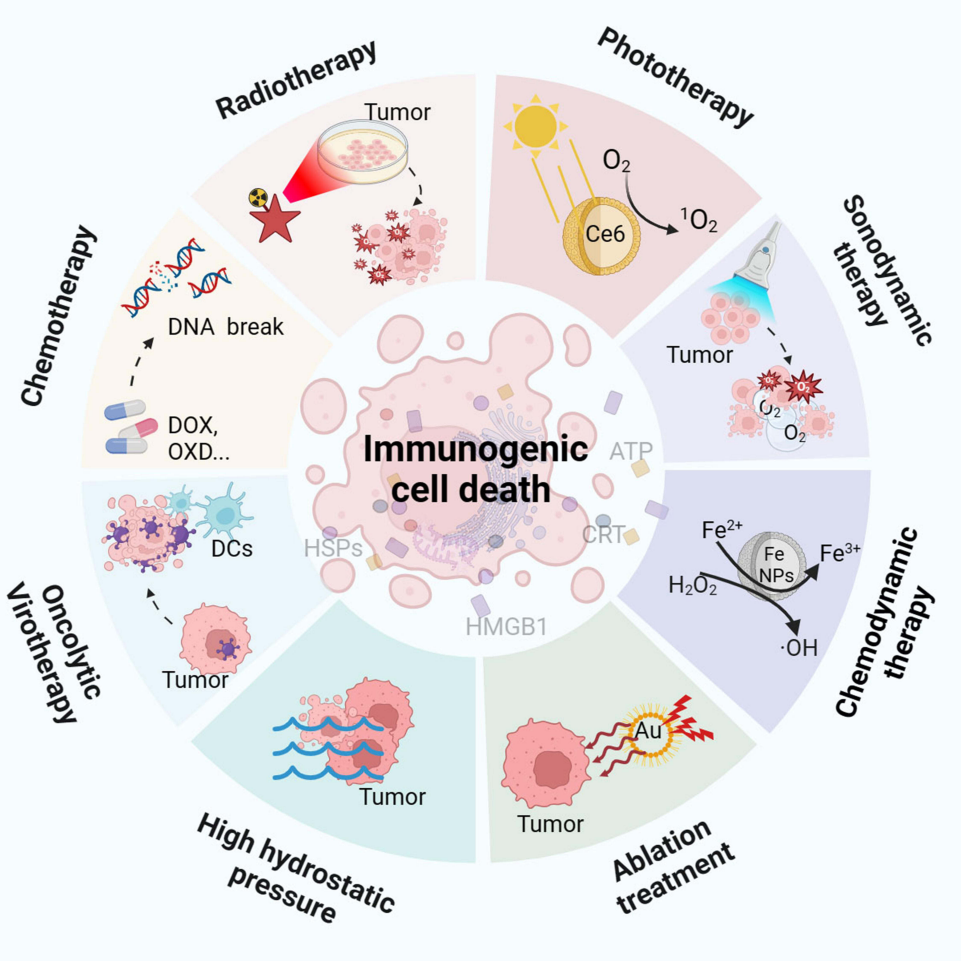

Figure 2 Overview of immunogenic cell death inducers. Created with BioRender.com.

anti-tumor immune effects. Of particular interest is paclitaxel's ability to induce ICD via TLR4-independent and -dependent pathways, highlighting its importance for future drug development in the field of cancer therapeutics.[53] Some other chemotherapeutic agents may not induce ICD but still exhibit immunogenicity under specific conditions, albeit to a lesser extent. Combining non-ICD-inducing chemotherapeutic agents like cisplatin with compounds that trigger ER stress has been reported to induce ICD.[54]

The precise characterization of chemotherapy-induced ICD or immunogenic modulation remains unclear in terms of structure and nature. Although cisplatin shares structural similarities with the typical ICD inducer OXA, it fails to activate the robust ER response necessary for CRT surface exposure and subsequent induction of ICD.[49] Bezu et al have proposed eIF2α phosphorylation as a specific marker of ICD and developed an algorithm correlating it with the physicochemical properties of various anticancer drugs by analyzing the cellular stress response. However, in vivo experiments are required to validate such predictions definitively.[55] Presently, all chemotherapeutic agents capable of inducing ICD exhibit CRT exposure, ATP secretion, and HMGB1 release from tumor cells as common features.[28] Additionally, performing vaccination assays using immunocompetent mice and homologous tumor cells is the most reliable approach to determine whether a drug is an ICD inducer.[56]

Radiotherapy

Radiotherapy is a therapeutic modality that utilizes ionizing radiation, including high-energy photon radiation (such as X-rays and gamma rays) and particle radiation (such as alpha particles, beta particles, and electrons), to directly or indirectly interact with intracellular substances for therapeutic effects.[57] Initially, the cytotoxic or cytostatic activity of X-rays and γ-rays was attributed to their direct action on cells through ionizing radiation. However, accumulating preclinical and clinical evidence suggests that the therapeutic effects of radiation also arise from local and distant bystander effects, demonstrating the immunological potential of radiotherapy.[58,59] Radiation induces DNA damage through direct action or production of ROS, leading to endoplasmic stress response.[57,60] During radiotherapy, molecules such as ATP, CRT, HMGB1, and HSP 70 are exposed on the surface of dead cells and trigger ICD by migrating to extracellular sites.[61] Furthermore, radiotherapy stimulates the secretion of pro-inflammatory cytokines and chemokines, including IFN, IL-1, TNF, and CXCL16, which promote the maturation of DCs.[62] These immunogenic cellular stress responses induced by radiotherapy modify the tumor phenotype and enhance the susceptibility of surviving tumor cells to immune targeting. This is achieved through increased expression of TAA (such as CEA and MUC1) and antigen processing and presentation mechanisms (such as MHC-I, peptide transporter proteins, chaperonins, and immunoproteasome subunits).[63–66]

It is worth noting that not all remodeling of the tumor microenvironment by radiotherapy results in immune activation. Certain effects of radiotherapy, such as increased tissue hypoxia, aggregation of M2-type macrophages,[67] accumulation of immunosuppressive Treg cells,[68] and upregulation of PD-L1 on the tumor cell surface,[61] can promote tumor growth. Interestingly, by carefully adjusting the dose and schedule of radiotherapy, it is possible to strike a balance between DCs, immunosuppressive myeloid cells, and Treg cells, effectively promoting ICD.[69,70] However, it should be acknowledged that radiotherapy-induced systemic immune responses are infrequent and insufficient to meet clinical requirements. In recent years, novel approaches involving high-Z element-based nanomaterials, such as HfO_2 nanoparticles (NBTXR3), Gd-based nanoparticles (AGuIX), and nanoscale metal-organic frameworks (Hf-DBP nMOFs), have emerged as radiosensitizers with advantageous properties.[71–73] Among these, AGuIX with a size of less than 5 nm has been shown to be effective in inducing ICD in irradiated B16 tumour cells, thereby triggering DCs maturation and activation of a systemic T-cell response.[74] AGuIX has been entered into a Phase III clinical trial as a radiosensitising agent for the treatment of brain metastases and as an agent for magnetic resonance imaging.[75]

Phototherapy

Phototherapy (PDT) relies on the utilization of photosensitizers (PS) to generate ROS, such as cytotoxic $^1O_2$, ·OH, and other related components, resulting in oxidative stress-induced cell death.[76,77] Tumor cells with a low oxidative stress threshold are particularly susceptible to ROS-mediated damage. Among the known inducers of ICD, hyp-PDT is the foremost Type II inducer and the most potent ROS-based inducer of ER stress.[78] Common photosensitisers include

phenothiazine dyes (analogs of methylene blue and toluidine blue), cyanines such as merocyanine 540 and polycyclic aromatic compounds, including hypericin and hypocrellin.[79] Hypericin, when photo-activated, leads to the production of reactive oxygen species (ROS), which disrupts the function of ATP2A2 (sarcoplasmic/endoplasmic reticulum calcium ATPase 2), causing disturbances in ER-Ca^{2+} balance and subsequent induction of ER stress.[78] Recent findings indicate that different PSs used in PDT selectively induce oxidative stress damage to specific organelles (eg ER, mitochondria, and lysosomes), resulting in the release of dying tumor cell debris.[80] This, in turn, triggers ICD via ER stress-induced exposure of CRT. Conventional photosensitisers are limited to shallow absorption of light tissue penetration, oxygen dependence and poor photosensitiser stability. Furthermore, the accumulation of PS in the ER and the impact of PDT treatment on the tumor microenvironment (eg, induction of severe local hypoxia) can limit the efficacy of tumor immunotherapy. Recent research efforts have increasingly emphasized the structural modification of conventional photosensitizers to enhance their absorption properties in the near-infrared (NIR) region.[81] Specifically, there is a growing focus on optimizing photosensitizers to utilize photons within the NIR-II window, which offers greater tissue penetration depth and signal-to-noise ratio in biological tissues. This holds significant potential for advancing applications in in vivo biological imaging.

In contrast to PDT, which utilizes light to sensitize oxygen molecules and generate ROS for cell death induction, photothermal therapy (PTT) employs photothermal conversion nanomaterials that convert light energy into heat energy under NIR light irradiation, effectively targeting and eliminating primary tumors. This minimally invasive therapeutic strategy enables precise control of thermal therapy by local application of photosensitizers and administration of low-intensity NIR radiation, thereby minimizing damage to non-targeted tissues.[82,83] Various light-absorbing materials, such as organic dyes,[84–86] noble metal nanostructures,[87–89] carbon nanotubes,[90,91] and semiconducting polymers,[92–94] can be employed for PTT. Importantly, PTT not only achieves tumor cell destruction through direct heating but also promotes ICD and triggers systemic antitumor immune responses. These immune responses involve redistribution and activation of immune effector cells, cytokine expression and secretion, and transformation of memory T lymphocytes. Additionally, recent studies have highlighted the advantages of utilizing the second near-infrared biological window (NIR(II), 950–1350 nm) for effective PTT. NIR(II) reduces photon scattering, decreases background interference, and enhances penetration depth, making it highly promising for clinical applications of PTT.[95,96]

Sonodynamic Therapy

Sonodynamic therapy (SDT) is a novel technique used for tumor treatment that involves the activation of drugs, known as acoustic sensitizers, through ultrasound. This activation triggers the production of ROS, which induces local cytotoxicity and leads to cancer cell death.[97] In contrast to PDT, SDT overcomes the limitations of PDT in terms of penetration depth.[98] The main mechanism of SDT is the cavitation effect induced by ultrasound (US), in which bubbles are formed by cavitation nuclei in a liquid due to ultrasound exposure.[99] These bubbles expand and eventually collapse, creating extreme conditions characterized by high temperatures (>5000 K), high pressures (>800 atm), and acoustic luminescence.[100] These conditions effectively stimulate the acoustic sonosensitizers to produce ROS, thereby enabling SDT to induce ICD and activate anti-tumor immune responses through the ROS-mediated apoptotic pathway in cancer cells.[101] The selection of sonosensitizers plays a crucial role in enhancing the efficiency of ROS generation using ultrasound.[102] Thus far, both organic and organic materials have been developed as sonosensitizers. Studies have investigated the effects of various inorganic materials, such as porphyrin derivatives,[103] Rose Bengal, doxorubicin, erythrosine. These sensitizers are widely utilized in SDT due to their extensive π-electron conjugation systems, exceptional catalytic properties, and broad optoelectronic properties. Organic ultrasound sensitizers commonly used are fat-soluble, resulting in short circulation times and limited accumulation and retention in tumors.[104] Xue et al delivered IR780 molecules to mitochondria, inducing oxidative stress through ultrasound-triggered ROS amplification, leading to increased exposure of CRT and release of HMGB1.[105] This process resulted in a more potent ICD effect, effectively suppressing primary and distant tumor growth. In contrast to organic nanomaterials, inorganic nanomaterials possess unique physicochemical properties that can be harnessed to create highly effective acoustic sensitizer. ZrO_{2-x} NPs with abundant defects can enhance the separation of US-triggered electron (e^-)-hole (e) pairs arising from a decreased band gap, enabling a high quantum yield of ROS for cancer therapy during SDT.[106] To date, a good number of inorganic

nanostructures with acoustic activation capacities, including TiO_{2-x} NPs,[107] transition metal oxide NPs[108] and noble-metal NPs (Au, Ag and Cu)[109] have been employed for SDT applications. However, the effectiveness of conventional acoustic sensitizers in inducing ICD is limited by the yield of ROS and their in vivo bioavailability.[110]

Chemodynamic Therapy

In comparison to other ROS therapies such as PTT and SDT, chemodynamic therapy (CDT) employs an iron-based Fenton reaction to generate highly cytotoxic hydroxyl radicals, leading to ICD and tumor inhibition.[111,112] This reaction is briefly described below using equations (1) and (2).[113]

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^- \left(k = 63M^{-1}s^{-1}\right) \quad (1)$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HO_2^{\cdot} + H^+ \left(k = 0.002 - 0.01M^{-1}s^{-1}\right) \quad (2)$$

CDT offers several advantages, including superior catalytic ROS generation, reduced dependence on external stimuli, the ability to penetrate deep tissues, and resistance to drug resistance. However, the effectiveness of CDT is limited by insufficient hydrogen peroxide and iron ion metabolism within the tumor microenvironment. To address this challenge, various Fenton-like reactions have been extensively studied in the context of oncology therapy, such as ferrocene (FcA), Cu^+ and Mn^{2+}.[114–116] Nevertheless, the efficacy of CDT is hindered by suboptimal metabolism of hydrogen peroxide and metal ions within the tumor microenvironment.[117] To overcome this challenge, several promising strategies have been implemented to augment CDT effectiveness. For instance, augmenting intracellular oxidative mechanisms and catalytic reactions in tumor cells contribute to the potent antitumor efficacy of the Fenton response.[117] Notably, Zhang et al demonstrated the utilization of Mo^{4+} incorporated onto the surface of MoS_2 nanosheets to expedite the conversion of Fe^{3+} to Fe^{2+}, consequently enhancing CDT therapy through a synergistic photothermal effect and co-catalysis.[118] It is worth mentioning that CDT frequently exhibits catalase-like activity, which is often coupled with the production of molecular oxygen along with ROS.

Similar to PDT and SDT, most ROS-generating processes consume oxygen and exacerbate hypoxia at the tumour site. Therefore, elevated levels of oxygen can enhance the generation of ROS induced by PDT and SDT, thereby amplifying oxidative stress.[108] In recent years, it has become necessary to develop catalytic sensitizers that can generate ROS independently of O_2 with high efficiency to induce ICD.[109]

Ablation Treatment

Ablation treatment, such as microwave ablation (MWA), radiofrequency ablation (RFA), and cryoablation, have emerged as effective local tumor treatment methods. By utilizing thermal energy, these techniques induce irreversible damage or coagulative necrosis of tumor cells, offering a precise and minimally invasive treatment option. An intriguing aspect of local ablation techniques is their ability to induce ICD.[119–122] RFA has been found to induce a deficiency in regulatory T-cells, inhibiting the Th2 response and significantly reducing levels of Th2 cytokines, including IL-4, IL-6, and IL-10.[123] The levels of HSP70 in human liver biopsy material[120] and in the sera of cancer patients[124] have been shown to be significantly higher after RFA. Extracellular HSPs are involved in various immune processes, acting as antigenic chaperones for APCs and as danger signals for the immune system through activation of DCs.[125] Additionally, MWA has been observed to activate macrophages, leading to increased production of IL-12, IL-2, IL-15, and IFN-γ.[126] These cytokines play a critical role in activating NK cells, ultimately inhibiting metastatic progression. It is important to acknowledge that tumor ablation is a complex process that not only triggers the appearance of danger signals, such as HSPs, but also stimulates the production of immunosuppressive signals like TGF-β or IL-10.[122] Similar to radiotherapy, the efficacy and immune response induced by thermal ablation depend greatly on the optimization of the thermal dose. Striking the right balance is crucial to effectively treat the primary tumor while inducing immune effects in distant tumors.

Furthermore, studies have revealed that ablation releases DAMPs from damaged cells, attracting neutrophils and monocytes to the ablation site. However, without additional stimulation by PRRs, DAMPs may be removed, resulting in the transition of initially recruited leukocytes from an acute inflammatory response to a repair phase.[127] In some cases,

this transition may even lead to a chronic inflammatory state that favors the tumor by altering macrophage metabolism.[128]

High Hydrostatic Pressure

High hydrostatic pressure (HHP), like temperature, plays a crucial role as an environmental variable in biological adaptation. Studies have revealed that when pressure reaches or surpasses 200 MPa, proteins undergo tertiary and quaternary structural changes, leading to the disruption of enzyme function. The use of HHP as a treatment for cancer was first explored in 1972 through a small clinical trial of hydrostatic cystodilatation for bladder cancer.[129] This pioneering study highlighted the potential application of HHP in oncological treatment.

Shinitzky et al demonstrated that the induction of systemic immune responses was achievable in melanoma cell-immunised mice through the inoculation of tumor cells treated with HHP.[130] In contrast, tumor cells that were not modified showed minimal effects on immune responses in the mice. Fucikova et al demonstrated that the apoptotic signaling pathways activated by HHP are similar to those stimulated by anthracyclines or photodynamic therapy.[131,132] By inducing the expression of specific cell surface markers associated with ICD, including heat shock proteins (HSP70, HSP90) and CRT, HHP triggers the release of HMGB1 and ATP. This effectively activates tumor-specific immunity against a wide range of primary human tumor cells and various cancer cell lines, such as leukemia, ovarian, and prostate cancers. The utilization of HHP in cancer treatment holds significant potential and warrants further investigation in the field of immunotherapy.

Oncolytic Virus

Oncolytic virus (OVs) is a promising approach that selectively targets and eliminates tumor cells while simultaneously stimulating the immune system to mount an anti-tumor immune response.[133,134] Currently used OVs vectors include poxvirus, adenovirus, and herpes simplex virus.[135–137] A study by Koks et al showed that in an in situ mouse glioma model, Oncolytic Newcastle Disease Virus (NDV) induces ICD, including surface exposure of CRT, HMGB1 release and increased expression of the PMEL17 cancer antigen, which elicits a long-lasting tumour-specific immune response.[138] Wang et al enhanced the anti-tumour effect on prostate cancer by combining STAT3 inhibitors with oncolytic NDV.[139] Araki et al found that the therapeutic potential of p53-expressing telomerase-specific oncolytic adenovirus OBP-702 exhibited efficacy in inducing ICD in human pancreatic ductal adenocarcinoma (PDAC) cells with varying levels of p53 expression.[140] This induction of ICD was mediated through the regulation of p53-induced apoptosis and autophagy, as well as the secretion of extracellular ATP and HMGB1 proteins. Other oncolytic viruses, such as measles virus and coxsackievirus B3, also release danger signaling molecules that induce ICD in infected cells in vitro.[141,142] However, the efficacy of OVs is still limited by latent antiviral mechanisms, the intrinsic physical barriers of the tumor, and the complex tumor microenvironment. Further research is warranted to overcome these challenges and optimize the therapeutic potential of OVs in the field of cancer immunotherapy.

ICD-Based Nanoparticle Design

Similar to an in situ cancer vaccine, it is essential to localize the ICD inducer within the tumor. Furthermore, a single induction approach is often inadequate to elicit a robust ICD effect and eliminate the tumor. In recent years, nanoparticles have emerged as a promising vehicle for achieving this goal. The enhanced permeability and retention (EPR) effect of nanoparticles enables the targeted delivery of ICD inducers to tumor tissues. Inorganic nanoparticles can effectively confine the energy field to the tumor site through mesoporous loading, minimizing damage to healthy cells. Notably, nanoparticles with inherent magnetic and photothermal effects demonstrate promising applications in targeting and real-time monitoring. Additionally, organic nanocarriers possess excellent biocompatibility and surface-functionalization capabilities to overcome biological barriers.

Therefore, the field of nanobiotechnology leverages nanosynthetic processes to offer promising strategies for restoring or augmenting ICD (Figure 3). This approach involves several key components: (1) inhibition of immunosuppressive signals such as PD-1/PD-L1 and CD47;[143,144] (2) facilitation of the release of DAMPs to enhance immunostimulation, including the use of autophagy activators, inhibitors of CD39/CD73, ATP, and CRT delivery;[145–148] (3)

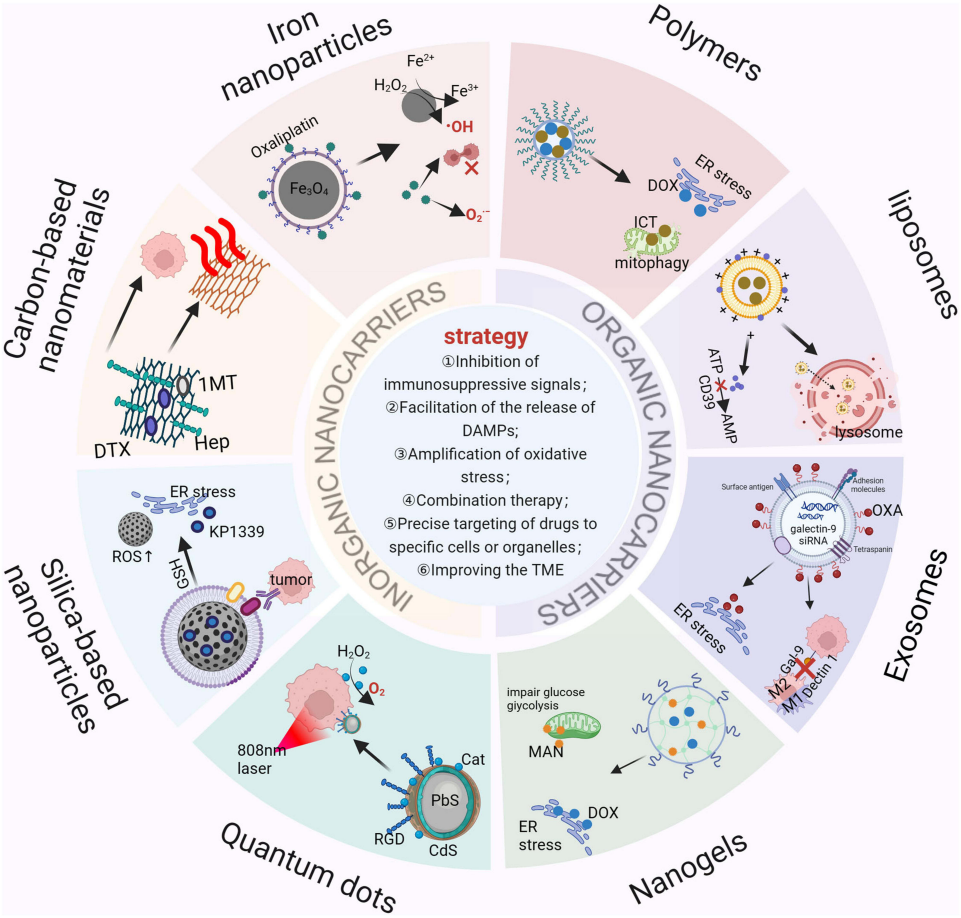

Figure 3 Nanomedicine design for restoring or enhancing the effects of immunogenic cell death. Created with BioRender.com.

amplification of oxidative stress to boost immune stimulation by disrupting the endogenous antioxidant system within tumors;[149] (4) alleviation of limitations associated with single inducers of ICD, such as local hypoxia and restricted penetration depth characteristic of PDT; (5) precise targeting of drugs to specific cells or organelles.[150] In the subsequent sections, we will analyze nanosystems capable of inducing ICD by combining the unique characteristics of multiple nanomaterials, aiming to provide insights for advancing tumor immunotherapy and the clinical translation of cancer nanodrugs.

Nanomedicine-Induced Immunogenic Cell Death Enhances Tumour Immunotherapy

Application of Inorganic Nanocarriers in Enhancing ICD Effect

In the biomedical field, there is widespread utilization of common inorganic nanoparticles, such as metal NPs, carbon-based NPs, and silicon-based NPs, as carriers for nanodrugs (Table 1). Inorganic nanocarriers demonstrate unique optical, magnetic, and electrical properties that are dependent on their physical attributes such as size, morphology, and density.[151] As a result, they have significant potential for improving the delivery of ICD drugs, consequently enhancing their anti-tumor effectiveness through either covalent or non-covalent bonding to the nanocarriers' surfaces.

Iron-Based Magnetic Nanoparticles

Iron-based magnetic nanoparticles, comprising pure iron nanoparticles and iron oxide magnetic nanoparticles, exhibit both intrinsic magnetic and biodegradable properties capabilities.[166] The Fenton reactions catalyzed by Fe^{2+} and Fe^{3+} have expanded the application of iron-agent magnetic nanoparticles in antitumor. Chen et al[152] developed tumor-targeted

Table 1 Inorganic Nanoparticle-Mediated Immunogenic Cell Death

Delivery System	ICD Inducer and Amplifier	Cytokines or DAMPs	Immune Cells Infiltration	Advantages	Model	Ref
Magnetic NPs	Fe_3O_4 + Oxaliplatin (IV)+ α-enolase targeting peptide (ETP)	CRT, HMGB1	↑DCs maturation; ↑$CD4^+$, $CD8^+$ T cells	Tumour-targeted accumulation; amplification of ROS generation; reversal of immunosuppression	4T1 (Balb/c mice)	[152]
	Fe_3O_4+PFP+Gox+ K7M2-WT (K7M2) osteosarcoma cell membranes	——	——	Facilitates oxygen delivery; promotes H_2O_2 production and favours the Fenton reaction; synergises photothermal therapy, CDT and starvation therapy	K2M7 (BALB/c mice)	[117]
	Fe+ HA@ $Cu_{2-x}S$+ Doxorubicin (DOX)	ATP, CRT, HMGB1	↑DCs maturation; ↑$CD4^+$, $CD8^+$T cells	Peroxidase-like activity that promotes H_2O_2 production leading to high ·OH production and relief of tumour hypoxia; sustained promotion of T-cell immune responses	CT26 (BALB/c mice)	[153]
Gold NPs	AuNPs+ Fluidic liposomes	CRT, HMGB1	↑DCs maturation; ↑ $CD8^+$ T cells	Using NIR(II) PTT to trigger ICD to enhance cancer immunotherapy.	4T1 (Balb/c mice)	[95]
	AuNCs+Dihydrolipoic acid	IL-12, TNF-α, IFN-γ	↑$CD4^+$ T cells, NK, DCs	Direct excitation by low-dose X-ray radiation; ROS production even in hypoxic conditions; Ultra small size for fast removal	Hepa1-6 (C57BL/6 mice)	[154]
	B16F10 cell+$HAuCl_4$ +DCs	HMGB1, HSPs, IFN-γ, TNF-α, IL-6	↑DCs maturation; ↑$CD4^+$, $CD8^+$ T cells	Using cells to synthesise immunocompetent nanoparticles with increased targeted delivery	4T1 (Balb/c mice) and B16F10 (C57BL/6 mice)	[155]
Carbon-Based NPs	SWNTs+ anti-CTLA-4	IL-1β, IL-12, IL-6, TNF-α	↑DCs maturation; ↑$CD8^+$ T cells	Eliminated the activity of Tregs in tumours and upregulated the number of CD20 tumour-infiltrating B cells	4T1 (Balb/c mice)	[156]
	GO+Hep+ Docetaxel (DTX) + 1-methyl-D-tryptophan (1MT)	CRT, HSP70, HMGB1	↑DCs maturation; ↑$CD4^+$, $CD8^+$ T cells; ↓M2 macrophages	Enhanced tumour infiltration by being delivered deeper into the tumour via the blood and lymphatic pathways; remodelling of the TME to enhance immune cell infiltration	B16F10 (C57BL/6 mice)	[157]
Silicon-Based NPs	MON+KP1339	CRT, HMGB1, TNF-α, IFN-γ, IL-6	↑DCs maturation; ↑$CD4^+$, $CD8^+$T cells	Response to GSH-controlled release; MON increases ROS levels to amplify chemotherapy-induced ICD	4T1 (Balb/c mice)	[158]
	MSN+aCD47+DOX	CRT, ATP, HMGB1, TNF-α, IFN-γ, IL-6	↑DCs maturation; ↑$CD3^+$, $CD8^+$T cells	Blockade of the CD47-SIRPα axis inhibits "don't eat me" signalling and enhances phagocytosis by macrophages	4T1 (Balb/c mice) and B16F10 (C57BL/6 mice)	[143]
	Silica NPs+ Polydopamine+ JQ-1	TNF-α, IFN-γ, IL-6	↑DCs maturation; ↑$CD4^+$, $CD8^+$T cells	The increased surface roughness of polydopamine nanoparticles significantly elevated cellular internalization.	B16F10 (C57BL/6 mice)	[144]

Quantum Dots	PbS/CdS ODs+ Catalase + RGD peptides+ PEG	CRT, ATP, HMGB1,	↓M2 macrophages; ↓Tregs; ↑$CD3^+$, $CD8^+$ T cells; ↑DCs maturation	Catalysing H_2O_2 decomposition to relieve tumour hypoxia for RGD-guided precision radiotherapy	4T1 (Balb/c mice)	[159]
	Ag_2S QDs+ Bifidobacterium bifidum (B,b)	CRT, TNF-α, IL-6,	↓M2 macrophages;	Enhanced nanomedicine tumour penetration and increased antigen capture	4T1 (Balb/c mice)	[160]
Upconversion NPs	UCNP + Chlorin e6 (Ce6)+ Imiquimod (R837)	TNF-α, IFN-γ, IL-12	↑$CD4^+$, $CD8^+$ T cells	Designed a type of multitasking nanoparticle based on UCNPs to trigger cancer immunotherapy by NIR-induced PDT.	CT26 (Balb/c mice)	[161]
	UCNP+ Indocyanine green (ICG) + Bengal (RB) + DSPE-PEG-mal	CRT, HMGB1, TNF-α, IL-6, IL-12	↑DCs maturation; ↑$CD8^+$ T cells	Increased tumour protein antigen capture: PDT and PTT combination therapy	4T1 (Balb/c mice)	[162]
	UCNP +TPEBTPy	CRT, HSP70, HMGB1, IFN-γ	↑DCs maturation; ↑$CD4^+$, $CD8^+$ T cells	Different functions of nanoparticles by controlling near-infrared light intensity	B16F10 (C57BL/6 mice)	[163]
LDHs	LDHs+ 2',3'-cyclic guanosine adenosine monophosphate	IFN-γ and CXCL10	↑DCs maturation; ↑$CD8^+$ T cells and NK cells	As-prepared LDHs-cGAMP could effectively enter cancerous or immune cells, inducing a stronger type I interferon (IFN-I) response.	Hepa1-6 (C57BL/6 mice)	[164]
	FeOOH+Cu-LDHs+ STA-9090	CRT, Hsp90	↑$CD3^+$, $CD8^+$T cells;	Sensitisation to photothermal therapy by overexpression of HSP90; amplification of ROS production by PTT in combination with CDT	4T1 (Balb/c mice)	[165]

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core-shell magnetic nanoparticles (ETP-PtFeNP) to enhance the induction of ICD loaded with oxaliplatin (IV) prodrugs. Fe_3O_4 serves as a carrier for chemotherapeutic drugs and targeted agents. Upon targeted accumulation and phagocytosis, the released Fe_3O_4 undergoes Fenton reactions, triggering highly toxic ROS in cooperation with oxaliplatin, which disrupts the redox balance, enhances the ICD effect, and improves the antitumor efficacy. As the production of ROS consumes a lot of oxygen making the tumour microenvironment hypoxic, limiting the performance of tumour immunotherapy. Wang et al[117] developed a tumor microenvironment adaptive nanoplatform (M-mFeP@O_2-G) using Fe_3O_4 as a carrier loaded with perfluoropentane (PFP) and glucose magnesium oxide (Gox). The inclusion of PFP facilitated the delivery of O_2, supporting Gox in oxidizing glucose to generate abundant concentrations of H_2O_2. This approach aimed to enhance the efficacy of CDT within the tumor site. Nanocatalytic therapy (NCT) has emerged as a promising non-invasive approach for tumor treatment. NCT employs reagents that can convert endogenous H_2O_2 into highly toxic ·OH, causing irreversible damage to proteins or DNA. This, in turn, leads to apoptosis and necrosis of tumor cells. Recently, Zhu et al demonstrated the synthesis of $Cu_{2-x}S$ nanomaterials through the reaction of Cu and S, which exhibited both photothermal catalysis and nanocatalysis properties resembling peroxidase and catalase enzymes, respectively.[153] Subsequently, Fe and DOX were incorporated into HA-modified $Cu_{2-x}S$ nanomaterials, enabling the nanomaterials to exhibit photothermal effects and peroxidase-like activity under near-infrared light irradiation. This combination effectively stimulated DCs maturation and polarization towards M1-type macrophages by providing a continuous supply of H_2O_2, thereby triggering potent ICD-inducing effects. Furthermore, the administration of anti-PD-L1 maintained T-cell immune activation.

Gold Nanoparticles

Gold nanoparticles (AuNPs) have gained significant prominence in the field of biomedicine due to their small size, ease of preparation, modifiability, rapid photothermal conversion, and high X-ray attenuation coefficient.[154] Gold nanoparticles are utilized as photothermal therapeutic agents (PTAs) primarily due to their higher photothermal conversion efficiency (PCE) attributed to the localized surface plasmon resonance (LSPR) on their surfaces.[167] The absorption peaks of plasmonic PTAs can be further adjusted to the biological transparency window through precise modification of their anisotropic shape.[168] Controlled aggregation of metallic nanoparticles offers a valuable approach for manipulating their optical properties, as the inter-particle plasmonic coupling induces a redshift in the tunable LSPR.[169] Wang et al successfully orchestrated the self-assembly of AuNPs on fluidic liposomes to develop near-infrared (II) light-responsive PTT transducers.[95] These transducers demonstrated a superior ability to induce ICD more uniformly and deeply compared to both near-infrared and red light. Notably, in solid tumors, the transducers exhibited a more pronounced tumor-suppressive effect than oxaliplatin. Notably, this delivery system significantly augments $CD8^+$ T cell infiltration at a depth of 6 mm beneath the tumor surface, which effectively addresses the immune escape challenges arising from insufficient lymphocyte infiltration resulting from PTT in the core and deeper regions of solid tumors. Engineered AuNPs have the ability to influence immune responses, including cytokine secretion and antibody production.[168] Moreover, the stability of AuNPs can be enhanced through absorption or chemical linkage with stabilizers like surfactants, enabling further modification of ligands or other molecules. In the realm of radiation therapy, gold nanostructures are widely employed as radiosensitizing materials owing to their potent X-ray attenuation capability. Notably, a dihydrolipoic acid-coated gold nanocluster (AuNC@DHLA) developed by Zhu et al exhibits a smaller size compared to conventional nanoscintillators, and it facilitates efficient ROS treatment through electron transfer mode (O_2^- and $HO^{-\bullet}$) instead of energy transfer mode.[154] This unique attribute enables the generation of effective ROS even under hypoxic conditions, thereby enabling effective treatment of solid tumors in vivo. Peptides, proteins, and nucleotides can be easily attached to gold nanoparticles through sulfhydryl or amine groups, resulting in the acquisition of diverse antigenic and adjuvant properties. This biomimetic synthesis approach holds great potential for advancing nanoparticle biosynthesis and its therapeutic applications, offering a non-invasive and efficient pathway for the development of nanomedicine. For the first time, Zhang et al developed a novel intracellularly generated nanoformulation to obtain AuNP@B16F10 using the cytosolic action of mouse melanoma B16F10 cells, which was subsequently made into AuNP@DC_{B16F10} by DCs biocamouflage action to improve its immunogenicity, thus realizing the combination of PTT and immunotherapy.[155]

Carbon-Based Nanomaterials

Carbon-based nanomaterials have gained significant attention in the field of biomedical nanocarriers due to their noteworthy characteristics, including a substantial specific surface area, high NIR absorption, efficient photothermal conversion and facile synthesis methods.[90] Among the various carbon-based nanomaterials investigated, carbon nanotubes (CNTs) and graphene oxides (GOs) have been the subject of extensive research. He et al reported the utilization of a graphene oxide- hyaluronic acid (NGO-HA) coupled with NIR laser for the treatment of melanoma skin cancer.[170] The transdermal delivery facilitated by the interaction between the conjugate and hyaluronic acid (HA) receptors effectively mitigated potential in vivo side effects associated with NGO, ultimately resulting in complete tumor tissue ablation.

Numerous studies have been conducted to explore the potential of CNTs and GO as immune adjuvants.[171,172] CNTs, including single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs), have been extensively investigated for various biomedical applications, including photothermal cancer therapy. Recent research on the interaction between nanotubes and the immune system has shown that CNTs possess the ability to activate both innate and adaptive immune responses, making them potential adjuvants.[173,174] Wang et al experimentally demonstrated that polyethylene glycolated SWNTs possess immune-adjuvant properties that promote DC migration and maturation.[156] They further showed that combining these SWNTs with a CTLA-4 blocking antibody (anti-CTLA-4) significantly inhibited the activity of regulatory T cells (Tregs) within tumors and increased the number of CD20 tumor-infiltrating B-cells. This combination therapy resulted in reduced tumor burden and improved survival rates in subcutaneous and lung metastasis models. In a mouse model of 4T1 lung metastatic tumors, the combination treatment of SWNT-based PTT with anti-CTLA-4 treatment led to long-term survival (57% survival at 50 days). In contrast, the group that received CTLA-4 blockade plus surgery only had a 25% survival rate, and none of the mice survived with surgery or SWNT-based PTT alone without anti-CTLA-4 injection. GO possesses a large surface area, an aromatic structure with π-π stacking interactions, electrostatic interactions with drug molecules, high thermal conductivity, and the ability to cross the plasma membrane.[175] However, free graphene oxide can induce autophagy-associated cell death and may be potentially toxic, limiting its application.[176] To overcome this limitation, Du et al proposed the functionalization of GO using heparin (Hep) for transdermal delivery.[157] Through π-π coupling, GO loaded with doxorubicin (DTX) and an IDO inhibitor (1MT) resulted in the development of a nanopreparation (D-1/GH) that effectively induced ICD signaling and exhibited potent antitumor effects. The combination therapy using this nano-formulation demonstrated superior inhibition of tumor growth compared to commercially available taxotere administered intravenously.

Silica-Based Nanoparticles

Silica-based nanoparticles include silicon nanoparticles, silica nanoparticles, and silica-coated nanoparticles, have emerged as promising carrier tools for delivering proteins or drug molecules to support cancer immunotherapy. Mesoporous organosilica nanoparticles (MON) are highly promising due to their tunable structure, large surface area, controlled matrix degradation, and responsive drug release capabilities.[103] In a recent study by Zhang et al, a coordinated responsive diselenide-bridged ruthenium compound (KP1339) was loaded onto MON for cancer chemoimmunotherapy.[158] The diselenide component enabled the controlled release of KP1339 through both ligand and redox response to GSH. Notably, high doses of MON exhibited a dual effect by significantly increasing levels of ROS while decreasing levels of GSH. This resulted in the induction of ER stress, which acted as an ICD amplifier, enhancing the anti-tumor immune response to KP1339, the chemotherapeutic agent. Luo et al developed a co-delivery nanocarrier, namely aCD47-DMSN, by encapsulating DOX within the mesoporous cavity of mesoporous silica nanoparticles (MSN) and immobilizing aCD47 on the surface of microspheres (Figure 4).[143] The purpose of incorporating aCD47 was to inhibit the CD47-SIRPα axis, thereby disabling the "do not-eat-me" signal, and concurrently enhance the exposure of CRT induced by DOX. This augmentation of CRT acted as an "eat-me" signal, promoting ICD. Upon intravenous administration of aCD47-DMSN in 4T1 and B16F10 mouse tumor models, an improved phagocytic response by macrophages was observed, leading to robust anti-tumor effects. Another approach employed by Yan et al[177] involves the construction of a layered structure encapsulating hydroxycamptothecin (HCPT) using alternate coatings of calcium carbonate (ACC) and silica layers. This self-regulatory model takes advantage of the silica hydrolysis kinetics to achieve sustained drug release within the tumor. By enabling controlled release of chemotherapeutic agents, this approach

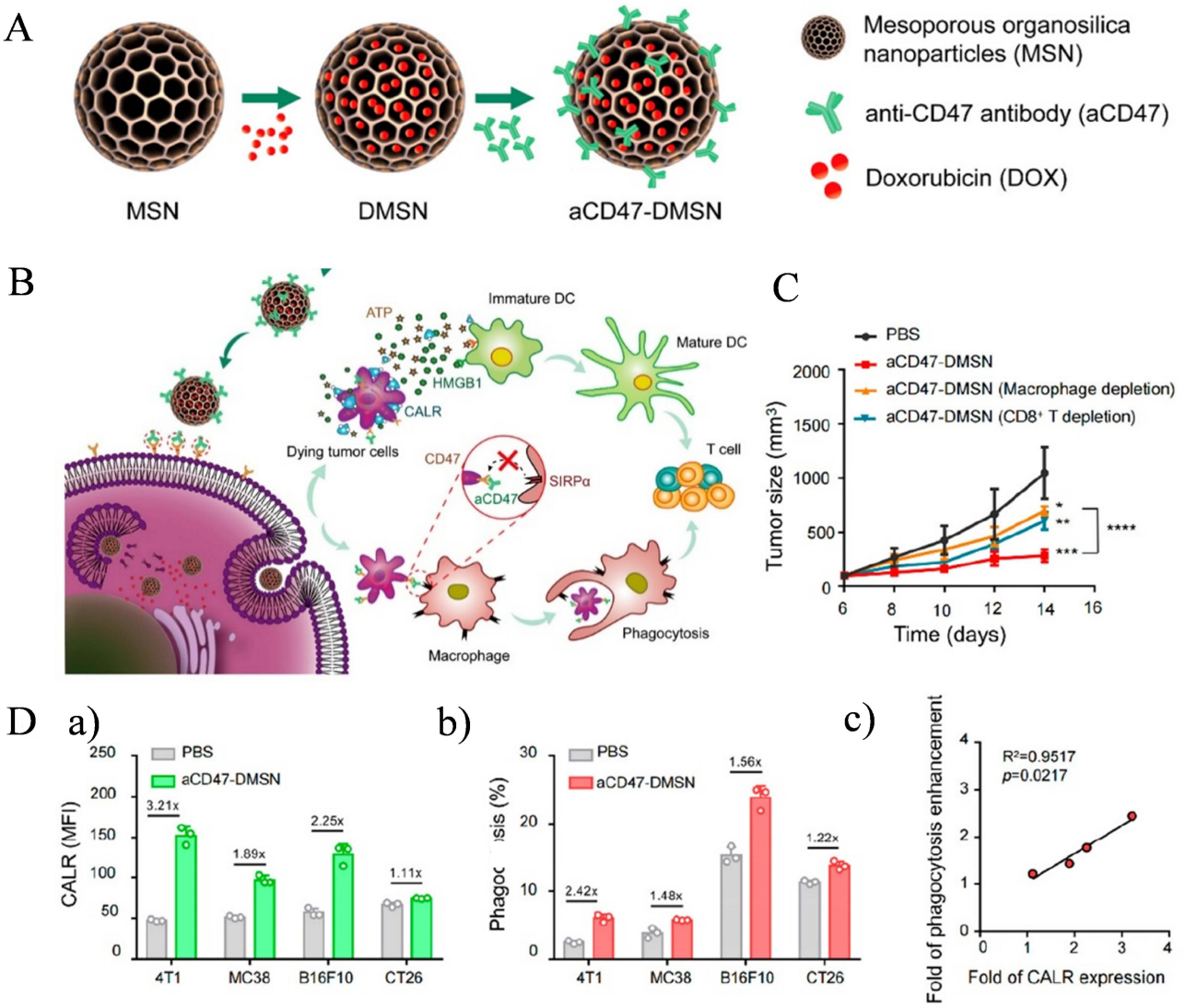

Figure 4 (**A**) aCD47-DMSN was constructed by the loading of DOX within the mesoporous cavity while adsorbing aCD47 on the surface. (**B**) Mechanism of action of aCD47-DMSN. (**C**) Average tumor growth curves after the treatments (n = 5, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001). (**D**). Level of CALR exposure a) and BMDMs phagocytosis b) under basal condition or aCD47DMSN treatment. c) The correlation between the fold of CALR expression and phagocytosis enhancement after aCD47-DMSN treatment. Reprinted with the permission from Luo JQ, Liu R, Chen FM, et al. Nanoparticle-Mediated CD47-SIRPα blockade and calreticulin exposure for improved cancer chemo-immunotherapy. *ACS Nano.* 2023;17(10):8966–8979. Copyright © 2023 American Chemical Society.[143]

enhances the therapeutic effect while minimizing side effects. The surface roughness of nanoparticles plays a crucial role in their cellular uptake and intracellular behavior, which ultimately affects the therapeutic efficacy of the loaded agents. On this basis, Xue et al utilized silica nanoparticles as carriers for a photothermal agent called polydopamine and the protein 4 (BRD4) inhibitor JQ-1, aiming to eradicate melanoma by combined photothermal and immunotherapy.[144] By etching silica nanoparticles with hydrofluoric acid (HF), the surface roughness was significantly increased, resulting in enhanced cellular uptake. This facilitated the effective delivery of JQ-1 into residual tumor cells, leading to the inhibition of PD-L1 expression after phototherapy and assisting T cells in eliminating residual cancer cells.

Quantum Dots

Quantum dots (QDs) are semiconductor nanocrystals composed of II–VI or III–V groups with physical dimensions less than the bulk exciton Bohr radius (2–10 nm). The QDs exhibit numerous interesting optical and electronic properties.[178] They possess favorable photostability and can be easily modified, making them highly valuable in the field of cancer diagnosis and treatment. QDs, such as Pb and Ag, emit light in the long end of the second near-infrared window (NIR-IIb) range, enabling high-

resolution imaging of deep tissues. To facilitate this application, Li et al developed a QD-Cat-RGD nanoprobe by modifying PbS/CdS QDs with catalase (Cat), arginine-glycine-aspartic acid (RGD) peptide, and poly(ethylene glycol) (PEG).[159] The incorporation of high atomic number atoms, specifically Pb, in the nanoprobe conferred favorable radiosensitizing properties. Additionally, Cat catalyzed the decomposition of H_2O_2, alleviating tumor hypoxia and enabling precise radiotherapy guided by RGD to enhance the immunocidal effect of ICD. The anaerobic microenvironment within tumors presents an ideal habitat for anaerobic bacteria, which have demonstrated effective tumor targeting and penetration. Zhao et al capitalized on this characteristic by combining the tumor penetration capability of Bifidobacterium bifidum (B,b) with the photothermal conversion effect of QDs.[160] This combination resulted in the generation of abundant tumor-associated antigens, effectively enhancing the immune response. Notably, the close interaction between B.b and tumor-associated macrophages facilitated the polarization of macrophages toward the M1 phenotype, creating a favorable tumor microenvironment that further augmented the effectiveness of photothermal therapy. By employing mannose-derived CDs nanoparticles, TAAs released after MWA treatment could be captured, thereby facilitating effective targeting of APCs.[179] Consequently, a robust anti-tumor immune response was induced, resulting in the inhibition of primary tumor growth as well as significant suppression of metastasis.

Upconversion Nanoparticles

UCNPs comprise a crystalline host matrix, which is doped with lanthanide ions. The combination determines the ability to absorb near-infrared light and convert into high-energy photons across a wide range of wavelengths, from ultraviolet to visible light.[180–182] The advantages of utilizing UCNPs include reduced phototoxicity, improved signal-to-noise ratio, and enhanced light penetration depth, making them promising candidates for various biomedical applications.[183]

Although PDT has the potential to induce ICD, it is still limited by the penetration depth of visible light.[181] To address this challenge, Xu et al developed multitasking UCNP-Ce6-R837 nanoparticles, wherein UCNPs were loaded with Ce6 and R837 to enable deep PDT-enhanced immune responses under NIR illumination.[161] Concurrent administration of CTLA-4 blockers resulted in the induction of long-term immune memory and prevention of tumor recurrence. Song et al delivered indocyanine green (ICG) and rose of Bengal (RB) as the core of UCNP to enhanced the uptake and presentation of APC by capturing tumor protein antigens released after in situ phototherapy via maleimide modification (Figure 5).[162] This strategy amplifies the combined effects of PDT and PTT. Mao et al undertook a study in which they combined the aggregation-induced emission (AIE) photosensitizer TPEBTPy with upconverted nanoparticles (UCNPs).[163] The purpose was to harness the ability of UCNPs to convert deep-penetrating near-infrared (NIR) light into visible wavelengths, matching the absorption range of TPEBTPy. This strategy enabled effective PDT treatment while also offering potential for bioimaging applications. Notably, the hybrid nanomaterial generated high levels of ROS when administered via intratumoral injection and upon exposure to high-power NIR irradiation. Under low-power NIR irradiation, the nanomaterial induced the generation of low doses of ROS, which functioned as crucial signaling molecules promoting the maturation of APCs. Furthermore, this hybrid nanomaterial exhibited the ability to capture released antigens and transport them to the lymph nodes. Additionally, Chen et al utilized UCNPs wrapped in TAMs membranes to deplete the colony-stimulating factor 1 (CSF1) secreted by tumor cells.[184] This depletion obstructs macrophage polarization into the M2 phenotype, thereby enhancing the immunotherapeutic effects of PDT.

Other

Layered double hydroxide nanoparticles (LDHs) are lamellar structured materials with two-dimensional (2D) characteristics, extensively studied as carriers for drug/gene delivery. LDHs offer numerous advantages, such as high anion-exchange capacity, customizable particle sizes, and enhanced cellular uptake.[185,186] Transient and feeble are typical features of RFA-induced antitumor immunity. Chen et al prepared RFA-based LDHs-cGAMP complexes, which effectively promoted DCs activation to inhibit the progression of poorly immunogenic hepa1-6 hepatocellular carcinomas by activating the cGAS-STING pathway and adsorbing RFA-generated TAAs, generating sustained immune stimulation (Figure 6).[164,187] Achieving effective ablation of tumours through PTT requires raising the temperature of cancerous tissue above 45°C. However, the repair of thermogenic (38–42°C) cell damage by Hsp, which are overexpressed by cancer cells, poses a challenge.[188] To address this, Li et al developed a nanohybrid (FeOOH@STA/Cu-LDH) wherein FeOOH nanodots were anchored as ROS inducers on the surface of Cu-LDHs, which act as photothermal agents.[165]

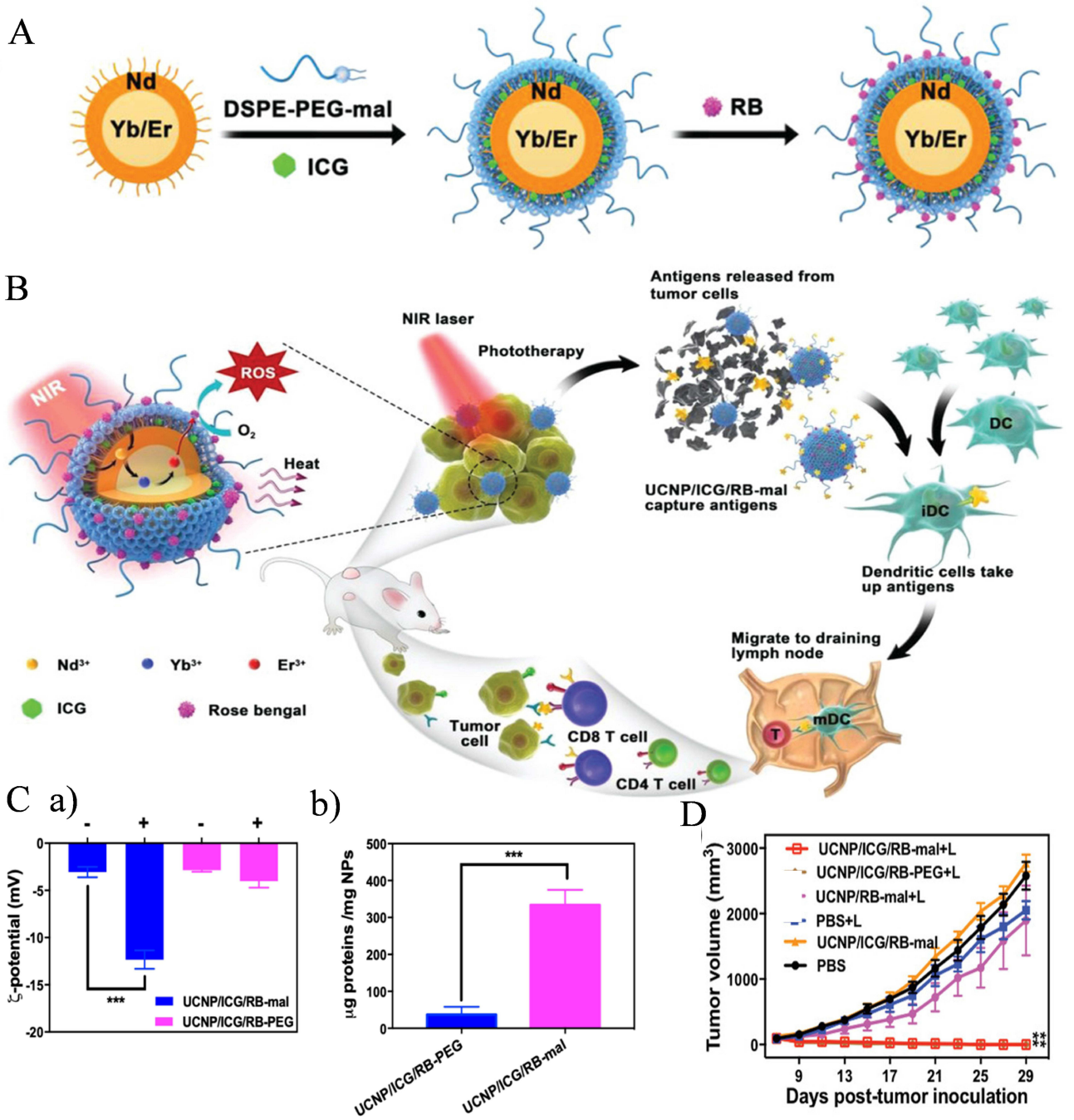

Figure 5 (**A**) Schematic drawing showing the fabrication process of UCNP/ICG/RB-mal. (**B**) Schematic illustration of both fabrication and mechanism of near-infrared (NIR)-triggered antigen-capturing nanoplatform for synergistic photo-immunotherapy. (**C**) a) The zeta potential of UCNP/ICG/RB-mal or UCNP/ICG/RB-PEG before and after antigen capture (n=4, ***p < 0.001); b) Quantification of protein captured by nanoparticles (n=4, ***p < 0.001). (**D**) Average tumor-growth curves of different treatment groups of mice with orthotopic 4T1 tumors (n = 6, **p < 0.01 vs PBS group). Reprinted from Wang M, Song J, Zhou F, et al. NIR-triggered phototherapy and immunotherapy via an antigen-capturing nanoplatform for metastatic cancer treatment. *Adv Sci*. 2019;6(10):1802157. © 2019 The Authors. Published by WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[162]

Additionally, the Hsp90 inhibitor (STA-9090) was embedded in the intercalation layer of Cu-LDHs. Notably, the bilayer hydroxide containing copper converts the energy of NIR laser into heat, elevating the temperature to a fever-type range (40–42°C). This temperature, in combination with the FeOOH-mediated Fenton reaction, amplifies ROS production, resulting in a significant exposure of CRT to tumour cells. Remarkably, even in the absence of immunosuppression, the amplification of ICD extends the therapeutic effect beyond the targeted site, promoting systemic anti-tumour immunity.

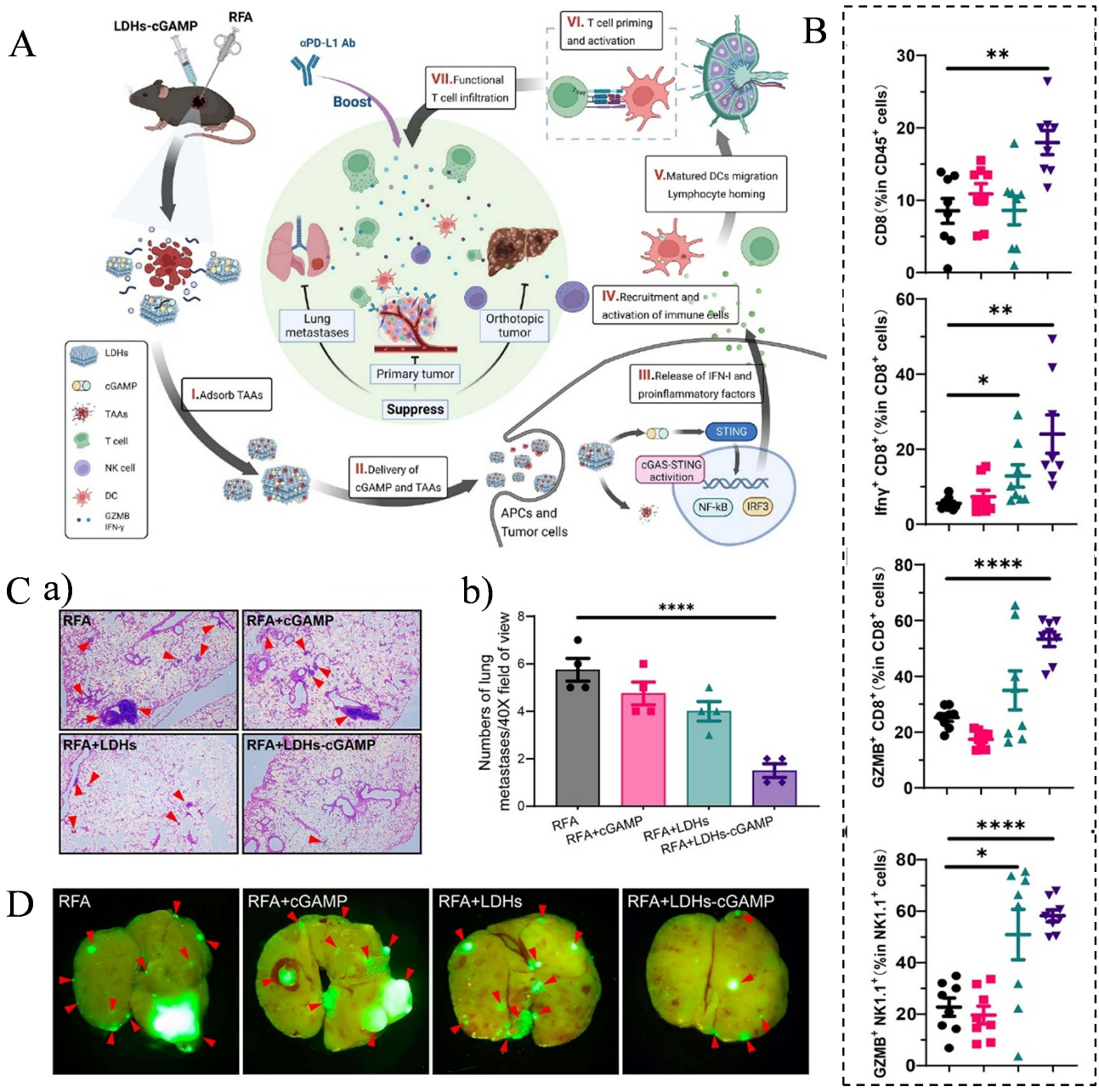

Figure 6 (**A**) LDHs-cGAMP adsorbed TAAs released by RFA-induced tumour cell death, which was internalised by the cells and activated through the cGAS-STING pathway. Meanwhile, the formed nanovaccine stimulates APCs and promotes an immune response. (**B**) Nanovaccine could enhance infiltration of immune cells into tumors (n=8, *p < 0.05; **p < 0.01; ****p < 0.0001). (**C**) a) Representative HE staining of lung metastases and b) the corresponding quantitative analysis results (n=4, ****p < 0.0001). (**D**) The results of lung metastases observed by SFM (green light represents metastases). Reprinted with the permission from Tian Z, Hu Q, Sun Z, et al. A booster for radiofrequency ablation: advanced adjuvant therapy via in situ nanovaccine synergized with anti-programmed death ligand 1 immunotherapy for systemically constraining hepatocellular carcinoma. *ACS Nano.* 2023;17(19):19441–19458. Copyright ©2023 American Chemical Society.[164]

Application of Organic Nanocarriers in Enhancing ICD Effect

Organic polymeric materials possess exceptional properties that render them highly suitable for various applications in the field of nanodelivery. Notable examples of such materials encompass poly (lactic-ethanolic acid copolymers), liposomes, exosomes, vesicles, and cyclodextrins (Table 2). These materials exhibit distinctive structures that offer stabilization to functional groups, specific ligand binding, and facilitate the formation of block copolymers. The multi-functionality exhibited by these materials facilitates the efficient delivery of water-insoluble drugs and holds great promise in significantly enhancing the efficacy of nanodrug delivery strategies for ICD.[189]

Table 2 Organic Nanoparticle-Mediated Immunogenic Cell Death

Delivery System	ICD Inducer and Amplifier	Cytokines or DAMPs	Immune Cells Infiltration	Advantages	Model	Ref
Polymers	PLGA-PEG-AEAA+ Icaritin +DOX	ATP, mtDNA, CRT, HMGB1, IFNγ, TNFα, IL-12	↑DCs maturation; ↑$CD4^+$, $CD8^+$ T cells; ↓M2 macrophages; ↓Tregs;	Induction of mitochondrial autophagy and apoptosis for ICD; prolongation of nanomedicine retention time	Hepa1−6 and B16F10 (C57BL/6 mice)	[146]
	PCL-P (L-arg) +IDO1 siRNA +Mitoxantrone (MIT)+ mPEG-PLL-DMA	CRT, HMGB-1, ATP, IFN-γ, TNF-α	↑DCs maturation; ↑CD4, CD8, IFN-γ CD8 T cells; ↓Tregs;	Efficient release of nanomedicines in tumour cells via ICD-activated charge switching; inhibition of the IDO pathway enhances ICD	4T1 an D CT26 (Balb/c mice)	[190]
	Carboxymethyl chitosan (CMCS) + PD-L1 siRNA+DOX	CRT, HMGB-1, ATP	↑CD4+, $CD8^+$ T cells;↓Tregs;	Efficient release in tumour cells; amelioration of DOX-induced PD-L1 upregulation	4T1 (Balb/c mice)	[189]
liposomes	1,2-dioleoyl-3-trimethylammonium-propane (DOTAP)+ HG13539-ACR	CRT, IFN-γ	↑DCs maturation; ↑M1 macrophages; ↑$CD3^+$, $CD8^+$T cells	Repeatedly induces CRT expression, enhances ICD and synergises with Focused Ultrasound (FUS).	B16F10 (C57BL/6 mice)	[145]
	Cationic liposomes+ OXA+ POM-1 (sodium polyoxotungstate)	CRT, HMGB1, ATP, IFN-γ	↑DCs maturation; ↑$CD3^+$, $CD4^+$, $CD8^+$ T cells; ↓Tregs	Interference with the ATP-ADO pathway to maintain immunostimulatory ATP levels	B16F10 (C57BL/6 mice)	[147]
	Indocyanine green (ICG) +Pardaxin peptide	CRT, ATP, HMGB1	↑DCs maturation; ↑$CD4^+$, $CD8^+$ T cells;	Targeted ER enhances PDT effect	EG7 (C57BL/6 mice)	[191]
Exosomes	Bone marrow mesenchymal stem cell (BM-MSC) + OXA+Galectin-9 siRNA	CRT, HMGB1, IFN-γ	↑$CD8^+$ T cells	Reversal of immunosuppression by blocking the galectin-9/dectin-1 axis	PANC-02 (C57BL/6)	[192]
	PpIX+NLS peptide	——	——	Dual-stage photomodulation of plasma membrane and nucleus-targeted photodynamic therapy for in situ generation of ROS and precise destruction of cell nuclei	4T1 (Balb/c mice)	[193]

Nanogels	Gemcitabine (GEM) + aPDL1	IL-6, IFN-γ	↑$CD3^+$, $CD8^+$ T cells	Control of drug release by ROS response and scavenging of ROS inhibits M2-type macrophage polarisation; inhibits immune checkpoint blockade	4T1 (Balb/c mice)	[194]
	Au NPs+ Toyocamycin+ poly(amidoamine) dendrimer	CRT, HMGB1, TNF-α, IFN-γ	↑$CD4^+$, $CD8^+$ T cells; ↓Tregs	Responsive dendrimeric NGs tackle tumors through a multi-pronged chemoimmunotherapy strategy targeting both cancer cells and immune cells.	Pan02 cells	[195]
	Pheophorbide A (PPA) + PD-L1 siRNA	IFN-γ	↑DCs maturation; ↑$CD8^+$ T cells	Increases photosensitiser water solubility and promotes 1O2 production; downregulates PD-L1 expression	B16F10 (C57BL/6 mice)	[196]
Cyclodextrin polymers	Cyclodextrin + Ginsenoside Rg3 + Quercetin (QTN)+ Folate (FA)	CRT, ATP, HMGB1	↑DCs maturation;	Promotes ROS production and enhances ICD	CT26 and HCT116 (Balb/c mice)	[197]
	Cyclodextrin-grafted hyaluronic acid (HA-CD) + Pyropheophorbide a (Ppa)+ JQ1	CRT, HMGB1, IFN-γ	↑DCs maturation; ↑CD8/CD4 T cells ratio	Blocking c-Myc transcription, inhibiting glycolysis and down-regulating PD-L1 expression on the surface of tumour cells	PANC-02 (C57BL/6)	[198]
	β-cyclodextrin+ DOX	CRT, HMGB1	——	DOX-based chemotherapy was enhanced due to the transport performance and tumor-specific release of this supramolecular nanocage.	4T1 (Balb/c mice)	[199]
Cell membrane	Plumbagin (PLB)+ Dihydrotanshinone I (DIH)+ Sodium bicarbonate	CRT, ATP, HMGB1, IFN-γ, IL-12, TNF-α,	↑DCs maturation; ↑M1 macrophages, NK cell; ↑$CD4^+$, $CD8^+$ T cells; ↓Tregs	Biomimetic nano-formulations improve in vivo toxicity, pharmacokinetics and tumour delivery; induction of ROS enhances chemotherapy-induced ICD	HCC (C57BL/6)	[200]
	Bacterial outer membranes (BM)+ Tumor cell membranes (TM)+ Glutathione (GSH)+ Te nanoparticles	CRT, ATP, HMGB1, IFN-γ, IL-12, TNF-α,	↑DCs maturation; ↑$CD3^+$, $CD8^+$ T cells;	Stimulation of APCs maturation and CTLs secretion to synergise ICD effects with radiotherapy sensitisers	4T1 (Balb/c mice)	[69]

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Polymers

Polymeric nanoparticles are colloidal particles with submicron size that serve as carriers for encapsulating or adsorbing agents within a matrix or onto a surface. These NPs find extensive utilization in biomedical applications, with both natural Polymers like sodium alginate and chitosan, and synthetic polymers such as poly(ε-caprolactone) (PCL), poly (lactic-co-glycolic acid) (PLGA), and poly(vinyl imide) (PEI) being commonly employed.[201] Among these, PLGA emerges as a highly successful biodegradable polymer. In vivo, PLGA undergoes hydrolysis leading to the formation of biodegradable metabolite monomers like lactic acid and glycolic acid. Yu et al employed a solution replacement technique to encapsulate Icaritin (ICT) and DOX within PLGA-PEG-AEAA, with the primary goal of improving systemic circulation and enabling targeted drug delivery through pH-responsive controlled release at the tumor site.[146] Notably, the inclusion of Epimedium resulted in improved anti-hepatocellular carcinoma (HCC) effects by synergistically inducing mitochondrial autophagy and apoptosis, which complemented the ICD effects induced by DOX. Under normal physiological conditions, PCL can undergo hydrolysis of its ester bonds, resulting in minimal to no toxicity within the human body. Shi et al developed cationized micelles composed of poly(ε-caprolactone)-poly(L-arginine) (PCL-P(L-arg), PPA) to encapsulate IDO1 siRNA and MIT.[190] Furthermore, they employed electrostatic interaction to encapsulate microacidic tumour microenvironment-responsive poly (ethylene glycol)-poly(L-lysine)-2,3-dimethylmaleic anhydride (mPEG-PLL-DMA, PLM) onto the PPA micelles. The hydrophilic PLM chains, which carry a negative charge, EPR effect of the nanoparticles, leading to prolonged blood circulation. Subsequently, the larger-sized nanoparticles were converted into MIT/siR-PPANPs with a positive charge within the microacidic environment, facilitating enhanced tumour penetration. Moreover, P(L-Arg) plasmonic sponges allowed for lysosomal escape, enabling efficient release of the chemotherapeutic drug MIT and IDO inhibitors within tumour cells, thereby demonstrating satisfactory tumour penetration ability. Inhibition of the IDO1 pathway through DO1 siRNA enhanced the anti-tumour effect of MIT-induced ICD, highlighting its potential for treating primary and distant tumours, reducing metastasis, promoting dendritic cell maturation, increasing CTLs numbers, and down-regulating Tregs levels in tumour tissues. In a study by Song et al, pH/reducing dual-responsive micelles were developed using GE11-modified carboxymethyl chitosan (CMCS) as a targeting peptide.[189] The micelles were prepared through nanoprecipitation, with PD-L1 siRNA and DOX encapsulated in the hydrophobic core. The subsequent release of PD-L1 siRNA inhibited immune escape, while DOX-induced ICD further enhanced tumour immunotherapy. This combination strategy demonstrated promising outcomes in weakly acidic and reducing environments, leading to the proliferation of NK cells within peripheral blood mononuclear cells (PBMC) and enhanced efficacy of chemotherapeutic drug-induced ICD.

liposomes

Liposomes are the phospholipid bilayer-enclosed spheres formed via self-assembly in water under a driving force of hydrophobicity.[202] Notably, lipids and phospholipids, being fundamental constituents of biological membranes, exhibit a propensity to interact with cell membranes, thus facilitating the phagocytosis of antigen-loaded nanoparticles. Sethuraman et al employed liposomes as a platform to develop a drug delivery system that encapsulates CRT plasmids.[145] This innovative approach, known as calcium reticulation nanoparticle (CRT-NP), facilitates the amplification of ultrasound-triggered ICD in tumors through the direct Introduction of a full-length clone of human CRT. The results demonstrate promising prospects for clinical translation in the treatment of melanoma. Fu et al utilized electrostatic interactions to immobilize a CD39 inhibitor (POM-1) onto liposomes containing OXA.[147] Upon reaching the tumor site, POM-1 exhibited strong binding affinity towards CD39, thereby disrupting the ATP-ADO pathway and preserving immunostimulatory ATP levels. This system effectively suppressed the growth of in situ tumors, lung metastases, and postoperative recurrent melanoma models through a dual mechanism involving the induction of ICD and alleviation of immunosuppression. Notably, it also facilitated the establishment of long-term immune memory.

Liposomes, unlike other nanocarriers, are vesicles composed of a lipid bilayer at ambient temperature. When the phase transition temperature (Tc) of liposomes consisting a type of phospholipids closely aligns with the ambient temperature, their membranes will display heightened permeability and have the potential to release their cargo abruptly.[203] Researchers such as Guo et al[204] have utilized emerging nanomaterials in their studies. They introduced tLyP-1 (CGNKRTR) modified liposomes to achieve targeted action against breast cancer. Through the co-delivery of

perfluoropentane, an acoustic sensitizer, and chemotherapeutic drugs, these liposomes were able to interfere with mitochondrial energy metabolism and induce chemotherapy sensitization. Guo et al also employed the pardaxin peptide to modify liposomes, resulting in the construction of viral non-viral nanovectors (Par-Lipo), which exhibited targeted ER-enhanced PDT effects (Figure 7).[191] Reactive carriers play a crucial role in controlling drug release. In the presence of ROS, unsaturated phospholipids within liposomes undergo a conversion process, resulting in the generation of hydrophilic peroxides. Yang et al devised a novel strategy to construct photoactivated liposomes containing the photosensitizer Ce6 and the chemotherapeutic drug Pt (IV).[205] Upon PDT, the ROS-induced action leads to structural disruption of the liposomes, facilitating the on-demand release of the Pt (IV) prodrug from the nanodrug. Subsequently, the released Pt (IV) undergoes reduction to highly cytotoxic Pt (II), further augmenting the effectiveness of PDT in tumor eradication. To enhance biocompatibility and prolong the circulation time in the bloodstream, the liposomes were modified with polyethylene glycol. Notably, Song et al employed polyethylene glycolized liposomes to encapsulate hydrogen peroxide or catalase (CAT), thus effectively preventing protease-mediated degradation during the delivery of the nanodrug.[206] Many liposomes deliver drugs to tumor cells through processes such as membrane fusion or endocytosis, often resulting in the disintegration of the liposomes. Liu et al introduced a nanoparticle (IERL) with a stable nanostructure and a bioactive surface achieved by polymer modification on the liposome surface.[203] The findings demonstrated that IERL-P, featuring a reinforced liposome structure, effectively captured produced TAAs and facilitated their transfer from endolysosomes to the cytoplasm in DCs upon laser irradiation. This mechanism prevented TAA entrapment in endolysosomes, leading to successful inhibition of tumor growth and a robust antitumor effect in vivo.

Exosomes

Exosomes are generated through an inward budding process within cells, including tumor cells, bacteria, and tumor-associated macrophages, resulting in the formation of intracellular vesicles.[207] These vesicles then progress to multivesicular bodies and are subsequently released outside the cell. Exosomes are characterized by their cup-shaped morphology, with a size ranging from 30 to 150 nm and a lipid bilayer structure.[207] Importantly, exosomes encapsulate a diverse array of molecules including proteins, lipids, DNA, and RNA derived from the parent cell, carrying essential information that contributes to their remarkable biocompatibility, ability to overcome biological barriers in vivo, and specific targeting of recipient cells.[208,209] Consequently, exosomes have garnered significant attention as promising carriers for drug delivery and have shown potential in numerous immunological applications.[210]

The association between dectin-1, a key innate immune receptor found on macrophages, and galectin-9 has been shown to induce the polarization of macrophages into the protumorigenic M2 phenotype.[192] In a study conducted by Zhou et al, exosomes were utilized as carriers for drug delivery.[192] Due to the close interaction between bone marrow-derived mesenchymal stem cells (BM-MSCs) and pancreatic ductal adenocarcinoma (PDAC) tumor tissues, exosomes derived from BM-MSCs (referred to as iEXO-OXA) were employed to transport both OXA, a chemotherapeutic agent, and galectin-9 siRNA, effectively enabling targeted delivery to pancreatic cancer in an in vivo setting. The co-administration of galectin-9 siRNA successfully disrupted the galectin-9/dectin-1 axis, thereby reversing the immunosuppressive effects induced by M2-type tumor-associated macrophages (TAMs) and enhancing the ICD effects of tumor chemotherapy. In vivo experiments corroborated that iEXO-OXA exhibited preferential accumulation at the tumor site, protected encapsulated genes, facilitated the activation of anti-tumor immunity, and prolonged the circulation time in the bloodstream. In another study by Cheng et al, engineered exosomes were combined with PDT, effectively circumventing endocytosis/lysosomal effects and achieving efficient localized PDT therapy targeting the nucleus.[193] This was achieved by directing nanoparticles to the plasma membrane via exosomes, triggering photochemical internalization. Subsequently, nuclear transport was facilitated in the presence of nuclear localization signal (NLS) peptides. Under secondary light exposure, the chimeric protein-engineered exosomes (ChiP-Exo) generated ROS inside the nucleus, leading to disruption and enhanced synergistic PDT, ultimately resulting in significant anti-tumor efficacy. This subcellular dual-targeting strategy, based on the amalgamation of exosomes and PDT, presents a promising approach to precise tumor therapy.

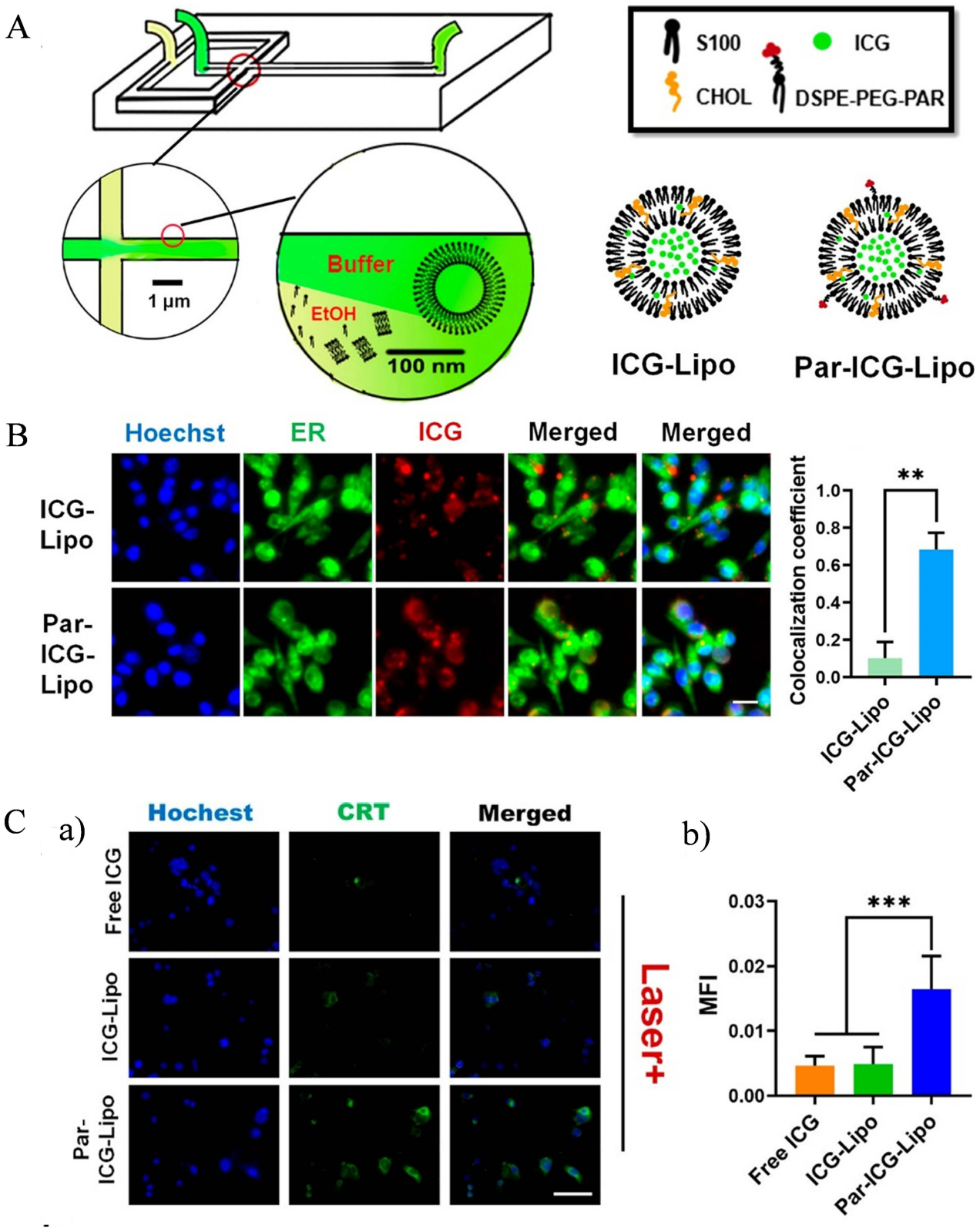

Figure 7 (**A**) Preparation of liposomes using a "self-assembly" mechanism in a microfluidic device with a focusing pipeline. (**B**). Par-ICG-Lipo colocalized almost completely with the ER (n=3, **p < 0.01). Scale bar: 20 μm. (**C**). a) Par-ICG-Lipo-mediated PDT significantly induces CRT exposure (ecto-CRT). b) Quantitative analysis of CRT exposure in B16 cells (n=3, ***p < 0.001). Scale bar: 100 μm. Reprinted with the permission from Liu X, Liu Y, Li X, et al. ER-Targeting PDT converts tumors into in situ therapeutic tumor vaccines. *ACS Nano*. 2022;16(6):9240–9253. Copyright ©2022 American Chemical Society.[191]

Nanogels

Nanogels are hydrogel nanoparticles composed of cross-linked polymer networks with a three-dimensional structure.[211] Unlike other nanocarriers such as polymers, liposomes, and exosomes, nanogels exhibit a rapid phase transition and have the ability to entrap substances within their network. Nanogels can be fabricated from natural polymers (eg, polysaccharides, peptides, and nucleic acids), synthetic polymers (eg, polyethylene glycol and poly n-isopropylacrylamide), or a combination of both through chemical cross-linking via covalent bonding or physical cross-linking via non-covalent bonding.[212] They are characterized by high stability, low toxicity, environmental responsiveness, prolonged circulation in the bloodstream, and biocompatibility.[213]

Wang et al developed a nanoplatform using PVA-TSPBA hydrogels for the responsive release of gemcitabine (GEM) and anti-programmed death-ligand 1 (aPDL1).[194] Within the tumor's high ROS microenvironment, the nanogels disassembled, facilitating drug release to activate ICD and inhibit immune checkpoint blockade. Moreover, the ROS-responsive nanogel system not only modulates therapeutic drug release but also acts as a ROS scavenger, impeding M2 macrophage differentiation and augmenting immunogenicity. In another study, Zhang et al developed a biomimetic nanogel co-loaded with Au NPs and Toy by incorporating reactive chemical groups into the nanogel structure (Figure 8).[195] This nanogel demonstrated responsiveness and tumor-specific targeting in the acidic tumor microenvironment. Released Toy promotes apoptosis of cancer cells via ER stress amplification to ICD for maturation of DCs. With Au NPs, not only can tumour-associated macrophages be induced to convert from M2-type to anti-tumour M1-type to re-regulate immunosuppressive TME, but also Au-mediated tumour CT imaging can be achieved. Particularly, self-assembled nanogels are capable of effectively encapsulating non-aggregated proteins and releasing them while preserving their native structure, thus exhibiting a molecular chaperone function attributed to the dynamic hydrophobic interaction aggregation. DNA nanostructures have emerged as novel non-cationic carriers for delivering genes and small molecule drugs. Building upon this, Guo et al synthesized nanogels co-encapsulating photosensitizers and small interfering RNAs (siRNAs) through nucleic acid hybridization.[196] The exceptional water solubility inherited from nucleic acids in this system facilitated the production of $^1O_2$ during PDT, resulting in significant ICD in tumor cells. Furthermore, the released siRNA down-regulated programmed cell death-ligand 1 (PD-L1) expression in tumor cells, synergistically promoting antitumor efficacy and effectively inhibiting both primary and distal tumors.

Cyclodextrin

Cyclodextrins (CD) are cyclic oligosaccharides that occur naturally as a result of starch hydrolysis by amylase.[214] Their unique structure, consisting of a hydrophobic inner cavity and a hydrophilic outer surface, allows for the encapsulation of small hydrophobic drug molecules or hydrophobic portions of macromolecules.[215] This results in the formation of water-soluble host-guest inclusion complexes, with the CD acting as the host and the hydrophobic drug molecule as the guest. This process imparts new physicochemical properties to the drug while preserving its intrinsic characteristics. Amongst the cyclodextrins, β-CDs are especially favored in pharmaceutical applications due to their modest water solubility and sufficiently large cavity size.[216]

In a recent study by Sun et al, a nanoformulation named CD-PEG-FA.Rg3.QTN was developed.[197] This formulation effectively exerted immunotherapeutic effects in a mouse model of colon cancer by encapsulating ginsenoside Rg3 and quercetin (QTN) after modifying cyclodextrin. The co-delivery of cyclodextrin facilitated the generation of ROS by QTN, which in turn enhanced the release of DAMPs induced by Rg3 and triggered the maturation of DCs. Additionally, when combined with PD-L1 inhibitors, this system significantly improved animal survival rates. Furthermore, Xu's research group employed a host-guest complexation strategy between β-cyclodextrin-grafted hydantoin (HA-CD) and an amantadine (AD)-modified prodrug to deliver JQ1 and pyropheophorbide a (Ppa) to tumors.[198] This approach effectively blocks c-Myc transcription, inhibits glycolysis, and downregulates PD-L1 expression on the surface of tumor cells, thereby promoting photoimmunotherapy of pancreatic cancer. The modification of the hydroxyl group of CD and the incorporation of various elements can facilitate the creation of a versatile drug delivery system. In a study by Hu et al, a GSH-responsive supramolecular nanocage was developed using polycyclodextrins (Figure 9).[199] This innovative design resulted in a nanocage with enhanced stability and drug-carrying capacity. Moreover, the redox equilibrium in the tumor microenvironment could be disturbed due to GSH depletion, further preventing the extrusion of DOX. This disruption

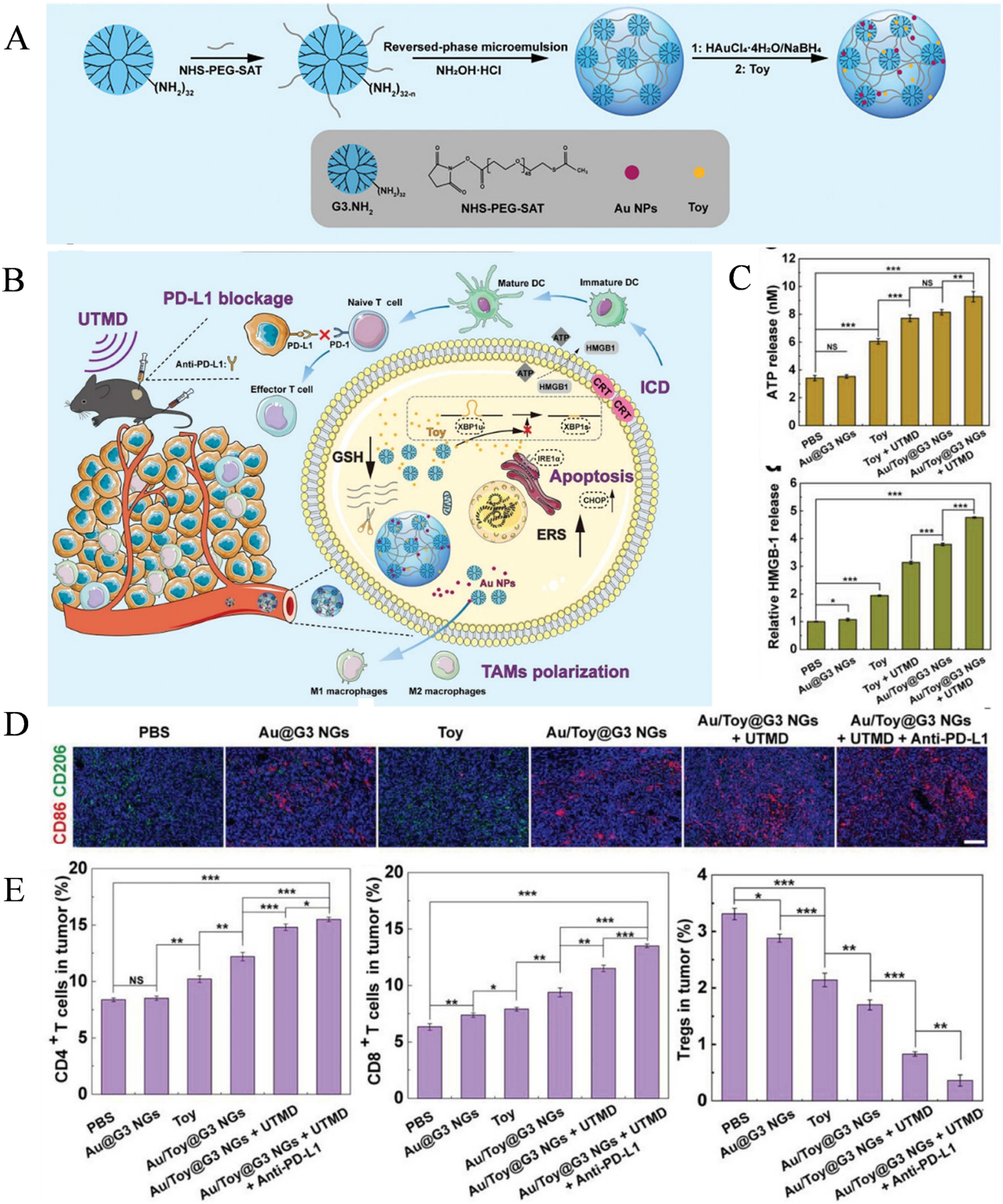

Figure 8 (**A**) Construction of Au/Toy@G3 NGs. (**B**) Au/Toy@G3 NGs for UTMD-enhanced chemoimmunotherapy and CT imaging of pancreatic tumor in combination with anti-PD-L1-mediated ICB. (**C**) The content of ATP and HMGB-1 secreted in the culture medium of cells treated by the Au/Toy@G3 NGs + UTMD reaches the highest level among all groups, suggesting the enhanced ICD effect through UTMD-facilitated improved chemotherapy of the hybrid NGs (n=3, *p < 0.05, **p < 0.01, and ***p < 0.001). (**D**) Au NPs could efficiently convert TAMs from M2 to M1-type. Scale bar: 100 μm. (**E**) Au/Toy@G3 NGs effectively increased the proportion of tumour-infiltrating CTLs, including CD4, CD8 T cells and Tregs (n=3, *p < 0.05, **p < 0.01, and ***p < 0.001). Reprinted from Zhang G, Zhan M, Zhang C, et al. Redox-responsive dendrimer nanogels enable ultrasound-enhanced chemoimmunotherapy of pancreatic cancer via endoplasmic reticulum stress amplification and macrophage polarization. *Adv. Sci.* 2023;10(24):2301759. © 2023 The Authors. Advanced Science published by Wiley-VCH GmbH.[195]

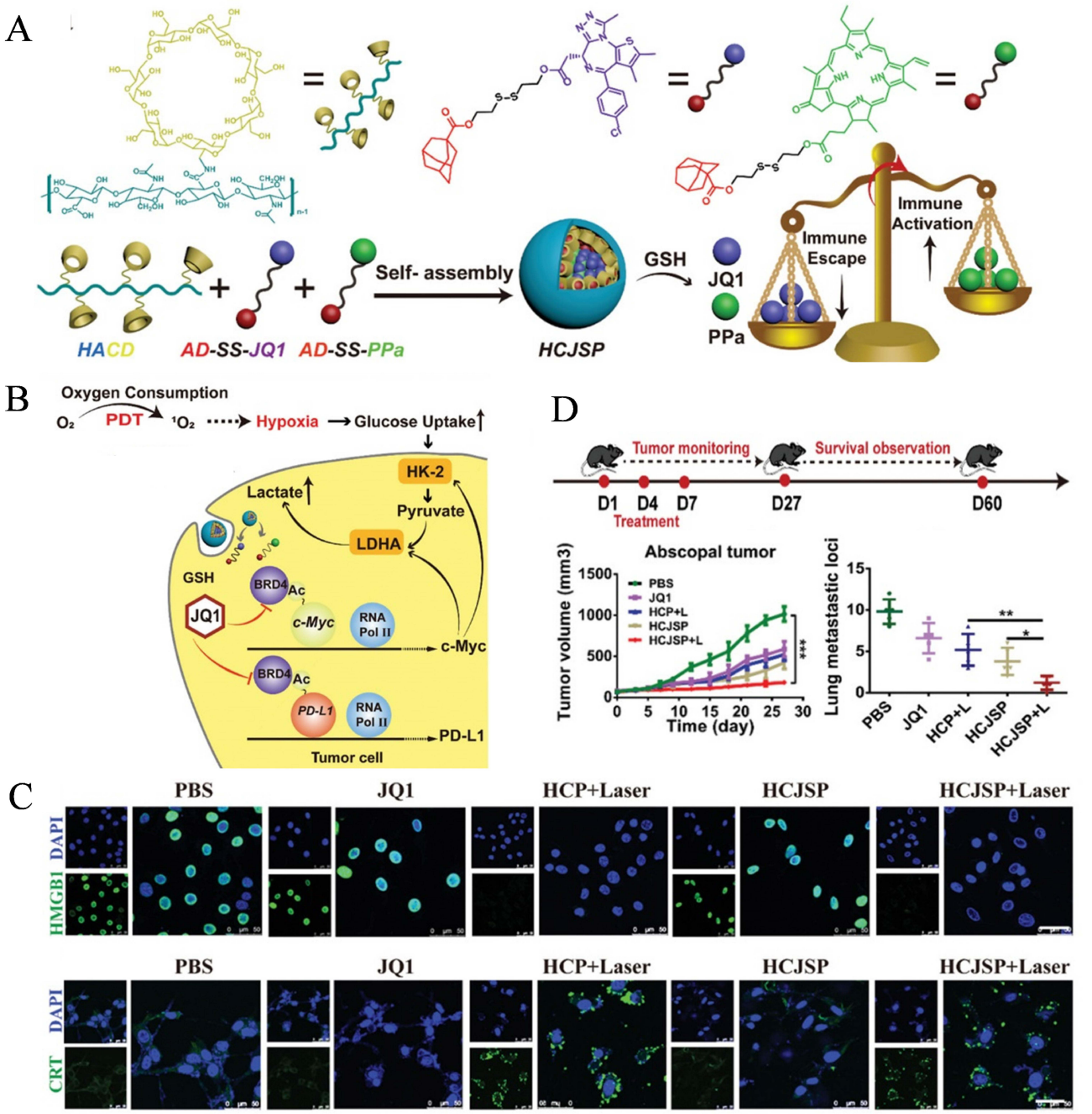

Figure 9 (**A**) Schematic illustration of the HCJSP prodrug nanoparticle prepared via the host–guest interaction between HA-CD and AD-SS-JQ1 and AD-SS-PPa. (**B**) BRD4i JQ1 can relieve PDT-promoted glycolysis and immunosuppressive tumor microenvironment by impeding the transcription of c-Myc and the downstream genes of the c-Myc pathway, including HK-2 and LDHA. Meanwhile, JQ1 can specifically downregulate IFN-γ-inducible PD-L1 expression on the surface of the tumor cells for combating PDT-inducible adaptive immune evasion. (**C**) Membrane exposure of CRT and extracellular efflux of HMGB1 as well-known hallmarks of ICD were determined in Panc02 cells in vitro. Scale bar: 50 μm. (**D**) Biodistribution and antitumor effect of the prodrug nanoparticles in vivo (n=3, *p < 0.05, **p < 0.01, and ***p < 0.001). Reprinted from Sun F, Zhu Q, Li T, et al. Regulating glucose metabolism with prodrug nanoparticles for promoting photoimmunotherapy of pancreatic cancer. *Adv Sci*. 2021;8(4):2002746. © 2021 The Authors. *Advanced Science* published by Wiley-VCH GmbH.[198]

amplified the release of DAMPs and promoted ICD, ultimately leading to effective tumor suppression and prolonged survival.

Others

Cell membrane bionanotechnology is a novel technique that aims to replicate the properties of cell membranes. This method involves the integration of natural cell membrane properties with those of the inner core material, thereby

preserving the original physicochemical characteristics of the nanoparticles. By harnessing the functionalities of proteins and polysaccharides present on the cell membrane surface, this approach enables the nanoparticles to evade immune system attacks, leading to enhanced biocompatibility.[217] Moreover, it facilitates prolonged circulation and enables targeted delivery within living organisms. Han et al employed mannitol-coated erythrocyte membranes as nanocarriers to encapsulate Plumbagin (PLB), dihydrotanshinone I (DIH), and sodium bicarbonate.[200] The incorporation of DIH-induced ROS synergistically potentiated the ICD effects of PLB, resulting in significantly enhanced efficacy of hepatocellular carcinoma (HCC) immunotherapy. Furthermore, it has been observed that the amount of antigens present on tumor cell membranes is often insufficient to adequately activate APCs. In order to overcome this limitation, Pan et al[69] developed a hybrid mimetic nanoplatform called MGTe, which combined tumor cell membranes (TM) with bacterial outer membranes (BM). This innovative platform aimed to amplify the activity of glutathione (GSH)-modified Te nanoparticles (GTe) by enhancing APC maturation and stimulating CTLs, thereby triggering an antitumor immune response.

Application of Organic-Inorganic Hybrid Nanocarriers in Enhancing the Antitumor Effect of ICD

Hybrid materials formed through the self-assembly or clustering of organic ligands and metal ions, facilitated by ligand bonding, have emerged as promising candidates for drug delivery applications, particularly in PDT, RT, and CDT.[218,219] These materials offer a combination of advantageous properties from both organic and inorganic components. Among them, MOFs have demonstrated great potential in PDT. Nanoscale metal-organic frameworks (nMOFs) are nanocomposites consisting of metal ions and organic ligands. These materials possess a unique crystalline structure with tunable pore sizes, diverse chemical compositions, and various topologies. As a result, nMOFs serve as versatile platforms for drug encapsulation, macromolecule loading, and PDT, among other biomedical applications. One notable advantage of nMOFs is their ability to directly incorporate PS as building blocks, enabling high loading capacity without self-quenching. Moreover, the porous nature of nMOFs facilitates the diffusion of ROS, thereby enhancing the efficiency of PDT compared to other nanoparticle formulations. Ni et al used Hf-DBP nMOFs for radiotherapy to enhance the radiotherapy-induced ICD effect by surface modification of the toll-like receptor-7 (TLR-7) agonist imiquimod and an anti-CD47 antibody (referred to as IMD@Hf-DBP/αCD47).[73] NMOFs-based radiotherapy induces the ICD effect by exposing CRT to the surface of tumour cells as an “eat-me“ signal that generates ROS and releases anti-cd47 antibodies to block the ”do not-eat-me” signalling pathway and promote antigen presentation. At the same time, the TLR-7 agonist imiquimod polarises M2 macrophages into pro-inflammatory (anti-tumour) M1 macrophages, reversing the immunosuppressive microenvironment, significantly enhancing the therapeutic efficacy of tumour eradication. Even so, IMD@Hf-DBP/αCD47 alone only inhibited in situ tumour growth, and in combination with an anti-PD-L1 immune checkpoint inhibitor resulted in complete ablation of both primary and distant tumours in CT26 colorectal homozygous mice. Shao et al reported the development of nanoparticles, denoted as TPZ/UCSs, consisting of UCNP and a porphyrin-based MOF.[81] The core-shell structure of TPZ/UCSs facilitated efficient energy transfer from UCNP to the PS, resulting in enhanced NIR photoactivation efficiency. Additionally, the porous structure of the MOF, when loaded with TPZ, enabled activated chemotherapy in response to hypoxia, thereby achieving a synergistic effect through combined chemical-photodynamic therapy.

In recent years, the use of microorganisms including bacteria, fungi, actinomycetes, and yeasts has gained significant attention for the synthesis of nanoparticles.[220] This approach offers a sustainable alternative to conventional chemical synthesis methods, which often require toxic reagents and high energy input. Numerous studies have demonstrated the biosynthesis of metal nanoparticles using various cell lines, such as HeLa (human cervical cancer), MCF-7 (human breast cancer), SKNSH (human neuroblastoma), HEK-293 (human embryonic kidney), and MCF10 (epithelial cells).[221] Qin et al proposed a novel strategy involving the use of tumor cells as a nanoplatform for the synthesis of AuNPs and subsequent formulation of biomimetic cargo-carrying vesicles.[222] In their study, mouse colorectal cancer cells MC38 were employed as the parental cells for generating tumor cell-derived AuNPs. The synthesized AuNPs, referred to as Au@MC38, retained the bioinformation of the original cells and exhibited excellent homologous targeting ability and

biocompatibility. Notably, Au@MC38 demonstrated the ability to amplify irradiation-induced DNA damage and ROS production. This amplification effect facilitated the induction of ICD in tumor cells and triggered an immune response.

Application of Carrier-Free Nanoformulations in Enhancing ICD Antitumor

Conventional carrier-assisted drugs present potential therapeutic risks due to their intricate preparation process, limited drug loading capacity, poor degradability, and propensity for inflammatory irritation. In recent years, self-delivery systems have emerged as promising candidates for clinical therapy by capitalizing on the chemical structures of specific drugs. Due to the production of various reducing substances by tumor cells, the efficacy of RT is greatly diminished as these substances counteract the oxidative environment by quenching free radicals. Hence, the use of high Z-element X-rays alone for RT sensitization is not satisfactory. To overcome this challenge, Huang et al developed a strategy by uniformly incorporating hemin into Gadolinium-based nanoparticles (Gd-NCPs) through carboxyl and conjugated π-bonds, resulting in multifunctional H@Gd-NCPs (Figure 10).[71] In the presence of H_2O_2, H@Gd-NCPs exhibited

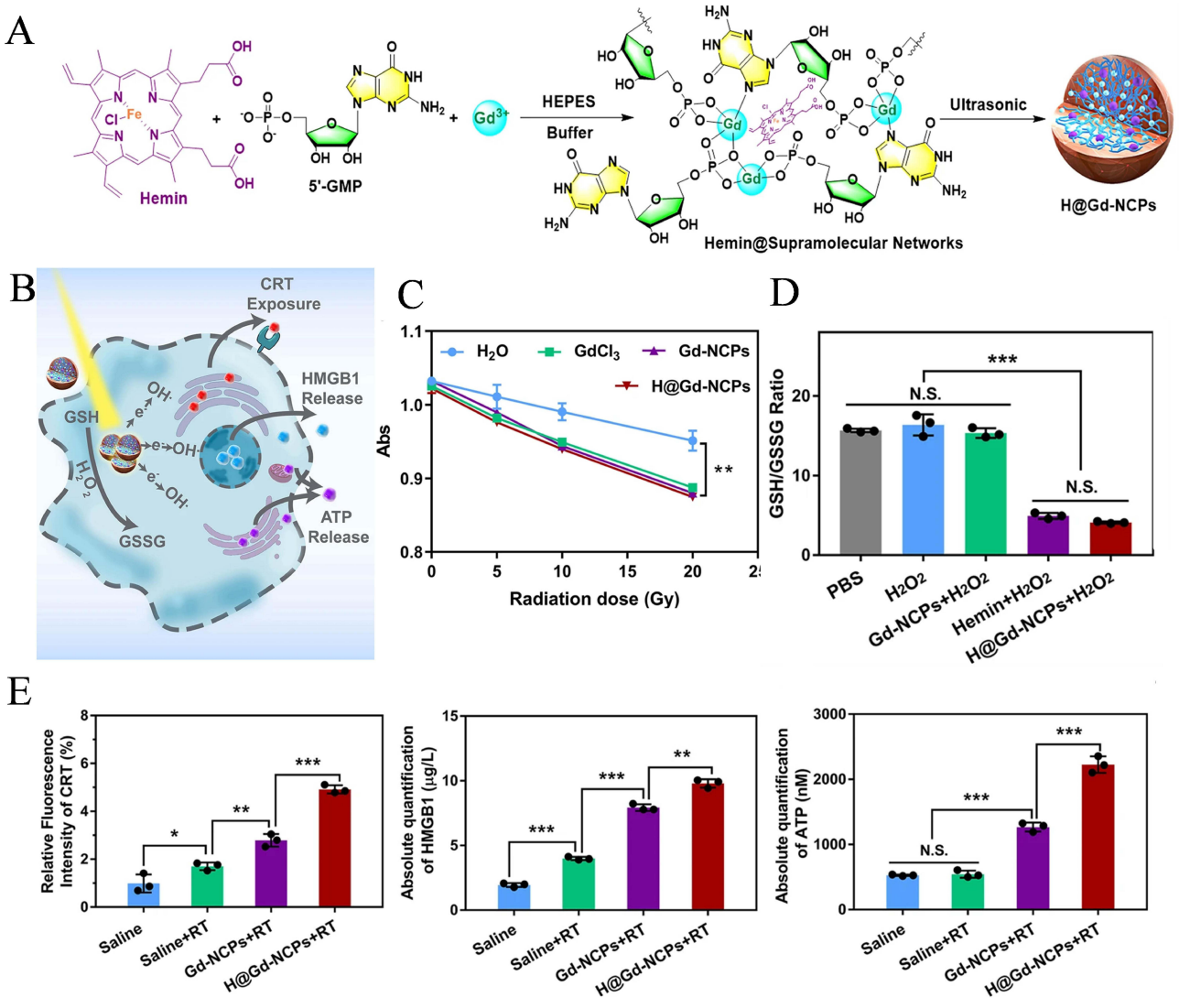

Figure 10 (**A**) Schematic illustration of the preparation of nanoscale coordination polymers H@Gd-NCPs. (**B**) The mechanism of H@Gd-NCPs for radiosensitization via amplifying intracellular oxidative stress to potentiate checkpoint blockade immunotherapies. (**C**) Gd in a free state or nanoparticles could enhance X-ray absorption and energy deposition to promote •OH generation (n = 3, **p = 0.0049). (**D**) H@Gd-NCPs could dramatically decrease the intracellular GSH/GSSG ratio in CT26 colorectal tumor cells ((n = 3, ***p = 0.0001). (**E**) Amplification of oxidative stress could induce potent immunogenicity (exposure of CRT, the release of HMGB1 and ATP) (n=3, *p < 0.05, **p < 0.01, and ***p < 0.001). Reprinted from Huang Z, Wang Y, Yao D, Wu J, Hu Y, Yuan A. Nanoscale coordination polymers induce immunogenic cell death by amplifying radiation therapy mediated oxidative stress. *Nat Commun*. 2021;12(1):145. Creative Commons.[71]

Hemin's peroxidase-like activity and had the ability to scavenge glutathione (GSH). This led to enhanced cellular oxidative stress, subsequently inducing ICD and the release of DAMPs, including HMGB1. The released DAMPs, in turn, activated DCs and stimulated a systemic anti-tumor immune response. In a 4T1 metastatic breast cancer model, the combination of H@Gd-NCPs and RT significantly prolonged the survival of mice by synergizing with the Treg cell-targeting antibody αCTLA-4. Additionally, the introduction of Fe^{2+} into the system facilitated the Fenton reaction, where Fe^{2+} catalyzed the conversion of H_2O_2 into highly toxic·OH and oxygen.[223] This not only relieved tumor hypoxia but also enabled tumor CDT. Furthermore, Fe^{2+} had the ability to reverse the phenotype of TAMs from M2 to M1, effectively altering the tumor immunosuppressive microenvironment (TIM) and activating an anti-tumor immune response.[224] Drawing inspiration from the crucial role of ATP as an "eat-me signal" in ICD, Zhang et al developed a multifunctional ICD amplifier for chemo-sensitizing immunotherapy.[148] They modified the D-ribose unit of ATP and co-assembled it with DOX and ferrous ions (Fe^{2+}) to form a nano-amplifier (PADO-Fe) through π-π stacking and coordination effects. PADO-Fe amplified the cascade effect of CDT-induced ICD by enhancing the "find-me signal", increasing DC recruitment and maturation, and activating the immune response not only in the primary tumor but also in distant tumors.

Conclusion and Perspective

The limited immunogenicity of tumor cells presents a challenge for the widespread application of immunotherapy. In response to this limitation, the induction of ICD has been proposed as a potential solution. Various studies have demonstrated that the induction of ICD can lead to improved anti-tumor efficacy. The use of ICD inducers has shown promise in enhancing the effectiveness of cancer treatment in both preclinical and clinical settings. To overcome the limitations associated with individual ICD inducers, the combination of these agents with functionalized nanoparticles utilizing NDDSs is being explored as a promising strategy to enhance cancer therapy efficacy.[225,226] The unique properties of nanomaterials can serve as versatile tools, such as carriers, stimuli-responsive agents, and drug release modifiers, to manipulate the tumor immune microenvironment and promote or enhance the induction of ICD in tumor cells. The future directions of this field may be as follows.

It is imperative to recognize that existing ICD inducers represent only a fraction of the potential in this area, and efforts to develop more efficacious inducers should continue to advance. Exploring a clear mechanism between the ICD process and the immune response helps us to better design target-oriented nanobiomaterials. For instance, strategies involving the combination of iron death and lipid peroxidase have been explored to enhance the release of DAMPs and promote a cascading chain reaction.[226] Many researchers suggest that employing nanotechnology-based multimodal synergistic therapies to induce or augment ICD holds substantial promise for improving cancer treatment outcomes.[225,226] Current strategies involve integrating immunotherapy with ICD inducers, such as combining PTT with immunomodulatory agents like checkpoint inhibitors,[227] IDO-1 inhibitors,[228] and immune adjuvants,[229] which have demonstrated notable therapeutic efficacy in clinical settings. Furthermore, the use of specific nanomaterials that respond to external stimuli, such as light, heat, and magnetism, allows for controlled drug release, facilitating precise drug delivery and localized amplification of ICD efficacy. These innovative approaches hold significant promise for the advancement of future ICD inducers.

However, it is important to acknowledge that the commercialization and clinical translation of nanosystems still present challenges that need to be addressed. The efficacy of therapeutic agents in activating and inhibiting ICD heavily relies on the administered dose and timing, including the schedules of other treatments such as radiotherapy and thermal ablation. Therefore, the selection of optimal doses and controlled release strategies for nanoparticles in combination therapies is critical. Furthermore, while many complex nanosystems have been designed to activate or enhance the ICD effect, biosafety, quality control, and scale-up production aspects need to be considered for the clinical implementation of nanosystems. Cell membranes from immune cells, including DCs, macrophages and NK cells, can provide nanoplatforms with immunogenic antigens, functional peptides and recognition receptors to facilitate vaccine delivery and antigen presentation for cancer chemotherapy. To facilitate the clinical translation of nanosystems with ICD-induced effects, the classification of individual tumours and elucidation of tumorigenesis mechanisms can greatly contribute to nanomedicine development and precision therapy.[148] Several nanodelivery systems with ICD inducing effects have been developed, although direct comparisons between these systems have not been made. The photoacoustic cavitation effect, which

generates photoacoustic shock waves and reconstructs them as images of the tumor, enables visualization of the tumor area and the dynamic distribution of nanoprobes.[230] This approach could enhance real-time image guidance and facilitate phototherapy using nanoplatforms.

Given the side effects associated with tumour immunotherapy, we believe that the development of an ICD amplification strategy complemented by immunotherapy holds potential for increasing tumour cure rates and enhancing prognostic outcomes in the future.

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Disclosure

The authors declare no conflicts of interests in this work.

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