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Recent advances in Cell-Membrane Camouflaged Nanoparticles for Cancer

Phototherapy

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Abstract: Phototherapy including photothermal therapy (PTT) and photodynamic therapy (PDT) employs phototherapeutic agents to generate heat or cytotoxic reactive oxygen species (ROS) has garnered particular interests for cancer therapy. However, the main challenges faced by conventional phototherapeutic agents include easy recognition by the immune system, rapid clearance from blood circulation, and low accumulation in target sites. Cell-membrane coating has emerged as a potential way to overcome these limitations, because it has proved that the abundant proteins on the surface of cell membranes can be inherited to the cell-membrane camouflaged nanoparticles. This review summarizes the recent advances in the development of biomimetic cell membrane camouflaged nanoparticles for cancer phototherapy. Different cell-membrane coating approaches are available, and different source of cell membranes including red blood cell (RBC) membrane, cancer cell membrane, platelet membrane, macrophage membrane, stem cell membrane, fibroblast cell membrane and myeloid-derived suppressor cell (MDSC) membrane can be used to coat the nanoparticles. After cell-membrane coating, the photophysical properties of the original phototherapeutic nanoparticles remain nearly unchanged; but, the coated nanoparticles are equipped with additional physiological features including immune escape, in vivo prolonged circulation time, or homologous targeting, depending on the source of cells. Moreover, the coated cell membrane could be ablated from phototherapeutic nanoparticles under laser irradiation, leading to the release of encapsulated drugs and further synergetic therapy. By combining other supplementary agents to normalize tumor microenvironment, cell membrane coating could further enhance the cancer therapeutic efficacy. Challenges and perspectives of cell membrane camouflaged nanoparticles in cancer phototherapy are discussed.

1. Introduction

Cancer has been one of the major life-threatening diseases to the human being for centuries.^[1] The conventional cancer therapies include surgery, chemotherapy, and radiotherapy.^[1c] Surgery is unable to completely resect all the tumor tissues resulting in a high recurrence rate, chemotherapy often lacks selectivity to cancer cells and causes serious side effects to normal organs, and radiotherapy often damages healthy cells and tissues near cancer cells.^[2] In recent years, new treatment modalities with enhanced efficacy and reduced adverse effects have received considerable attention.^[3] One of the examples is phototherapy, including photothermal therapy (PTT) and photodynamic therapy (PDT).^[4] Phototherapy is a noninvasive approach that relies on the phototherapeutic agents in conjunction with light irradiation to selectively kill cancer cells with minimal toxicity to normal tissues in the dark.^[5] PTT employs photoabsorbing agents to generate heat under near-infrared (NIR) laser irradiation, resulting in cancer cells thermal ablation.^[6] PDT involves the generation of cytotoxic reactive oxygen species (ROS), such as singlet oxygen ($^1\text{O}_2$), from photosensitizers (PSs) under the light of a specific wavelength to oxidize adjacent biomolecules and consequently kill cancer cells.^[7] In addition to small molecule agents, many nanomaterials including gold nanostructures,^[8] silver nanoparticles,^[9] carbon nanotubes,^[10] magnetic nanoparticles,^[11] two-dimensional materials,^[12] quantum dots,^[13] porphyrins,^[14] metal organic frameworks (MOF),^[15] NIR dyes encapsulated nanoparticles^[16] and semiconducting polymer nanoparticles (SPNs)^[17] have been widely developed for PTT and PDT.

With innate non-toxicity in the dark and light-induced toxicity, nanoparticles-based PTT and PDT have improved therapeutic specificity and reduced toxic adverse effects as compared with the traditional chemotherapy and radiotherapy.^[18] However, there are several disadvantages that limit the application of nanoparticles-based PTT or PDT in clinics. For example, once injected into the body, nanoparticles are often recognized as intruders by

immune system, leading to an immune response against nanoparticles.^[19] Meanwhile, nanoparticles are likely to be picked up and cleared out by the mononuclear phagocyte system (MPS) during blood circulation, resulting in shortened circulation time and limited therapeutic effects.^[20] At last, although non-targeting nanoparticles can passively target the tumor through enhanced permeability and retention (EPR) effect,^[21] it is estimated that only 0.7% (median) of the administered dose of nanomedicine is delivered to the tumor sites, while the rest is accumulated in healthy organs.^[22] Thus, surface modification of nanoparticles is a common strategy to achieve immune escape, prolong blood circulation and enhance tumor targeting.^[23] Among many coating materials, poly (ethylene glycol) (PEG) coating of nanoparticles is the current gold-standard.^[24] However, it is found that anti-PEG immunoglobulin M antibodies are induced after the first injection of PEG-modified nanoparticles, leading to the rapid clearance of the second dose of PEGylated nanoparticles from blood circulation.^[25]

Recently, surface modification of nanoparticles using cell membrane is an emerging strategy to endow nanoparticles with excellent biointerfacing property, which has attracted many attentions in nanomedicine field, including drug delivery,^[26] imaging,^[27] detoxification,^[28] vaccination^[29] and phototherapy.^[30] The cell membrane camouflaged nanoparticles are composed of two parts: a synthetic nanoparticle core and a layer of the natural cell membrane.^[31] The synthetic nanoparticle cores could be inorganic/organic nanoparticles with different biological and therapeutic functionalities, while the layer of natural cell membrane could innately mimic the antigenic diversity of the source cells, leading to a series of source cells-relevant functions such as immune escape and long circulation.^[32]

Herein we summarize recent advances in the development of biomimetic cell membrane camouflaged nanoparticles for cancer phototherapy (**Figure 1**). The sources of natural cell membranes, the type of nanoparticles core, and their coating approaches are summarized and compared in **Table 1**. The advantages of nanoparticles camouflaged with RBC membrane, cancer cell membrane, platelet membrane, macrophage membrane, stem cell membrane,

fibroblast cell membrane or myeloid-derived suppressor cell (MDSC) membrane are sequentially discussed. The immune escape ability, in vivo prolonged blood circulation time, homologous tumor targeting ability and the phototherapy efficacy of cell membrane camouflaged nanoparticles are discussed in details and compared with the uncoated original nanoparticles. At last, potential challenges and perspectives of developing cell membrane camouflaged phototherapeutic nanoparticles are covered.

Figure 1. Cell membrane camouflaged nanoparticles for cancer phototherapy. A series of cell membranes are used to coat onto the surface of phototherapeutic nanoparticle cores. RBC membrane features the evasion of immune clearance of phototherapeutic nanoparticles. Cancer cell membrane endows phototherapeutic nanoparticles with immune escape and homologous targeting abilities. Platelet membrane facilitates the evasion of immune clearance and specific adhesion to injured tumor tissues of phototherapeutic nanoparticles. The other cell membranes such as macrophage membrane, stem cell membrane, fibroblast cell membrane and MDSC membrane offer many unique properties including immune evasion and tumor targeting functionality to phototherapeutic nanoparticles.

Table 1. Summary of the sources of cell membranes, nanoparticle cores and coating approaches of cell membrane camouflaged nanoparticles for cancer phototherapy (CPTT: chemo-photothermal therapy; CPDT: chem-photodynamic therapy).

Source of cell membranes		Phototherapy type	Nanoparticle cores	Coating approach	References
RBC membrane		PTT	Gold nanoparticles	Top-down	33
			Fe ₃ O ₄ magnetic nanoparticles	Microfluidic electroporation	35
			Fe ₃ O ₄ magnetic nanoclusters	Top-down	39c
			Gold nanocages	Top-down	40
			Melanin nanoparticles	Top-down	41
			Polypyrrole nanoparticles	Top-down	42
		CPTT	DiR-loaded membranes / PTX-loaded polymeric nanoparticles	Top-down	43
			DOX-loaded Prussian blue/manganese dioxide nanoparticles		45a
			DOX-loaded mesoporous Prussian blue nanoparticles		45b
		PDT	Hypocrellin B-loaded magnetic mesoporous silica nanoparticles	Top-down	46
			ICG and perfluorotributylamine-loaded HSA nanoparticles		48
			Methylene blue-loaded Hemoglobin and polydopamine complexes		52
		CPDT	Methylene blue and cisplatin loaded gelatin nanogel	Top-down	53
			PTX and 5,10,15,20-tetraphenylchlorin loaded polymeric nanoparticles		54
	MCF-7 cells	PTT	ICG-loaded PLGA nanoparticles	Top-down	56
	4T1 cells	CPTT	DOX-loaded gold nanoclusters	Top-down	57
	RBC and B16		DOX-loaded CuS nanoparticles	Top-down	34

Cancer cell membrane	hybrid cells				
	HeLa cells	PDT	Al (III) phthalocyanine chloride tetrasulfonic acid loaded MOF	Top-down	58
	4T1 cells		Catalase and glucose oxidase loaded porphyrin MOF	Top-down	59
Platelet membrane		PTT	Fe ₃ O ₄ magnetic nanoparticles	Top-down	65
			Gold nanorods	Microfluidic electroporation	66
Macrophage membrane		PTT	Gold nanoshells	Top-down	70
Stem cell membrane		PDT	ZnPC and MC540 loaded silica shell coated UCNP	Top-down	73
Fibroblast cell membrane		PTT&PDT	SPNs	Top-down	77
MDSC membrane		PTT	Fe ₃ O ₄ magnetic nanoparticles	Top-down	85

Table 2. Summary of the differences, advantages and disadvantages of different cell membrane camouflaged nanoparticles in cancer phototherapy.

Different source of cell membranes	Common features	Unique advantages	Disadvantages
RBC membrane	Abundant availability; Facile extraction and coating to nanoparticles; In vivo immune evasion;	Long circulation time;	Low ability for active targeting to tumor
Cancer cell membrane		Homologous targeting to source cancer cells	Shorter circulation time than RBC
Platelet membrane		Targeting to specific tumors with overexpression of surface markers “CD62p, CD47, and CD44 receptors”; Specific adhesion to injured vessels or tumor tissues.	Only targeting to limited types of tumor;

Macrophage membrane		Targeting to specific tumors with overexpression of surface marker “CD49d”, such as MCF-7 tumor and 4T1 tumor.	Only targeting to limited types of tumor
Stem cell membrane		Tumor tropism	Shorter circulation time than RBC; Low specificity
Fibroblast cell membrane		Homologous targeting to cancer-associated fibroblasts	Part targeting to normal fibroblast
MDSC membrane		Active targeting to MDSC-riched tumor	Immunosuppression towards tumor

2. Cell Membrane Coating Approaches

The cell membrane camouflaged nanoparticles could be prepared through different approaches including top-down approach and microfluidic electroporation approach (**Figure 2**). The top-down approach is a well-reported method to obtain the cell membrane camouflaged nanoparticles.^[32-33] Briefly, purified cells are first subjected to initial hypotonic treatment to remove their intracellular contents. Then, the emptied cells are washed and extruded through polycarbonate porous membranes, generating cell membrane-derived vesicles. To obtain cell membrane camouflaged nanoparticles, cell membrane-derived vesicles are then fused with nanoparticles by mechanical extrusion through ~100 nm pores for several times. The mechanical force imposed by the extrusion process facilitates the fusion of cell membrane vesicles over nanoparticles, leading to the cell membrane camouflaged nanoparticles (Figure 2a). The hybrid cell membrane coating nanoparticles could be obtained through similar coating technology.^[34] The membrane vesicles are first derived from different cells and then fused together by sonication. The obtained fused membranes are coated onto a single nanoparticle to

combine the functionalities from both cell membranes through sonication (Figure 2b). More recently, a microfluidic chip system for electroporation has been developed to fabricate cell membrane camouflaged nanoparticles.^[35] The reported system comprises five different parts: two inlets, a Y-shaped merging channel, an S-shaped mixing channel, an electroporation zone and an outlet. The nanoparticles and cell-membrane derived vesicles are injected into this system through inlets, and completely merged and mixed through the Y-shaped merging channel and S-shaped mixing channel. In the electroporation zone, the electric pulses between two electrodes could promote the entry of nanoparticles into cell-membrane derived vesicles and further obtain the cell membrane camouflaged nanoparticles through the outlet (Figure 2c).

Figure 2. Schematic illustration of the preparation process of cell membrane camouflaged nanoparticles. (a) Top-down approach. Membrane vesicles are first derived from cells. Then the membrane vesicles are coated onto the surface of nanoparticles through extrusion. (b) Top-down approach. Membranes vesicles are derived from different cells and then fused together by sonication. The obtained fused membranes are coated onto the surface of nanoparticles

through sonication. (c) Microfluidic electroporation approach. Membrane vesicles are first derived from cells. Then nanoparticles and membrane vesicles are completely merged and flow through the electroporation zone. The electric pulses between two electrodes promote the entry of nanoparticles into cell-membrane derived vesicles to obtain the cell membrane camouflaged nanoparticles. Panel a reprinted with permission from Ref. [33]. Copyright 2013, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

3. RBC Membrane Camouflaged Nanoparticles

RBCs, also known as erythrocytes, are the most abundant cells in the blood.^[36] The retention time of RBC is up to 120 days in humans.^[37] The membrane of RBCs is an ideal surface modification material for nanoparticles, because there are many natural “self-markers” including CD47 proteins, various membrane proteins, glycans, acidic sialyl moieties on the membrane surface of RBCs, which can decrease uptake of nanoparticles by reticuloendothelial system (RES), provide the nanoparticles with long circulation time and enable nanoparticles to escape immunogenic clearance.^[38] The RBC membrane camouflaged nanoparticles are the first reported cell membrane biomimetic system, and currently the most popular natural carriers in biomedical applications.^[32, 39]

It has been reported that RBC membrane coating approach improved phototherapy.^[33, 39a] In the first study, Zhang group demonstrated the coating of natural RBC membranes on the surface of gold nanoparticles using a top-down approach.^[33] After membrane fusion, a slight increase in particles size from 70 to 86 nm and an increase in surface zeta potential of particles from -42 to -35 mV were observed (**Figure 3a**). A spherical core-shell structure with AuNPs as the thin shell was also visualized by transmission electron microscopy (TEM) (**Figure 3b**). After coating, the RBC cell membrane precluded the binding between the thiolated fluorescent dye and the gold nanoparticle cores, and subsequently restored the fluorescence emission (**Figure**

3c). Using polystyrene microspheres conjugated with two distinct anti-CD47 antibodies, it was demonstrated that the RBC membrane was not only coated on the surface of AuNPs but also arranged in the right-side-out orientation (Figure 3d). At last, RBC@AuNPs significantly evaded macrophage uptake compared to the original AuNPs, which was beneficial for reducing in vivo clearance (Figure 3e&f).

Figure 3. (a) Diameters and surface zeta potentials of AuNPs before and after RBC membrane coating. (b) The representative TEM image of RBC@AuNPs under negative staining with uranyl acetate. (c) Fluorescence spectrum of i) FITC-thiol, ii) FITC-thiol mixed with RBC@AuNPs, and iii) FITC-thiol mixed with bare AuNPs. (d) An antibody binding study. TEM images of RBC@AuNPs incubated with i) anti-CD47 (exoplasmic) antibody-modified polystyrene microspheres and ii) anti-CD47 (cytoplasmic) antibody-modified polystyrene

microspheres. The bare AuNPs were incubated with iii) anti-CD47 (exoplasmic) antibody-modified polystyrene microspheres and iv) anti-CD47 (cytoplasmic) antibody-modified polystyrene microspheres. Scale bars = 1 μm . (e) RBC membrane coating inhibits macrophage uptake. Bright field microscopic images of J774 murine macrophage cells incubated for 30 min in i) culture medium, ii) RBC@AuNPs and iii) the original AuNPs. (f) Quantitative analysis of macrophage uptake of RBC@AuNPs and the original AuNPs. Reprinted with permission from Ref. [33]. Copyright 2013, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

In order to validate in vivo PTT application of RBC-membrane camouflaged nanoparticles, Yang and co-workers fabricated gold nanocages (AuNCs) through a galvanic replacement between silver nanocubes and HAuCl_4 .^[40] The surface of AuNCs was wrapped using poly(vinylpyrrolidone) (PVP, ~50000) to obtain PVP@AuNCs. RBC@AuNCs were obtained by fusing the RBC-membrane-derived vesicles and PVP@AuNCs based on the top-down approach (**Figure 4a**). Because the coating of RBC membrane on AuNC surface may hinder the heat diffusion into water environment during laser irradiation, the photothermal maximum temperature of RBC@AuNCs was slightly lower than that of PVP@AuNCs under the same condition (**Figure 4b**). With laser irradiation at 850 nm for 5 min, both average size and zeta potential of RBC@AuNCs changed towards those of PVP@AuNCs, demonstrating that laser irradiation partially ablated the RBC membrane of RBC@AuNCs. This phenomenon facilitated the heat diffusion during photothermal conversion and afforded the faster and larger temperature rises generated by NIR-irradiated RBC@AuNCs. Through heating and cooling in four cycles, the maximum temperatures of PVP@AuNCs remained nearly the same, yet the maximum temperatures of RBC@AuNCs was gradually close to that of PVP@AuNCs (**Figure 4c**). These results indicated that repeated laser irradiation hardly affects the AuNC cores of RBC@AuNC, but could damage the RBC membrane coating, affording more effective photothermal conversion for in vivo cancer treatment. With the help of RBC-membrane coating,

RBC@AuNCs showed dramatically enhanced blood retention time in comparison with PVP@AuNCs (Figure 4d). The circulation half-life of RBC@AuNCs was calculated to be 9.5 h, which is much longer than that for PVP@AuNCs (1 h). Due to the excellent circulation half-life, RBC@AuNCs exhibited higher accumulation (8.34% ID/g) in the tumor at 24 h in comparison with PVP@AuNCs (4.37% ID/g) (Figure 4e). Moreover, RBC@AuNCs displayed a significantly decreased accumulation in liver and lung in comparison with PVP@AuNCs due to the absence of immunogenic clearance after RBC-membrane coating (Figure 4e&f). Obviously, RBC@AuNCs have combined the superior photothermal properties of the AuNC cores with long in vivo circulation lifetime derived from RBC membrane, leading to significantly increased tumor accumulation and enhanced PTT efficacy compared to PVP@AuNCs (Figure 4g&h).

Figure 4. (a) Schematic illustration of the preparation procedure of RBC membrane camouflaged gold nanocages (RBC@AuNCs), and PTT in mice. (b) The temperature of RBC@AuNCs and PVP@AuNCs as a function of laser irradiating time and laser power intensity (850 nm laser). Controls are PBS irradiated with an 850 nm laser at 2.0 W cm^{-2} . (c) The photothermal heating and natural cooling cycles of PVP@AuNCs and RBC@AuNCs (850 nm laser, 1 W cm^{-2}). (d) Blood retentions of RBC@AuNCs and PVP@AuNCs for 24 h. (e,f) In vivo biodistribution of PVP@AuNCs and RBC@AuNCs at (e) 24 h and (f) 48 h after injection. (g) IR thermal images of tumor-bearing mice under laser irradiation for different time after injected with PVP@AuNCs and RBC@AuNCs (850 nm laser, 1 W cm^{-2}). (h) Tumor growth curves of mice after injection of PBS, PVP@AuNCs, and RBC@AuNCs with laser irradiation (850 nm laser, 1 W cm^{-2}). * and ** indicate $p < 0.05$ and $p < 0.01$, respectively. Reprinted with permission from Ref. [40]. Copyright 2014, American Chemical Society.

In another example, a microfluidic electroporation approach instead of extrusion was developed to fabricate RBC membrane camouflaged Fe_3O_4 magnetic nanoparticles (RBC@MNs).^[35] The obtained RBC@MNs exhibited the capability for both tumor magnetic resonance imaging (MRI) and PTT of tumors under irradiation due to the effective magnetic and photothermal conversion effects of the magnetic nanoparticle cores and the long blood retention and circulation time of the RBC membrane. Moreover, it was demonstrated that the RBC@MNs fabricated by microfluidic electroporation approach showed significantly better antitumor efficacy than that prepared by conventional extrusion owing to the complete cell membrane coating. Similarly, RBC membrane was used to coat melanin nanoparticles^[41] and polypyrrole nanoparticles^[42] for improved PTT.

Furthermore, because cell membrane could be ablated from photothermal nanoparticles, the RBC membrane camouflaged photothermal nanoparticles were used for controlled drug delivery upon laser irradiation. Li and co-workers reported a new NIR-responsive RBC

membrane camouflaged nanoparticle for a synergetic CPTT to treat tumor.^[43] A lipophilic membrane dye 1,1-dioctadecyl-3,3,3,3-tetramethylindotricarbocyanine iodide (DiR) was embedded into the lipid bilayer of RBC membrane to obtain DiR-loaded RBC membrane (RBC-DiR). Paclitaxel (PTX), was loaded in 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) incorporated polymeric nanoparticle cores to obtain PTX-loaded polymeric nanoparticle cores (PTX-PN). The RBC-DiR@PTX-PN was then fabricated by coating DiR-RV onto the surface of PTX-PN using the top-down approach(**Figure 5a**). Under 808 nm laser irradiation for 5 min, the structure of RBC-DiR@PTX-PN was destroyed (**Figure 5b**), thus the PTX release was accelerated, leading to 45% PTX release within 30 min (**Figure 5c**) and 100% PTX release after 72 h (**Figure 5d**). The fluorescence of DiR in the RBC-DiR@PTX-PN was used for in vivo tumor imaging. Due to the existence of RBC membrane, RBC-DiR@PTX-PN showed longer circulation lifetime that was 12.3-fold higher than that of free dye. With laser irradiation, tumor accumulation of RBC-DiR@PTX-PN was 2.1-fold higher than that without laser irradiation (**Figure 5e**). Thereby, the RBC-DiR@PTX-PN showed a synergetic chemo-photothermal therapy, with a complete inhibition of primary tumor and a 98% suppression of lung metastasis in vivo, demonstrating a versatile nanosized drug delivery system for cancer therapy. Similarly, RBC membrane was used to coat other photothermal agents such as indocyanine green (ICG),^[44] and Prussian Blue^[45] for combined cancer chemo-phototherapy.

Figure 5. (a) Schematic illustration of the NIR-triggered drug release of the RBC biomimetic nanoparticles (RBC-DiR@PTX-PN). (b) Representative TEM images of RBC-DiR@PTX-PN before (top) and after (bottom) laser irradiation (808 nm, 3 W cm⁻²). Scale bar = 50 nm. (c,d) In vitro drug release behavior from RBC-DiR@PTX-PN at 37 °C, 43 °C water bath, and 37 °C after laser irradiation for 5 min and monitoring for (c) 30 min and (d) 72 h, respectively. (808 nm, 3 W cm⁻²) (e) In vivo biodistribution of PTX in Taxol, and RBC-DiR@PTX-PN with or without NIR laser irradiation at 0.5, 1, 4, 8, and 24 h after injection, respectively. (808 nm, 3 W cm⁻²) ***p* < 0.01. Reprinted with permission from Ref. [43]. Copyright 2016, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

To enhance tumor accumulation of PS molecules, cell membrane coating approach has been developed to improve PDT efficacy in a similar strategy as that for PTT. For instance, magnetic mesoporous silica nanoparticles (MMSNs) adsorbed with Hypocrellin B (HB), a type of PS, were subsequently cloaked with RBC membrane.^[46] Using a $^1\text{O}_2$ detecting sensor, 9,10-anthracenediylbis(methylene)dimalonic acid (ABDA), it was demonstrated that HB-loaded RBC@MMSNs could effectively generate $^1\text{O}_2$ under irradiation of 560 nm light. Upon laser irradiation, HB-loaded RBC@MMSNs exhibited successful in vitro PDT after incubation with HeLa cells. In vivo, the accumulation of RBC@MMSNs in the tumor was higher than that of MMSNs, due to the long circulation lifetime of the RBC membrane. With the help of magnetic field (MF), RBC@MMSNs showed the highest accumulation in tumor among these groups, due to the magnetic properties of RBC@MMSNs. Thus, in the presence of laser irradiation and MF, HB-loaded RBC@MMSNs could completely suppress tumor growth with negligible side effects.

A major challenge in PDT is that PDT intrinsically requires oxygen to convert to ROS. Because the internal tumor microenvironment is hypoxic, the therapeutic efficacy of the treatment is limited by the lack of oxygen.^[47] To address this issue, oxygen self-enriched human serum albumin (HSA) nanoparticles encapsulating ICG and perfluorotributylamine (PFTBA) were fabricated, and RBC vesicles extracted from RBC membranes were coated around the nanoparticles to obtain biomimetic RBC nanoparticles (RBC@IPH).^[48] The obtained nanoparticles showed reduced uptake into macrophages and long in vivo circulation halftime due to the coating of RBC membrane, and the enhanced $^1\text{O}_2$ production due to the addition of PFTBA in nanoparticles, leading to enhanced in vivo PDT.

Hemoglobin (Hb), the oxygen-transport metalloprotein abundant in RBCs (~270 million Hb molecules in each RBC), has been widely explored as the oxygen supplier in biomedical applications.^[49] However, Hb is easy to be oxidized during in vivo circulation, especially in the environment enriched of H_2O_2 , resulting in the decline of oxygen-carry capacity, accompanied

by the generation of toxic substances.^[50] The special antioxidative enzymes in natural RBCs such as catalase (CAT) and superoxide dismutase (SOD) can counteract this adverse effect.^[51] Based on this, Zhang group fabricated a type of artificial RBCs which are rich in Hb for the self-oxygen-supplied PDT.^[52] Through the polymerization of dopamine in the presence of Hb, the Hb and polydopamine (PDA) complexes (PDA-Hb) were formed. PDA in the complexes acts as the antioxidant to protect Hb from oxidant damage. Methylene blue (MB) as the photodynamic agent was absorbed by PDA-Hb complexes to form PDA-Hb-MB. Finally, the RBC membrane derived from nature RBC were coated onto the surface of PDA-Hb-MB to obtain the RBC@PHM (**Figure 6a**). The average mass of Hb per RBC@PHM was ~10-fold higher than that of natural RBC. The oxygen-carrying capability and oxygen-releasing capability at the hypoxia environment of RBC@PHM were found similar with that of Hb (**Figure 6b**). In the presence of PDA, the oxygen-carrying capacity of RBC@PHM was unaffected when pretreated with H₂O₂, while an obvious decline of dissolved oxygen was observed when Hb was pretreated with H₂O₂ (**Figure 6c**). RBC@PHM could generate much more ¹O₂ than MB alone under laser irradiation, indicating the oxygen supply significantly enhanced ¹O₂ generation (**Figure 6d**). Treatment of H₂O₂ had no effect on the ¹O₂ generation efficiency of RBC@PHM, but dramatically affected the ¹O₂ generation efficiency of Hb, demonstrating the antioxidative capability of RBC coating on PDA. The RBC membrane in the RBC@PHM also enabled low immune responses with less uptake by macrophages. Thus, RBC@PHM could effectively generate intracellular ¹O₂ upon laser irradiation in both normoxic and hypoxic environments compared with other control nanoparticles. Therefore, RBC@PHM could successfully ablate cancer cells in vitro with laser irradiation under both normoxic and hypoxic conditions. In vivo, the RBC@PHM efficiently accumulated in the 4T1 tumor site and improved the hypoxia environment through superior antioxidization and admirable oxygen-carrying capability during in vivo circulation, leading to the lowest expression of the hypoxia-

related protein in the tumor site (Figure 6e). Thus, RBC@PHM boosted the PDT efficacy and caused almost complete tumor elimination with minimal systematic toxicity (Figure 6f).

Figure 6. (a) Schematic illustration of RBC@PHM for cancer therapy. (b) The oxygen concentration in PBS after adding oxygen-presaturated Hb, RBC@BSA-PDA, and RBC@PHM with an equivalent content of $4\ mg\ mL^{-1}$ Hb. (c) Relative changes of dissolved oxygen after the addition of H_2O_2 -pretreated Hb or RBC@PHM compared with the non-pretreated controls. (d) 1O_2 detection using RNO assay after different treatments. (e) In vivo immunofluorescence staining of pimonidazole and HIF-1 α in the tumors after different treatments for 24 h. The scale bar = $50\ \mu m$. (f) Relative tumor volume changes during 20 days after different treatments. ($660\ nm$, $0.22\ W\ cm^{-2}$) * and ** indicate $p < 0.05$ and $p < 0.01$,

respectively. Reprinted with permission from Ref. [52]. Copyright 2018, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

ROS generated by PS is not only applied for PDT but also applied to trigger drug release for chemotherapy. To this end, a PS methylene blue (MB) and a chemotherapeutic drug cisplatin (Pt) were loaded into gelatin nanogel core, then coated with RBC membrane to obtain a nanovesicle (RBC@MP).^[53] After confirming the successful coating of RBC@MP through sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and western-blotting analysis, it was demonstrated that the RBC@MP could decrease macrophage uptake when compared to the bare nanogels (MPNGs). Upon laser irradiation for 150s, strong fluorescence intensity was observed indicating the MB and Pt could be rapidly released from RBC@MP, while only slight MB and Pt were released from RBC@MP without laser irradiation. With laser irradiation, RBC@MP caused a remarkable temperature increase and less effective $^1\text{O}_2$ generation compared to MPNGs. This is because MB in RBC@MP is in the aggregation state that preferentially converts light to heat while free MB performs a good fluorescence and photodynamic capability. When incubated with 4T1 cells for 4 h, RBC@MP colocalized with the lysosomes and then entered the cytosol after laser irradiation, leading to efficient cancer cell eradication. In vivo, strong photoacoustic signals were detected in the tumor of RBC@MP-treated mice, while no signal was observed in free drugs-treated mice, indicating the significant accumulation of RBC@MP in the tumor. After continuous laser irradiation, the tumor temperature of RBC@MP-treated mice increased dramatically, leading to the activation of RBC-MP to release MB and Pt. Meanwhile, the released MB could effectively generate $^1\text{O}_2$ upon laser irradiation. Thereby, RBC@MP could successfully restrict primary tumor growth and inhibit the pulmonary metastasis without obvious side effects.

In a similar work, Xie and co-workers reported RBC membrane camouflaged dimeric prodrug nanoparticles for synergistic photodynamic/chemotherapy.^[54] The inner core of the

reported nanoparticle was first prepared by co-encapsulation of ROS-responsive PTX dimer (PTX₂-TK) and PS 5,10,15,20-tetraphenylchlorin (TPC) into copolymer methoxypoly(ethylene glycol)-block-poly(D,L-lactide) (PEG-*b*-PDLLA) through solvent exchange method. Then, the inner core and RBC-membrane derived vesicles were coextruded through 450 nm porous membranes to obtain RBC membrane camouflaged nanoparticles (RBC@M(TPC-PTX)). The core-shell structure of RBC@M(TPC-PTX), the increased size, and changes in zeta potential validated the successful coating of RBC membrane. The SDS-PAGE assay indicated the membrane protein markers were successfully reserved during the preparation of RBC@M(TPC-PTX). Therefore, RBC@M(TPC-PTX) significantly evaded the macrophage uptake compared to naked nanoparticles. It was determined that RBC@M(TPC-PTX) could effectively generate ROS in both solution and HeLa cells. Therefore, upon laser irradiation, the thioketal linker in RBC@M(TPC-PTX) was cleaved by the generated ROS, leading to PTX release and a marked increase of cytotoxicity in vitro by a synergetic therapy of PDT from TPC and chemotherapy from PTX. Notably, a 4.6-times higher local concentration of PTX₂-TK in tumor site of the RBC@M(TPC-PTX) group was observed compared to that of the naked nanoparticles group. Finally, upon laser irradiation, the RBC@M(TPC-PTX) group showed the strongest antitumor effect with no obvious systemic toxicity, due to the significance of cell membrane coating.

4. Cancer Cell Membrane Camouflaged Nanoparticles

RBC membrane camouflaged nanoparticles discussed in the previous section showed reduced macrophage uptake, long circulation time, and evasion of immune clearance. However, RBC membrane does not endow any active targeting ability to tumor. In tumors, cancer cells possess some unique properties such as antigenic display and homologous binding, which are firmly attributed to their plasma membrane proteins on the surface including N-cadherin, galectin-3, or epithelial cell adhesion molecule (EpCAM).^[29, 55] Encouraged by this, nanoparticles surface functionalization with homotypic cancer cell membrane could compete

for the replication of surface antigenic diversity, obtaining immune escape and homologous targeting abilities, which can be leveraged for highly specific and effective cancer therapy.^[29]

The homologous targeting ability of cancer cell membrane camouflaged nanoparticles was first demonstrated by Zhang group using melanoma cells membrane-coated PLGA nanoparticles.^[29] The authors demonstrated that cancer cell membrane camouflaged nanoparticles showed much stronger binding efficiency to the original cancer cells compared to RBC camouflaged nanoparticles and naked nanoparticles. This concept was further expanded for multiple techniques imaging and photothermal therapy using ICG nanoparticles.^[56] ICG dye was loaded into poly(lactic-co-glycolic acid) PLGA to form the core, then coated with PEGylated MCF-7 cancer cell membranes to obtain CC@ICG by extrusion (**Figure 7a**). CC@ICG showed comparable fluorescence and photoacoustic imaging properties, and higher photothermal conversion efficiency compared to free ICG. SDS-PAGE and western blot analysis indicated CC@ICG possessed similar cellular adhesion molecules including EpCAM, N-cadherin, and galectin-3, compared with MCF-7 cell lysate, which play important roles in homologous binding and adhesion. The targeting ability of CC@ICG to different cells including MCF-7 cells, 293T cells, MCF-10A cells, HepG2 cells, A549 cells, and MDA-MB-231 cells were investigated. The highest uptake efficiency in MCF-7 cells of CC@ICG among these cells confirmed the homotypic binding ability of CC@ICG (Figure 7b&c). Moreover, when incubated with MCF-7 cells, CC@ICG also presented higher uptake efficiency in comparison with that of PEGylated control nanoparticles and free ICG, resulting in enhanced photothermal cytotoxicity of CC@ICG. In vivo, due to the EPR effect and homotypic active targeting, CC@ICG showed significant fluorescence and photoacoustic signals in the tumor area in comparison with that of PEGylated control nanoparticles and free ICG (Figure 7d). After i.v. injection of CC@ICG, the tumor temperature increased up to 55.3°C upon laser irradiation, leading to complete remission of the tumor with no recurrence in 18 days, owing to the highest accumulation of CC@ICG in the tumor area. On the contrary, no apparent antitumor efficacy

was observed for the free ICG and PEGylated control nanoparticles groups with laser irradiation because of the rapid clearance and insufficient accumulation in tumor.

Figure 7. (a) Schematic illustration of the preparation process of CC@ICG. (b) Cellular uptake in different cells after incubation with CC@ICG. (c) Mean fluorescence intensity of different cells measured by flow cytometry after incubation with CC@ICG. (d) NIR fluorescence images and PA images of MCF-7 tumor-bearing mice at different time points after injection of different agents. Reprinted with permission from Ref. [56]. Copyright 2016, American Chemical Society.

Beyond homotypic active targeting the primary tumor, the cancer cell membrane camouflaged nanoparticles are capable of active targeting metastasis and combination with photothermal ability to trigger drug release. In one example, 4T1 cancer cell membranes were coated on the surface of chemotherapeutic drug DOX-incorporated gold nanocages to obtain CC@DAuNC.^[57] CC@DAuNC showed a similar increase in local temperature compared to the bare AuNCs, demonstrating that DOX and cell membrane coating had no effects on the photothermal conversion efficiency. Upon laser irradiation, the remarked temperature rise of CC@DAuNC could not only destroy the cancer cells due to hyperthermia but also destruct the membrane coating of CC@DAuNC to release the encapsulated drug, significantly accelerating the release kinetics compared to that without laser irradiation. The source 4T1 cells incubated with CC@DAuNC exhibited significantly higher uptake compared to other control groups, indicating the homotypic binding ability of CC@DAuNC. Moreover, the laser irradiation-induced hyperthermia enhanced the permeability and fluidity of the membranes on 4T1 cells and accelerated drug release from CC@DAuNC, further enhancing the signal of DOX in 4T1 cell. The combination of the homotypic binding ability and phototoxicity of CC@DAuNC with accelerated drug release profile enabled the highest cytotoxicity to 4T1 cells. In vivo, CC@DAuNC exhibited highest DOX accumulation in the tumor region, due to EPR effect and the homotypic targeting ability. Notably, accumulation of DOX in lung tissues was dramatically increased after CC@DAuNC injection versus free DOX, indicating that the homotypic targeting capability to the metastatic 4T1 tumor in the lung tissues after cancer cell membrane coating. Finally, the primary tumor volume was dramatically suppressed and the metastases were significantly decreased, with no obvious side effects during the experiment period, after intravenous injection of CC@DAuNC paired with irradiation.

RBC membrane coated nanoparticles exhibited extended in vivo circulation time, while cancer cell membrane coated nanoparticles displayed significantly homotypic targeting to source tumor. Therefore, a hybrid cell membrane coating approach that fused RBC and cancer

cell membrane onto a single nanoparticle is desirable to combine the functionalities from both cell membranes. In one case, RBC and B16-F10 cell membranes were fused together to achieve enhanced functionality (**Figure 8**).^[34] To confirm this fusion, B16-F10 cell membrane was first labeled with a Forster resonance energy transfer (FRET) pair of dye. With increasing amount of RBC membrane hybridized into the B16-F10 cell membrane, the fluorescence was gradually increased, demonstrating the successful fusion (Figure 8b). SDS-PAGE analysis, western blot analysis, and immunogold TEM imaging further indicated that the hybrid membrane contained membrane protein markers from both RBC and B16-F10 membranes. The hybrid membranes were then coated onto DOX-loaded copper sulfide nanoparticles (DCuS NPs) to obtain RBC-B16@DCuS NPs (Figure 8a). The obtained hybrid membrane camouflaged nanoparticles exhibited a strong absorption at 1064 nm, leading to a high photothermal conversion under a 1064 nm laser irradiation (Figure 8c) and concentration-dependent photoacoustic signals (Figure 8d). When incubated with different cell lines, the hybrid nanoparticles displayed starkly superior uptake in B16-F10 cells compared to other cell lines, revealing the homotypic targeting capability to the source cells (Figure 8e). Similar to the previous examples, the DOX release profile from RBC-B16@DCuS NPs had a typical photothermal and pH-related effect (Figure 8f). In vivo, the hybrid nanoparticles showed longer circulation time than the B16-F10 cell membrane coating nanoparticles due to intrinsic properties of RBCs (Figure 8g). Thus, the hybrid nanoparticles exhibited an enhanced tumor accumulation compared to RBC or B16-F10 membrane solo coated nanoparticles (Figure 8h). Finally, with 1064 nm laser irradiation, the hybrid nanoparticles could effectively control tumor growth without obvious adverse effects, owing to the hybrid membrane and the synergistic PTT/chemotherapy.

Figure 8. (a) Schematic illustration of the preparation process of RBC-B16@DCuS NPs. (b) The fluorescence intensity of B16-F10 membrane doped with DiD and Dil when mixed with different amounts of RBC membrane. (c) The temperature of water, CuS, RBC-B16@CuS, and RBC-B16@DCuS NPs ($50 \mu\text{g mL}^{-1}$) as a function of laser irradiating time. (d) PA intensity of RBC-B16@CuS NPs in different concentrations. (e) Mean fluorescence intensity of different cell lines after 4 h incubation with Dil labeled RBC-B16@CuS NPs. (f) In vitro DOX release behavior from RBC-B16@DCuS NPs at pH 7.4 and 5.0 with or without NIR laser irradiation (1064 nm , 1.0 W cm^{-2}). (g) Blood retention time of CuS NPs, RBC@CuS NPs, B16@CuS NPs, and RBC-B16@CuS NPs over a span of 24 h after i.v. injection. (h) In vivo biodistribution of CuS NPs, RBC@CuS NPs, B16@CuS NPs, and RBC-B16@CuS NPs at 24 h after injection. Reprinted with permission from Ref. [34]. Copyright 2018, American Chemical Society.

The PDT efficiency could be optimized based on the cancer cell membrane targeting approach. In one example, a CAT and Al (III) phthalocyanine chloride tetrasulfonic acid (defined as PS) loaded porouszeolitic imidazolate framework (ZIF) was coated with HeLa cell

membrane to obtain a biomimetic platform (CC@CAT-PS-ZIF).^[58] This biomimetic platform exhibited more efficient nanoparticle uptake in the source cells (HeLa cells) due to the homotypic binding properties, in comparison with limited uptake in the COS7 cells, SCC-7 cells, and 4T1 cells. When nanoparticles were incubated with HeLa cells and irradiated, the efficient intracellular $^1\text{O}_2$ generation was observed by CLSM. The combination of efficient nanoparticles uptake and intracellular $^1\text{O}_2$ generation induced efficient apoptosis in HeLa cells. In vivo, the embedded CAT in this biomimetic platform significantly improved the tumor hypoxic condition *via* catalyzing intracellular H_2O_2 into O_2 . Compared to the uncoated nanoparticles, the introduction of cell membrane enhanced tumor accumulation due to the homotypic binding to source cells, and had long circulation lifetime in the blood due to immune escape. Therefore, CC@CAT-PS-ZIF showed strongly effective PDT with the help of CAT compared to other control groups. The up-regulated caspase-3 expression and down-regulated Bcl-2 expression in tumor tissues were detected after treatment with CC@CAT-PS-ZIF under laser irradiation than that in other control groups, revealing the increased apoptotic cells in tumor tissue.

This O_2 self-sufficient strategy was further modified by the same group through combining cancer targeting starvation therapy. In this work, cancer cell membrane derived from 4T1 cells were coated around a porphyrin metal-organic PCN-224 framework embedded with both CAT and glucose oxidase (GOx) to obtain a cascade bioreactor (CC@CGP).^[59] GOx could decompose intracellular glucose, resulting in the cancer starvation therapy.^[60] When CC@CGP was treated with glucose, a dramatic pH drop was detected, indicating glucose decomposition by GOx in CC@CGP to produce gluconic acid and H_2O_2 . In the presence of H_2O_2 , dramatic oxygen production was observed, signifying the CAT in CC@CGP could catalyze the H_2O_2 and subsequent production of oxygen to improve tumor hypoxic environment. The abundant $^1\text{O}_2$ was produced when laser irradiated to CC@CGP in the presence of H_2O_2 , compared to other control groups. Moreover, due to the homotypic binding properties of CC@CGP towards

source cells (4T1 cells), a higher accumulation of CC@CGP was found in 4T1 cells rather than B16F10 cells, HepG2 cells, and COS7 cells. Further, the macrophage uptake of CC@CGP was dramatically decreased compared with the bare nanoparticles. In vivo tumor accumulation ability was also enhanced by the homotypic cancer cell membrane coating. Therefore, using the 4T1 tumor-bearing mouse model, CC@CGP indeed mitigated the tumor hypoxic environment, thus led to almost complete suppression of tumor with no obvious side effects for 14 days under laser irradiation, indicating the successful synergistic starvation therapy and PDT.

5. Platelet Membrane Camouflaged Nanoparticles

Platelets (PLTs) are produced from the bone marrow cells megakaryocytes.^[61] The basic function of PLTs is to contribute to hemostasis, as PLTs are circulating sentinels that target to vascular injury sites to trigger repair processes and preserve the integrity of blood circulation.^[62] The recognition and interaction between PLTs and circulating tumor cells (CTC) have received considerable interests due to their critical contribution to tumor metastasis.^[63] PLTs can cover CTC to help CTC escape from immune clearance in blood circulation and spread to new tissues. This function of PLTs is related to their surface marker proteins including P-Selectin (also known as CD62p), CD47 and CD44 receptors.^[26c, 64] Utilization of their surface marker proteins, PLT membranes have the potential to be used for coating onto the surface of nanoparticles to possess flexible properties including evasion of immune clearance and specific adhesion to injured vessels or tumor tissues, which are beneficial to nanomedicine application.

In one example, Fe₃O₄ magnetic nanoparticles were coated with PLT membrane through top-down approach for enhanced MRI and PTT of tumors.^[65] The T₂-weighted relaxation rate value (R₂) and photothermal conversion effects of PLT camouflaged magnetic nanoparticles (PLT@MNs) are close to that of the bare nanoparticles, indicating the negligible effect of membrane coating on MRI and photothermal functionalities. PLT@MNs showed a similar macrophage uptake to RBC membrane coated nanoparticles and highly preferred uptake by MCF-7 cancer cells, demonstrating the immune escape and cancer cells targeting abilities after

PLT membrane coating. In vivo, using MCF-7 tumor-bearing mouse model, PLT@MNs showed similar in vivo circulation time to the RBC membrane coated nanoparticles, and reduced MPS uptake compared to the bare nanoparticles. The obvious darkening effect at 24 h in MRI and a higher dose of Fe at 48 h through quantitative analysis with ICP-AES in the tumor site confirmed the improved tumor accumulation and targeting ability of PLT@MNs compared to other control nanoparticles. Thereby, PLT@MNs exhibited significantly higher tumor temperature rise compared to other control groups. By applying an MF near the tumor, the tumor temperature could be further increased. The effective PTT effect of PLT@MNs + MF + laser group completely eliminated the MCF-7 tumors. In addition, the authors demonstrated that PTT could increase the targeting ability of PLT@MNs to the tumor, which may be contributed to that PLTs actively seal to the damaged blood vessels by PTT due to the self-healing ability of PLTs.

To further investigate the phenomenon of enhanced targeting ability of PLT membrane camouflaged nanoparticles to the tumor sites during PTT, the same group fabricated a gold nanorods (AuNRs)-loaded PLTs (PLT@AuNRs) *via* electroporation process to investigate the self-reinforcing characteristic of PLT-based nanoparticles in PTT (**Figure 9a**).^[66] In vivo, PLT@AuNRs showed longer systematic circulation over 48 h with lower organ MPS accumulation compared with bare AuNPs (Figure 9b). Notably, compared to without laser irradiation, more PLT@AuNRs accumulated in tumor site after subsequent doses of injections with laser irradiation, possibly because PLT@AuNRs had self-healing ability to actively target the injury site of tumor caused by PTT (Figure 9c). Thus, the maximum tumor temperature of PLT@AuNRs treated mice was successively increased after each treatment (Figure 9d), leading to enhanced PTT effects *via* this self-reinforcing characteristic of PLT@AuNRs (Figure 9e&g). Moreover, the negligible body weight loss of PTT treatment group compared with the PBS group demonstrated biosafety of this novel self-reinforcing PTT therapeutic strategy (Figure 9f).

Figure 9. (a) Schematic illustration of the preparation process of PLT@AuNRs and self-reinforcing characteristic of PLT@AuNRs in PTT. (b) Blood retention time of different nanoparticles over a span of 72 h after i.v. injection. (c) Tumor accumulation of PLT@AuNRs after subsequent doses of injections with or without laser irradiation (808 nm, 2 W cm⁻²). (d) Representative in vivo IR thermal images of tumor-bearing mice before and after each treatment. White circles indicate the tumor sites. (e) Tumor volume changes after different treatments. (f) Mice body weight change after different treatment (808 nm, 2 W cm⁻²). (g) Representative TUNEL and Ki-67-stained tumor slice images of mice after different treatments. Scale bar: 50 μm (TUNEL-stained tumor slices) 25 μm (Ki-67-stained tumor slices). ** and *** indicate $p < 0.01$ and $p < 0.001$, respectively. Reprinted with permission from Ref. [66]. Copyright 2017, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

6. Other Cell Membrane Camouflaged Nanoparticles

6.1. Macrophage Membrane Camouflaged Nanoparticles

Macrophages are one type of white blood cells, can help to perform immune functions. Macrophages display many unique properties that facilitate immune evasion and site-specific targeting to inflammation or tumor, thus macrophage membranes have potential to perform as coatings in cancer nanomedicine.^[67] For instance, CD49d is a surface marker that is expressed in macrophage membranes.^[68] Meanwhile, CD49d is also a primary ligand to vascular cell adhesion molecule 1 (VCAM-1) expressed by some cancer cells such as MCF-7 cancer cells and 4T1 cancer cells.^[69] Therefore, macrophage membranes could specifically bind to some cancer cells during in vivo circulation.

In one example, gold nanoshells (AuNSs) were formed through mesoporous silica nanoparticles (MSNs) templating approach.^[70] The AuNSs were also loaded with NIR dye, cyanine 7, for in vivo imaging. After coating with macrophage membrane, the obtained macrophage membrane coated AuNSs (MPC@AuNSs) showed an obvious core-shell structure, and similar absorption peak compared to bare AuNSs. When incubated with 4T1 cells, an enhanced cellular uptake of MPC@AuNSs was confirmed by CLSM imaging and flow-cytometry analysis compared to bare AuNSs. Therefore, MPC@AuNSs could efficiently kill 4T1 cells in vitro under laser irradiation. In vivo, MPC@AuNSs showed significantly prolonged systematic circulation over 48 h compared to the uncoated nanoparticles, resulting in an enhanced accumulation of MPC@AuNSs in the tumor site. When used to treat 4T1 tumor-bearing mice, MPC@AuNSs can effectively suppress tumor growth under laser irradiation.

6.2. Stem cell Membrane Camouflaged Nanoparticles

Stem cells can differentiate into other types of cells, therefore stem cells have been widely used in medical field, especially for regenerative medicine applications.^[71] Stem cells have some special properties, such as tumor tropism, and thus can be applied in drug delivery field.^[72] Likewise, stem cell membrane camouflaged nanoparticles have shown similar targeting functionality to tumor. Recently, stem cell membrane coating has been employed as an

improvement strategy for photo-based applications.^[73] The stem cell membranes were derived from bone-marrow-derived mesenchymal stem cell membrane. The upconversion nanoparticles (UCNPs) were first coated with a mesoporous silica shell, then two PSs were loaded into the shell, subsequently coated by stem cell membranes to obtain final nanoparticles. The stem cell membrane camouflaged nanoparticles showed good cytocompatibility and blood compatibility when incubated with normal hepatocyte cells or mouse blood. In addition, the stem cell membrane camouflaged nanoparticles exhibited enhanced uptake when incubated with HeLa cells compared with the bare nanoparticles, indicating the cancer cell targeting capability from stem cell membrane. When injected into tumor-bearing mice, the accumulation of stem cell membrane coated nanoparticles in tumor was significantly higher than that of the bare nanoparticles. Meanwhile, less accumulation in liver indicated reduced clearance of the stem cell membrane camouflaged nanoparticles by MPS. Combining the injection of nanoparticles with laser irradiation could significantly improve the photodynamic anticancer efficacy, leading to complete control of tumor growth without obvious side effects.

6.3. Fibroblast Membrane Camouflaged Nanoparticles

Activated fibroblasts (AFs), termed cancer-associated fibroblasts (CAFs) are a major component of tumor stromal cells that synthesize the extracellular matrix (ECM) and collagen in the tumor microenvironment.^[74] CAFs play an important role in tumor progression, angiogenesis, proliferation, and migration.^[75] Therefore, the CAFs also represent a molecular target for cancer treatment.^[76] Recently, our group developed a biomimetic SPNs camouflaged with activated fibroblasts cell membranes for improved cancer phototherapy (**Figure 10**).^[77] SPNs are an emerging category of organic photonic nanomaterials made from optically active π -conjugated semiconducting polymers (SPs) and have shown the advantages of good biocompatibility.^[78] The structural versatility and excellent optical properties of SPNs allow them to be applied in a series of imaging applications including fluorescence, chemiluminescence or photoacoustic.^[79] Moreover, SPNs showed superior photothermal

conversion efficiency and photodynamic capability, which could be applied in phototherapy.^[4d, 17, 80] The activated fibroblast cell membranes were derived from normal fibroblasts after treatment with transforming growth factor (TGF- β 1) to activate them into AF cells (Figure 10b). The SPNs were obtained through nanoprecipitation in the presence of poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) (PEG-*b*-PPG-*b*-PEG) and a NIR absorbing SP, poly(cyclopentadithiophene-*alt*-benzothiadiazole) (PCPDTBT) (Figure 10a). The optical, photothermal and photodynamic properties of the SPNs did not change after coating with AF cell membrane. Reasonably, the AF@SPNs showed enhanced uptake in the AF cells compared with the bare SPNs and cancer cell membrane camouflaged SPNs (CC@SPNs), due to the homologous targeting ability of AF@SPNs. In vivo, using 4T1 tumor model, AF@SPNs had much stronger fluorescence (Figure 10c&d) and photoacoustic signals (Figure 10e&f) in the tumor area in comparison with that of the bare SPNs and CC@SPNs, due to EPR effect and homologous targeting ability of AF@SPNs towards cancer-associated fibroblasts. Therefore, with laser irradiation, AF@SPNs showed the best in vivo PTT&PDT effect compared to the bare SPNs group and CC@SPNs group, leading to almost complete tumor elimination with minimal systematic toxicity, implying enhanced phototherapy efficiency and favorable biocompatibility of cancer-associated fibroblast membrane camouflaged SPN-mediated phototherapy.

Figure 10. (a) Chemical structures of PCPDTBT and PEG-*b*-PPG-*b*-PEG used for the preparation of SPNs. (b) Schematic illustration of preparation process of AF@SPN. (c) In vivo NIR fluorescence images of 4T1 tumor-bearing mice at different time points after i.v. injection of different nanoparticles. White dashed circles indicate the tumor sites. (d) Quantification of fluorescence intensities in tumor area as a function of postinjection time after i.v. injection of different nanoparticles. (e) Representative PA maximum imaging projection of 4T1 tumors in living mice at different time points after i.v. injection of different nanoparticles. (f) Quantification of PA intensities at 680 nm in tumor area as a function of postinjection time after i.v. injection of different nanoparticles. * $p < 0.05$. NS indicates no significance. Reprinted with permission from Ref. [77]. Copyright 2018, American Chemical Society.

6.4. Myeloid-Derived Suppressor Cell (MDSC) Membrane Camouflaged Nanoparticles

MDSCs are a heterogeneous population of immune cells from the myeloid lineage.^[83] They are not present in healthy individuals but strongly appear in pathological situations such as chronic inflammation, infection and cancers.^[84] MDSCs also play a major regulator in immune suppression in cancer including tumor angiogenesis and metastases.^[84] Since MDSCs expeditiously expand in tumor environment, targeting these cells could be an attractive therapeutic strategy. Recently, MDSC membrane camouflaged nanoparticles show the advantages of evasion of immune clearance and active targeting tumor microenvironment, which could be used for improved cancer phototherapy.^[85]

In one example, magnetic Fe₃O₄ nanoparticle (MNP) was coated with MDSC membrane to obtain MDSC@MNP. When incubated with RAW264.7 murine macrophage cells, the cellular uptake of MDSC@MNP was 5-10-fold lower than the original MNP, indicating the immune escape capability of MDSC@MNP. The body weight, blood biochemistry of the MDSC@MNP-treated mice showed no significant difference compared to PBS group, demonstrating the excellent biocompatible in vivo. The MDSC@MNP group showed significantly higher accumulation in tumor and lower accumulation in liver and spleen than the original MNP group, indicating the active targeting to the tumor microenvironment and decreased MPS uptake. With laser irradiation, the tumor temperature of MDSC@MNP-treated mice increased dramatically, inducing immunogenic cell death, reprogramming tumor-associated macrophages, and reducing tumor metabolic activity, thus leading to enhanced antitumor effect.

7. Conclusions and Perspectives

This review summarizes the recent advances in cell membrane camouflaged nanoparticles for cancer phototherapy. Phototherapy requests photoabsorbing agents or PSs to be effectively accumulated in tumor site for the generation of sufficient heat or cytotoxic ROS to ablate cancer cells. However, similar to other nanomedicines, traditional phototherapeutic nanoparticles usually experience issues of early recognition by the immune system and quick clearance from blood circulation, leading to low accumulation in the targeting site. The cell membrane coating approach is a feasible way to overcome these limitations by providing a unique biological interface. This cell membrane coating approach does not affect biological activity,

photophysical property of the original uncoated phototherapeutic nanoparticles. Moreover, because the coated cell membrane could be ablated from phototherapeutic nanoparticles under laser irradiation, it enables light-triggerable release of encapsulated drugs for synergetic and combined therapy.

The cell membranes were herein discussed include RBC membrane, cancer cell membrane, PLT membrane, macrophage membrane, stem cell membrane, fibroblast cell membrane and MDSC membrane. RBC membrane has many natural “self-makers” including CD47 proteins, glycans, and acidic sialyl moieties, which contribute to the evasion of immune clearance of RBC membrane camouflaged nanoparticles. The plasma membrane proteins such as N-cadherin, galectin-3 or EpCAM on the surface of cancer cell membranes display some unique properties including antigenic display and homologous binding, which endow cancer cell membrane camouflaged nanoparticles with immune escape and homologous targeting abilities. The surface marker proteins of PLT including P-Selectin, CD47, and CD44 receptors facilitate the absence of immunogenic clearance and specific adhesion to injured tumor tissues of the PLT membrane camouflaged nanoparticles. The other cell membranes such as macrophage membrane, stem cell membrane, fibroblast cell membrane and MDSC membrane also endow many unique properties including immune evasion and tumor targeting functionality to these cell membrane camouflaged nanoparticles. By adjusting the source of cell membranes, the functionalities of cell membrane camouflaged nanoparticles including immune escape, in vivo prolonged circulation time or homologous targeting can be achieved. By hybridizing different cell membranes, the functionalities from those cell membranes can be further integrated into one type of nanoparticles. Thereby, by utilizing the cell membrane coating approach, increased accumulation of nanoparticles in the tumor site can be achieved, thus improving cancer therapeutic effect. Moreover, by combining other supplementary agents such as CAT or Hb to normalize tumor microenvironment, cell membrane coating approach could further lead to the enhanced treatment in cancer therapy.

However, there are some important issues that should be addressed for further improvement of cell membrane coating approach. First, the integrity of cell membrane and the nanoparticle core should be maximally retained to keep the functionality during blood circulation. However, how to precisely characterize the integrity of cell membrane camouflaged nanoparticles *in vivo* has not been uncovered. Second, although cell membrane camouflaged nanoparticles display unique advantages such as evasion of immune clearance and tumor-relevant targeting, they are incapable to penetrate inside the tumor area due to dense ECM and elevated interstitial fluid pressure (IFP) in the tumor microenvironment.^[81] Modifying the cell membrane camouflaged nanoparticles with some peptides or ligands could enhance their penetration ability to effectively kill deep-seated cancer cells.^[82] Last, although the cell membrane camouflaged nanoparticles show *in vivo* good biocompatibility and minimal cytotoxicity to healthy organs, their long-term biological effects to living organisms require careful investigation. Especially, the biological safety of cancer cell membrane in the nanoparticles to the healthy organs should be investigated carefully since there are still a large proportion of administrated cell membrane camouflaged nanoparticles accumulated in healthy organs after the improvement of tumor-targeting strategy.

Conflict of Interest

The authors declare no conflict of interest.

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Cell-membrane camouflaged phototherapeutic nanoparticles are equipped with immune escape, in vivo prolonged circulation time and homologous targeting, while their phototherapeutic activities remain nearly unchanged. This review highlights the recent advances in the development of biomimetic cell membrane camouflaged nanoparticles for cancer phototherapy in living animals.

Keyword: Cell membrane, Biomimetic nanoparticles, Photothermal therapy, Photodynamic therapy.

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Recent advances in Cell Membrane Camouflaged Nanoparticles for Cancer

Phototherapy

ToC figure: