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Cell membrane-coated nanocarriers: the emerging targeted delivery system for cancer theranostics

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Cancer is a leading cause of death worldwide. The use of nanocarriers (NCs) has generated significant interest to improve cancer therapy by targeted delivery. However, conventional NCs in general lack specificity and have poor biodistribution, resulting in low efficacy in cancer therapy. To circumvent this problem, there has been an increasing focus on cancer cell membrane-coated NCs (CCMCNCs), which can deliver therapeutics directly to tumor cells. CCMCNCs comprise active cancer cell surface adhesive molecules combined with other functional proteins, and offer extended blood circulation with robust cell-specific targeting, ensuring enhanced intratumoral penetration and higher tumor-specific accumulation of NCs. In this review, we discuss the preparation, homologous targeting mechanisms, and application of CCMCNCs in targeted cancer therapy.

Introduction

Cancer is a major global public health issue and the global burden is projected to reach approximately 14.6 million cases by 2035 [1]. Patients with cancer are mostly treated with one or a combination of three options: chemotherapy, radiation therapy, and surgery [2]. Conventional cancer therapeutics are generally delivered as free drugs via the systemic circulation, often with low efficacy and adverse effects. These inherent limitations of conventional cancer therapeutics have encouraged the development and application of various NCs for effective and safe cancer therapy [3]. NCs are often engineered to be subnanometer in size to benefit from the enhanced permeability and retention (EPR) effect of tumor tissues, or engineered with targeting ligands, such as antibodies, peptides, and aptamers, to enhance their specific accumulation in tumors [3–7]. However, complexities, such as tumor heterogeneity, abnormal tumor microenvironments, and physiological barriers, have hindered the bench-to-bedside translation of NCs [3,8].

Recently, biomimetic functionalization of NCs to provide them with superior biocompatibility and robust targeting towards desired tissues has received increased research attention [9–11]. In particular, CMCNCs have demonstrated promising results in preclinical studies [9,11]. CMCNCs comprise a cell–material hybrid nanoplatform that combines the advantages of natural and synthetic elements [12]. On the inside is a nanomaterial core, capable of being loaded with therapeutics, including drugs and/or genes, or imaging agents, whereas the outside encompasses proteolipid vesicles derived from cell membrane sources [9,10,12]. These proteolipid vesicles are approximately 50% protein by mass and also contain many complex glycan structures and abundant lipids [13].

Initially, red blood cell (RBC) membrane-coated NCs were fabricated using a combination of RBC membrane-derived lipid vesicles and poly(lactic co-glycolic acid) NCs (PLGA-NCs) via a co-extrusion approach [14]. Further advances have led to remarkable progress in cell membrane-coating technology, resulting in NCs coated with membranes derived from platelets, leukocytes, mesenchymal stem cells, and cardiac stem cells [15–18]. Each cell

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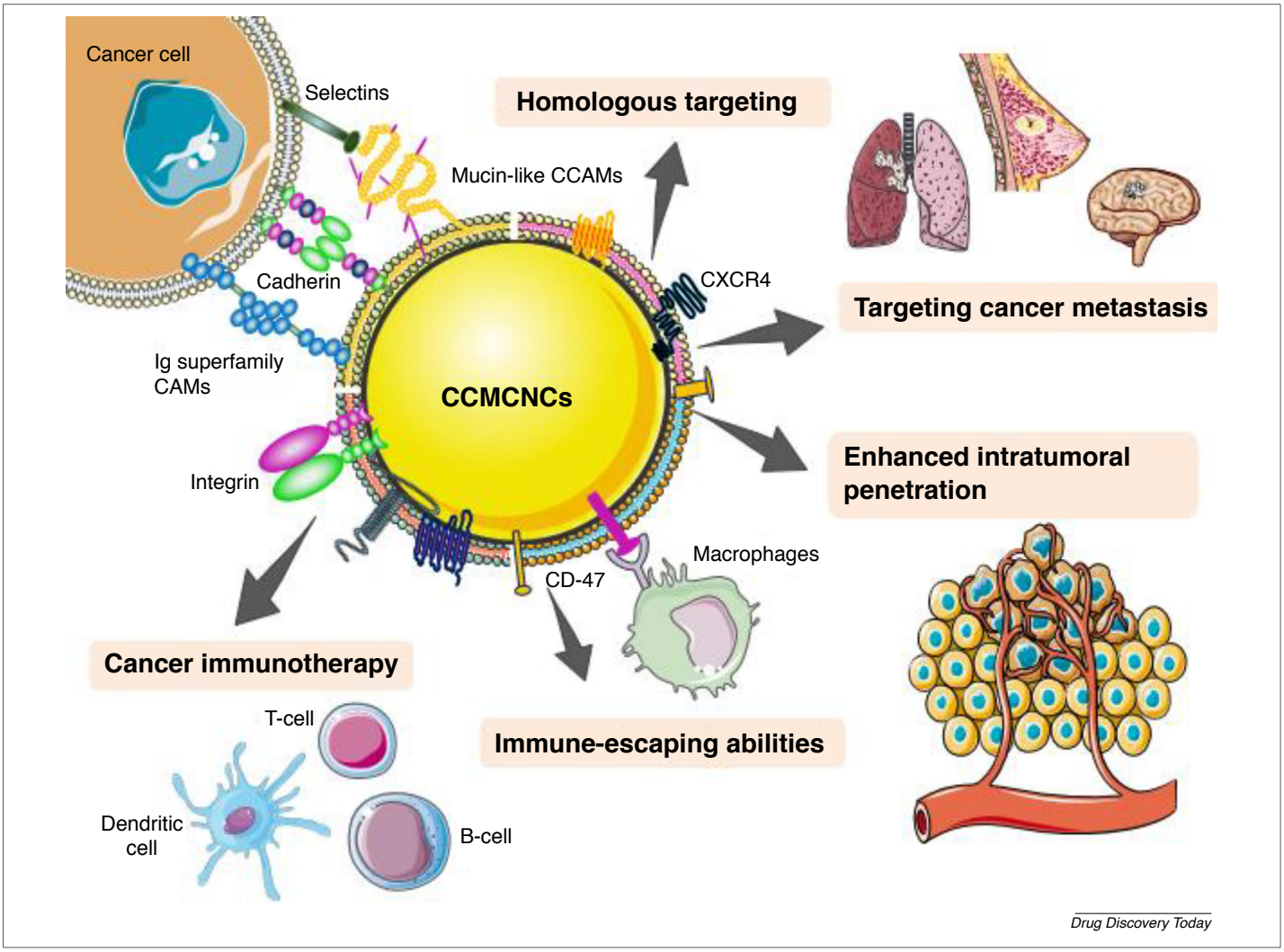

FIGURE 1

Schematic overview of the advantages and application of cancer cell membrane-coated nanocarriers (CCMCNCs) for the targeted delivery of nanotheranostics in cancer therapy. The figure details the various proteins involved in the interaction of CCMCNCs with cancer cells in achieving targeted delivery through adhesive proteins, approaching metastasis in various organs through homologous targeting, antigen specific targeting of T cells in immunotherapy, and enhanced intratumoral penetration and immune escape from macrophages through CD47 antigens.

source has its own unique protein–lipid composition that is critical for its physiological effects, such as immunological effects and natural targeting. Among these diverse cell sources, cancer cells have gained primary importance in cancer therapy because of their homologous binding to the source cells and their natural immune-evading properties [19–21]. In this review, we mainly focus on recent advances in the development of CCMCNCs for the targeted delivery of anticancer therapeutics and theranostics.

Preparation of CCMCNCs

CCMCNCs have been the subject of numerous promising preclinical studies owing to their unique cancer-targeting properties. The major concern surrounding CCMCNCs is their preparation. On a small scale, CCMCNCs can be fabricated through simple top-down fabrication methods. The proteolipid vesicles of cancer cell membranes (CCMs) are purified by multiple centrifugation steps after initial treatment with hypotonic cell lysis or mild mechanical processes, such as homogenization and/or sonication [22]. Anticancer therapeutics or theranostic-incorporated NCs are prepared by conventional methods, such as emulsion solvent evaporation, or via a self-assembly process [23–25]. Finally, the surface engineering of the CCM on NCs can be achieved by extrusion or electrostatic attraction [19]. CCMCNCs prepared by top-down procedures, (Fig. 2) exhibit many characteristics, including excellent stability, ability to load diverse therapeutics and theranostics, and flexibility in additional surface engineering with targeting molecules. However, the preparation of CCMCNCs needs further exploration. In particular, scale-up and process optimization are essential to meet the requirement of translational studies [26]. Laboratory-scale preparation methods involving multiple manual steps can induce process variability, which could significantly affect the physiochemical and biological characteristics of the resulting CCMCNCs [27]. The difficulty in manufacturing CCMCNCs in a reproducible and scalable manner also discourages their clinical translation [9].

To overcome these difficulties in CMCNC preparation, a microfluidic-assisted fabrication process was attempted [27]. Microflui-

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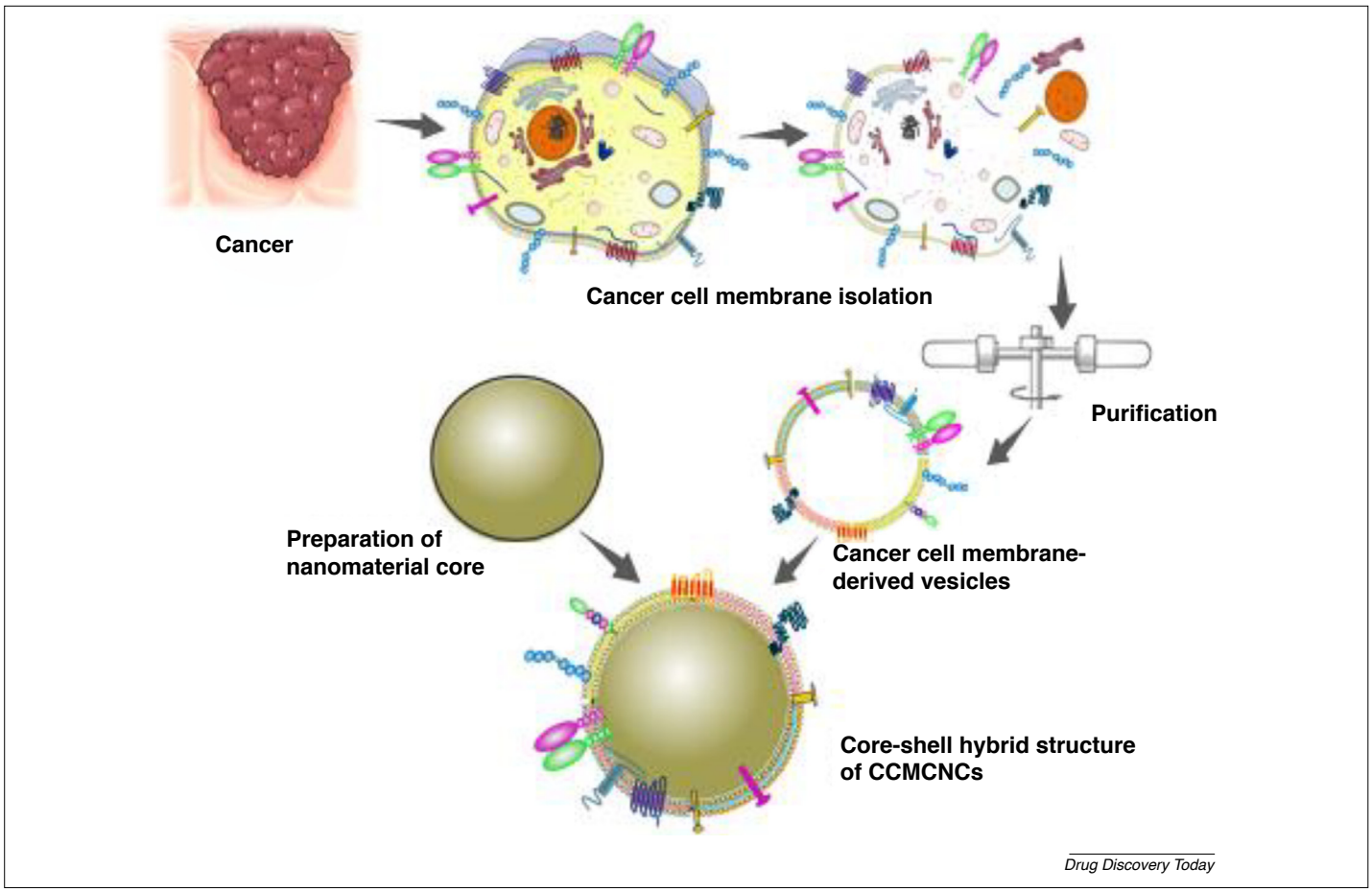

FIGURE 2

A generalized schematic representation of the various steps involved in the preparation of cancer cell membrane-coated nanocarriers (CCMCNCs). In this strategy, the membrane-derived extracellular vesicles are selectively isolated by centrifugation and then subjected to an extrusion procedure to functionalize the nanocarriers.

dic-based CMCNCs preparation enables enhanced mixing and precise fluidic modulation inside microchannels, thus allowing the flow-mediated fabrication of CMCNCs in a controllable manner [28]. In a recent study, Rao *et al*. demonstrated that a microfluidic electroporation method could be used for the efficient synthesis of CMCNCs. The magnetic nanoparticle (MNP) core and RBC membrane-derived vesicles were infused into a microfluidic device. When the blend of MNPs and the RBC membrane-derived vesicles flowed through the electroporation zone, electric pulses successfully promoted the encapsulation of MNPs within the RBC vesicles [29]. The researchers further investigated the *in vivo* performance of RBC membrane-coated MNPs in animal models. The RBC-MNPs prepared by the microfluidic electroporation approach exhibited significantly better treatments effect than those prepared by conventional methods [29].

Homotypic adhesion of cancer cells and CCMCNCs

Cancer development and progression is a multistep process in which cancer cell adhesion molecules (CCAMs) have a pivotal role in the development of recurrent, invasive, and distant metastasis [30]. CCAMs comprise membrane receptors, including cadherins, selectins, integrins, the immunoglobulin superfamily (Ig-SF), and lymphocyte-homing receptors (e.g., CD44), which are critical for cell–cell and cell–matrix interactions [31]. Cadherins, whose main function is cell–cell adhesion, have been well studied for their role in cell signaling during critical processes such as epithelial-to-mesenchymal transition (EMT), cell migration, and gene regulation through catenin pathways [32]. By contrast, integrins are involved in both cell–cell and cell–extracellular membrane (ECM) interactions and have shown cell- and tissue-specific functions. Integrins, such as integrin beta-1 (ITβ1), ITα1, ITα2, ITα5, ITβ3, ITβ4, and ITβ5, are highly expressed in the plasma membrane of various cancer cells [33]. Furthermore, integrins have a crucial role in cell proliferation, differentiation, and migration because of their ability to transfer signals from the ECM to the cell. Selectins and Ig-SF members are mainly involved in immune cells and platelets. Apart from these CCAM proteins, mucoprotein 1 (Muc1), which is not generally defined as a CCAM, also has a central role in cancer cell adhesion [34]. All or some of these CCAMs are involved in either intravascular cell–cell heterotypic (between cancer and other types of cell) or homotypic (between cancer cells) adhesive interactions, leading to the establishment of metastatic deposits. Earlier studies demonstrated that metastatic cell homotypic aggregation and heterotypic adhesion represent two coordinated steps of the metastatic cascade, mediated largely by similar molecular mechanisms, specifically by interactions of

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the tumor-associated Thomsen–Friedenreich glycoantigen (TF-Ag) with galectin-3 [35,36]. TF-Ag is a disaccharide galactose β1-3*N*-acetyl galactosamine that is attached to proteins by α-*O*-serine or *O*-threonine linkages [36]. Galectin-3, a unique chimera-type member of the β-galactoside-binding soluble lectin family, is present in both normal and cancer cells, and has a crucial role in the regulation of cell adhesion [36]. It is involved in accelerating the detachment of cancer cells from the primary tumor site and promoting cell adhesion and survival from anoikis in the blood stream. The occurrence of the oncofetal TF antigen and the increased expression of galectins are both common features in cancer [36]. Numerous experimental results have revealed that the galectin–TF interaction promotes heterotypic and homotypic aggregation in cancer progression and metastasis [36,37]. Additionally, cancer cells with high metastatic potential have a higher capability to form homotypic multicellular aggregates than their low metastatic counterparts. Furthermore, galectin-1 was found to bind to CCAMs, including cluster of differentiation 44 (CD44) and CD326 [38,39].

Additionally, CD47, a ubiquitous 50-kDa, integrin-associated five-spanning transmembrane protein that belongs to the Ig-SF is critically responsible for the immune-evading properties of cancer cells [31,40]. CD47 interacts with signal regulatory protein-α (SIRP-α) expressed by macrophages and dendritic cells [40,41]. The binding of SIRP-α with CD47 results in the phosphorylation of the cytoplasmic tail of SIRP-α, leading to the binding and activation of protein phosphatases that block phagocytosis, possibly through the inhibition of motor protein myosin-IIA accumulation at the phagocytic synapses [42]. CD47, a 'don't eat me' signal for immune cells, is overexpressed on the surface of most of cancers [43]. Recent studies have reported methods for the functionalization of synthetic NCs to membranes with CD47 antigens [44–46]. These NCs have the same density of the biomarker on the cell. Notably, the CD47 proteins were shown to be oriented almost exclusively in a right-side-out fashion, with the extracellular portion displayed on the particle surfaces because of the electrostatic repulsion between the negatively charged NC core and the negatively charged sialyl moieties residing on the exoplasmic side of the membranes [9,44]. As a result of this right side-oriented membrane coating, macrophage uptake of the CMCNCs was significantly inhibited *in vitro* [12]. Additionally, NCs coated with cancer cell-derived membranes, or synthetic peptides designed from CD47 antigen had a prolonged circulation time *in vivo* [46]. Another study demonstrated that coating NCs with CD47 enabled selective evasion of phagocytic clearance by distinct macrophages [47]. In Table 1, we detail selective examples of CCM-associated adhesive molecules. Over all, CCM functionalization on synthetic NCs can evade immune clearance and exhibit homotypic targeting behavior, which extensively improves their cancer-specific accumulation and retention ability [31].

CCMCNCs for the targeted therapeutics delivery

Despite significant improvements and innovations in cancer nanomedicine, effective treatments for cancer remain a major challenge [48]. For instance, a recent meta-analysis reported that an average of just 0.7% of any injected NP dose reaches tumors [49]. CCM-coating (CCMC) strategies have been suggested to solve this potential problem by enhancing homologous targeting and the intratumoral penetration of NCs to the primary tumor as well as their metastatic spread [19–21]. In addition, CCMC on the NC surface represents a valuable strategy that might prevent the premature release of therapeutics in the bloodstream and increase tumor-specific accumulation, thereby avoiding adverse effects [10]. The application of the CCMC method to a variety of NC surfaces has demonstrated the engineering flexibility of the platform [19,50–53]. Individual formulations can be customized and tailored to address the specific needs of cancer treatment [31,52–54]. Recent advances in material sciences, preparation methods, and computational models to study the mechanisms of controlled therapeutic release have led to the ability to create tunable NC systems capable of localized and sustained delivery, facilitating enhanced therapeutic indices of anticancer therapeutics [27,55,56]. Fang *et al*. first explored a homotypic targeting strategy for MDA-MB-435 cancer cell-targeted drug delivery, where they coated PLGA NPs with plasma membranes derived from the same type of cancer cells [19]. The resulting core-shell NPs had breast cancer (MDA-MB-435) cell surface adhesion domains and exhibited a strong homotypic affinity for the source cancer cells, resulting in 20- and 40-fold higher cellular uptake than naked PLGA-NPs and RBC membrane-coated NPs, respectively [19]. Circulating tumor cells (CTCs) prefer to form aggregates, mediated by homotypic adhesion molecules, to prevent anoikis in the circulation and establish metastatic nodules [35,57,58]. Sun *et al*. developed a smart nanoplatform based on the homotypic aggregation of metastatic cancer cells. They used 4T1 metastatic breast CCMs for functionalization on paclitaxel (PTX)-loaded polymeric NCs comprising poly-caprolactone (PCL) and pluronic copolymer F68 [31]. These 4T1-CCMCNCs retained CAMs, including TF-antigen, E-

TABLE 1

Selective CCM-associated proteins critically responsible for the adhesion of cancer cells and cancer cell-derived extracellular vesicles

CCM-associated adhesive protein family	Selective proteins
Cadherins and catenin	Cadherin-1, 2 and 19; protocadherin; catenins (α, β, and γ); desmoglein (DSG2 and DSG3); desmocollin (DSC2 and DSC3)
Integrins	αvβ3, αvβ5, α5β1, α6β4, α4β1, and αvβ6
Ig-SF CAMs	ALCAM, Contactin, ICAM, MCAM, NCAM
Tetraspanins and CD44	CD9, CD151 and CD44
Integrin-associated proteins	CD47
Non-Ig-SF CAMs	EpCAM
G proteins and GPCRs	CXCR4, CD97

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cadherin, CD44, CD326, and the self-signaling protein CD47. The authors showed that the 4T1-CCMCNCs were preferentially targeted to breast cancer cells, but not lung fibroblast and macrophage cells. Additionally, the accumulation of PTX in primary tumor and metastasized pulmonary tissue increased by 3.3- and 2.5-fold, respectively, when delivered using 4T1-CCMCNCs instead of uncoated NCs [31]. Zhu *et al*. devised doxorubicin (DOX)-attached magnetic Fe_3O_4-NCs (MNCs) coated with membranes of human squamous carcinoma (UM-SCC-7) cells [20]. The authors demonstrated the homologous adhesion and enhanced cellular internalization of MNP@DOX@CCMCNCs to the source cancer cells by coating the MNP@DOX with the specific cell membrane derived from a variety of cancer cell lines, including UM-SCC-7 and HeLa (human cervix carcinoma) cells [20].

Interestingly, these studies proved that the self-recognition of the same cancer cells consequently led to highly tumor-selective self-targeting to the homologous tumors *in vivo*, even in competition with heterotypic tumors. Personalization of cancer-targeted therapy using a patient's own cancer cells to coat the NPs could enhance the delivery of therapeutics to the site of cancer metastasis [59]. Gdowski *et al*. demonstrated a new bioinformatics strategy for the target validation and personalized design of CCMCNCs to treat bone metastatic prostate cancer [59]. They used The Cancer Genome Atlas (TCGA) database of patients with metastatic prostate cancer to identify targets and used that information to design personalized CCMCNCs [59].

Applications of CCMCNCs in cancer treatment

Nanotheranostics

Cancer nanotheranostics (CNTs) is a relatively new and rapidly growing field that combines the advantages of cancer diagnosis with therapy [60]. The ability to bundle both therapeutic and diagnostic capabilities into a single package offers exciting prospects for the development of cancer nanomedicine [61]. Nanotheranostics, including semiconducting quantum dots (e.g., CdSe), metallic (e.g., Au), magnetic (e.g., Fe_3O_4), metal-organic frameworks, and multifunctional NCs have opened a new horizon for applications in both cancer diagnosis and therapy [62,63]. However, their biomedical applications have been limited because of their surface properties, which are often recognized and rapidly cleared by immune cells [54]. Currently, surface engineering of NCs with lipids and polyethylene glycol (PEG) or RBC membrane-derived lipid vesicles has been used to enhance the biocompatibility and extend the blood circulation time of CNTs [64]. Despite the clinical translation of an increasing number of PEG-engineered NCs, the accelerated blood clearance (ABC) phenomenon has been reported [65,66]. Although RBC membrane coating has been proven to enhance circulation half-life, RBCs do not have targeting molecules and are not suitable for tumor-specific targeting [67]. As a potential solution, CCMCNCs have been exploited to enhance the circulation and targeting efficiency of CNTs [21,54]. As discussed above, CCAM and CD47 on the CCMCNCs offer homologous targeting and enhanced circulation [31]. Co-delivery of anticancer therapeutics and diagnostics within CCMCNCs has been shown to have promising synergistic anticancer effects in various experimental studies [52]. For instance, Chen *et al*. developed CCMC indocyanine green (CCMC-ICG) NCs for homologous targeting with dual-modal imaging (fluorescence and photoacoustic imaging) and photothermal therapy [50]. The CCMC on ICG-coated NPs (ICNPs) provided enhanced homologous tumor binding and led to high accumulation of ICG nanoprobes in the tumors, resulting in real-time dual-modal imaging, with high spatial resolution and enhanced photothermal effects [50]. In another study, Rao *et al*. developed CCM-cloaked upconversion nanoparticles (UCNPs), a lanthanide-doped nanocrystal that can convert near-infrared (NIR) radiation to visible light, representing a promising new generation of CNTs. Incorporation of CCMs with UCNPs exhibited immune system-evading properties, and homologous targeting capabilities with remarkable NIR fluorescence emission performance [54]. Sun *et al*. decorated DOX-loaded gold nanocages (AuNs) with 4T1 breast cancer cell-derived membranes to achieve concurrent tumor imaging and dual-modality treatment [21]. Upon NIR irradiation, the AuNs produced heat that eradicated surrounding cancer cells via a hyperthermia effect. The produced hyperthermia triggered DOX release from the CCMC DOX-incorporated AuNs (CDAuNs) to improve chemotherapy against breast cancer cell metastasis [21]. Li *et al*. developed a novel biomimetic nanoplatform comprising the bioreductive drug tirapazamine (TPZ)-loaded porphyrinic metal organic framework PCN-224 with a homologous 4T1 CCMC (TPZ@PCN@Mem) for tumor-targeted combination therapy. The prepared TPZ@PCN@Mem nanotheranostic platform exhibited favorable immune evasion and selective accumulation in tumor tissues [52]. The versatile theranostic nanoplatform (TPZ@PCN@Mem) generated large amounts of reactive oxygen species (ROS) under light irradiation to kill tumor cells, whereas the hypoxic tumor conditions, aggravated by photochemical oxygen depletion, resulted in the accelerated activation of the delivered TPZ for bioreductive chemotherapy [52]. This combination of photodynamic therapy (PDT) and hypoxia-activated chemotherapy with homologous cancer targeting was efficient for both primary tumor ablation and distal tumor metastasis inhibition [52].

Nanobioreactors

Tumors renew their energy metabolism to support their rapid proliferation, survival, metastasis, and resistance to cancer treatments. Since the discovery of the Warburg effect, numerous studies have shed light on several aspects of cancer energy metabolism, with the goal of finding new cancer treatments [68]. Glucose oxidase (GOx), which converts glucose into gluconic acid and H_2O_2, is potentially useful for synergistic cancer starvation and oxidation therapy [69]. Ying *et al*. developed a cancer-targeted cascade bioreactor for synergistic starvation and PDT by embedding GOx and catalase in the CCMC porphyrin metal-organic framework (MOF) of a porous coordination network (PCN-224). Porphyrin-based Zr-MOF PCN-224 was used as the nanophotosensitizer, and also as a nanocarrier for GOx and catalase. CCM-derived lipid vesicle functionalization on the GOx and catalase-loaded PCN–224s yielded superior biocompatibility, immune system-evading properties, and homotypic targeting behavior to the cancer-targeted cascade bioreactor (mCGP) [53]. Once internalized by cancer cells, the mCGP promoted microenvironmental oxygenation by catalyzing the endogenous H_2O_2 to produce O_2, which would subsequently accelerate the decomposition of intracellular glucose and enhance the production of cytotoxic singlet oxygen ($1O_2$) under light irradiation. This would further improve

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therapeutic efficiency by synergistic starvation therapy and PDT. The amplified synergistic effects of long-term cancer starvation with PDT efficiently inhibited tumor growth after a single administration [53]. Similarly, Balasubramanian *et al*. developed a biomimetic nanoreactor comprising undecylenic acid-modified thermally hydrocarbonized porous silicon (UnPSi) NPs that provided a favorable microenvironment for entrapped horseradish peroxidase (HRP) and isolated CCM materials derived from MDA-MB-231 breast cancer cells. The enclosed membranes could function as artificial organelles inside cells to counteract the oxidative stress involved in an array of human diseases. Enzyme activities and kinetics analyses showed enhanced substrate affinities and reaction rates compared with those of the free enzymes, suggesting that the nanoreactors had high catalytic activity. Furthermore, the authors demonstrated that the CCMC nanoreactors were cytocompatible and readily integrated with cells while remaining intact and being intracellularly stable.

Tumor hypoxia has been proven to cause resistance to chemotherapy [70]. To acclimate to a hypoxic microenvironment, tumor cells increase the transcriptional activity of hypoxia-inducible factor-1 alpha (HIF-1α), which is involved in angiogenesis, invasion, and metastasis of tumor cells. HIF-1α has also been implicated in resistance to chemotherapy by enhancing the expression of P-glycoprotein (a membrane efflux pump) that recognizes different cancer therapeutics and transports them out of the cells, causing chemotherapy failure. To mitigate this issue, recently, Tian *et al*. developed CCMCNCs with a polymeric core encapsulating hemoglobin (Hb) as an oxygen carrier and DOX [71]. The designed CCMCNCs preserved CCAMs on the surface of the NCs for homologous targeting and have the oxygen-carrying capacity of Hb for O_2-interfering chemotherapy. The authors showed that the designed CCMCNCs not only accomplished higher tumor specificity and lower toxicity by homologous targeting, but also significantly reduced the exocytosis of DOX by suppressing the expression of HIF-1α, multidrug resistance gene 1, and P-glycoprotein, consequently offering safe and highly efficient chemotherapy [71].

Cancer immunotherapy

The immune system has the natural capacity to detect and kill tumor cells. This property of the immune system can prevent the development of many cancers. The rapidly advancing field of cancer immunology has produced several new methods of treating cancer, called immunotherapies, which increase the strength of the immune response against cancer. Immunotherapies either stimulate the activities of specific components of the immune system or counteract signals produced by tumors that suppress immune responses. Immunotherapeutic strategies, including oncolytic viruses, adoptive transfer of *ex vivo* engineered immune cells (activated T, dendritic, and natural killer cells), and administration of antibodies or recombinant proteins that either stimulate the immune cells or block the immune checkpoint pathways, such as monoclonal antibody blocking of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD1), are now being described at a breathtaking pace [72,73]. In addition, the development of cancer vaccines has attracted great interest in recent decades [74–76]. In particular, nanovaccine platforms mimicking the key features of surface molecular organization and physiochemical properties, such as the size and shape of biological entities, has emerged as a new concept in cancer vaccine development [77–79]. Integrating synthetic NCs with CCMs holds tremendous potential for cancer immunotherapy. CCMC offers a full array of tumor-associated antigens (TAAs) to immune cells, thereby stimulating robust tumor-specific immune responses [12,19,80]. Fang *et al*. initially developed a CCMC nanovaccine platform by coating the membranes of human melanoma cancer cells on immunological adjuvant-loaded PLGA NPs [19]. This cancer nanovaccine platform enabled the colocalization of numerous tumor antigens, together with immunological adjuvants, in a stabilized particulate form, which facilitated the uptake of membrane-bound tumor antigens for efficient presentation and downstream immune activation [19]. Additionally, the CCMC nanovaccine platform holds more promise as cancer vaccines than do individual TAAs because the immune cells can elicit immune responses to several TAAs [81]. In a recent study, Fontana *et al*. developed multistage nanovaccines based on breast CCM (MDA-MB-231)-coated immunoadjuvants (acetylated dextran-coated porous silicon) for cancer immunotherapy [80]. The breast cancer cell (MDA-MB-231) membrane-coated thermally oxidized porous silicon (TOPSi@AcDEX@CCM) nanoplatform promoted the expression of co-stimulatory signals (CD80 and CD86) in immune cells and enhanced the secretion of proinflammatory cytokines (Interferon-γ) in peripheral blood monocytes (PBMCs), thereby provoking a Th1-mediated immune response [80]. In another study, Jin *et al*. demonstrated the potential application of human primary glioblastoma CCM (U87)-coated PLGA-NPs in cancer immunotherapy [51]. Subcutaneous injection of these U87-CCMC NPs triggered a tumor-specific immune response by inducing $CD4^+$, $CD8^+$ T lymphocytes in the lymph nodes and spleens of a Balb/c mouse model [51]. Interestingly, Noh *et al*. designed immunomodulatory tumosomes using tumor cell-derived antigens and immunostimulatory lipid (3-*O*-desacyl-4′-monophosphoryl lipid A (MPLA) as adjuvant tumor cells, together with conventional synthetic lipids. These multifaceted tumosomes delivered the cancer antigens along with immunostimulatory adjuvants to prime a long-term adaptive immune response in tumor-draining lymph nodes as well as in the spleen. Furthermore, injection of this hybrid tumosome led to the cessation of cancer growth [82]. In a recent study, Kroll and co-workers applied the concepts of cancer cell mimics nanotechnology to improve the efficacy of tumor cell vaccines. These authors provide exciting evidence that encapsulating vaccine adjuvants in CCMC nanocarriers can be an efficient method of stimulating anticancer immunity [83].

Concluding remarks and future perspectives

Biomimetic engineering strategies have the potential to greatly enhance the biocompatibility and functionality of diverse NC platforms [9,27,84]. In particular, integrating synthetic NCs with functional CCMs is becoming more important in the cancer-targeted delivery of therapeutics and theranostics [9,19,44,51]. These CCMCNCs can interact with homologous cancer cells using their CCAMs, enabling the therapeutics or theranostics to act specifically on tumor cells, without adversely affecting healthy cells (Fig. 1). In addition, CCMC on NCs also provides a camouflaging effect on the NCs via their self-signaling protein (CD47), thereby enhancing the circulation half-life of the NCs. CCMs have

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TABLE 2

Summary of CCM-derived vesicles currently used for coating various NPs for therapeutic deliveries targeting cancer cells

Cancer cell line	Core material	Therapeutics/Theranostics	Application	Refs
B16-F10 and MDA-MB-435	PLGA-NPs	MPLA	Targeted drug delivery; cancer immunotherapy	[19]
UM-SCC-7	MNPs	DOX	Targeted drug delivery	[20]
4T1	AuNs	DOX	Targeted-triggered drug delivery	[21]
4T1	Polymeric NPs	PTX	Targeted drug delivery	[31]
MCF-7	Polymeric NPs	ICG	Fluorescence and photo-acoustic imaging; photothermal therapy	[50]
4T1	Porphyrinic metal organic frameworks, such as PCN-224	TPZ/PCN-224	Photodynamic therapy; hypoxia-amplified bioreductive therapy	[52]
4T1	PCN-224	GOx and catalase/PCN-224	Cancer-targeted synergistic starvation; photodynamic therapy	[53]
MDA-MB-435	UCNPs	UCNPs	Targeted cancer imaging	[54]
MCF-7	PLGA-NPs	Hb and DOX	Targeted oxygen interference therapy for breaking hypoxia-induced chemoresistance	[71]
MDA-MB-231	Acetylated dextran (AcDEX)-coated silicon NPs	Model antigen (Trp2) CCM-associated proteins as antigens	Cancer nanovaccines	[80]
B16-F10	NA	MPLA and dimethyldioctadecyl ammonium	Cancer immunotherapy	[82]
A549	Tumor cell-derived microparticles	Oncolytic adenovirus	Cancer biotherapy	[72]
H22	Tumor cell-derived microparticles	DOX/methotrexate (MTX) and cisplatin	Chemotherapy	[86]
A549	Tumor cell-derived microparticles	Cisplatin	Chemotherapy	[85]

the full array of TAAs that stimulate the enhanced cancer antigen-specific immune response, possibly enhancing current cancer immune therapies. Furthermore, the application of the CCMC method to a variety of nanomaterials has demonstrated the engineering flexibility of the platform. Individual formulations can be custom made and tailored to address the specific needs to treat a certain cancer. The NC core can be modified to implement precise characteristics to aid the efficient and effective delivery of therapeutics. Furthermore, CCMCs can be selected for each specific treatment protocol. For example, CCMs can be utilized as a targeting strategy for solid tumors (e.g., breast cancer and prostate cancer) and potentially, circulating and metastatic cancers.

Looking forward, CCMCNCs could also be endowed with additional properties that are not native to the cell membrane through additional surface functionalization procedures or genetic engineering of the source cells to overexpress proteins of interest (POIs), or by combining the membranes of two different cell types, which might add another degree of freedom to the CCMCNC platform.

Despite current progress in preclinical research of CCMCNCs, numerous challenges need to be addressed before translating from bench to bedside. First, the source of CCM could raise several problems. For example, numerous cancer-associated proteins are present on CCMCNCs. Among these, only a few are responsible for robust targeting, whereas others are liable to induce immune responses and adverse effects. To identify the potential proteins and remove the unwanted proteins would enhance the performance of CCMCNCs in targeted cancer therapy. In general, the preparation of CCMCNCs is complex and the yield of final product is low. Alternatively, extracellular vesicles (EVs), subnano-sized membrane vesicles released by tumor cells, have been investigated for their potential application in therapeutics and theranostics delivery systems for antitumor therapy [72,85,86]. In Table 2, we detail recent preclinical investigations on the CCM-derived vesicle-based therapeutics delivery system. However, there is an urgent demand to simplify and scale up the preparation process of CCM-derived vesicles for robust clinical translation. Commercialization and clinical investigation of cancer nanomedicine has accelerated in recent years, although CCMCNCs are still relatively new. We predict that these CCMCNCs will soon be subject to significant translational studies. To accommodate this, a shift in focus from preclinical development to clinical translation will need to occur, because methods and workflows for reliable scale-up of CCMCNCs fabrication will become increasingly important. Recent developments in microfluidic technologies could be used to tackle the manufacturing issues and might speed up the clinical translation of novel cancer nanomedicines.

Overall, as researchers continue to explore CCMC strategies, new and exciting platforms will be developed with the potential to drastically alter the present scenario of cancer nanomedicine. In the future, although numerous challenges need to be systematically investigated, we believe that these biomimetic cell membrane-coated nanomaterials could open an exciting new area in precise diagnosis and therapy for various human diseases, including cancer.

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