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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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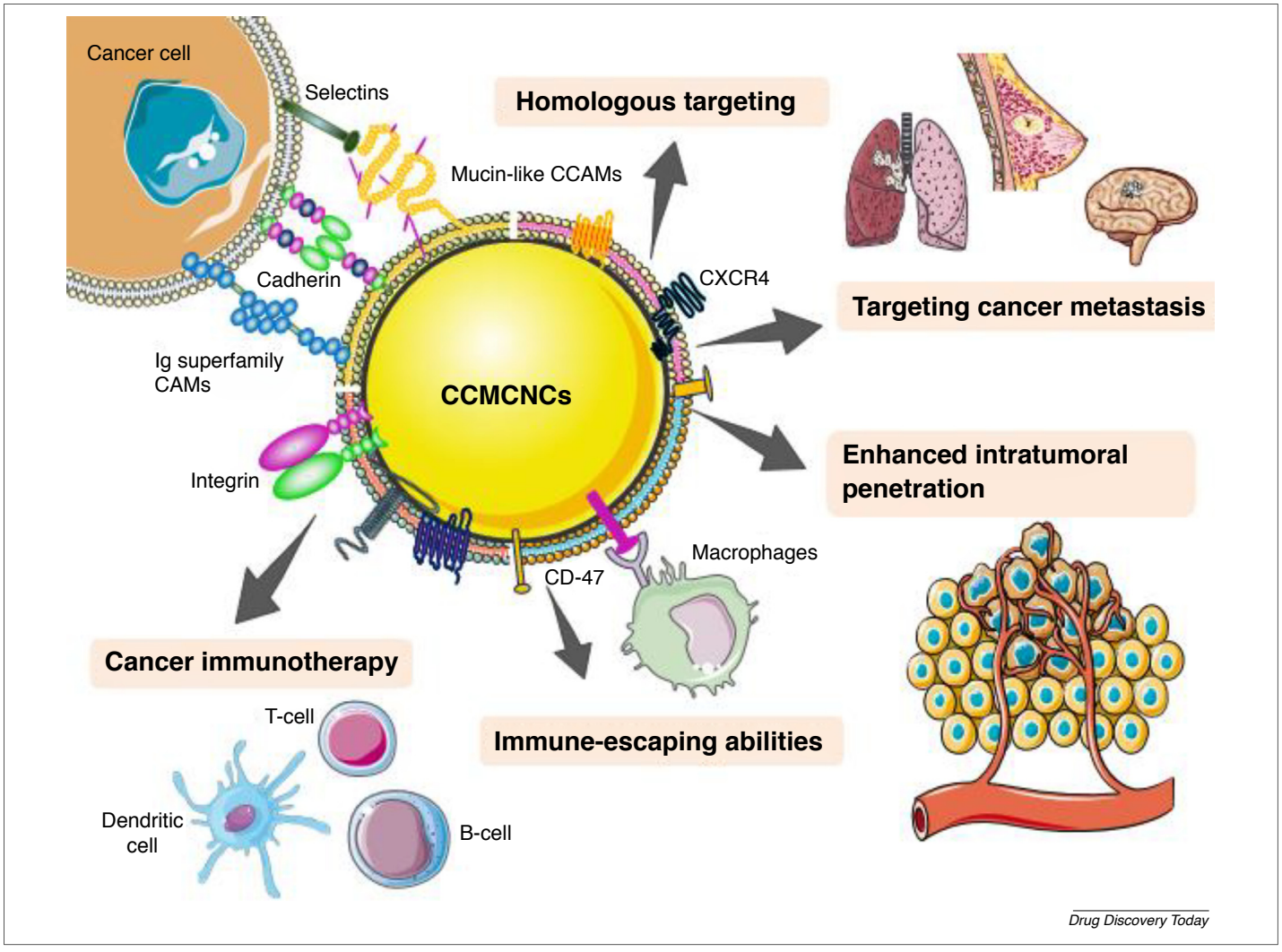

FIGURE 1

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-