Commentary

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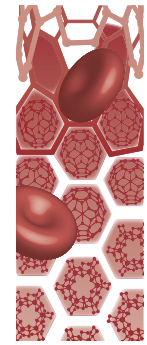

Dressing of multifunctional nanoparticles with natural cell-derived membranes for the superior chemotherapy

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"The inherited intrinsic properties of these membranes make them exceptional; they mimic the parent cell's characteristics and have been reported to be successful in superior cancer therapy"

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Nanocarriers are advanced therapeutic vehicles designed to carry therapeutics in a nano-sized core for superior efficacy [1]. Recently, researchers have been attracted to the study of advanced approaches in cancer therapy, such as hybrid phototherapy/chemotherapy, as they can allow diagnosis and treatment in a single modality [2]. Several limitations are associated with conventional cancer treatment approaches; for example, surgical removal carries the risk of off-target tissue damage and bleeding, and radiotherapy and chemotherapy are associated with many adverse side effects leading to low specificity of the therapy for cancer and multidrug resistance [3]. Conventional nanocarriers for cancer therapy have short residence times in systemic circulation and, most importantly, are considered a foreign body by the immune system and are often expelled from systemic circulation even before reaching the target site [4,5]. These limitations have motivated scientists to overcome the poor targetability and accumulation of chemotherapeutics in the target tissues.

To overcome the limitations of conventional nanocarriers, many research groups have recently developed unique nanocarriers with surfaces that have been modified by incorporating specific ligands [6,7]. These nanocarriers are encapsulated by membranes derived from innate cells to reduce immunorecognition and sequestration of the nanocarriers by immune cells, thereby maintaining prolonged circulation of therapeutics (in membrane-coated nanocarriers) in the blood [8] and improving their deposition and accumulation in the targeted cancerous cells [9]. In addition, the incorporation of specific ligands improves the targetability of membrane-coated nanocarriers to the target site, which endows superior chemotherapeutic efficacy compared with conventional nanocarriers [10].

Clinicians have considered various anticancer drugs for the treatment of different cancers. Notably, different drugs such as alkylating agents, nitrosoureas, antimetabolites, antitumor antibiotics, topoisomerase inhibitors and mitotic inhibitors are being used to treat various cancers [11,12]. The outcomes of these established drugs have been promising during clinical trials, and, therefore, these are currently used as first-line treatments for cancer [11]. Traditional chemotherapeutics offer a higher survival rate and better chemotherapeutic effects compared with modern offerings involving nanocarrier technologies, but the side effects and long-term consequences of chemotherapy, such as gastric distress, vomiting, hypersensitivity, cardiovascular toxicity (for cisplatin) and peripheral neuropathy (for taxanes),

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remain a significant cause of concern for patients and clinicians. Furthermore, metronomic therapy with anticancer agents becomes more limited over time and has resulted in the emergence of drug resistance [3]. In addition, the established classes of drugs such as platinum-based chemotherapeutics resulted in hypersensitivity reactions in a group of patients; a study by Ruggiero *et al.* reported that children administered carboplatin for the treatment of solid tumors exhibited hypersensitivity in almost 50% of cases [13]. Another case where cisplatin resulted in severe side effects in the form of cardiovascular disease after the concurrent use of this drug was shown by Herradon *et al.* [14]. Therefore, to improve the therapeutic efficacy, biosafety and bioavailability of these drugs, many studies have investigated the role of novel drug-delivery systems (NDDS) in cancer therapy. These NDDS have been combined with other modalities (imaging, diagnosis and treatment) to form combinatorial cancer therapies in which the movement of a drug can be precisely monitored in systemic circulation in preclinical and clinical studies.

For diagnosis and treatment, various multifunctional nanocarriers such as polymeric nanoparticles, liposomes, magnetic nanoparticles and lipid-based nanoparticles (solid-lipid nanoparticles and nanostructured lipid nanocarriers) have been investigated and described in the literature as having superior therapeutic efficacy compared with conventional therapies [15–17]. This superiority over conventional therapies involves various advantages, including higher drug payload, better permeation, higher drug solubility and superior bioavailability [18]. These advantages attracted scientists to consider these nanocarriers for the delivery of therapeutics; however, liposomes seem ineffective in cancer therapy due to several limitations, including poor structural integrity leading to the leakage of drug content and instability during long-term storage [19,20]. Polymeric and metallic nanoparticles also have several limitations, for example, higher toxicity and poor biocompatibility with the biological milieu [20]. Most of these nanoparticles were investigated in trials and failed due to severe side effects and toxicities. Nonetheless, a few of these nanoparticles have been translated from laboratories to clinics and successfully approved by the US FDA for biomedical applications [21]. The limitations of polymeric and metallic nanoparticles necessitate the development of such nanocarriers that mitigate and reduce immune rejection and toxicities, increase the circulation time of the nanocarriers in systemic circulation, increase the targeting ability to the target site and improve quality biodistribution. The development of nanocarriers by biomedical engineering enables the exploration of the potential of these nanoparticles to overcome various complications associated with the conventional approach.

The construction of biomimetic nanoparticles is achieved by encapsulating the nanocarrier in a natural cell membrane, such as a red blood cell membrane, white blood cell membrane, leukocyte membrane, platelet cell membrane or cancer cell membrane [22–24]. These membranes can be separated and extracted by various lysis techniques, such as repeated freezing and resuscitation, hypotonic treatment and mechanical extrusion, without altering the intrinsic properties of the membranes [25,26]. The inherited intrinsic properties of these membranes make them exceptional; they mimic the parent cell's characteristics and have been reported to be successful in superior cancer therapy [27,28].

This strategy of encapsulating drug-loaded nanocarriers in a natural cell membrane, which replicates the complexities of the parent cell, offers many benefits. The advantages of these nanoconstructs are that they effectively dodge immune clearance and provide long blood circulation times [29]. Some inherent membrane proteins can also help them to target the cancer cells. For example, CD47 protein is crucial and plays a main role in enhancing the circulation of membrane-coated nanocarriers. In addition, the unique ability of CD47 to exert a 'do not eat me' signal helps the membrane-coated nanocarriers escape immune invasion via the mechanisms of the reticuloendothelial system and opsonization [30]. Such mechanisms reduce the off-site targeting and immune clearance, thereby increasing the retention of these nanocarriers in the blood for a longer period and ultimately, enhancing the accumulation of therapeutics at the target site [31,32].

One important point that cannot be overlooked is the retention of membrane functionalities (i.e., proteins and lipids) throughout the construction of the nanocarriers [33,34]. These functionalities provide an additional boost to the performance of the nanoparticulate system due to the presence of intrinsic functionalities of the membrane. As discussed with respect to CD47, this strategy offers remarkable stealth and immune evasion; it can also improve the targetability of nanocarriers to the cancerous cells, thereby reducing toxicities on noncancerous cells and off-target sites, and, therefore, increasing overall therapeutic efficacy [18]. The strategy can also allow the carriers to respond to environmental stimuli such as pH, redox potential as local stimuli responsiveness, magnetic field, light and ultrasound [35]. To illustrate the case, Zhang *et al.* designed macrophage-membrane-coated nanocarriers for tumor-targeted chemotherapy. The mechanism of drug release from these nanocarriers is followed by the response to the endosomal pH change of the tumor. This strategy showed improved therapeutic effects inherited from both membrane-derived tumor accumulation and step-by-step controlled drug release [36]. In another case, redox stimuli,

the difference between diseased cells and the normal cell environment activates the nanocarrier to target and release the drug at the specific site. In inflamed disease conditions, the innate inflammation-directed chemoattract ability of macrophages could migrate the nanocarriers to accumulate in inflammatory tumor tissue, thereby contributing to successful chemotherapy [37].

To design these nanoparticulate systems and their functionalization utilizing intrinsic functionalities involves various methods such as lipid insertion, membrane hybridization, metabolic engineering and genetic modification. The lipid insertion method usually incorporates a functional ligand through a lipid anchor. In this method, insertion onto the membrane relies on the physical method rather than chemical interaction, which avoids the alteration in intrinsic properties of the membrane by the chemical method [38]. Second, the membrane hybridization technique is quite complex, in which cell membranes are derived from two different cells such as red blood cells, white blood cells and specific tumor cells for boosting the chemotherapy. This method usually aims to reduce the undesirable binding of nanocarriers around the target site. However, the complexity of this method restricts its application even in preclinical models [39].

In the case of metabolic engineering, the natural biosynthetic pathway is altered and harnessed for activation and expression of a ligand onto cell membrane-coated nanoparticles. The method requires a thorough understanding of the biochemistry of the cellular metabolism of that specific cell membrane, which has undergone further modification with the metabolic substrate [40]. Therefore, this method is also considered a restricted method for biomedical engineers to incorporate ligands on the cell membrane. Last, the gene modification technique is an advanced method that induces and actives new functions by altering the expression of proteins and genes on the cell membrane. This method can effectively express the desired ligands with high affinity to the target cells, ultimately improving targetability [41]. Recently, the genetic modification technique has been combined with CRISPR/Cas9 technology, which endowed an efficient, economical and faster approach to editing the cell membrane's genes and enhancing the tumor cells' targetability by membrane-coated nanocarriers [42]. Therefore, biomedical engineers have widely explored and applied these methods to enhance the functionalization of the natural cell membrane, which supports superior chemotherapy.

To construct these nanocarriers, the initial step is to extract the membrane from the mother cell by removing the intracellular components without altering the intrinsic properties of the membrane. The removal of intracellular content can be achieved by freeze-thaw, discontinuous sucrose gradient treatment and electroporation. The freeze-thaw method is mostly preferred to extract the cell membrane from nonnucleated cells, such as red blood cells and platelets. Although, the process of membrane extraction at -80°C (freeze) and at 37°C (thaw) in repeated cycles can damage the integrity of the membrane, resulting in the loss of membrane structure, reduced protein stability and reduced overall functionalities of the membrane [10,22]. The discontinuous sucrose gradient method is the commonly preferred method by biomedical engineers for the lysis of the cell membrane. This technique is employed for the removal of intracellular biomolecules, vesicles and nuclei. The electroporation technique lysis the mother cell by exposing cells to electric fields. Exposure to a strong field can irreversibly reduce the integrity of cell membrane by deteriorating lipid symmetry and causing protein denaturation [43].

The coating of the membrane onto the nanocarrier is achieved by other methods such as physical extrusion, sonication methods and microfluidic techniques [44]. This entire process of membrane removal from the parent cell and coating it over the nanocarrier is delicate. Therefore, special attention should be paid when choosing a method for constructing such multifunctional nanocarriers, due to the retention of proteins and natural ligands on the cell membrane, which is of prime importance when considering such a strategy for developing nanodecoys. The membrane coating strategy has been reported extensively in the literature. It provides various advantages such as suppressing the reticuloendothelial system uptake, prolonging the nanoconstructs' circulation lifetime, improving the vasculature permeability of the tumor and improving biomedical targeting and imaging [45].

A report published in *Nature* unraveled the relationship between the red blood cell membrane-coating nanoparticulate system and its internalization into target cells. The main objective of this study was to evaluate a fluorescence quenching assay to probe the extent and integrity of cell membrane coating over nanocarriers. The findings surprised biomedical engineers as they demonstrated that almost 90% of such nanocarriers were partially coated, which directly affected the uptake of nanocarriers to the target site, as the nanocarriers uptake starts with an initial adhesion of nanocarrier to the target cell and interaction with the lipids, proteins and other components of the cell membrane [46]. Notably, the clathrin-mediated pathway is involved in the uptake of these membrane-coated nanoparticles. Also, the higher extent of coating of the cell membrane on the nanocarrier allowed higher cellular uptake due to the interaction of caveolin and lipid rafts in endocytosis and the fusion of membrane-coated

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nanocarriers [47]. Furthermore, the molecular simulation in the experimental investigation exhibited the endocytic mechanism for the internalization into the target site. Therefore, this strategy revealed an effective and successful approach for superior chemotherapy [46].

Similarly, another investigation by Xue *et al.* described the role of the neutrophil in the cloaking of paclitaxel (PTX)-loaded liposomes (PTX-LPs) for targeting postoperative malignant glioma. These researchers constructed PTX-loaded liposomes and successfully exploited the neutrophil's native ability to effectively transverse the blood–brain barrier or blood–brain tumor barrier by incubating PTX-LPs with neutrophils. The physiological functions of these nanocarriers were determined by various activities, including the expression of a specific protein (CD11b), chemotaxis and superoxide anion production, determined using flow cytometry. In addition, other studies were performed, such as drug release at the target site, evaluation of inflammatory cytokine expressions and brain targetability to ensure a successful approach to the suppression of postoperative glioma. The investigation is based on the inflammation-responsive strategy. The inflammation that occurs due to the removal of brain tumors results in the release of inflammatory factors in the blood, such as IL-8 and TNF-α, which upregulate neutrophils and acts as a chemoattractant for constructed liposomes. These PTX-loaded LPs migrated along the chemoattractant gradient in the blood and infiltrated tumor cells in the inflamed brain in a spontaneous and demand manner. The treatment with these liposomes endowed inhibitory effects on tumor recurrence in the glioma mouse model [48]. Cao *et al.* constructed celastrol-loaded polymeric nanoparticles with a neutrophil membrane for superior chemotherapy [49]. The study's outcomes demonstrated that proinflammatory cytokines such as TNF-α and IL-1β were significantly downregulated by these nanocarriers, which resulted in the traversing of the pancreas's blood barrier and enhancing the targeting ability to the tumor site [49]. Therefore, the ability to recognize chemokines and proinflammatory makers enables its wide application in targeting tumor cells [48,50].

These nanocarriers mimic the biological milieu of the target site and are known for their immune escape and targeting ability. Considering their biomimetic strategy, cancer cell membranes have also been used to design such nanocarriers, since the membrane retrieved from the mother cancer cells has intrinsic functional abilities. Cancer cell membranes show a range of antigen and tumor-specific adhesion moieties such as MUCO1, gal-3, integrins and cadherins. Such intrinsic unique antigens play an important role in immune invasion and self-protection. Numerous studies have demonstrated the application of the cancer membrane coating technique and its superior effect in cancer therapy by improving the targeting to the site, prolonging the blood circulation time of the nanocarrier and its unique ability of immune invasion. Hence, these advanced nanoconstructs have been proven effective in superior cancer therapy; however, their translation from laboratory to clinic requires further exploration and investigation.

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