Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2022.42.006724

Cell Membrane Nano Vesicles as Drug Carriers: Biomedical Applications

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ARTICLE INFO

Received: February 18, 2022

Published: March 01, 2022

Citation: Mahfuzul Islam. Cell Membrane Nano Vesicles as Drug Carriers: Biomedical Applications. Biomed J Sci & Tech Res 42(2)-2022. BJSTR. MS.ID.006724.

Keywords: Inflammation; Nanotechnology; Cell Membrane-Derived Vesicles; Membrane Engineering; Drug-Delivery Systems

Abbreviations: RBCs: Red Blood Cells; EVs: Extracellular Vesicles; CARs: Chimeric Antigen Receptors

ABSTRACT

The biofunctionalization of nanoparticles (NPS) is a critical step in delivering specific therapeutic agents. Although nanotechnology has progressed, it still falls short of simulating the complex intercellular connections that happen under physiological settings in human bodies. Because cell membrane-derived vesicles contain the intrinsic functions and signaling networks of their parent cells, they can overcome a wide range of challenges encountered in the living cell. Furthermore, the many natural combinations of membranes obtained from distinct cell sources broaden the variety of cell membrane-derived vesicles, resulting in an altogether new category of drug delivery systems. Vesicles produced from cell membranes can transport therapeutic substances within their interiors or coat drug-loaded core nanoparticles' surfaces. When compared to synthetic nanomaterials, emerging concepts have been investigated to utilize human cells to manufacture cell membrane-formed nanoparticles (NPS). This is because cells retain innate capacities to interact with human tissues. Neutrophils, red blood cells (RBCs), platelets, and monocytes have all been used to generate therapeutic nanoparticles (NPs) to treat vascular disease and cancer. These innovative drug delivery platforms can improve patient quality of life. Throughout this study, we will explore numerous cell membrane-nanoparticle designs and uses in nanomedicine and the idea of cell membrane-nanoparticles and their future implications.

Introduction

Cell therapy replaces damaged tissue or cells with intact and living cells obtained from the patient (autologous cells) or a donor (allogeneic cells). Cell therapy may have its origins in 1931 when Swiss physician Paul Niehans attempted to cure a patient by injecting calf embryos. Various cell types have been engineered as novel therapeutics for multiple diseases and conditions due to evolving research and emerging innovative technologies [1-3]. Cells such as erythrocytes, platelets, cancer cells, leukocytes, stem cells, and bacteria may be used. Among these, erythrocytes have a high degree of biocompatibility when used as autologous cells or carriers of therapeutic agents [4,5]. Platelets have been extensively studied as novel drug delivery carriers for enhanced efficacy due to their critical roles in hemostasis and thrombosis and their newly discovered role in the development and metastasis of tumors [6,7]. Synthetic nanoparticles (NPs) have been used to diagnose and deliver drugs to patients suffering from various diseases [8-15]. NPS are synthesized from a variety of materials, including lipids [16,17], polymers [18], proteins [19-22], and metals [23-25]. NPS are frequently conjugated with targeting ligands or antibodies to deliver them to pathological sites in the body [26]. However, the biofunctionalization of NPs is insufficient to replicate the complex and multicellular interactions found in the human body, potentially limiting the efficacy of drug delivery via those nanotechnologies [27,28].

Intercellular communication is critical for survival and homeostasis maintenance in all multicellular systems.

Communication occurs via two major pathways: direct cell-cell interactions and the secretion of soluble signaling molecules by cells. Recent research indicates that an additional mechanism, mediated by extracellular vesicles (EVs), plays a critical role in regulating intercellular interactions over short and long distances [29,30]. To effectively treat cancer, drug delivery systems targeting tumor cells have been developed via the design of targeting ligands conjugated to the surface of nanoparticles [31-34]. Arginine-glycine-aspartic acid (RGD) is a peptide that binds to fibronectin [35] specifically. RGD [34,36] is also a specific ligand for integrin v3, which plays a critical role in tumor angiogenesis and metastasis [37], according to studies. Integrin v expression is significantly higher on endothelial cells lining tumor blood vessels than normal endothelial cells [38]. Integrin v3 is highly expressed on various tumor cells, promoting tumor metastasis [39] and facilitating the migration of immune cells into tumor tissues [40]. Thus, using RGD to deliver therapeutics to integrin v3 may be a novel strategy for tumor intervention [38,41,42]. Despite the remarkable progress described above, cell-based therapeutics face numerous obstacles before being widely adopted for clinical use with increased efficacy [43,44]. One of the most critical impediments is the inability to control the fate of injected cells *in vivo*, which is critical for increasing the percentage of cells reaching target tissues and decreasing off-target accumulation. Therapeutic cells transplanted into the recipient's body may encounter undesirable host immune responses and frequently lose their therapeutic activity due to immune surveillance [45]. Another critical issue is that injecting drugs or drug-loaded nanoparticles into cells may cause damage to the cell membrane and alter the cell phenotype. Some cases may even be cytotoxic to the carrier cells [46].

Leveraging Cell Membranes to form Nano Vesicles as Efficient Drug Delivery Systems

Cell therapy has enormous potential for treating a variety of diseases. For example, genetically engineering isolated T cells from patients with chimeric antigen receptors (CARs) redirected T cell specificity and ushered in a new era of cancer treatment. The exciting news is that the US Food and Drug Administration recently approved CD19-specific CAR T cells to treat children and young adults with B-cell acute lymphoblast leukemia [47]. Additionally, clinical trials involving cell transplantation are being conducted to address cell function deficiencies [48,49]. Additionally, novel strategies for tissue engineering utilizing stem cells are currently being developed at various stages [50]. However, these approaches are frequently constrained by the difficulty of meeting clinical-scale demand for donor cells, as well as the lifelong requirement for immunosuppressive or other adjuvant drugs that enhance cell efficiency but have undesirable side effects [51]. To this end, cell engineering methods have been proposed to address concerns about rejection by host immune systems by immunoisolating the cells using microcapsules or three-dimensional scaffolds [52-54]. Although promising, complications arise due to the foreign-body response induced by the implant materials, which manifests as immune cell recruitment, fibrous deposits, restricted nutrient passage, and eventual cell death.

Additionally, additional work is necessary to evaluate the accuracy of transplantation and the extent of engrafted cells to optimize the therapeutic outcome [55]; as a result, other transformative cell engineering technologies are in high demand for biomedical applications. CCells' ability to communicate with one another and their environment enables them to perform complex tasks and adapt sophisticated biological entities in the body system. As a classic example, the various proteins on the membrane of red blood cells (RBCs) facilitate information exchange with phagocytes, thereby alleviating complement-mediated attack and prolonging circulation [56]. Furthermore, it has already been illustrated that the recruitment of specific cells in response to chemokines contributes to immune responses, disease development, and tissue formation [57]. Using the knowledge gained from these processes, efforts have been made to incorporate therapeutic constructs into natural cells to develop the next generation of delivery platforms [57-59] As a further evolution," top-dow" procedures have been proposed in which synthetic nanomaterials are disguised as cellular membranes to recapitulate the original cells' critical functions and thus increase nanomaterials' utility [60-62]. These approaches to cell engineering alleviate the host immune response and preserve the complexity and, most importantly, the biological functions of innate cells, conferring enhanced therapeutic efficacy. This Account will highlight recent research conducted in our laboratory that focuses on newly developed cell engineering technologies for cancer immunotherapy, targeted drug delivery, and diabetes treatment.

Cell Membrane Surface Repertoire / Different Sources/ Utility and Bio Functionality

It's a hot scientific area right now, and exosomes play a vital part in transmitting information from cell to cell. Exosomes, as previously said, have the potential to be a next-generation biological instrument for the delivery of therapeutic compounds in the body. The ability to target the brain due to BBB permeability is one of the advantages of exosomes, which also have several advantages, including infinite secretion, artificial encapsulation of biofunctional molecules, controlled expression of synthetic proteins in exosomal membranes, (iv) low cytotoxicity, (v) regulated immunogenicity, (vi) efficient use of cell-to-cell communication routes, and (vii) low

cytotoxicity. There are several problems to exosome-based delivery systems, including inadequate cell targeting and absorption effectiveness and insufficient cytosolic release of exosomal contents. Because of this, significant advances in the design of advanced exosome-based delivery systems are necessary shortly. Biofunctional peptide-modified exosomes were used to design and demonstrate a novel drug delivery system, completed and demonstrated. A pH-sensitive fusogenic peptide is used to promote the cytosolic release of exosomal contents in this approach, which is based on arginine-rich cell-penetrating peptide-modified exosomes for active macropinocytosis and intracellular delivery of therapeutic compounds [63]. Understanding the dynamic architecture of cell membranes is the most difficult component of membrane research to accomplish. However, it was not until the 1970s that it was discovered that lipids and proteins could migrate laterally inside the lipid bilayer, signaling that cell membranes function as fluids [64]. Asymmetrical lipid organization in the bilayer's two leaflets was also demonstrated at the time [65], and this was confirmed afterward. Specific flippases are responsible for flipping lipids from one leaflet to the other to preserve the correct asymmetry under conditions of excessive energy consumption [66]. It was Vittorio Luzzati, in the 1960s, who found another remarkable property of lipid bilayers, demonstrating that they could fold into a variety of variants with distinct symmetries [67]. These are three-dimensional structures with a high curvature, which periodically exhibit periodic cubic structures. This extraordinary property indicated that lipids have an unrivaled ability to construct a wide range of architectural structures in their environment. Additionally, the move from a planar bilayer structure to cubic membranes needs little energy, allowing cells to self-organize and self-organize dynamically in a large number of situations. Until recently, the only polymorphism that has found its way into biology has been cubic membranes [68,69].

Extraction of Cell Membrane & Formation of Nano Vesicles

Considering that they have a hollow core structure, cell membrane-derived vesicles are an excellent choice for coating material for various therapeutic cargo-loaded nanoparticle formulations. The coating of therapeutic nanoparticles made of various materials and forms, as well as the encapsulation of tiny molecules within their interior, have been accomplished using cell membrane-derived vesicles in recent years. Molecular core nanoparticles entrapped in cell membranes are designed to function either as drug transporters or as a therapeutic agent in and of themselves [70]. By coating a nanoparticle with the cell membrane, developers can take advantage of the synergistic properties afforded by the cell membrane and the core components to create new products. When loaded with drugs, nanoparticles with lipid bilayer structures, such as those found in cell membrane-derived vesicles, may operate as an additional physical barrier, inhibiting the release of the loaded drug(s) from the nanoparticle core [71]. Drugs encapsulated in polymeric core nanoparticles that have been successively coated with cell membranes have been shown to have a prolonged release after being injected. One investigation discovered that RBC vesicles released more than 50% of the encapsulated doxorubicin in the first 16 hours [72] after being implanted. Doxorubicin was encapsulated in a polylactic acid core and then coated with an RBC membrane, which was demonstrated to delay the release, with 50 percent release observed after 36 hours [73]. Due to the difference in release kinetics, it has been determined that the cell membrane can operate as a diffusion barrier. Encasing nanoparticles within vesicles formed from cell membranes makes it feasible to increase medication loading in the body. When PLGA nanoparticles were wrapped around cell membrane-derived vesicles, it was demonstrated that the doxorubicin loading content increased to 21 percent [74], as opposed to a maximum loading content of 10 percent when cell membrane-derived vesicles were not wrapped around a nanoparticle core [75]. A variety of small compounds, including doxorubicin [76], indocyanine green [77], and clarithromycin [78], as well as macromolecules, such as glucose oxidase [79] and growth factors [80], have been enclosed in core nanoparticles for delivery. One more benefit of using a cell membrane coating is that it improves the biocompatibility of the underlying material. Because cell membranes are composed of biodegradable and naturally occurring lipids, proteins, and carbohydrates, cell membrane coatings may potentially lower the cellular toxicity of the core material used in the coating. Metal [81,82], carbon [83], and gold [84] nanoparticles are among the nanoparticles that have been covered with cell membranes, according to the researchers. Immune cell opsonization and phagocytosis of plasma proteins have been demonstrated to be reduced when a cell membrane coating is applied [85]. This results in a longer circulation period for the core material. The ability of cell membrane-derived vesicles to adopt a variety of morphologies depends on the cell membrane's fluidity. Core materials can be coated with cell membrane-derived vesicles in various shapes, including spherical [86], nanocube [87], and nanorod. In one application, iron oxide/manganese oxide nanocubes were coated with U-251MG cancer cell membranes to improve delivery to tumor tissues [87].

Characterization of the Nanovesicles

Vesicle size, polydispersity index, and zeta potential were determined at 25 1 **°C** using the Dynamic Light Scattering method and a Zetasizer Nano ZS instrument (Malvern Instruments, United Kingdom) [88,89]. Before being characterized at a scattering angle of 90°, samples were diluted with filtered phosphate buffer saline and then characterized again at the same angle. When determining

the surface charge of drug-loaded vesicles, the Zetasizer Nano ZS was used (Malvern Instruments, Malvern, UK). After 60 seconds of investigation, the average zeta potential of the vesicles was calculated, which provided insight into the morphology of nano-transfersomes. When using an 80 kV voltage setting for transmission electron microscopy (JEM-1011, JEOL, Tokyo, Japan), pictures of nano-transfersomes can be obtained. An appropriate thin layer of the nano-transfersomes drop was allowed to develop and cure adequately on a copper grid. The samples were inspected with a transmission electron microscope [90]. The effectiveness of entrapment is determined (percent). This study used an Ultra Centrifuge (OptimaTM Max-E) to test the effectiveness of entrapment of EM-loaded nanotransfersomes vesicles for one hour at 40,000 rpm and four degrees Celsius [91]. It was necessary to properly separate the supernatant and quantify it using the HPLC method [92]. The entrapment efficiency was calculated with the help of the equation shown below.Regarding percent entrapment efficiency, the formula is (T - C)/T 100, where T signifies total electromagnetic field and C means electromagnetic field detected exclusively in the supernatant.

Future Prospects

We reviewed the present state of the art in cell membrane-covered nanoparticles and highlighted significant biological applications from a biomedical standpoint. Cell membrane-specific functions and qualities such as lengthy circulation time, immune evasion, antibioadhesion, and tissue-specific targeting are transferred to synthetic materials through biomimetic techniques. The goal of the biomimetic strategy is to produce cell-like nanoparticles utilizing a top-down assembly approach that bridges the gap between synthetic materials and biological entities, further motivating the design of theranostic systems in terms of their physical structure. A further advantage of the proposed technique is that it is free of chemicals and includes the bioactivity of membrane-related components into the nanoparticle surface-engineering process. Meanwhile, the amazing diversity of parent cells (RBCs, platelets, stem cells, cancer cells, immune cells, and microbes) provides a plethora of coating types that can be conjugated with nanoparticles for various biomedical applications due to the incredible diversity of parent cells. Cell membrane-covered nanoparticles will have many benefits over their uncoated counterparts in future applications such as *in vivo* drug delivery, bioimaging, and cancer therapy. More to the point, most synthetic nanoparticles can be covered by cell membranes, resulting in biomimetic platforms that are biocompatible and immunogenic regardless of their hydrophobicity, surface potential, size, or morphology. The use of a single kind or conventional types of cell membranes as coating materials, on the other hand, may restrict the range of functions available to the coating. As coating components in the future, it is recommended that mixed cell membranes or novel cell or bacterial membranes be utilized. Therapeutic nanoparticles will work better *in vivo* if they have a variety of integrated components that contain a wide range of biological moieties and functionalities. When considering the inclusion of ligands into cell membrane coatings to boost synergistic performance in biomedical applications, consider ligands made of antibodies, DNA/RNA, peptides, proteins, and enzymes, among other things. Furthermore, cell membrane-covered synthetic nanoparticles are still hampered by complex preparation procedures, easy deactivation, large-scale synthesis, and challenging preservation; these difficulties should be explored and solved in the future, as well as by the limitations of current technology. Research into cell membrane-covered nanoparticles should also focus on translating findings from experimental studies to therapeutic applications.

Conclusion

This article discusses nanoparticles' many designs and applications with various cell membranes in nanomedicine. Because these nano systems were initially designed to extend their circulation time. They were initially examined using red blood cell membranes, as these cells are known to circulate for extended periods in the blood. Due to this technology's adaptability, it has been applied to the membranes of a range of different cell types, including white blood cells, platelets, cancer cells, mesenchymal stem cells, and beta cells. By leveraging this cellular diversity and unique features and the capacity to use a variety of nanoparticles and drug delivery systems, an entirely new sector of nanocarrier manufacture with multiple uses has opened up. Notably, cell membranes possess a variety of features, including the ability to regulate physical contact, immunological evasion, and homologous targeting. The remarkable technology demonstrated here is that the nanoparticles' coating preserves the cell membrane's characteristics. Membrane-coated particles may be utilized to prevent autoimmunity to a specific antigen in the future. As a result, the application possibilities for these nanocarriers are practically endless and undiscovered. Coating nanoparticles with cell membranes has generated substantial interest in the clinical area due to membranes' immunomodulatory properties in treating diseases such as bacterial infections and cancer. Indeed, it has been demonstrated that injection of these coated nanoparticles enhances antigen-specific immunity. Additionally, this coating technology makes nano vaccines, which promote broad immunity to attack specific targets. We believe that nanocarriers will be created for use in medicine to promote human health in the future. To summarize,

this technique possesses several advantages and cellular diversity, enabling it to be applied to a wide variety of medical conditions. As a result, it has not been deployed fully in a clinical context.

Conflict of Interest

No conflict of interest with any institution/organization.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2022.42.006724

Mahfuzul Islam. Biomed J Sci & Tech Res