Biomimetic and Biologically Originated Nanoparticles for Drug Delivery Applications: A Brief Overview and Update

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ABSTRACT

Biomimetic and biologically originating nanoparticles are an exciting new form of drug delivery system. Examples of biologically originating nanoparticles include exosomes and other extracellular vesicles, lipoproteins, ferritins, and virus-like nanoparticles. These nanoparticles can range anywhere from 5 nm up to 1000 nm and can come in different configurations depending on the nature of the nanoparticle. Various types of drugs can be loaded into these nanoparticles including hydrophobic, hydrophilic, small molecule, and nucleic acid drugs. Specific loading techniques have been developed for each nanoparticle specie. These naturally occurring nanoparticles all undergo a similar processing process, in which they are collected, purified, and functionalized for use as drug delivery systems. The scale and relative availability within our own bodies presents a significant difficulty to using biological nanoparticles for commercial applications. Using recombinant nanoparticles, produced by bacterium and other microorganisms, is a viable alternative to human derived nanoparticles, but does require more processing to become functional. Although there are many advantages to using biologically originating nanoparticles for drug delivery, such as high target specificity, great biocompatibility, and biodegradability, they are limited by their stability, scalability, and safety as they are largely unstudied compared to current drug delivery models. Further work must be done to fully characterize and fully realize the potential of these nanoparticles.

Introduction

Nanomaterials have been a focus of innovation in the field of material science over the past decades [1]. Nanomaterials of interest include nanotubes, nanofibers, and nanoparticles (NPs) [1]. The type of nanostructure is highly dependent on the material the structure is synthesized from; for example, nanotubes are made from graphene sheets, whereas nanofibers are commonly formed from polymers in industry [2,3]. NPs are microscopic spheres characterized by having a diameter of less than 100 nm [1]. Industrial applications of NPs range from energy-based research, environmental applications, and as catalysts [4]. Traditionally these nanomaterials have been synthetically produced by industry, but there are also examples of naturally occurring NPs synthesized within our own bodies and other organisms, which has become a recent topic of interest within biomaterial and tissue engineering [5].

Biologically originating NPs are biologically manufactured by organisms using biological materials; this is an important distinction to make to differentiate between biological NPs and natural NPs [6]. Biologically originating NPs have various biomedical applications, such as biomarkers, contrast agents, and as drug delivery systems [7]. Biologically originating NPs are synthesized in various parts of the organism and can be broadly defined into two groups: intracellular structures; and extracellular assemblies [5]. Intracellular structures are found within the cell and are typically cellular organelles, such as the magnetosome [5]. As the name suggests, extracellular structures can be found in the extracellular environment, such as lipoproteins [5]. Biologically originating NPs have various functions within the living organism, making them better suited to specific biomedical applications than others [5]. Generally, biologically originating NPs all have a similar structure; a macromolecular core (ex. nucleic acids, proteins, etc.)

encapsulated by an outer membrane [5]. This nanostructure makes biologically originating NPs a very attractive engineering model for drug delivery [8]. In addition, biologically originated NPs have inherent advantages over physiochemically produced NPs; these include improved cytotoxicity and biocompatibility, more pharmacologically active, reproducible and scalable, and environmentally friendly [5, 9].

This review aims to give an overview of the biologically originating NPs used in drug delivery systems, including (1) a description of their chemical and physical structure; (2) where they are biologically produced; and (3) advantages and disadvantages in drug delivery systems. Further, current applications of biological originated NPs will be covered, with a critical evaluation of future trends of the technology.

Classifications of Biological Nanoparticles

Exosomes

Exosomes are nanoscale vesicles that are secreted from many different types of cells within the body [5]. Exosomes are an example of an intracellular structure biologically originated NPs, and are a specific type of extracellular vesicle (EV). Exosomes are formed through the budding of endosomal membranes found throughout the intracellular environment [10]. Within the cell, exosomes are contained within multivesicular bodies (MVB) and are released into the extracellular environment when the MVB fuses to the cell's plasma membrane [11]. Exosomes are comprised of a phospholipid bilayer surrounding a macromolecule core, such as various nucleic acids or lipids [5]. Exosomes range in size from 40 nm - 150 nm in diameter; exosome membranes are highly rich in cholesterols and sphingolipids and feature a variety of membrane-associated proteins [5, 12]. Membrane-associated proteins found within endosomes can include endosome-associated proteins like Rab proteins and lipid raft-associated proteins like flotillin [13]. These membrane-associated proteins help make exosomes effective platforms for drug delivery. For example, lipid raft-associated proteins can help pharmacological signalling pathways [14].

Exosomes have many different functions, depending on the cell type from which they are secreted. For example, exosomes secreted from mesenchymal stem cells (MSCs) carry mRNA, proteins, lipids, and other functional macromolecules to target cells, transmitting signals and facilitating bulk transfer from the MSC [15]. Generally, exosomes facilitate intercellular communication by transporting chemical messengers and nucleic acids [11]. Exosomes use receptor-ligand interactions to bind to their target cells membrane [11]. Once the exosome binds and fuses to the target cell, they enter the cell through endocytosis, releasing their contents once inside the recipient cell, propagating the chemical signal and affecting cellular processes [11].

Exosomes are attractive drug delivery models due to their physical and chemical structure [11]. Due to the biological origin of exosomes, they avoid phagocytosis, lysosomal engulfment, and do not initiate an immune response within the host. Due to the ligand-receptor relationship, exosomes exhibit excellent specificity [16]. Exosomes are easy to isolate from biological fluids; they can be isolated using differential centrifugation, filtration, size-exclusion chromatography, polymer precipitation, and immunomagnetic isolation [11]. The phospholipid bilayer of exosomes effectively protects the contents, reducing drug degradation before reaching the target cell [11]. As well, it is relatively easy to load exosomes with therapeutics. Loading can be done through incubation, freeze-thaw cycle, sonication, extrusion, electroporation and simple mixing [11]. Due to their hydrophilic core, exosomes are readily loaded with water-soluble therapeutics. The physiological function of exosomes as chemical and nucleic acid messengers makes them an effective delivery model for interference RNAs (siRNA) [11].

Exosomes readily take up a variety of therapeutics, are biocompatible, and are extremely specific in the cells they affect. Further, research has shown exosome compatibility between different species [17]. Using allogeneic exosomes for the synthesis of drug-loaded exosomes makes it a very commercially attractive option, with easy scalability.

Lipoproteins

Lipoproteins (LPs) are spherical biological nanoparticles produced within the intestines and the liver [18]. LPs are composed of a hydrophobic lipid core surrounded by a hydrophilic phospholipid membrane [19]. Within the membrane are embedded apolipoproteins which are used to bind other lipids. LPs can be categorized into five different classes depending on the composition, density, and size of the molecule. The smallest LPs are the high-density lipoproteins (HDLs) which can be as small as 5 nm, while the largest class, the chylomicrons, can be as large as 1000 nm [18]. Intestinal-originating LPs facilitate lipid transfer from the intestines to be stored by various tissues around the body, whereas liver-originating LPs carry lipids from tissue stores to the liver to be catabolized [18]. Because of the hydrophilic membrane surrounding LPs they are excellent molecules for transporting hydrophobic materials within aqueous solutions. LPs interact with fat metabolizing cells through receptor interactions, such as the scavenger receptor class B type 1 (SRB1). These receptors can be over expressed within cancer cells and atherosclerotic plaques, making LPs an attractive drug delivery model [18].

Biological lipoprotein genesis can be endogenous, occurring within the hepatic cells of the liver, or exogenous using dietary lipids for LP synthesis within the intestines. Both endogenously and exogenously originating LPs are important molecules in lipid metabolism within the body. LPs can also be synthetically produced by combining lipids and peptides in solution. By varying the relative compositions of the lipid and peptide components the size and density of synthetic LPs can be controlled and tailored to mimic those of naturally occurring LPs. LPs can be found and isolated from various biological fluids from within the body including blood, lipoaspirate, cerebral spinal fluid, and conditioned media [18]. LPs are easily separated from the majority of other components of these fluids due to the size and density of LPs. Due to the similarity in size and density of exosomes and LPs it is difficult to obtain an isolated sample of LPs when both of these nanoparticles exist in solution [18]. In order to avoid exosome contamination further separation must be done using ultracentrifugation, tangential flow filtration, size exclusion chromatography, and immune-based precipitation [18]. Synthetic LPs do not require the same filtration and isolation techniques as their biological counterparts but are limited by the cost and complexity of the synthesis process.

Although similar to liposomes, lipoproteins are significantly different in that they contain a hydrophobic core and apolipoprotein containing membrane. These differences make LPs an attractive drug delivery method that could replace the use of liposomes as a drug delivery model [18]. Liposomes can be used as drug delivery methods to treat fungal infections as well as to carry chemotherapeutics in cancer therapy; the clinical applications of liposomes are severely limited by their short circulation times, which can cause a host immune response [18, 20]. LPs are an alternative to liposomes and can be loaded with a range of both hydrophobic and hydrophilic drugs due to the heterogenous, hydrophobic core-hydrophilic membrane, structure of LPs [18]. Hydrophobic, lipophilic therapeutics can be incorporated into the core of the LP, while hydrophilic therapeutics can be chemically conjugated onto the LP membrane [21, 22]. Low-density lipoproteins (LDLs) and HDLs are the primary LPs used for drug delivery as they easily penetrate tissue due to their size and show target selectivity through receptor-ligand interactions [18]. Examples of therapeutic agents that have been delivered by LPs include chemotherapy, nucleotides, imaging agents, and anti-human immunodeficiency virus drugs [18].

Lipoproteins can be used to carry a variety of drugs, show good stability in circulation, and avoid host immune response. They show target selectivity when treating cells which overexpress LP receptors, such as in certain cancer cells. Commercial scalability of biological and synthetically synthesized LPs is limited by the cost of synthetic LP manufacturing and contamination of biologically originating LPs by exosomes [18].

Ferritin

Ferritin is a globular protein complex made up of 24 subunits which is used to store intracellular iron [23]. There are two different subunits which make up the ferritin complex, the heavy chain which gathers iron and the light chain which stores the iron. Ferritin self assembles to form nanosized spherical cages approximately 12 nm in diameter with

an internal core of 8 nm in diameter [24]. Where ferritin is found in the extracellular environment, in serum, it can be an indicator of inflammation and is associated with some forms of cancer. Cells bind ferritin through the human transferrin receptor 1 (TfR1), which causes the ferritin to be absorbed through endocytosis into the cell [24]. Ferritin sequesters iron from the body into its hollow core, protecting the host from the toxic pro-oxidative effects of iron, and stores it until it is needed [24]. Ferritin can be engineered to store therapeutics and diagnostic molecules in its core instead of iron, making it an attractive biologically originating nanoparticle for drug delivery [25]. Ferratin can be easily loaded with small molecule therapeutics and can exhibit specificity through binding target receptors to the surface [24].

Many organisms naturally produce ferritin, making it an easily produced and scaled nanoparticle [25]. The purification efficiency of natural ferritin poses a difficulty when used for commercial applications, making recombinant ferritin advantageous in large scale applications. Bacterium, such as *Escherichia coli*, have been used to produce recombinant ferritin for drug delivery applications and are easily purified and loaded. Ferritin can be loaded with both small molecule therapeutics and metal nanoparticles, as an imaging agent [24]. Techniques for ferritin loading include pH-induced disassembly, salt-induced disassembly, diffusion-based encapsulation, and surface conjugation [24]. Further, ferritin can be modified to respond to certain stimuli by surface ligand conjugation, accelerating the rate of ferritin breakdown and thus the rate of drug elution [24].

Ferritin is a very stable nanoparticle which can be used to deliver both hydrophobic and hydrophilic small molecules therapeutics [24]. It is easily scaled and uniform in size, making it an attractive nanoparticle. Ferritin is limited in its target specificity, but through genetic engineering these properties are being improved and new ligands are being explored to combat this [24].

Virus-Like Nanoparticles

Virus-like nanoparticles are derived from viral coat proteins, envelope proteins, or core proteins [26]. Although derived from viral components they are non-contagious and biocompatible, as they lack any viral genetic information. They have applications in vaccine development as well as cancer therapeutic delivery methods [26, 27]. They can range in size from 20 to 200 nm and can vary in shape from helical to globular, depending on the virus the nanoparticle is derived from [26]. Virus-like nanoparticles can exhibit strong immune-responses from T and B cells, making them effective models for vaccines. Because of their size and the nature of viral derived nanoparticles, they are easily taken up by antigen-presenting cells (APCs) [26]. The vaccine applications for virus-like nanoparticles are limited by the size of the nanoparticle, as larger particles aren't as readily distributed and can conglomerate at the site of injection [26]. Virus-like nanoparticle vaccines can be categorized into three groups depending on their structure: enveloped virus-like nanoparticles, non-enveloped virus-like nanoparticles, and chimeric virus-like nanoparticles [26].

Virus-like nanoparticles can also be engineered as a delivery method for cancer therapeutics [27]. Virus-like nanoparticles can be loaded with therapeutics through assembly of covalently linked molecules; co-assembly, both pre-programmed and nonspecific molecular interactions; templating assembly; or through diffusion of small molecular therapeutics. Various types of therapeutic can be loaded into virus-like nanoparticles, including small molecules and nucleic acids (ex. mRNA, siRNAs) [27].

Although useful in drug delivery and disease treatment, virus-like nanoparticles are limited in their clinical capacity by poor stability and high production costs [26]. The purification and processing of virus-like nanoparticles add a lot of embedded costs. Optimization of this process may make virus-like nanoparticles a viable commercial drug delivery model in the near future [26].

Clinical Applications of Biological Nanoparticles for Drug Delivery

Cancer therapy

Cancer is the second leading cause of death and is a major problem globally; new therapeutic methods have emerged to tackle the problem. The conventional method is through chemotherapy; however, this method indiscriminately kills both normal and cancer cells. Therefore, studies seek new methods for the precise therapy of cancer. Nanoparticle-based drug delivery systems are being increasingly used in studies of cancer treatments with the benefits of precise cancer cell targeting, good pharmacokinetics, prevention of drug resistance, and reduction of side effects from conventional treatments [28]. Nanoparticles used as drug delivery systems in cancer are usually chosen and designed based on the size and characteristics of the target tumour. Mechanically, they target tumour cells through the carrier effects of nanoparticles and the position effect of the targeting substance [28]. Then drugs within the nanoparticles would be released into tumour cells, exhibiting cytotoxic effects. Nanocarriers could enter the tumour site through two mechanisms: by taking advantage of the persistent enhanced permeability and retention (EPR) effect of the tumour environment or through ligand binding of the receptors on the surface of nanoparticles [28].

Targets of cancer drugs are mostly intercellular, where drugs are required to cross the cell membrane before they can act on the tumour cells. However, premature degradation and poor water solubility make it difficult to achieve desirable therapeutic effects. Biological nanoparticles such as exosomes, which contain a lipid bilayer that can protect the drug content in vivo, are therefore a great alternative. The interaction between the recipient cells and exosomes membrane proteins makes it easy for them to enter the cells. Studies were performed on various cancers. A study found that exosomes loaded with cisplatin can prolong the lives of ovarian cancer mice without side effects on the kidney or liver that would have been caused by administering cisplatin alone [29]. Another study demonstrated that macrophage-derived exosomes could load paclitaxel with better stability and efficiency and effectively inhibit Lewis Lung Carcinoma cell proliferation [29]. Moreover, exosomes acquired from tumour cells are found to deliver drugs back to the tumour cells more accurately than standard therapeutics. Test results showed that prostate cancer cell-derived exosomes more effectively deliver paclitaxel into the prostate cancer cells [30].

The fact that lipoprotein receptors are overexpressed in some tumours allows lipoprotein-based drug delivery systems to deliver chemotherapeutic drugs to cancer cells. Cancer cells also rely on cholesterol uptake carried by endogenous lipoproteins as needed for accelerated membrane synthesis [31]. Passive loading was used to load drugs into lipoproteins where high density lipoproteins HDLs were found to incorporate cancer drugs more efficiently than LDLs, but results are subjected to change according to the type of drugs loaded [31]. Paclitaxel-loaded HDLs have shown a significant decrease in the half-maximal inhibitory concentration dose (IC50) compared to direct free administration in breast, prostate and ovarian cancer cell lines. Drugs can also be conjugated to lipoproteins [31]. For example, synthetic LDL chemically conjugated to paclitaxel through oleate can improve therapeutic effects in glioblastoma multiforme cell lines. Effects are more pronounced in cancer cells that exhibit high levels of LDL receptors in which a similar study shows LDL conjugated paclitaxel shows more enhanced toxicity in glioblastoma than hepatocarcinoma [31].

Biomimetic nanoparticles such as tumour-targeting-cell-membrane-based nanoparticles are membrane-camouflaged nanoparticles that mimic native cell types to remain in the circulation longer to reach tumour sites [32]. For example, red-blood-cell-based nanoparticles express CD47 markers on the surface to prevent being cleared out. Targeting was also improved with the presence of leukocyte proteins (e.g. LFD-1 and Mac-1), where leukocyte-based nanoparticles were found to improve doxorubicin delivery in melanoma and breast cancer in mice model [32]. Platelet-coated membranes that target circulating tumour cells take advantage of the interaction between tumour cells and platelets present during metastases. A study shows that treatment using these biomimetic nanoparticles in doxorubicin delivery shows a more significant accumulation of drugs within breast cancer tumours [32].

These studies highlight the success in using biological and biomimetic nanoparticles in cancer drug delivery by increasing targeting accuracy and accumulation within cancer cells for a higher cytotoxic effect.

Cardiovascular disease

Cardiovascular disease (CVD) is another disease that costs many lives every year. Poor solubility and stability of drugs, off-target effects and short systemic circulation give rise to challenges for free drugs to give desirable therapeutic effects. Nanoparticles become a powerful tool to deliver therapeutics for CVDs stably.

Lipoproteins are endogenous carriers for insoluble substances such as fat or cholesterol in the aqueous environment of blood. Although lipoproteins are involved in CVD progression, it can also reverse CVD and atherosclerotic events by acting as a drug delivery system. In a study, HDL nanoparticles were loaded with simvastatin, enabling specific drug delivery to the site of atherosclerotic plaques [33]. They were tested on Apo E knockout mice and showed high drug levels at the site, inhibiting plaques' formation and decreasing inflammation. Another drug, tanshinone IA, was loaded into HDL particles in another study. In vivo HDL was remodelled into a spherical shape, and drugs were delivered to foam cells in atherosclerotic lesions, where results show a strong anti-atherogenic effect in animal models [33].

The bloodstream has always been a barrier when designing nanoparticle carriers. Nanoparticles are always being removed from the bloodstream. One of the most successful attempts to overcome the rapid clearance of nanoparticles from the bloodstream is by incorporating polyethylene glycol [34]. However, detrimental effects may happen after multiple administrations where the host immune response may be activated. The solution to this would be using biomimetic nanoparticles. Most biomimetic nanoparticles are designed to target the activated endothelia that occur in inflammation [34].

With the expression of CD47, erythrocytes have a long-circulating time that prevents it from undergoing phagocytosis initiated by the mononucleate phagocyte system. Erythrocyte-membrane-coated polymeric spherical nanoparticles were therefore designed to elongate the circulation time. It is found that this design elongated the circulation time of nanoparticles by 2.5 folds [34]. In the same study, it was found that loading rapamycin, an immunosuppressive drug that inhibits smooth muscle cell proliferation, in this nanoparticle design enhances the accumulation of drug at atherosclerotic plaques and slows down atherosclerosis progression and improve toxicity profiles [34].

Leukocytes contain markers CD45 and CD47 that also increase their blood circulation time. In an attempt to avoid clearance by the mononucleate phagocyte system, leuko-like vectors were made by coating leukocyte membranes onto the nanoparticle [34]. Leukosomes were later made to enhance therapeutic effects by purifying leukocyte membrane proteins and integrating them onto the walls of lipid bilayer nanoparticles. Rapamycin was delivered into the body; the release of the drug was localized to the atherosclerotic region of the aorta. It was found to reduce vascular inflammation in Apo E deficient hypercholesteraemic mice [34].

Even with much advancement in localizing targeting, increasing the circulation time, and preventing unwanted clearance for the delivery of drugs for CVD, there are currently no nanoparticles clinically available for CVD. More work is needed to determine their capability of active targeting, the stability, storage conditions and contamination control measure before being clinically used.

Infectious Diseases

Infectious diseases are a severe public health crisis, causing symptoms ranging from asymptomatic to deadly. Infectious diseases caused by viruses, fungi, bacteria, and parasites are responsible for many deaths and hospitalizations worldwide. Although antibiotics such as small-molecule drugs and peptides have been developed to combat various specific infectious diseases, antiviral and antibacterial agents have severe side effects due to their systemic exposure [35]. Moreover, new bacteria and viruses are constantly emerging; the rapid emergence of drug-resistant agents and the presence of novel pathogens is why infectious disease remains a serious global health problem [35].

Nanotechnology is a new strategy to overcome the drawbacks of antibiotics and antiviral drugs while potentiating their therapeutic benefits. When treating infectious diseases, antibiotics and biomimetic and biological nanoparticles provide greater complexity, functionality, and biocompatibility [35]. Various antibiotic structures can be trapped in, absorbed, or covalently conjugated with nanoparticles [35]. Nanoparticles have been studied to improve the effectiveness of therapeutics by prolonging circulation time, increasing drug stability and relative availability, targeting infection sites and modulating drug release in response to relevant biochemical signals such as changes in pH or bacterial toxins [35]. Evidence has shown that nanoparticle-based strategies can reduce or even reverse resistance development by changing the delivery route, promoting intracellular uptake, and regulating drug pathogen interactions [35].

Cell membrane-based-biomimetic nanoparticles, such as EVs, have created a new class of treatment, with the critical approach of targeting the source of infection, neutralizing pathogenic mechanisms and modulating immune cells involved in anti-pathogenic responses. Nanoparticles mimicking platelets, epithelial cells and even bacteria have been studied to achieve specific targeting. Overactivation of platelets causes thrombi, a niche where bacteria are protected from the immune system [36]. Utilising this feature of bacteria, platelet-coated nanoparticles can effectively deliver antibiotics. Platelet-coated nanoparticles carrying docetaxel and vancomycin are found to have significant antimicrobial activity in mice that are systemically challenged with a methicillin-resistant strain of bacteria [36]. Another method is to deliver antibiotics using gastric epithelial cell membrane nanoparticles. These nanoparticles present the surface antigens the bacteria would recognize on host cells [37]. Upon recognizing particular proteins, bacteria internalize the nanoparticles that carry lethal antibiotics [37]. Clarithromycin-loaded gastric epithelial cell nanoparticles have demonstrated superior therapeutic efficacy compared to free drop counterparts and their nanoparticle control group [37].

Nanovesicles derived from neutrophil-like cells (HL-60 cells) are another biological nanoparticle used for drug delivery. HL-60 cell-derived nanovesicles, loaded with the anti-inflammatory agent TPCA-1, were used to treat mouse models of lipopolysaccharide-induced lung inflammation by targeting lung vasculature [38]. Results show a significantly decreased inflammatory cytokine expression and neutrophil infiltration [38]. In another study done by the same group, intravenously administered piceatannol-loaded HL-60 cell nanovesicles dramatically reduced local and systemic inflammation of lipopolysaccharide-induced models of acute lung injury and sepsis [39].

There are still tremendous challenges precisely targeting bacteria or infected cells and delivering antibiotics. Exosomes are effective nanoparticles that facilitate the targeted delivery of antibacterial agents. A study showed that exosomes enhance curcumin delivery, a hydrophobic anti-inflammatory drug to activate monocytes in vivo [40]. In a study using mouse models of lipopolysaccharide-induced brain inflammation and lipopolysaccharide-induced septic shock, curcumin-loaded exosomes show more significant protective effects compared to free drugs [41]. On top of that, exosomes can effectively deliver exogenous siRNA to monocytes and lymphocytes. Exosomes successfully delivered an exogenous miRNA-155 mimic was successfully delivered to macrophages by exosomes, which significantly inhibited lipopolysaccharide-induced inflammation [42].

Different nanoparticles have been used to treat infectious diseases. However, there is more extensive use of nanotechnologies or more specifically virosomes or virus-like particles, in the development of vaccines. Other uses of nanoparticles in infectious diseases, such as directly neutralizing toxins from pathogens, are also common.

Neural Diseases

Treatment of brain disorders has been challenging, mainly because of the blood-brain barrier, pharmacokinetics and toxicity of drugs. Therefore, biomimetic nanoparticle drug delivery systems have been developed to change the pharmacokinetics and biodistribution of drugs improving efficacy of the treatment while reducing side effects [43]. They are found to have increased biocompatibility and longer circulation time. Most importantly, in brain disorders, they enable blood-brain barrier penetration and increase drug concentration at the target site. Common methods for nanoparticles to cross the blood brain barrier are through paracellular pathways, passive transmembrane diffusion, carrier-mediated transports, receptor-mediated transcytosis and adsorptive mediates transcytosis [43].

Exosomes have been used in various brain disorders as a drug delivery vehicle. Macrophage secreted exosomes can breach the blood-brain barrier and release the cargo at the desired site in the brain. An example would be edaravone, which is used to protect neuronal cells as an ischemic stroke treatment [44]. The bioavailability of edaravone was improved by loading into exosomes, showing a prolonged half-life [44]. In a study of encephalitis, exosomes were used to deliver brain-derived neurotrophic factors. In the presence of inflammation, the uptake of exosomes was promoted, facilitated by the upregulation of intercellular adhesion molecules. This allowed more exosomes to cross the blood-brain barrier showing increased drug levels within the brain [45]. Reduced levels of antioxidants, such as catalase, have been observed in patients with Parkinson's Disease, which may lead to oxidative stress and neurodegeneration [46]. Catalase encapsulated in exosomes has been found to have prolonged blood circulating effects and improved delivery, increasing the efficacy of small molecules in combating Parkinson's [46]. Alzheimer's disease is associated with the phosphorylation of tau, forming extracellular inflammatory plagues. Curcumin regulates tau phosphorylation; however, it has low bioavailability and poor water solubility. Curcumin-loaded exosomes have shown improved stability, solubility, bioavailability, and ability to cross the blood-brain barrier. Studies on curcumin-loaded exosomes have found high concentrations of curcumin in brain tissue successfully inhibiting tau phosphorylation and improving neuronal function in murine Alzheimer's Disease models.

Biological and biomimetic nanoparticles give greater precision and allow drug molecules to cross the blood-brain barrier, and they hold great potential. However, since the brain is a complex and sophisticated organ, more studies are needed to confirm the stability of these treatments.

Future Directions

Significant progress has been made in biological and biomimetic nanoparticles, paving a new way for delivering drugs into the body. Advancements in engineering allow these nanoparticles to be engineered with features that improve targeting and stability. Fine-tuned properties could also further facilitate immune-modulatory interaction [47]. Work in this field has demonstrated the broad applications of drug delivery systems in various diseases. These nanoparticles have the ability to pass through the body without activating the immune system, but their interaction with the surrounding cells also allows them to directly communicate with cells involved in the disease [47].

Despite the many advantages of these nanoparticles, there are still existing challenges to be faced before transitioning into the clinical setting. Engineering and ex vivo treatments are needed to allow the incorporation of therapeutic substances, which make it challenging to maintain the integrity of the original natural particles. Altering the natural structure may result in more rapid drug clearance from the blood. And therefore, further optimization of these particles is needed. The degradability of these nanoparticles should also be considered when designing them. Engineers must prevent these nanoparticles from staying inside the body for too long, causing side effects, but not so short that they do not produce the wanted results.

Also, these nanoparticles come from natural cells, which give possible batch-to-batch inconsistencies. It may be difficult to ensure consistency with current fabrication techniques. Researchers need to develop quick and effective screening assays to confirm the incorporation of wanted features and the functionality of nanoparticles. Membrane proteins are also an essential part of biomimetic nanoparticles, such as membrane-coated nanoparticles, needed for signalling and binding to specific sites. Undesirable consequences may be caused due to the incorporation of unwanted proteins. Therefore, it is essential to determine the unwanted proteins and effectively remove them.

The safety of some nanoparticles is also an important factor. Nanoparticles that originate from pathogens such as viruses may potentially be immunogenic. Their application is still limited due to the possible risks. The pathogenic component should be removed effectively, and its safety must be thoroughly addressed before use. And although other examples, such as the heavily studied exosomes, do not originate from dangerous pathogenic organisms, technologies or production, storage and quality control are flawed, and there is yet any consensus on the technical standards [31]. Different techniques cause inconsistencies in results and affect the safety outcomes of products.

Conclusion

There are many different kinds of biomimetic and biological nanoparticles, including exosomes, extracellular vesicles, lipoproteins, ferritins, and virus-like nanoparticles to name a few. These nanoparticles have great potential at increasing the efficacy, accuracy and specificity of drugs in diseases such as cancer, cardiovascular diseases, infectious disease and brain disorder. These particles can express extreme specificity and stability. However, there are still challenges and problems to be dealt with before this technology can be widely used in the market, including safety, structure, scalability, and quality control. Most of these nanoparticles are naturally occurring within our own bodies, expressing great biocompatibility and a low host immune-response. Isolating and purifying these naturally occurring nanoparticles is often the limiting factor when trying to commercialize drug delivering nanoparticles. To aide in production, recombinant nanoparticles manufactured by bacterium and other microorganisms can be used to increase production capacities. Although most trials of biologically originating nanoparticles is currently in the preclinical phase, they are an exciting new technology at the cutting edge of tissue engineering which may cataclysmically change how drugs and medicine is administered.

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