Survey of Lipid Nanoparticles Characteristics and Conjugates on the Mechanisms of Drug Delivery for Cancer Treatment

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Lipid nanoparticles are one of only the few FDA approved, and highly bio-compatible vessels for targeted drug delivery via bloodstream and have shown to be particularly effective for the cancer treatment of various types. These nanoparticles exhibit several key characteristics which make them ideal candidate for this purpose, such as, biocompatibility, non-toxic nature, easily modulable to target specific cells and allowing controlled release of the drugs, etc. However, as they travel in the bloodstream and eventually reach the target tumor, they undergo various biological phenomena, e.g. interaction with proteins, segregation of liver and other parts of body, etc. that degrade their effectiveness. This paper is a short review of various important phenomena and mechanisms that lipid nanoparticles undergo during targeted drug-delivery for cancer treatment, which were used to highlight key features of an ideal nanoparticle suitable for intravenous mode of drug administration for cancer treatment. Furthermore, modifications made to these nanomedicines to enable an effective drug-delivery have been discussed along with their corresponding limitations.

Introduction

Nanoparticles have been extensively studied for their application as vehicles for drug delivery for cancer treatments for the past few decades due to significant advantages they offer over the traditional methods for effective treatments of certain critical ailments such as cancer. Various kinds of nanoparticles that have been studied include gold nanoparticles, quantum dots, polymeric nanoparticles, carbon nanotubes, lipid and liposomal nanoparticles, etc. Amongst these, lipid nanoparticles, liposomal, and certain polymeric nanoparticles are the only kinds approved by FDA for the targeted drug delivery and gene therapy [1,2]. The human body has various mechanisms due to which drug delivery can become less effective or ineffective and cause a variation in the responses to treatments, such as unfavorable immune responses to the nanoparticles or drugs. This uncertainty regarding the body's response to the delivery method can create further risk for a patient, especially if the patient is in a treatment in which the drug delivery is not targeted. For example, cancer cells may develop the ability to recognize drugs as toxic agents and, facilitated by ATP-binding cassette transporter proteins, flush them from the intracellular cytoplasm, leaving them ineffective. Breast cancer cells have been noted, often to have a particular resistance protein called ABCG2, responsible for drug efflux in breast cancer cells [3]. The patient may even face further risk from the drug delivery if the body's mechanisms, such as the reticuloendothelial system, filters the nanoparticles from the bloodstream and thus cause the drugs to be released in an organ, such as the liver, in which there is no cancer and cause damage to its healthy tissue. Through the creation of different characteristics- such as size, shape, and surface characteristics- nanoparticles can be given the ability to evade those mechanisms and thus allow the drug to be effective. Each type of nanoparticle has its own uses, benefits, and drawbacks, and thus are suited for different situations.

Nanoparticles are generally categorized into three categories: Organic, hybrid, and inorganic. Examples of inorganic nanoparticles are gold nanoparticles, quantum dots, and silica nanoparticles. They are an area of interest in study due to their unique physical and chemical properties, easily modifiable surface chemistry, and more feasible manufacturing. However, they have found limited application in cancer treatment due to their poor biocompatibility and biodegradability [4]. Amongst these, gold nanoparticles have garnered interest, and generally are more biocompatible, although they have a tendency for aggregation. They are prepared in three different ways but usually produced by solution phase synthesis using hydrogen tetrachloroaurate alongside a reduction step and sometimes stabilized by a cap of citrate which can also reduce aggregation. Gold nanoparticles have found uses in various modes of cancer treatment, such as gene therapy, photothermal therapy and immunotherapy, and even as a probe for imaging [5].

Hybrid nanoparticles are a combination of organic and inorganic material, and thus both of their benefits and drawbacks. Lipid-polymer hybrid nanoparticles have demonstrated promise in certain types of cancers, with both components addressing some of the weaknesses of the other component. Due to the lipid shell, which is generally PEGylated, they display better

Inorganic	Polymeric	Organic
Gold NP	Polymersome	Liposome
Silica NP	Dendrimer	Lipid NP
Quantum dot	Polymer Micelle	Emulsion
Iron Oxide NP		

Fig. 1 Table shows various kinds of nanoparticles being studied for drug-delivery [6].

avoidance of the reticuloendothelial system and biocompatibility, and the polymer core allows for better retention of the drug and overall stability [7]. However, these nanoparticles still exhibit certain limitations. For example, the polymer lacks good biodegradability, and the lipid shell shows relatively low stability.

Organic nanoparticles have been the most extensively studied and applied types of nanoparticles for cancer drug delivery, especially due to their biocompatibility both in delivery and the excretion of the unused drug from the body. The first nanoparticle approved for drug delivery was the liposome, which contains an outer lipid layer and a core consisting of either a hydrophobic or hydrophilic drug. Liposomes are composed of a phospholipid shell that can self-assemble to form a closed bilayer structure in aqueous environments. Due to this, they are effective in preventing degradation of the enclosed drug molecules [8]. They have also been found equally effective in the delivery of other treatments, such as nucleic acids for gene therapy [4]. Also, liposome or lipid nanoparticles (LNPs) have been found to be more effective for certain cancers involving solid tumors and treatments, such as breast cancer [9].

Despite all the developments and the intended primary objective of targeted delivery of drugs using the nanoparticles, it has been found that, less than 1% of nanoparticles end up in the tumor region, with most being eliminated through opsonization, the reticuloendothelial system, or by uptake by organs such as the liver, causing damage and toxicity to those systems [10]. This paper surveys important mechanisms that affect effective transport, compatibility to immune system as well as intake of the drug carrying lipid nanoparticles at the targeted region of the body, such as formation of protein corona, the degree of specificity of the targeted area, physical characteristics etc. Based on the ideal characteristics of nanoparticles for the targeted drug delivery via intravascular administration of medications, this work highlights important areas that need further improvements.

Discussion

a **Protein Corona and Polymer Coatings**
Liposomes, like all other nanoparticles, activate various body mechanisms and interact with plasma proteins, often leading to the formation of a protein corona unique to the characteristics and components of that liposome. A protein corona can disguise the nanoparticle from those mechanisms, such as macrophages, but could also activate an immune response if it is composed of certain complement proteins [10]. Complement proteins are a system of over 30 proteins which attach to foreign objects within the body and can initiate both an activate and innate immune response, even being able to kill pathogens by themselves through the membrane attack complex [11]. It is generally found that once administered intravenously, lipid nanoparticles tend to accumulate in the liver due to their interactions with plasma proteins, which drastically reduces the circulation time of these nanoparticles [12].

Certain polymer coatings not only could help in preventing certain immune agents from recognizing the nanoparticles as foreign objects, but also significantly increase the circulation time and thus enhance the probability of the lipid nanoparticles to reach the targeted tumorous region [6]. Polyethylene Glycol (PEG) has been found to be effective in keeping nanoparticles better hidden from the immune system due to its characteristics such as high hydrophilicity and electrical neutrality. High hydrophilicity would allow the nanoparticles to avoid aggregation, avoid detection by the reticuloendothelial system, and move through the bloodstream more easily, due to its ability to interact with the aqueous content of the body [13]. Additional details about electrical neutrality have been discussed in the section "Physical Characteristics." Lipid nanoparticles can be easily cleared from the body due to their non-covalent intermolecular interactions, however that can also make them unravel in the process of delivery. This early unraveling can also be prevented by PEG, giving the nanoparticles a longer circulation time with a protective coating, helping in delaying their unraveling [6].

A study by Berger et al. examined the impact of various lipid-PEG on protein corona formations. They found that at the point at which the PEG coating of the lipid nanoparticles degraded, there was a rapid increase in the size of the nanoparticles from the proteins and a significant decrease in the protein concentration of fetal bovine serum in which the nanoparticles were immersed [14]. These findings indicated that the PEG coating provided a useful barrier for the lipid nanoparticle structures from the adsorption of proteins in their surrounding environments. Additionally, they found that certain types of lipid nanoparticles can help reduce the degradation of the PEG. For example, C18 acyl chain LNPs were found to have had minimal change in their size and the surrounding protein concentration, while the C14 LNPs, with shorter chains, had rapid desorption of the PEG membrane and increased its size due to accumulation a protein corona [14]. Thus, the effectiveness of

PEG can be aided through certain types of LNPs, which can lead to longer lifespans of the nanoparticles and better stealth against the innate and active responses of the immune system.

However, it is important that the molecular ratio of PEG be adjusted properly because high ratio of PEG could impede the activity and reduce intake of the medication [15]. In addition, PEG coated LNPs could induce pseudo-allergies due to reactogenicity [16]. Nevertheless, PEG remains the most effective coating material to increase the circulation time of LNPs in the blood stream and promote a targeted drug-delivery.

b **Target Specificity of Nanoparticles and Targeting Ligands**

As stated in prior paragraphs, most of the nanoparticles delivered through the bloodstream do not make it to the tumor, ending up eliminated by macrophages or through uptake by other organs, causing damage to them alongside other toxic side effects. However, the uptake of nanoparticles by the tumor can be improved by utilizing two main routes: (a) Passive targeting, and (b) Active targeting [17]. Passive targeting involves no modification in the characteristics of the drug carrying lipid nanoparticles. Therefore, it can target both malignant as well as healthy tissues with equal vitality. The propensity to accumulate at different tissues depends upon the inherent physical, chemical and energetic tendencies of these LNPs. To minimize the adverse impact due to the leakage to such healthy tissues, intratumoural administration of these nanoparticles is most common, which is conducted under the premise that drug can be constrained to the tumor region. Various factors that control the diffusion are, vasculature organization of tissues and tumor regions, the extent of lymphatic drainage and the density of extracellular matrix (ECM). Tumor regions typically have high ECM and bad vasculature organization [18]. However, this approach would be limited to the tumors that are accessible to such a treatment methodology. Also, only those medications can be administered whose leakage to healthy tissues can be tolerated by the body.

Active targeting is the most important approach for ensuring a reliable way of drug-delivery and is dependent upon finding the tumor specific antigen (TSA), which can bind to another molecule and thus facilitates the absorption of drug carrying lipid nanoparticles into the tumorous region. These targeting ligands specifically target receptors expressed on tumor cells, or largely expressed on tumor cells, and thus help to minimize the cytotoxic damage of the nanoparticles to non-cancerous cells [19]. Unfortunately, finding TSA exclusive to the given type of tumor is rare. Therefore, another option that is frequently explored is to determine tumor-associated antigens (TAA). These antigens are over-expressed in the targeted tumor type but are not entirely exclusive to them. Folic acid, carbohydrates, peptides, aptamers, and antibodies are several types of targeting ligands that have been researched and found, each with their own benefits and drawbacks for both TSAs and TAAs [20].

Folic acid is a small-molecule vitamin which is necessary in cell growth and proliferation, and while all normal cells require it, folate receptors are overexpressed in many cancer types including breast, ovarian, and lung cancers [21]. Due to this fact, alongside its biocompatibility, through conjugation with the surface of the nanoparticle, folic acid can be used to target those types of cancer cells. However, since it aids with cell growth it may aid the cancer in its own growth alongside not being a perfect targeting factor [20]. Carbohydrates are another type of ligand which can find many receptors on the targeted cells and have the advantage of existing as several types and in abundance. Examples of ones targeting overexpressed receptors would be hyaluronic acid, galactose, and lactate. Another strategy utilizes the fact that cancer cells have an increased metabolism, and thus an increased necessity for glucose [20]. So, a variety of glycoconjugates have been extensively studied to have a cancer-selective uptake and aid in reducing cytotoxicity to other organs. However, as with folic acid, they are not perfectly targeted and can still be picked up by other cells. Additionally, due to their complexities they could still attract a protein corona.

Peptides are generally used to make system reactive nanoparticles. For example, a nanoparticle bonded to peptides that unravel in an environment with a certain pH can help reduce premature drug release. If a nanoparticle reaches a cancer cell, it is brought inside its membrane through the process of phagocytosis, due to being a large particle. In this process, it is engulfed by a vesicle and then broken down by digestive enzymes [22]. To avoid entrapment inside the vesicle and decomposition and thus reducing the efficacy of the drug molecules or siRNA for treatment, studies have found that certain peptides can aid in escaping these vesicles. One study by Nguyen et al. has constructed a peptide called acidity-triggered rational membrane (ATRAM), that in acidic conditions attaches to the membranes and disrupts them. As vesicles tend to become acidic due to digestive enzymes, the peptide allows nanoparticle treatment to escape into the cytosol and be more effective [23]. Additionally, since cancer cells tend to be more acidic than their normal counterparts, the peptide aids with reducing cytotoxicity in non-cancerous regions by avoiding early release in the non-acidic environments

of healthy tissue.

With regard to an important component of the post-targeted delivery is the effectiveness of the internalization of the medicine into the tumor. It is known that m-RNA must reach the cytoplasm for the treatment to be effective. There might be different complex mechanisms to facilitate or retard this transfer, and there is a limited understanding of the involved mechanisms. Nevertheless, it is recorded from multiple studies that efficient release of the drug from lipid nanoparticles promotes its faster internalization, which is proportional to the payload of the nanomedicine[24].

c **Physical Characteristics**

There are various other physical characteristics of nanoparticles which also influence their ability to reach their targeted area alongside surface morphology. For example, the effectiveness of a lipid nanoparticle is also dependent on its stability, size, shape, surface charge, and other additional factors[25]. All these factors can influence the ability of the nanoparticle to physically move through the body's blood vessels and avoid detection from the body's immune agents. The surface charge of a nanoparticle can greatly influence its interactions with other components within the body. For example, positively charged nanoparticles can avoid being tagged by phagocytes and are more easily accepted by target cells due to their negatively charged membranes. However, they can also have harmful effects such as hemolysis. In contrast, negatively charged LNPs can have longer circulation time, but may find it difficult to enter the target cell due to the repulsive forces from the negatively charged membrane[26]. One solution to this problem could be to have a neutral charge for the cell. Another solution, as Du et al. have found, is pH dependent surface charge modifiers, that allow the nanoparticles to have the attraction and stealth benefits of a positively charged nanoparticle without causing toxic effects on the surrounding environment[27].

An optimum size between 10 nm – 100 nm can aid LNPs in having the ability to evade kidney clearance and liver filtration, leak through blood vessels to accumulate at the targeted sites, increase cellular uptake mechanism, reduce aggregation in blood, and avoid immune agents[28]. For example, it was found by Jasinski et al. that nanoparticles with a diameter less than 5 nm tend to be filtered by the kidneys and nanoparticles with a diameter greater than 100 nm were cleared out by the liver, engulfed by macrophages, or lodged in healthy tissue[29]. Large nanoparticles also have a lesser ability to move through thinner blood vessels, which may inhibit their ability to reach the targeted area, and this trait is also influenced by the flexibility of the nanoparticles. There are also different types of endocytosis that occur upon cellular uptake based upon the size of the nanoparticle. They can affect the intracellular distribution of the drug and hence its effectiveness[21]. Additionally, there are other barriers to the uptake of nanoparticles, such as the blood-brain barrier, with nanoparticle distribution within the bloodstream. There haven't been consistent findings for the connection between exact nanoparticle size and brain-barrier uptake due to the role of many other factors, however Nowak et al. found that nanoparticles of size 200 nm tended to have the most uptake by cells in healthy mice, with the reasons being unknown[30]. Thus, there are a variety of factors to consider in terms of nanoparticle size that depend on the main goal and obstacles to nanoparticle drug delivery.

The key presumption behind the enhanced drug delivery with optimum size of LNPs and coating with PEG is that the blood circulation activity is relatively aggressive in the tumorous region. Therefore, the probability of reacting with the desired tumor by utilizing the reactivity of TSA/TAA would be higher. However, it is known from mouse models that less than 1% of LNPs administer intravenously reach the targeted solid tumors. It is an important area that needs further research in terms of possibly utilizing other modes of drug administration, etc.

Even after the delivery of LNPs to the targeted tumor, the penetration of LNPs is another important phenomenon that controls the response of the medication. Since LNPs are typically 50 nm – 150 nm, their uniform distribution within the tumor cells poses a challenge due to their relatively large size[31]. Approaches to utilize the acidic environment in the vicinity of tumorous region to have a pH mediated break-down of LNPs into smaller particles could be one of the potential ways to enhance the penetration of LNPs[32].

The response of the human body to LNPs is very complex and varied. However, despite the limited efficacy of LNPs reaching the targeted tumors, the overall understanding of the characteristics of nanoparticles for an efficient intravenous drug delivery to the target region is that they should be biocompatible and biodegradable to avoid the adverse responses to the nanoparticle and causing long-term serious side-effects. This is one of the major reasons as to the widespread adoption of LNPs as drug-delivery vehicles, with their composition made of naturally occurring materials and non-covalent bondings. Furthermore, the body should not immediately flag or eliminate the nanoparticle through the immune system, liver clearance, kidney filtration, various barriers, etc. This can be achieved through achieving an optimum size of LNPs (10-100 nm), applying surface coatings such as PEG, which can aid in enhanced times spent in the blood circulation and avoiding the formation of protein corona. In addition, it is important to make sure that the nanoparticle can make it to the cancerous region without prematurely releasing the drug or

breaking down, which can be achieved by adding surface coatings for improved stability, environment responsive release mechanisms such as pH and temperature, and being composed of flexible materials for proper mobility through small blood vessels. Finally, the nanoparticle needs to target the cancerous region specifically, rather than being picked up by other cells, tissue, or organs. Targeting ligands can help target overexpressed receptors on cancer cells and either neutral or positively charged nanoparticle surfaces can aid with increasing the affinity of nanoparticles towards the target TSA or TAA. Also, to enhance the drug release in the tumor tissues, enhancing the payload could be an important factor that needs consideration in the LNPs.

PEG Coating	Targeting Ligands and stabilizers	Physical characteristics	Drug absorption at Tumor
Decreased Protein corona	Better target specificity	10-100 nm ideal size	Smaller size (<20 nm) ideal
More time in blood circulation	Less impact on healthy tissues	(+) charge bad for transfer via blood	Need to break down large LNPs
Less segregation to unintended regions	Reduced premature drug release	(-) charge bad at tumor location	
		pH-modulated charge preferred	

Fig. 2 Table shows key characteristics of LNPs needed to have an effective drug delivery

Based on the status of the development of targeted drug-delivery using LNPs, it can be mentioned that despite significantly increasing the time spent in the blood circulation and increasing their availability, it could be difficult to significantly increase the actual intake of the targeted drugs and finding alternate pathways could be useful. Also, enhancing the targeting efficacy by developing suitable drugs as well as maximizing payloads for their efficient drug delivery, and finally size reduction post-delivery for a uniform absorption within the tumor are some of important areas that need further research for effective treatments of different types of cancers.

Conclusion

Nanoparticles-based drug-delivery has proved to be an exciting and rapidly developing approach for the treatment of cancers. Amongst various types of nanoparticles available, LNPs are the most popular because of several advantages that they offer. For the intravenous administration of the targeted drug-delivery, there are a variety of aspects through which the effectiveness of lipid nanoparticles can be improved within the bloodstream, each having its own benefits and drawbacks. In this process, despite developing an overall empirical understanding of ideal characteristics of nanoparticles, the actual realization has proven to be difficult due to the innate significant complexities involved. The key directions of research efforts should include, most importantly, determining the exclusively over-expressed gene for a reliable tumor specificity for the development of a potent medicine, ensuring more effective drug-delivery as well as effective absorption of drugs post-delivery by the solid tumors.

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