Review Article

A Systematic Review on Advanced Drug Delivery Technologies to Target the Lymphatic System

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ABSTRACT

Lymphatic systems maintains the body water balance, helps in the absorption of lipids, fatty acids, triglycerides, fat soluble vitamins and also play an important role in body's immune system. Lymphoedema, Lymphoma and several other diseases are associated with lymphatic system. In addition to these, lymphatic system acts as a channel in the metastasis of many cancers including melanoma, lung, prostate and breast and so on. It also plays a key role in spreading other diseases such as filariasis, anthrax, tuberculosis, leishmaniasis and HIV. Lymphatic drug delivery provides a great opportunity in the treatment of these complex diseases. Several advanced drug delivery technologies such as liposomes, carbon nanotubes, lipid nano particles have been explored. Poorly aqueous soluble drugs when administered orally absorb into systemic circulation via intestinal lymphatic duct. Therefore the bioavailability and localization of drugs, can be enhanced by these technologies coupling with the proper selection of the root of administration. Therefore, in recent years lymphatic system has been recognized as the optimum site for the drug delivery to enhance bioavailability of lipophilic drugs, to target immune system and also lymphatic system associated diseases and disorders. In this article the suitability of advanced drug delivery systems such as dendrimers, carbon nanotubes, and liposomes to target the lymphatic system were emphasized. The problems associated with these systems are also discussed.

Keywords: Dendrimers, carbon nanotubes, liposomes.

INTRODUCTION

Lymphatic system was described first in the 17th century by Gasparo Aselli in 1627.[1] It consists of lymphatic vessels which are similar to circulatory system's veins and capillaries, lymph nodules and nodes. Lymphatic vessels start as blind ended capillaries. They branch, interconnect and spread into almost all tissues except in central nervous system, eye and certain cartilaginous tissue. The lymphatic vessels collect excess interstitial fluid (lymph) and drain into venous system via thoracic duct present on the left side and or the right lymphatic duct.[2] The lymph is a clear liquid and has milky appearance, alkaline pH (7.4 – 7.8) with a specific gravity of about 1012-1025. It is composed of lymphocytes, fat globules, proteins (albumin -10 to 30 gms/liter, fibrinogen – 150 to 250 gms / liter, total fat – 10 to 60 gms / liter, triglycerides, cholesterol, chylomicrons, glucose, urea and electrolytes. The lymph flows throughout the body in continuous loop (one direction) upwards toward neck. Lymphatic circulation does not contain any central pump, but, depends on the local pressure effects and intrinsic contraction of the larger lymphatics.

The major functions of the lymphatic system are maintenance of body water balance, absorption of lipids, fatty acids, triglycerides, cholesterol esters, xenobiotics and fat soluble vitamins from the intestinal tract. In addition to this the lymphatic system plays an important role in body's immune system by transporting antigen presenting cells such as dendritic cells to the lymph nodes. A typical diagram showing lymphatic system was given in figure 1.

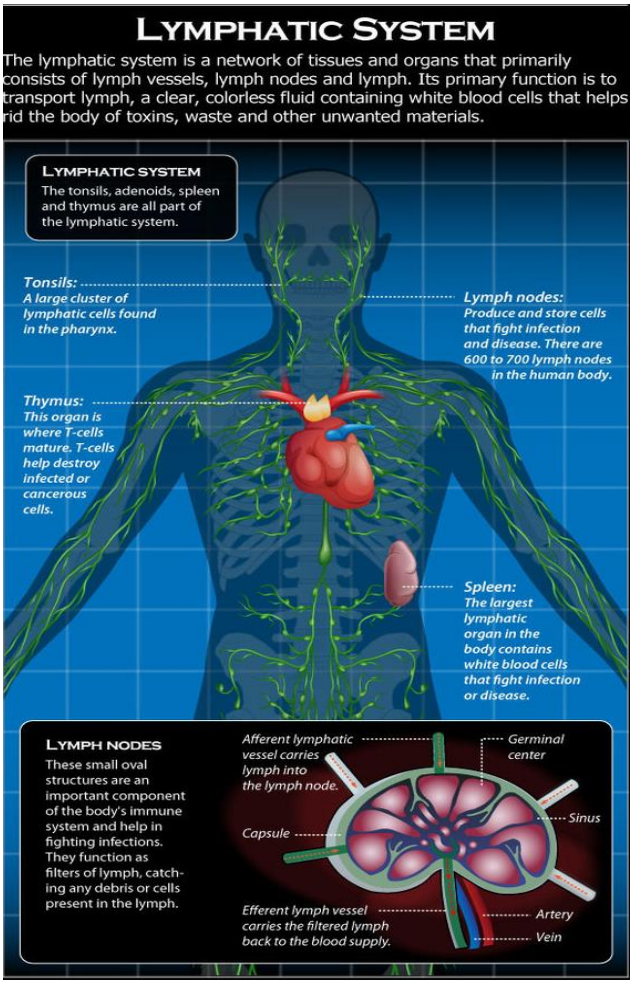

Figure 1: A typical diagram representing the lymphatic system

Diseases and disorders of the lymphatic system

Lymphoedema: lymphatic blockage leads to accumulation of fluid (lymph collect) in extracellular space and causes lymphoedema. It can be classified as primary lymphoedema and secondary lymphoedema. Primary lymphoedema again classified into lymphedema congenita, lymphoedema praecox and lymphoedema tarda. Lymphedema congenita is a severe form of lymphoedema. Secondary lymphoedema is caused by acquired lymphatic obstruction which in turn is caused by infiltration of regional nodes by tumor, surgical excision of regional nodes in treatment of malignancy and fibrosis after infectious or inflammatory processes or radiation. Lymphadenopathy-enlargement of the lymph nodes caused by infection, inflammation, or cancer Lymphoma-Lymphoma is cancer of the lymph nodes. It occurs when lymphocytes grow and multiply uncontrollably. Castleman disease is a group of inflammatory disorders that cause lymph node enlargement and can result in multiple-organ dysfunction. It is a similar to a lymphoma and is often treated with chemotherapy. It can be unicentric [one lymph node] or multicentric, involving multiple lymph nodes. Lymphangiomatosis is a disease involving multiple cysts or lesions formed from lymphatic vessels. It is thought to be the result of a genetic mutation. Lymphatic system not only acts as a major region for many diseases such as metastitial tuberculosis, cancer, filariasis, HIV, leishmaniasis but also spread through the lymphatic system[3]. A flow chart depicting the disorders of lymphatic system was given in **fig 2**

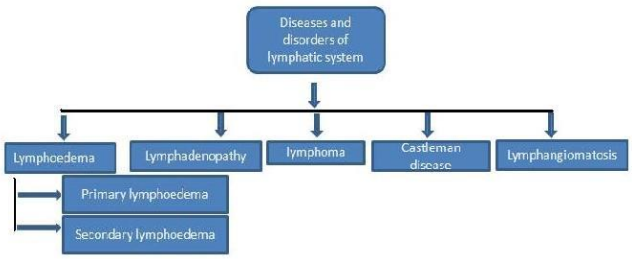

Figure 2: Diseases of lymphatic system

Rationality in lymphatic drug targeting

Lymphatic drug delivery is gaining importance in recent years and the rationality is explained below:

- It is possible to circumvent first pass effect through lymphatic drug delivery.
- Increased absorption of hydrophilic macromolecules and macroconjugates is possible through paracellular diffusion, because of the presence of single layered non fenestrated endothelial cells in lymph capillaries.
- In the intestinal region aggregated lymphoid follicles are present as peyer's patches. These patches offer a great opportunity to deliver the drugs to lymphatic system via oral route.
- Lipid formulations are better absorbed transcellularly into lymphatic system via chylomicron formation when given orally.
- Further by exploiting the anatomical features (its non uniform structure in various body regions) and physiological function (in clearing the particulate matter from the interstitium) several particulate drug delivery systems have been designed to target the regional lymph nodes.
- The progression of autoimmune diseases like HIV/AIDS, rheumatoid arthritis, rejection of organ transplants (for ex., kidney, lungs), chronic inflammatory disorders including psoriasis, atopic dermatitis takes place through lymphatic system.
- Thence, the lymphatic system can be considered as a potential target to deliver drugs for achieving an optimal therapeutic benefit.
- In this review various colloidal drug delivery systems to target the lymphatic system has been discussed.

Drug targeting approaches to lymphatic system

Liposomes

Liposomes are vehicles made up of phospholipids. They contain internal aqueous core surrounded by lipid bilayers. Phospholipids are amphipathic molecules in which hydrophilic head group orient towards aqueous phase whereas the hydrophobic tails orient towards lipid phase. Therefore both hydrophilic and lipophilic drugs can be entrapped within the liposomal vesicles. Liposomes as carriers have been studied extensively to deliver the drugs to lymphatic system. They are considered as most suitable carriers because of their excellent affinity towards biological membranes, selective targeting to lymphatic tissue by intra peritoneal, subcutaneous and intramuscular injections. Liposomal formulations can enhance the stability, bioavailability, and reduces the toxicity.

Cefotaxime is a third generation cephalosporin antibiotic with poor oral bio availability and short biological half life[4]. Cefotaxime liposomes were reported by Ling et al., using negatively charged phosphatidyl choline. *In vivo* bio availability of liposomal formulation of cefotaxime was compared with aqueous drug solution and a physical mixture of cefotaxime with blank liposomes in rats. The bioavailability of about 2.7 and 2.3 times in liposomal formulations was increased approximately compared to other. This increased bioavailability was partly due to the encapsulation of drug into liposomes as it protects the drug from low pH effects and partly due to increased localization of the drug at the intestinal lymphatics[5].

Doxorubicin and other anthracyclines are commonly used in the treatment of B-cell non-Hodgkin's lymphoma but their clinical use is hindered due to their cardiovascular toxicity like cardiomyopathy and congestive heart failure. Liposomal conjugation of doxorubicin preferentially

distributed into tumor tissue and reduces the tumor toxicity. Visani and Isidori in their study reported that the non pegylated liposomal doxorubicin efflux due to p-glycoprotein which is over expressed in non-Hodgkins's lymphoma is decreased. This causes increased circulation times in the blood and further internalization into tumor tissue by enhanced permeation and retention effect[6].

Lymphatic uptake is influenced by their particle size, surface charge and the composition. Zidovudine loaded surface engineered liposomes were investigated to enhance the lymphatic uptake specifically lymph node, spleen. Positively and negatively charged liposomes were prepared by incorporating stearylamine and dicetyl phosphate. The conventional liposomes and mannose coated liposomes were compared in drug release properties and a controlled drug release was reported with mannose coated liposomes. Surface engineered liposomes showed biphasic zidovudine release and organ distribution studies showed a high free zidovudine concentration in the spleen and lymph nodes and a reduced concentration in the serum (kaurcd 2008). Modified liposomes for lymphatic targeting were investigated. High molecular weight hyaluronic acid modified docetaxel loaded nanoliposomes and low molecular weight hyaluronic acid modified docetaxel loaded nanoliposomes were prepared by electrostatic attraction. The lymphatic drainage and lymph node uptake were evaluated by pharmacokinetics and distribution recovery of docetaxil. Using near infrared fluorescence imaging technique, the ability of cyanine dye (C7) – loaded low molecular weight hyaluronic acid liposomes (LMWHA-LPs/cy 7) to target the lymphatic system was studied. It is reported a high drug concentration in lymph nodes, longer retention times in hyaluronic acid modified liposomes and the lymph node uptake depends upon the density of hyaluronic acid instead of particle size[7].

However lymphatic absorption of liposomes is also hampered due to the possible interaction of liposomes with membrane surface interstitial proteins. These interactions increase the size of liposomes and settle at the administration site and could not be absorbed completely. Macrophage phagocytosis is decreased in PEGylated liposomes and therefore lymphatic uptake is reduced in case of PEGylated liposomes compared to unmodified liposomes. But the size of the PEGylated liposomes can be adjusted by modifying the PEG chains or lipid bi layer core of the carrier to enhance the lymphatic uptake. Liposomes are building up in lymphatic tissue due to phagocytosis or mechanical retention. This will cause damage to the normal lymph nodes. Mixing PEGylated lyposomes with a cationic polysaccharide lowers the drainage of liposomes into normal lymph tissue. Conventional liposomes cannot distinguish metastatic and normal lymph nodes and liposomal uptake by metastatic lymph nodes.

Dendrimers

Dendrimers are polymeric molecules with three dimensional net works. They are unique in their tree like branched structure and has been explored as targeted drug delivery systems in the nanomedicine field in various disorders[8]. Dendrimers consists of three components in their structure which include an initial core (a starting atom), interior layers with repeating units, exterior (terminal functionality). Dendrimers are classified into various types including poly (amidoamine) dendrimers (PAMAM), Poly (amidoamine-organosilicon) dendrimers (PAMAMOS), Poly (propylene imine) PPI dendrimers, Tecto dendrimer, multilingual dendrimers, Chiral dendrimers, Hybrid denrimers, amphiphilic dendrimers, micellar dendrimers, multiple antigen peptide dendrimers and frechet-type dendrimers.

Dendrimers with a range of molecular weights can be prepared. Dendrimers possess polyfunctional surfaces, therefore different types of drugs and pharmacokinetic modifiers can be attached. These unique properties make them useful in several biomedical applications. For example larger dendrimers in particular > 8 nm preferentially drain into the lymphatic capillaries after subcutaneous injection[9]. Lymphatic targeting can be enhanced with increasing dendrimer size and hydrophobicity. Large hydrophilic dendrimers escape from the systemic circulation into lymphatic system and re circulated into the systemic circulation, this enables the PEGylated dendrimers a long circulation times.

Gemma et al., studied the small molecule chemotherapeutics uptake into the lymphatic system after subcutaneous and intravenous administration as a simple solution, poly-lysine dendrimer, a PEGylated liposomes and various pluronic micellar formulations in thoracic lymph duct cannulated rats[10]. They observed an increased recovery of doxorubicin in the lymph over a period of 30 hrs and up to 685 fold and 3.7 fold of doxorubicin with dendrimer doxorubicin when compared to the solution and liposomal formulations respectively. Though dendrimers are potential in site specific drug delivery, they also posses certain toxicity issues. For ex., dendrimers with cationic functional groups interact with negative biological membranes caused cell lysis and integrity of biological membrane. Cationic dendrimers such as PAMAM dendrimers cause concentration and generation dependent cytotoxicity and hemolysis[8].

Carbon nanotubes

Carbon nanotube, the name itself indicates that it is a tube shaped material and made up of carbon. They belong to the Fullerene family in which carbon atoms joined together to form cages or tubes or balls. They possess unusual mechanical, electrical and thermal properties. They are good conductors of electricity, extremely light in weight and strong enough. They are hallow cylindrical structures and formed when graphine sheets containing sp^2 hybridized carbon atoms are rolled

up. They are two types single walled and multiwalled CNTs depending on the number of graphine sheets rolled and their diameter ranges from 0.4 to 3 nm and 2 to 500 nm respectively[11]. In recent years CNTs became more popular as nano metric vehicles for the temporal and site specific drug delivery and also for diagnostic purpose.

Multiwalled CNTs attached with polyacrylic acid were prepared by radical polymerization and made them highly hydrophilic. Fe_3O_4 based magnetite nanoparticles were adsorbed onto these CNTs by coprecipitation and gemcitabin was entrapped to target the lymphatic system. It is reported that after 3 hrs of subcutaneous injection CNTs were seen only in local lymph nodes[12]. In one study Yang et al reported magnetic CNTs which were non covalently functionalized by folic acid. The externally placed magnet guided the drug matrix to the regional lymph nodes where magnetic nanotubes retained and released the incorporated drug continuously[13]. Gemsitabin loaded CNTs were also reported by Ji et al. The authors demonstrated the ability of CNTs to deliver gemcitabin to lymph nodes under the guidance of magnetic field. The results revealed that chemotherapeutic drug delivery to lymph nodes via CNTs is more advantageous compared to another approach. This is also supported by another study with different approach involving the injection of MWCNTs subcutaneously into left rear foot pad of rat and observing the accumulation of CNTs using biopsy. The results showed the accumulation of MWCBTs in left popliated lymphnodes[14].

The solubility of CNTs is important prerequisite from the administration site to be absorbed, blood transportation, secretion and biocompatibility. But the presence of strong Π-Π interactions between the tubes, hydrophobicity of side walls of graphine sheets causes the CNTs to aggregate into bundles, and therefore the available surface area decreases for drug loading. The aqueous solubility of CNTs is an important obstacle due to their greater tendency to bundle together.

The biosafety of carbon nanotubes due to their non-biodegradability and non eliminatability is another important obstacle to use CNTs as drug delivery systems. If these problems associated with CNTs should are resolved, the CNTs are optimistic therapeutic cargos in delivering the drugs to lymphatic system.

Monoclonal antibodies

An antibody is a large protein molecule and also called as immunoglobulin. Antibodies are produced by the immune system in response to invading foreign pathogens. If the antibody is produced by a single clone of cells or cell line it is called as monoclonal antibody (mAb). These mAbs are used to treat many diseases including some types of cancers. Some antibodies work by themselves and they are named as naked antibodies. Ex., alemtuzumab is used in the treatment of chronic lymphocytic leukemia. Some antibodies are conjugated antibodies and prepared by joining with radioactive particle (radiolabeled antibodies) or chemotherapeutic drugs (chemolabeled antibodies). An IgG2a mAb was injected into mice intravenously and interstitially to mice. It was found that the antibody administered by interstitial injection localized more in lymph nodes confirming that antibody delivery can be optimized via lymphatic system[15].

Lipid formulations for lymphatic delivery

Drugs can be delivered to the lymphatic system by means of different mechanisms. For example the porous nature of lymphatic vasculature allows hydrophilic macromolecules and macromolecular conjugates into the lymphatic system. The presence of peyer's patches in the intestinal wall provide an entry point for the transport of lipids. To make use of this, several lipid based formulations such as lipid nanoemulsions, solid lipid nanoparticles, nano structured lipid carriers and so on are developed. Ghosh and Roy were extensively reviewed on this topic and listed out all nanoparticulate systems that can be used for lymphatic targeting[16].

CONCLUSION

Lymphatic system is essential in maintaining the body water balance, absorption of certain nutrients and lipophilic drugs. Several diseases and disorders are associated with the lymphatic system and some diseases spread through the lymphatic system. To target these diseases several advanced drug delivery technologies such as lipid based formulations, carbon nanotubes etc., are explored. In this review the possibilities and obstacles associated with lymphatic delivery of these technologies were analyzed.

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