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Lipoprotein nanoparticles in diagnosis and treatment of cancer

Abstract

Lipoproteins are natural endogenous nanoparticles synthesized by human liver that became an important part of Nano medicine. Due to their high compatibility, safety and stability, many studies have been conducted to investigate utilization of LDL and HDL as Nano vectors. Modified lipoproteins, synthetic recombinant lipoproteins as well as analogous Apo lipoproteins have been formulated for the same purposes. Applications of lipoprotein nanoparticles in targeted delivery of multiple cancer imaging probes and anticancer chemotherapeutic and photodynamic treatments will be briefed.

Keywords: nanoparticles, lipoproteins, LDL, HDL, anticancer, chemotherapy, drug delivery, photodynamic therapy, imaging, lipid nanotechnology

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Amira R Amin, Hatem K Amin

Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Helwan University, Egypt

Correspondence: Amira R Amin, Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Helwan University, Egypt, Email amira_amin_95@yahoo.com

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Abbreviations: NP, nano particle; LDL, low density lipoproteins ; HDL, high density lipoproteins ; SLDL, synthetic low density lipoproteins; LDL-Rl, low density lipoprotein receptor ; SR-Bi, scavenger receptor class B type I; DTPA, diethylene triaminepenta acetic acid; SPECT, single-photon emission computed tomography; MRI, magnetic resonance imaging; NIR, near infrared fluorophores

Introduction

Nanotechnology is introduced by Richard P. Feynman in 1960, since that time it has been a subject for investigation and application in various medical, industrial, and environmental fields.[1] Nanoparticles are very tiny material within the size range of 1-1,000nm and many naturally existent organic and inorganic nanoparticles have been present before they were synthesized in labs.[2] Their great surface area and modifiable optical properties allowed the use of nanoparticles in various medical aspects such as bio-imaging, diagnosis and drug delivery for treatment of many diseases.[3] Cancer is one of the most hazardous clinical conditions associated with high mortality rates it's characterized by abnormal and uncontrolled cell division. More than 200 types of cancers are identified now and treated with radiation, chemotherapy and surgery. Targeted drug delivery can improve the therapeutic outcome of anticancer treatments achieving a selective effect on tumor cells and sparing other tissues from the toxic side effects improving their therapeutic index.[4] Nanotechnology was applied in oncology to provide alternative way for drug delivery and reduce tumor resistance.[5] Liposomal formulations are the simplest and most widely used type of nanomedicine since the approval of liposomal doxorubicin and daunorubicin for treatment of Kaposi's sarcoma in 1995 and currently they are used in breast and ovarian cancer.[6] Most nanomedicine focuses on Enhanced Permeability and Retention Effect (EPR) theory to enhance the pharmacokinetic profiles, permeability and distribution of anticancer therapy and improve drug behavior through ligand-mediated targeting.[7] Other nanomedicines in clinical development include polymeric conjugates, polymeric micelles and polymeric nanoparticles. Lipoproteins were found to be an excellent bionic Nano vectors particularly for lipophilic anticancer agents because of their high compatibility and stability as their tiny size decreases their elimination by the kidneys and allows their penetration through tumor fiber space[8] that's why lipoproteins have been used to incorporate and transport various hydrophobic compounds for therapeutic or imaging purposes. This review aims to summarize and discuss the application of natural, modified, simulated and recombinant lipoproteins in screening and treatment of cancer.

Discussion

Natural lipoproteins

LDL as a natural nanoparticle: LDL are natural nanoparticles synthesized in human liver from a hydrophobic core made unsaturated fatty acids, triglycerides, cholesterol and cholesterol esters and a hydrophilic shell made from phospholipids, cholesterol esters and a single molecule of ApoB-100 which is responsible of controlling their size at 22nm.[9] Their main function is to transport cholesterol through the systemic circulation. LDL receptor (LDL-R) is expressed in some natural tissues and malignancies, LDL is internalized inside cells through ionic interactions between the highly cationic binding site of the receptor and the anionic binding groups on the cell surface.[10] LDL can act as a carrier for many optical imaging agents, nuclear magnetic resonance probes, chemotherapeutic and photodynamic agents which is applied in treatment and diagnosis of cancer.[11] These lipophilic agents can be loaded on the LDL molecule either through weak van der Waals interactions to the surface of the particle (surface loading), covalent interactions with the phospholipid or the apolipoprotein (protein loading) or by intercalation of the agent within the core (core loading).[12] Covalent Protein binding was used by many investigators to incorporate radiotracers for various techniques as[13] who used technetium-99m (99mTc) radiolabeled LDL for cancer diagnosis by single-photon emission computed tomography (SPECT) on B16-melanoma relying on increased LDL uptake in tumor tissues during growing stages.[14] Surface loading has been used to enhance the delivery of fluorescent agents as pyro pheophorbide cholesteryl oleate that was found to be effective photodynamic therapy agent in certain tumors with high rates of expression of LDL receptor.[15] Carbocyanine and prototype contrast agent (PTIR267) which is suitable for MRI[16,17] and for diagnostic imaging of tumors and MRI contrast

agents as Amphiphilic gadolinium-DTPA chelate[18] the procedure could incorporate 180 molecules in each particle while it is found that chelation of Gadolinium with AAZTAC17 had better stability and enhancement.[19] Core loading is also used to deliver probes as pyro pheophorbide cholesterol esters and other near infrared fluorescent agents as well as photosensitizers as Chlorin, phthalocyanine, naphthalocyanine, and pyro pheophorbide photodynamic therapy agents.[12] Each of these techniques has its pros and cons, as covalent interaction with the apolipoprotein on certain residues can affect receptor interactions, while surface loading is associated with higher leakage rates and considerable non-receptor mediated delivery and nonspecific binding so, core loading appears to be the most successful technique.[20] LDL nanoparticles are also used to deliver photodynamic therapy as porphyrin photo activators e.g. phthalocyanines, benzoporphyrins and tetraphenyl porphyrins, Naphthalocyanine, Chlorophyll A and bacteriochlorophyll which are known for their poor bioavailability.[11]

HDL lipoproteins: HDL size is approximately 10nm-the smallest among all other lipoproteins - which has a good impact on its distribution, stability and pharmacokinetics that's why it may generally be preferred over LDL however, it lacks the preferential binding ability to vascular receptors and can bind to GIT receptors. HDL NP had been used in cancer therapy and imaging as LDL NP and they are even preferred in transporting siRNA as their surface receptor regulation inactivates lysosomal pathway and facilitates RNA manipulation.[8]

Synthetic lipoproteins: Lipoproteins could be directly isolated and used as a Nano vehicle after incorporation of the lipophilic compounds but many issues restrict their isolation as the choice of the loading technique, storage and safety.[21] Thus, synthetic lipoproteins were developed, their major advantage is allowing strict control on the ratio and structure of every compound incorporated in the synthetic lipoprotein, their size and dimensions hence, regulate physicochemical properties and achieve more specific targeting, retaining all the advantages of natural lipoproteins.

Recombinant LDL nanoparticles: Recombinant lipoproteins are synthesized from natural or recombinant lipoproteins along with various lipid molecules and the desired added molecules, recombinant LDL and HDL NP have long been formulated and proven to be an effective potential carrier for many therapeutic and fluorescent imaging agents[22,23] developed synthetic LDL nanoparticles core loaded by paclitaxel oleate which showed better delivery and destruction of glioblastoma multiforme cell lines, the enhancement of the cytotoxic effect was confirmed by in vivo study that used synthetic LDL NP for encapsulation of paclitaxel-alpha linolenic acid (PALA) in mice.[24] While the uptake of recombinant LDL NP into chronic myeloid leukemia cells and yielded promising selectivity toward malignant tissues.[25] On the other hand, a reconstituted Apo-B is used for the formation of synthetic LDL for delivery of hydrophobic drug as M4N (tetra-O-methyl nordihydroguaiaretic acid) and amphiphilic molecules.[26]

Recombinant HDL nanoparticles: Synthetic HDL lipoproteins were used as carriers for many chemotherapeutic agents as iododeoxyuridine and doxorubicin, which were efficiently transported within tumor fiber mass of malignancies that over expressed (SR-BI) HDL receptor.[8] Formulated HDL-like nanoparticles for PH responsive release of paclitaxel in acidic media, which enhanced PTX potency greatly. 10-hydroxycamptothecin delivery through recombinant HDL bionic vehicles brought about 3-fold reduction in IC50 than free drug.[27,28]

Simulated lipoprotein nanoparticles: ApoB-100, Apo-I, and Apo E structure complexity and difficulty of isolation is causing a concern during the synthesis of lipoproteins. This problem could be solved by the formation of analogue peptides with high resemblance of these lipoproteins facilitating lipoprotein nanoparticles production and accelerating their application.[29] Synthetic LDL nanoparticles is utilized with mimetic peptides for core loading of paclitaxel oleate[30] and Apo A-I mimetic peptide for the formulation of synthetic peptide HDL-mimicking peptide-phospholipid scaffold (HPPS) with similar binding properties of natural HDL nanoparticles on their (SR-Bi) receptors which can be applied for the delivery of various probes, chemotherapeutic agents.[31]

Modified LDL nanoparticles/Rerouting if LDL nanoparticles: LDL drug targeting is generally applicable and restricted only in tumors in which LDL-R are over expressed. However, multiple tumor specific receptors were identified. Therefore, it was found that modification of lysine residue in the side chain abolished the selective binding of LDL to LDL-R and enhance binding to other tumors. It was found that modification of lysine using folic acid allowed targeting to folic acid receptor (FR) which is over expressed in many tumors.[32] The principle was tested on nasopharyngeal carcinoma cells with high FR expression and found positive results however the uptake into cells decreased as the number of folic acid molecules added increased to more than 170 out of the 357 lysine amino groups.

Other applications

Lipoproteins nanoparticles is an important form of nanomedicine applied in treatment of many clinical conditions other than cancer. For example LDL nanoparticles are used for targeted delivery of antifungal and antibiotics,[33] botanical compounds with low bioavailability.[34] Lipoproteins are a promising part of soft nanotechnology, which could be applied in Alzheimer's disease. Synthetic HDL NP loaded with α-Mangostin which prevents amyloid beta aggregation and orally administered Apo A-I mimetic peptide that has the ability to bind to amyloid b-protein in the brain and prevent its accumulation in the brain to bring about better prognosis for Alzheimer's disease.[35]

Limitations

The main problem associated with lipoprotein application in diagnostic and therapeutic purposes is the nonspecific background binding to normal cell receptors such as the cells of reticuloendothelial system, modification of the nanoparticle size, dimensions and addition of molecules such as PEG to achieve more specific binding could reduce the problem but still can't eliminate it.[36] Furthermore, clinical application of lipoproteins requires developing of an efficient imaging technique to determine their exact distribution. The only available quantitative technique is radionuclide labelling but it's not reliable as the probe may alter the distribution of the nanoparticle itself and the conjugation between the label and nanoparticles is not stable under biological conditions inside the body.[37] Despite the promising results of the studies conducted on LDL nanoparticles as Nano vectors, their physicochemical properties and storage stability requires further investigations. For synthetic lipoprotein NP, deficiency of apolipoproteins due to difficult extraction and questionable purity is the main limitation that requires complex experimental conformation of the purity and quality of the obtained proteins. Pathogen free apolipoproteins are available commercially but increase the cost of production process.[36] Substitution of the complex apolipoproteins with the simulated ones with similar properties seems to facilitate

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nanoparticles productions. However, not enough studies had been conducted to ensure that these simulated lipoproteins don't trigger immune reactions.

Conclusion

Targeted delivery of anticancer therapeutic and imaging agents by Nano vectors brought about significant improvement of their efficiency and therapeutic index. Lipoprotein Nano particles are preferred as bionic Nano vectors because of their size range which promotes their stability and need not to be identified by the reticuloendothelial system with good safety profiles.[38] Many studies confirmed their efficacy in transporting anticancer chemotherapeutic agents as paclitaxel and doxorubicin, PDT agents as Naphthylocyanine and porphyrins and imaging agents in various imaging techniques as Ultrasound, MRI, NRI and SPECT.

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None

Conflict of interest

The author declares no conflict of interest.

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