Lipid Nanoparticles as Platforms for Theranostic Purposes

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Lipid nanoparticles (LNPs) are the first approved nanomedicines and the most well-studied class of nanocarriers for drug delivery. Currently, they are in the frontline of the pandemic fight as vaccine formulations and therapeutic products. However, even though they are so well-studied, new materials and new modifications arise every day that can improve their properties. Their dynamic nature, especially the liquid crystal state of membranes, is under constant investigation and it is that which many times leads to their complex biological behavior. In addition, newly discovered biomaterials and nanoparticles that possess promising effects and functionalities, but also toxicity and/or poor pharmacokinetics, can be combined with LNPs to ameliorate their properties.

Keywords: lipid nanoparticles ; liposomes ; biomaterials ; hybrid nanosystems ; functional ; theranostics ; nanotheranostics ; cancer ; clinical translation

1. Quantum Dots

Quantum dots (QDs) are semiconductor nanomaterials of size ranging between 1 and 10 nm that possess optical and electronic properties different from those of larger particles of bulk material, due to quantum mechanics. These size and composition-dependent properties render QDs very promising as materials in many application areas, including electronics, luminescence, catalysis and disease diagnostics [1]. QDs offer several advantages over other categories of fluorescent molecules. One of them is their broad absorption spectrum, combined with a narrow emission spectrum, enabling fluorescent multiplexed analysis and diagnosis. However, their lack of biocompatibility and potential toxicity limits their use in humans. An answer to this challenge is their combination with lipidic nanoparticles, for the development of functional systems for diagnostic or theranostic purposes [2].

Lopes et al., developed a hydroxyapatite-coated liposomal platform incorporating bupivacaine as a local anesthetic agent and CdSe QDs as a bioimaging agent. The formation of the hydroxyapatite coating was achieved by utilizing zwitterionic and negative phospholipids for preparing the liposomes and then adding calcium and phosphate ions to the suspension. The system would facilitate targeted delivery of the drug in situ, due to the HAP coating, as well as monitoring of in vivo drug distribution [3].

Multifunctional theranostic platforms can also integrate further modalities, such as active targeting properties to target tissues and cells. In the case of Demir et al., curcumin and carbon dot (CD)-loaded liposomes were surface-functionalized with anti-CD44 antibodies. CDs belong to the class of QDs, but have been reported to be more biocompatible, less toxic, photostable, and adaptable compared to them [4]. The final multifunctional liposomes exhibited superior effect on tumor cells compared to curcumin-loaded and curcumin/CD-loaded ones. Moreover, 3D holographic microscopy was used as an imaging tool to monitor the effect of the nanoparticles. The results were encouraging in further utilizing this theranostic platform for cancer therapy, equipped with real-time diagnosis.

Seleci et al., developed liposomes with membrane-incorporated CdSe/ZnS QDs and core-encapsulated topotecan. According to physicochemical, fluorescence microscopy and flow cytometry studies, the nanoparticles were effective in co-delivering the diagnostic and therapeutic molecules, as was evident from cellular uptake and distribution results [5]. In another study, Olerile and colleagues developed an NLC, loaded with CdTe/CdS/ZnS QDs and paclitaxel (PTX), as a parenteral theranostic DDS for cancer [6]. The nanoparticles were prepared by emulsion-evaporation and low temperature-solidification. The results from in vivo and ex vivo experiments suggested the targeted delivery of this nanosystem, with successful imaging and suppression of the tumor.

2. Inorganic Nanoparticles

LNP technology can be combined with inorganic nanoparticles that enable diagnosis and treatment. The resultant hybrid technologies are of great interest, since they combine the advantages of both classes of these nanoparticles, but have also helped in overcoming several of their individual limitations, such as solubility and toxicity issues. In addition, LNPs offer versatile solutions for the delivery of inorganic materials, where the latter can be encapsulated inside the aqueous pore, incorporated inside the membrane or attached on the surface, depending on the desired functionality and effect. Superparamagnetic iron oxide nanoparticles (SPIONs), gold, silver and palladium are some of the candidates for this technology [7].

Saesso et al., developed liposomes incorporating SPIONs and functionalized with anti-CD20, for crossing of the blood–brain barrier and active targeting in brain lymphoma [8]. Vibrating sample magnetometry confirmed the superparamagnetic properties of the nanosystem, while cellular uptake and apoptosis were achieved in B-lymphoma cells. Finally, delivery and anticancer effect in a BBB model confirmed the potential of these nanocarriers as theranostic tools.

Wereszczyńska and Zalewski combined fatty acid derivatives of gadolinium 3+ (Gd(III)) and zinc phthalocyanine (ZnPc) in a single liposomal formulation, with the purpose of concurrent diagnosis and treatment of cancer [9]. ZnPc acts as a photosensitizer for PDT and Gd(III) is an MRI contrast agent. The Gd(III) derivatives would self-assemble alongside the phospholipids, leading to orientation of Gd(III) towards the polar region, while ZnPc was incorporated inside the membrane, leading to relaxivity enhancement that might facilitate the reduction in Gd(III) dose and related toxic effects. This phenomenon is considered crucial for future development of efficient and safe MRI theranostics and is associated with the liposomal membrane structure and dynamics, altered after the incorporation of other biomaterials [10].

Gold nanoparticles are particles with unique properties that are utilized in various imaging, diagnostic and therapeutic applications, such as CT and surface-enhanced Raman Spectroscopy (SERS). These nanoparticles can be synthesized in a tailored, precise and reproducible manner, having spheric, cubic, rod-like, cage-like or other forms. In addition, their stability, safety and ease of modification are some of the attributes that render them appropriate for diagnosis and therapy [11]. Sonkar et al., designed and developed theranostic liposomes, incorporating docetaxel (DCX) and glutathione-reduced gold nanoparticles (AuGSH) and decorated with transferrin for active targeting of the receptor in in vitro and in vivo glioma models [12]. The result was the delivery of higher amounts of DCX and AuGSH to the brain and improved $AUC_{(0\text{-}4\ h)}$ values, compared to Docel™, while this platform was proposed as a promising nanotheranostic tool.

Another promising technology that has been integrated with LNPs, is metal–ligand coordination nanosystems, which are formed through interactions between metal ions and organic ligands. In cancer theranostics, MOFs have shown potential, as they can combine modalities of both metal ions, such as Fe^{3+}, as well as organic ligands, such as organic dyes. This enables the concurrent imaging by MRI and fluorescence. Lin et al. developed an indocyanine green (ICG)-Fe^{3+} coordination system for US-assisted theranostics of cancer, aiming to bypass the hurdles associated with sonodynamic therapy [13]. The complex was encapsulated inside a lipid layer, leading to a multi-level self-assembling supramolecular system, using a single-step multi-level approach. The complex was administered to hepatocellular carcinoma orthotopic mouse models, increasing ROS generation and the in situ conversion of the microbubbles to nanoparticles, promoting accumulation at the target site. Superior loading efficiency and bioavailability make this nanosystem promising for non-invasive multimodal imaging.

3. Photodynamic and Photothermal Therapy

PDT utilizes photosensitizer (PS) molecules for the elimination of tumor cells. After light irritation, PSs become excited and then through one of two processes (type I or II), produce radicals and reactive oxygen species (ROS) or singlet oxygen ($^1O_2$) from triplet oxygen ($^3O_2$), thus oxidizing cellular components [14]. Their overall physiological effect includes cell ablation, inflammatory and immune responses, as well as vascular damage. Though it offers many important advantages, including almost absent invasiveness, low toxicity and low drug resistance, the application of PDT in the clinical setting is still limited, owing to the lipophilicity, short half-life and lack in tissue specificity and targeting [15]. In addition, despite the drug resistance absence, some tumor cells are able to enhance their tolerance to ROS by upregulating glutathione expression [16]. LNPs constitute a rational approach in addressing the limitations of PDT, by solubilizing and stabilizing PS molecules, by offering targeted and modified delivery of the cargo, avoiding delivery to normal tissues and related toxicity, by co-loading with other diagnostic and therapeutic agents, and by protecting PSs from exposure to blood and immune components that might lead to their degradation [14].

On the other hand, PTT is a non-invasive type of treatment that employs photothermal agents, such as metal nanoparticles, inorganic nanomaterials and small molecular organic dyes which generate hyperthermia under near-infrared (NIR) laser irradiation and ablate cancer cells [17][18]. However, hyperthermia causes cells necrosis and inflammation, leading to therapy complications, as well as injuries and serious pains to patients. This issue is traditionally addressed by co-administrating nonsteroidal anti-inflammatory drugs (NSAID) [19]. LNPs can offer better solutions to this problem.

Skupin-Mrugalska et al., demonstrated that microfluidics can be a method of choice for the one-step production of theranostic liposomes with a high entrapment degree of therapeutic and diagnostic molecules [20]. In their case, an MRI agent and a PS were co-delivered to carcinoma cell lines. In another approach on PDT, Giurguis et al. developed tunable NIR-activable liposomes that contained lipid conjugates of a benzoporphyrin derivative or IRDye 700DX, with emphasis on the role of membrane composition in the functionality of these platforms [21]. They concluded that lipid conjugates of PSs can affect the outcome of PDT based not only on their photoresponsive behavior, but also on their chemical nature and conformation inside the membrane.

Panikar et al., enhanced the PDT potential of methylene blue (MB) by attaching it on NaYF4:Yb, Er nanoparticles (UCNPs) and subsequently encapsulating the complexes inside liposomes [22]. The final formulation exhibited enhanced ROS generation, while active targeting properties were achieved by membrane incorporation of a lipid derivative of their newly developed anti-HER-2 peptide. In another recent study, hypericin, a molecule for PDT and photodiagnosis, was incorporated in three different types of nanovehicles, based on the copolymer F127 and dipalmitoyl-sn-3-glycerol-phosphatidylcholine (DPPC) [23]. The aim was to improve its photophysical properties, by preserving its monomeric form. From the available platforms, the mixed copolymer–lipid system proved superior in most aspects.

Another promising candidate for PDT and PTT is porphyrin-lipid nanoparticles or porphysomes, which are vesicles composed of pyropheophorbide-conjugated phospholipids [24]. These nanoparticles are promising theranostic agents for a wide range of applications, including drug delivery, phototherapy, magnetic resonance imaging (MRI) and PET. They end up inside tumors due to the enhanced permeability and retention (EPR) effect and after their entrance into the cancer cells, they are disrupted into pyrolipid subunits. Both the intact and the disrupted state can be exploited for therapeutic purposes.

Previous studies would primarily focus on the use of porphysomes as PTT agents, suggesting that they can be utilized for PDT only though target-triggered activation. Guidolin et al. showed through animal studies that porphysomes are effective in PDT without any modification, by comparing them with Photofrin®, a porphyrin-based PDT agent that is clinically approved [25]. They concluded that multimodal diagnostic and therapeutic applications arise from the intrinsic structure of porphysomes and that they also enable concurrent PDT and PTT. What is more, skin photosensitivity, which is a limiting factor in PDT, may be significantly lower with porphysomes than with Photofrin®.

4. Thermosensitive Liposomes

Lysolipid-containing temperature-sensitive liposomes (LTSLs) are a promising endeavor in the area of drug delivery. They undergo gel-to-liquid crystalline phase transition under conditions of hyperthermia (HT), releasing their cargo in a spatiotemporal way [26]. In the case of ThermoDox®, this hyperthermia (40–42 °C) is induced by applying local radiofrequency ablation and high focused intensity ultrasound (HIFU) [27]. The product has undergone a Clinical Phase 3 for the treatment of hepatocellular carcinoma and is currently under Clinical Phase 1 for liver cancer. In fact, local HT has been employed in chemotherapy to enhance drug accumulation through tissue perfusion, as well as to sensitize tumor cells to treatment. With LTSLs, it is exploited to increase drug bioavailability and decreasing peripheral toxicity [28][29].

LTSLs can be combined with SPIONs or other metallic nanoparticles on a single hybrid nanoplatform [30][31][32]. In this way, thermo- and magneto-responsive behaviors can be integrated to offer multifunctionality. This is achieved by utilizing the classic phospholipid DPPC, the lysolipid 1-stearoyl-2-hydroxy-sn-glycero-3-phosphocholine (MSPC) that induces membrane pore formation during the thermoresponsive phase transition, and a component to promote interfacial stabilization and biological stability, such as PEG-lipid 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethyleneglycol)-2000] (DSPE-PEG2000) [33]. In addition, SPIONs, gold or copper sulfide nanoparticles, when incorporated inside the liposomal membrane, offer bioimaging. As a result, these lysolipid-containing temperature-sensitive magnetoliposomes (mLTSLs) initially act as MRI contrast agents and when they reach the target tissue, they are destabilized by hyperthermia, which originates from external sources or from the magnetic nanoparticles that are stimulated [34][35].

At the same time, local HT and the use of specific drug molecules, such as doxorubicin (DOX), have been associated with upregulation of cell death ligand 1 (PD-L1), which create an immunosuppressive environment inside tumor tissues [36][37]. Based on this, Ma et al. studied the beneficial effect of cell death protein 1 (PD1) blockade, in combination with photothermally activated mLTSLs with encapsulated DOX [38]. Drug delivery and MRI were achieved, while tumor growth was significantly reduced by coadministration of anti-PD1 monoclonal antibodies (mAb). In this case, the drug was delivered inside the liposomal core, while nitrodopamine palmitate-coated iron oxide nanoparticles (IO NPs) were incorporated inside the membrane.

One of the main challenges in the development of mixed/chimeric advanced drug delivery nanosystems (aDDnSs) is to have a well-defined, robust and scalable manufacturing process. The nanoscale is one factor that renders formulation difficult, while another is the complexity of the system. Cheung and colleagues managed to develop a SPION-incorporating LTSL through a scalable nanoprecipitation method, with high reproducibility and stability [33]. These nanoparticles offer multimodal imaging and targeted drug delivery, which are controlled through local hyperthermia and the SPION behavior, modulated, e.g., by a magnetic field or NIR irradiation.

5. Cell Membranes

The utilization of cell membranes as a tool to effectively deliver bioactive agents is the next step in terms of biocompatibility and biological stability. The cell membrane is essential in fundamental cellular functions, including compartmentalization, self-identification, bio-interfacing and signal transduction [39]. Cell membrane-based nanoparticles (CMBNs) are cell-material nanohybrids that combine the advantages of biomimicry and bio-functionality, being able to mimic and interact with the complex biological microenvironment [40]. Inside this technology, there are both synthetic and natural elements, where the latter are proteolipid vesicles that act as a “trojan horse”, camouflaging nanomaterials that carry drug molecules, genes or imaging agents. CMBNs are a new class of DDSs that integrate the unique biomimetic and functional properties of cell membranes and the engineering versatility of synthetic nanomaterials [41].

Depending on the intended application and target site, the membranes can originate from cancer cells, red or white blood cells, platelets, mesenchymal stem cells or neutrophils, with each class having its own advantages. For instance, cancer cell coating offers increased circulation and tumor affinity and homing, facilitating theranostics, while reducing any potential side effects [39][42]. The main mechanism that drives these particles is the affinity of the utilized membrane for the relevant tissue. One very important advantage of this new class of nanoparticles is that they can escape the immune system and have prolonged circulation time, which is a prerequisite for the EPR effect and tumor targeting [43].

Rao et al., prepared erythrocyte membrane-coated magnetic nanoparticles by microfluidic electroporation, instead of conventional extrusion [44]. The formulation was tested in vivo on MCF-7 human breast tumor xenografts and exhibited superior effect, apparently due to the achievement of better coating results. In particular, Fe_3O_4 nanoparticles and red blood cells were infused inside a microfluidic device, where electric pulses promoted the entry of the former inside the latter. The resultant nanoparticles exhibited superior magnetic and photothermal properties that were utilized for MRI and PTT in mice. Furthermore, serving scale-up and industrialization, the authors claim that the method offers accurate control of the size and function of the vesicles that are used for coating. At the same time, autologous extraction of RBCs, combined with a convenient production method, might facilitate personalized theranostics that will be compatible with each individual’s immune system.

Neutrophils are another promising approach in cell membrane-mediated drug delivery and find extensive application in glioma treatment, since they can penetrate the blood brain tumor barrier (BBTB) and are the most abundant immune cell class. In this context, Xue and co-workers developed neutrophils with encapsulated PTX-loaded liposomes for post-operative glioma recurrence [45]. The stimulus for the release of PTX from the neutrophils was the high concentration of inflammatory signals, leading to slower tumor recurrence and growth, as well as improved survival, even though the tumor regeneration was not prevented. Such studies pave the way for clinical exploitation of physiologically derived immune cells as DDSs.

The selective deprivation of nutrient supply and metabolic pathways of tumor cells can improve anticancer treatment. Li et al. designed and developed a cascade bioreactor that enabled concurrent starvation of cancer cells and PDT [46]. They achieved this by incorporating glucose oxidase and catalase molecules inside a porphyrin MOF of a porous coordination network, which was then camouflaged with a cancer cell membrane. Cancer cell targeting and tumor retention were enhanced, owing to the biomimetic camouflage, immune escape and homotypic targeting. From there on, cancer cell internalization was followed by the bioreactor promoting microenvironmental oxygenation, leading to decomposition of intracellular glucose and enhancement of cytotoxic singlet oxygen ($^1O_2$) under light irradiation. The results were

synergistic long-term cancer starvation and robust PDT, effectively inhibiting tumor growth after a single administration. In similar context, Chen and coworkers developed poly lactic-co-glycolic acid (PLGA) nanoparticles that incorporated ICG in the polymeric core and were coated with cancer cell membrane as a surrounding shell [47]. The nanoparticles exhibited homologous targeting, good photothermal properties and excellent imaging properties, based on fluorescence and photoacoustics. The membrane shell facilitated cell endocytosis, homologous targeting and in vivo tumor accumulation, while liver and kidney uptake were decreased. Finally, the nanosystems exhibited very efficient PT and elimination of the xenograft tumor, suggesting that cancer cell membranes are very promising as biomimetic components of DDSs for cancer imaging and therapy.

6. Lipoprotein Nanoparticles

Lipoproteins have the endogenous role of transferring hydrophobic molecules, such as cholesterol and other lipids, between different sites inside the organisms. Recently, the understanding of their function and role, alongside their biocompatibility and biomimicry, have led to the development of lipoprotein-inspired nanosystems, which are promising as DDSs for therapeutic, diagnostic and theranostic purposes [48]. Such nanosystems can circumvent the reticuloendothelial system, to have a prolonged circulation time, while their very small size allows them to efficiently penetrate tumors. In addition, lipoproteins have high affinity for endogenous receptors that can be found on cancer cells. Their structure includes a hydrophobic core, surrounded by a phospholipid monolayer that contains unesterified cholesterol and apolipoproteins [49].

Sheng et al., developed a nanoplatform, based on high-density lipoproteins (HDLs), in which they incorporated ICG for NIR-activated fluorescence imaging, PTT and PDT [50]. In addition, they decorated the nanoparticles with a tumor-homing iRGD peptide via conjugation, for active targeting. The peptide was attached by cross-linking, which led to the organization of a scaffold that could maintain the nanoparticle structure. The HDL-like nanoparticles could penetrate tumors, facilitating effective PTT and PDT under NIR light irradiation. At the same time, He and colleagues built a nanotheranostic system based on an HDL-mimicking peptide–phospholipid scaffold (HPPS), with hTfR (human TfR) monoclonal antibody (mAb) decoration, complexed siRNA, and the fluorophore DiR-BOA incorporated inside the core [51]. DiR-BOA acts as an imaging tool, while the nanoparticles could efficiently target and cause HEPG2 apoptosis.

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