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Editorial

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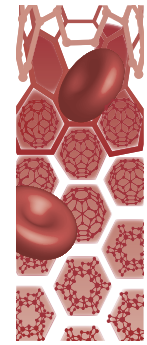

Natural and artificial phospholipid bilayer coatings on solid-state nanoparticles, current and future perspectives

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> "the development of phospholipid-coated solid-state nanoparticles is very promising and an increasing amount of research output is focusing on this topic, up to *in vivo* validations"

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In recent years, much research attention has been applied to the development and clinical application of lipid-based nanomedicines, such as the use of liposomes for drug delivery, of lipid nanoparticles for gene delivery, for example in COVID-19 vaccines, and of cell-derived extracellular vesicles (EVs).

EVs are nanosized lipid bilayer structures secreted by almost all eukaryotic cells. They are involved in membrane trafficking and intercellular communication, working as natural vectors for the delivery of various biomolecules, including lipids, proteins and nucleic acids. The surface protein profile, determined by the secreting cell type, determines EV-cell interactions and EVs generated from different sources demonstrate specific tropisms toward particular organs and tissues [1,2]. For this reason, EVs are intensively studied to better understand their innate targeting and cargo delivery characteristics, as well as a basis to develop nanomedicines for drug and gene delivery. For example, tumor-derived EVs are involved in cancer progression and organ-specific metastasis by mediating the transfer of oncogenic molecules between cancer and various recipient cells in either local or distant microenvironments. For these innate tropisms and targeting capabilities, EVs have been investigated as carriers for different anticancer agents. Encapsulation in EVs has allowed for the targeted delivery and increased therapeutic efficacy of different chemotherapeutics [3] and RNAs [4] and some EV-based drug-delivery formulations are currently in clinical trials [5,6]. However, the oncogenic potential of tumor-derived EVs still raises some concerns regarding their application. In addition to this, EVs greatly vary in terms of size, genetic content and protein expression depending on the physiological or pathological state of parental cells and are difficult and time consuming to isolate and purify, which poses a limit on their large-scale and reproducible production for pharmaceutic industries.

A wide variety of alternative solutions have been proposed to circumvent these challenges, which can be divided into two broad groups, top-down and bottom-up methods. Top-down methods can produce nano- or microvesicles by disrupting or extruding cell membranes [7], i.e., creating so-called membrane ghosts or nanoerythrosomes [8] when erythrocytes are involved. In contrast, bottom-up methods produce synthetic-natural hybrids, such as EVs fused with synthetic lipids, liposomes or both [9]. Until recently, the most research attention in the production of EV biomimetics has been on the latter, i.e., fully artificial liposomes mimicking EV functions in terms of targeting and cargo transfer, but with controllable and reproducible size and physicochemical features [10]. We believe that the bottom-up approach, which is still in its initial phases, could offer enormous opportunities in the field of EV biomimetics, aiming at the development of fully synthetic products much less complex in composition, but which still resemble their natural counterparts in terms of efficacy in aforementioned targeting and cargo transfer. The formulation of EV-mimicking nanostructures is based on the assumption that not all components of natural EVs are essential for their delivery functionality. This opens up the possibility of incorporating only essential structural and functional components, identifying them for example in tumor-derived EVs, which show strong tropism capabilities. By reproducing the key lipid and protein composition, it is possible to obtain artificial nanosystems

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that are simpler than natural EVs and can be customized with robust biological functionalities for the specific therapeutic outcome.

The role of lipid bilayers, either natural or artificial or a mixture of the two, can be regarded not only as carriers of molecules, like drugs, dyes or genetic material but also for encapsulating solid-state nanoparticles. Both organic and inorganic nanoparticles suffer from a lack of colloidal stability in biological media, either *in vitro* or *in vivo*, which must be strictly preserved to avoid their aggregation, premature degradation and rapid clearance. Colloidal stability is also helpful in guaranteeing the optimal biodistribution of nanoparticles, cell internalization processes and, more in general, the nanoparticle therapeutic and/or diagnostic activities in the target tissue. Among many proposed strategies to overcome this issue, we firmly believe that using phospholipidic bilayers to encapsulate solid-state nanoparticles holds great promise and can, in the future, become the standard for applying solid-state nanoparticles in nanomedicine. Lipid coating provides a defensive barrier between the core and the biological environment, ensuring the chemical and colloidal stability of nanoparticles by reducing the physical and chemical interactions with the surrounding media [11]. Also, the lipid bilayer can offer a barrier from inside to outside, preventing cargo leakage from carriers with open pores, like mesoporous silica nanoparticles, and avoiding off-target delivery [12]. Moreover, lipid bilayers increase the biocompatibility of coated nanoparticles, can serve as a substrate for conjugation with a variety of moieties for cell-specific targeting and improve interaction with target cell membranes, facilitating the internalization process thanks to their structural resemblance to these membranes [13].

However, efficient cell internalization needs to be coupled with effective intracellular release and redistribution of the therapeutic content. Indeed, most nanoparticles can enter cells via endocytosis, which consists of the invagination of the cell membrane and the production of internal membrane-bound structures (endosomes) enveloping the taken-up nanoparticles [14]. The effectiveness of nanoparticles as intracellular imaging probes or therapeutic agents can be impaired or even totally hindered due to the lack of endosomal escape, which prevents the therapeutic/imaging cargoes of nanoparticles from efficiently reaching the cytosol and cell subcompartments. In view of this challenge, different stimuli-responsive solutions were ideated to equip the nanoparticles with release mechanisms and overcome the endosomal membrane 'barrier'. Stimuli-responsive surface moieties, such as endosomolytic peptides, are capable of inducing osmotic pressure inside the endosome [15]. Also, photoactive molecules that enable the production of reactive oxygen species and destruction of the endosomal compartments [16–18] have been proposed as possible solution and employed in lipid bilayer coated porous nanoparticles loaded with cargo. Additionally, biodegradable nanoparticles, able to dissolve due to acidic pH or redox reactions were efficiently proposed as endosomal escape strategies [11,19]. Finally, recent advances proposed the use of fusogenic lipid bilayers, allowing to bypass the endocytosis mechanism while directly merging the lipid-coated nanoparticles with the cell membrane and achieving the intracellular cytosolic delivery of the therapeutic and imaging content [20]. In this respect, magnetic iron oxide nanoparticles [20], polymeric [21] and porous silicon nanoparticles [22] have been coated with a mixture of phospholipids including cell membrane-fusogenic ones, enabling their intracellular delivery directly to the cytosol.

We believe that the role of phospholipid bilayer, although established in the generation of nanocarriers for molecules both in research and clinical fields, is still in its infancy when considering the delivery of solid-state nanoparticles. Nonetheless, the development of phospholipid-coated solid-state nanoparticles is very promising and an increasing amount of research output is focusing on this topic, up to *in vivo* validations. The current advantages of using artificial lipid-based systems for enveloping nanoparticles are, of course, the control of their manufacture and reproducibility. However, efficient tissue targeting has yet to be demonstrated. The use of naturally derived cell membranes or EVs as a coating for solid-state nanoparticles holds promise due to the intrinsic low immunogenicity and tropism of biologically derived material, and hybrid liposomes/EV-coated NPs represent a promising research frontier that could yield significant advances. Finally, fully artificial EV biomimetics encapsulating solid-state nanoparticles with diagnostic or therapeutic capabilities is the ultimate goal, allowing to overcome the production and storage limitations of natural EVs and offering the brightest future for the development of safe and off-the-shelf nanosystems for the next generation nanomedicine.

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