Protein corona: Friend or foe? Co-opting serum proteins for nanoparticle delivery

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ABSTRACT

For systemically delivered nanoparticles to reach target tissues, they must first circulate long enough to reach the target and extravasate there. A challenge is that the particles end up engaging with serum proteins and undergo immune cell recognition and premature clearance. The serum protein binding, also known as protein corona formation, is difficult to prevent, even with artificial protection via "stealth" coating. Protein corona may be problematic as it can interfere with the interaction of targeting ligands with tissue-specific receptors and abrogate the so-called active targeting process, hence, the efficiency of drug delivery. However, recent studies show that serum protein binding to circulating nanoparticles may be actively exploited to enhance their downstream delivery. This review summarizes known issues of protein corona and traditional strategies to control the corona, such as avoiding or overriding its formation, as well as emerging efforts to enhance drug delivery to target organs via nanoparticles. It concludes with a discussion of prevailing challenges in exploiting protein corona for nanoparticle development.

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1. Introduction

Nanoparticulate drug carriers are used to preserve drug stability in physiological conditions and improve drug delivery to target tissues. The premise of using nanoparticles (NPs) is that the nano-sized particles have selective access to tumors with leaky vasculature via the enhanced permeability and retention (EPR) effect [1]. Additionally, NPs may be coated with antibodies, peptides, and proteins that bind to the overexpressed receptors in target tissues, which further enhance target-specific retention and uptake. However, few nanoparticle formulations translated to clinically applicable products, with the majority still suffering from premature clearance by the mononuclear phagocyte system (MPS) and suboptimal therapeutic benefits.

One of the critical challenges is that proteins in the physiological media bind to the NPs to form an assembly of various proteins on the surface, called protein corona (PC) [2]. The PC endows NPs with a new identity, distinct from the original physicochemical identity, driving the *in-vivo* fates of NPs in a manner that may be inconsistent with the design [3–6]. Therefore, PC is considered a missing link between *in vitro-in vivo* correlation of NP performance [7]. Understanding the nature of PC and its impact on the biological performance of NPs is critical to the successful development of NP products.

Since the initial recognition of PC and its impact on NP performance [8–12], numerous studies have investigated the relationship between PC profiles and NP attributes [9,13–16]. The early focus has been to develop analytical methods, identify the components of PC, and understand NP properties that govern the PC profiles [4]. With increasing data linking the PC profiles and *in vivo* performance of NPs, recent efforts are made to exploit the PC, instead of avoiding it, by identifying serum proteins promoting target-specific interactions and co-opting those proteins by design [17]. Several preclinical studies support that PC can help deliver drugs via NPs to specific organs, including the brain, which remains a tempting target. Once considered a *foe*, the PC deserves new attention as a potential *friend* to help improve NP-based drug delivery.

With the new perspective on PC, we intend to compile recent literature to understand the current state of the art and explore new opportunities to take NP technology to the next level. We will first summarize known issues of PC formation and traditional approaches to control PC and discuss emerging strategies to exploit PC for NP delivery, focusing on articles published in the last five years. The review will conclude with a discussion of prevailing challenges in using PC for NP development.

2. Protein corona on nanoparticles

Once NPs enter the circulation, they interact with different components of biological fluid, especially serum proteins. The NP surface is first covered by proteins abundant in blood, forming a "soft corona," which, over time, is replaced by high-affinity proteins to form a "hard corona" [18,19]. A common *in vitro* method to profile PC on NPs is to incubate them with plasma or serum for a certain time, elute and digest the surface-bound proteins, and analyze them by gel electrophoresis and LS-MS/MS. Prior to the elution of PC, the NPs are typically separated from the excess solution by centrifugation and washing [20]; therefore, most *in vitro* results tend to focus on hard corona, which survives centrifugation and subsequent washing steps. Recognizing the significance of dynamic environment on PC formation, recent studies investigate the PC formed *in vivo*, where the NPs are injected intravenously and retrieved from blood [21]. Magnetic separation [22] or size exclusion chromatography [23] are employed to separate NPs from the blood for analysis. To investigate soft corona and temporal evolution of PC, *in vitro* methods are complemented by additional analytical tools, such as microscopy [24], spectroscopy [25 26], zeta potential analysis [27,28], or click chemistry that immobilizes soft corona *in situ* [29]. Techniques used to analyze PC have been thoroughly reviewed in recent literature [30].

The composition and quantity of proteins bound to NPs vary with their size and surface chemistry [3,31]. A study with polystyrene NPs with differential sizes (50 and 100 nm) and surface chemistry (plain, carboxyl-modified, and amine-modified), incubated with human serum, detected > 80 plasma proteins in 88 % of the data sets, commonly involving immunoglobulins, lipoproteins, and complement proteins [3]. Selected proteins may be clustered according to their preference of size and surface chemistry, where the identity, lipid affinity, and post-translational modification of each protein contribute to the preference [3]. PC also depends on plasma composition and concentration [32,33]. In addition, the medical condition of a patient has a profound impact on PC profiles [34]. For example, PC-bound liposomes in pancreatic cancer patients are less negatively charged than those of other cancer patients or healthy individuals due to the enrichment of tumor antigen-specific autoantibodies [35]. These findings demonstrate the dependence of PC on biological factors and underscore the importance of simulating *in vivo* conditions (e.g., serum concentration, disease status, species) in PC analysis, which may be overlooked in conventional *in vitro* assays based on cell culture media with animal sera.

3. Effects of PC on NP performance

PC can alter the size and surface characters of NPs and confer different biological properties, causing unpredictable therapeutic outcomes. The following summarizes the influences of PC on NP functionality.

3.1. Colloid stability

There are mixed findings regarding the effects of PC on the colloidal stability of NPs. Some show that PC increases the risk of NP aggregation. Surfactant-stabilized gold nanorods (NR), precoated with PC by incubation with equine serum, undergo differential degrees of aggregation depending on the stabilizing agents and the media in which they are tested [36]. With cationically stabilized gold NRs by cetyltrimethylammonium bromide (CTAB) or oligofectamine, the PC caused aggregation in deionized water but not in RPMI cell culture medium. On the other hand, the gold NRs stabilized with neutral surfactant Brij56 or anionic phosphatidylserine remained stable in both deionized water and cell culture medium [36]. Others report that the aggregation depends on the type and concentration of proteins: polystyrene NPs aggregated in medium containing cow serum, less so in cow serum depleted of immunoglobulin G (IgG), and did not aggregate in medium with fetal calf serum (very low on antibodies). Supplementing IgG or fibronectin to fetal serum caused the aggregation, indicating the two proteins to be responsible [37]. The diverse conclusions on the colloidal stability of PC-coated NPs may be attributable to the variability of test conditions: The interactions of PC-coated NPs vary with the pH and ionic strength of the medium, which influence the charges of NPs and proteins [38–42], types of ions [39,43], and the protein to NP ratio (i.e., the protein concentration) [37,44].

Proteins with relatively large molecular weights (>40 kDa) and low isoelectric points (<pH 7.4), such as albumin, catalase, hemoglobin, glucose oxidase, and horseradish peroxidase, have shown to help disperse gold NPs, based on the steric hindrance and/or negative charges in physiological pH [45]. Therefore, serum albumin is actively exploited to improve the colloidal stability of NPs, such as gold NPs that can accommodate the protein via cysteine residues [45,46]. The albumin-coated gold NPs maintained colloidal stability in hypertonic conditions, extreme pHs [45], high concentrations, and the lyophilization process [46]. Nevertheless, the protective effect of surface-bound albumin varies with the type of NPs and ions in the media [43] and may not be generalized.

3.2. Cellular interaction

PC affects the cellular uptake of NPs in various ways. In many cases, the presence of PC, such as serum albumin, on the NP surface lowers the surface energy and decreases the NP–cell membrane interaction, thereby reducing the NP uptake [47,48]. The extent of NP uptake reduction varies with the NP size and the cell types. A study with gold NPs showed that the PC effect on particle uptake increased with the particle size, with 50 nm gold NPs being more affected than 5 nm and 20 nm gold NPs, and phagocytic cells were more affected than nonphagocytic cells [49]. In addition, the surface chemistry and softness of NPs influence the extent of the PC effect. In LNPs with two PEGylated acyl chains of different lengths (C18 vs C14), PC decreased the HepG2 cell uptake of LNPs with the C18 acyl chain but increased the uptake of LNPs with the C14 chain [50]. Also, solid NPs showed a significant decrease in the uptake by human keratinocytes and endothelial cells upon PC binding, whereas soft nanogels made of dendritic polyglycerol were not affected by PC [51].

PC can also enhance the cellular uptake of NPs. PC can help negatively charged NPs to overcome the electrostatic repulsion between the cell membrane and NPs. For example, PC helps neutralize the surface charge of citrate-coated silver NPs and allows them to enter mouse embryonic fibroblasts, increasing cytotoxicity [52]. Fibrinogen, immunoglobulins, and complements bound to NPs respectively interact with integrin receptor, Fc receptor, and complement receptors of macrophages to facilitate phagocytosis

of the NPs [53]. Apolipoproteins ApoE and ApoB-100 support the uptake of NPs by brain endothelial cells via the low-density lipoprotein receptor (LDLR) [54].

In addition, PC can change the uptake pathway of NPs. With gold NPs, PC interfered with classical caveolae- or scavenger receptor-mediated endocytosis or phagocytosis but promoted clathrin-mediated endocytosis. In hepatocellular carcinoma (HepG2) cells, clathrin-mediated endocytosis was favored in serum-containing medium, whereas caveolae-mediated endocytosis dominated in serum-free medium [49]. Our group has also observed a change in the endocytosis pathway from clathrin-mediated endocytosis to caveolae-mediated endocytosis due to the albumin binding to NPs via polydopamine surface (more in Section 6.1) [55].

The effect of PC on NP-cell interaction varies with the source of PC. For example, the adhesion of NPs to target cells was shown to be affected by PC differently according to the species from which the PC was obtained [56]. Here, organic and inorganic NPs (500 nm) were modified with sialyl Lewis A (sLe^A) to target selectin-expressing endothelial cells. When the NPs were added to selectin-expressing human umbilical vein endothelial cells (HUVEC) in laminar flow, their binding to the cells was significantly affected (almost eliminated) by porcine plasma but not by mouse plasma. The adhesion inhibition of PLGA particles was also observed in human plasma [57]. The differential effect of protein binding to HUVEC was attributed to the difference in PC composition: the sLe^A-modified PLGA NPs exposed to porcine plasma showed the binding of 150 kDa protein (likely IgG), like in human plasma, as well as > 250 kDa protein, but those exposed to mouse plasma did not. This study underscores that the effect of PC on cellular interactions and other behaviors of NPs discussed below should be interpreted in the context of species.

Given the species dependence, it is worthwhile to reconsider the reliability of animal models (typically mouse models) in predicting the clinical consequences of PC formation. Neutrophils are identified to be a major phagocytic cell population that contributes to NP clearance in blood [58,59]. Neutrophils showed a differential NP uptake pattern according to the medium in which the NPs were incubated: polystyrene NPs in human plasma were taken up by human neutrophils far more than those in bovine serum [58]. PC profiling and incubation with selected proteins suggest that complement components in human plasma bind to the NPs and mediate their preferential uptake by neutrophils [58]. PEGylated polystyrene NPs were even more prone to neutrophil uptake compared to naked (carboxylated polystyrene) NPs. This difference is attributable, ironically, to the stealth function of polyethylene glycol (PEG) (Section 4): naked NPs were covered with benign PC, including albumin, whereas PEGylated NPs acquired less PC, leaving room for complement protein binding. This study suggests that the PC effect studied in one species may not be extrapolated to others. Species difference in the cell population (e.g., neutrophils representing 50–70 % of circulating leukocytes in humans but 10–25 % in mice [60]) brings an additional layer of complexity in interpreting the consequence of PC binding to NPs.

3.3. Cytotoxicity

NP introduced to the body continuously interact with various types of cells, including blood cells, endothelial cells, and cancerous cells. The carrier itself may have detrimental effects to the cell viability. PCs can affect the extent of cytotoxicity of the NPs either positively or negatively.

Many studies report that PC reduces the cellular toxicity of NPs [61–67]. The PC layer can block NPs from contacting and damaging cell membranes and reduce their cellular uptake. For instance, CTAB-coated gold NRs destabilize the cell membrane and cause

necrosis; however, PC shielded the adverse effects of the cationic surfactant and reduced the toxicity on A549 cells [68]. Graphene oxide nanosheets induce reactive oxygen species (ROS) and directly damage the cell membrane via sharp edges [69,70]; however, 10 % FBS and bovine serum albumin PC reduced the damaging effect by making the edge of nanosheets dull and reducing their surface area available for lipid extraction [70]. Additionally, PC can scavenge ROS or reduce their production catalyzed by inorganic NPs. For example, titanium dioxide (TiO_2) nanotubes induce phototoxicity upon UV irradiation by catalyzing ROS production. However, serum proteins bound to TiO_2 nanotubes sequestered the photoinduced hydroxyl radicals and reduced phototoxicity [66]. Cadmium telluride quantum dots (CdTe QDs) impair mitochondrial activity by damaging the organelle membrane, resulting in ROS increase and ATP reduction. PC acquired in fetal bovine serum prevented the negative effects of QDs on mitochondria activities, alleviating the cytotoxicity to RAW 264.7 cells [71]. The PC-mediated reduction of ROS production and cytotoxicity has also been reported with ZnO NPs [72,73] and Fe_3O_4 NPs [74]. Meanwhile, the protective effect of PC may be dependent on the protein identity. Lysozyme, immunoglobulin G, and bovine serum albumin are shown to reduce the cytotoxicity of the poly(acrylic acid)-*block*-polystyrene polymersomes on HeLa and HEK 293 cells [75]. Similarly, serum albumin corona attenuated the platelet aggregation caused by carboxylate-functionalized carbon nanotubes; however, IgG and histone H1 corona aggravated the platelet damage in distinct manners [76].

Conversely, PC can exert adverse effects on cell functions. For example, human serum albumin adsorbed on ultrasmall gold nanoparticles (AuNPs) underwent conformational change leading to increased α-helicity. The albumin with altered conformation damaged the cell membrane and increased cytotoxicity to BRL 3A rat liver cells and 293 T embryonic kidney cells [77]. In another example, cadmium sulfide nanomaterials (CdS NMs) incubated with fetal bovine serum increased cytotoxicity to the cells while reducing macrophage uptake [78]. The apparently contradicting phenomenon was attributed to the PC-induced expression of FcγRIIB receptors [78], which activate protein kinase B/Caspase 3 pathway to induce apoptosis but also downregulate phagocytic activity of macrophages [79]. This study illustrates that cellular uptake is not always a prerequisite for increased cytotoxicity. PC formation can also lead to abnormal proliferation of the cells. PC formed on the nanoscale airborne particulate matter by serum incubation stimulated the generation of ROS, which activated α-smooth muscle actin expression, causing aberrant proliferation of human lung fibroblasts [80]. Similarly, SiO_2 NPs recruited transforming growth factor β1 (TGF-β1) from the supernatant of lung tissue homogenate, enhancing the epithelial-mesenchymal transition and the development of pulmonary fibrosis [81]. In blood, naked amorphous SiO_2 NPs (70 nm) bound to coagulation factor XII, which activated the coagulation cascade and caused fatal toxicity in mice [82,83].

3.4. Biodistribution

A prominent consequence of the altered NP-cell interaction due to PC is the loss of cell targeting function of the functional ligand. A seminal observation was made with Transferrin (Tf)-functionalized silica NPs, which lost the ability to specifically interact with cell Tf receptor (TfR) upon incubation in serum [84]. Similarly, polymeric NPs functionalized with HIV-1 *trans*-activating transcriptor (TAT) peptides (known to cross the blood–brain barrier, BBB) and antibodies to neural/glial antigen 2 (NG2) (known to target oligodendrocyte precursor cells, OPC) did not show enhanced brain delivery and OPC targeting, likely due to significant PC binding

[85]. A study with sLe^A-modified PLGA NPs suggests that IgA and IgM may be potential culprits [86]. As mentioned in Section 3.2, sLe^A-modified PLGA NPs lose the ability to bind to E-selectin-expressing endothelial cells when incubated in human plasma [57]. The NPs incubated in Ig-depleted plasma maintained the binding ability, holding Igs accountable for the loss of ligand function [86]. Restoration of IgA and, to a lesser extent, IgM to the Ig-depleted plasma caused the inhibition of NP binding to the target cells, indicating that the two Igs are involved. Despite the abundance, IgG did not have a significant effect on NP-cell interaction [86].

On the other hand, PC with an affinity for specific cell receptors may provide an opportunity to increase NP biodistribution to specific organs. For example, lipid nanoparticles (LNPs) are envisioned to recruit ApoE in circulation, which binds to the LDLR of hepatocytes [87–89]. The ApoE-mediated liver tropism uniquely qualified LNPs for the delivery of nucleic acids addressing liver diseases, such as hereditary transthyretin amyloidosis [90,91]. Serum proteins exploited for organ targeting are discussed in Section 6 with recent examples.

3.5. Immune responses

Some surface-bound proteins can activate immune systems, causing premature clearance of the NPs or promoting the release of proinflammatory cytokines [53,92].

3.5.1. Complement activation

Several dextran-based magnetic resonance imaging agents (Sinerem, Combidex, Feridex) have been withdrawn from clinical use due to the complement-related side effects [93]. Dextran-coated ferrous NPs are known to activate the lectin complement pathway, starting with lectin binding, followed by the adsorption of mannose-binding lectin (MBL)-associated lectin serine protease 1 (MASP-1), and MASP-2, and complement protein C3, then converted to the activated C3b [93,94]. A study with iron oxide NPs (IONPs) and liposomes describes that C3b binding involves immunoglobulins, which first bind to PC and are attacked by C3b. The initially bound C3b recruits convertases, which induce the cleavage of C3 near the surface, causing additional C3b binding [95]. The complement-bound NPs undergo increased binding/uptake by immune cells via corresponding receptors, such as complement receptor (CR)1/2 and CR3 [96].

Polymer coating of IONPs affects the complement protein deposition and corresponding production of proinflammatory cytokines [97]. Among IONPs with a bare surface, PEG, or PVP coating, incubated in human serum, IONP-PEG, but not the other two, showed increased C3a and C5a binding, indicating complement activation via the alternative pathway. IONP-PEG also augmented the IL-1β, TNF-α, and IL-6 levels and showed an increased presence in the spleen compared to the other IONPs. The differential effect of IONP-PEG was attributed to the pre-existing anti-PEG antibodies, which may have activated the immunoglobulin-mediated complement pathway [97]. Silica NPs show a similar dependence on polymer coating in complement activation and cellular uptake [98]. Poly(2-methyl-2-oxazoline) (PMOXA)-coated silica NPs showed more deposition of C3b and C3c α′ chain fragment 2 than the PEG-silica NPs or the uncoated NPs after human serum incubation. The C3 opsonized PMOXA-silica NPs promoted cellular uptake by human monocytes, polymorphonuclear granulocytes, and macrophages. However, the complement activation and macrophage uptake were not observed with mouse counterparts, indicating species dependence [98], consistent with the case shown in Section 3.3.

3.5.2. Effects on immune cells

Several studies report that PC can increase NP interaction with immune cells to increase proinflammatory cytokine production. For example, PC on black phosphorus nanosheets (BPNSs) and black phosphorus quantum dots (BPQDs), mostly (70–76 %) consisting of immune-relevant proteins, facilitated macrophage uptake of these NPs and the production of pro-inflammatory cytokines from the NP-treated macrophages [99]. Likewise, PC formed on PEGylated carbon nanotubes (CNT) induced the production of ROS and pro-inflammatory cytokines in macrophages and activated immune cells in the spleen [100]. Such immunostimulatory effects depended on the conformation of the bound proteins. IgG and α1 acid-glycoprotein underwent unfolding on the surface CNT, causing the production of inflammatory mediators, whereas fibrinogen and vitronectin - with no structural changes - had negligible effects on ROS production [100].

The effects on immune cells also depend on the surface chemistry of NPs. Gold NRs were modified with cetyltrimethyl ammonium bromide (CTAB), poly(diallyldimethyl ammonium chloride) (PDDAC), polyethyleneimine (PEI), polystyrene sulfonate (PSS), and PEG. Of these, PEI- or PDDAC-coated gold NRs increased the IL-1β production in macrophages upon PC binding, enriched with acute-phase proteins and complements [101].

PC may also reduce the proinflammatory effects. For example, PC-covered nanosilica (SiO_2) showed lower cytotoxicity and reduced production of IL-8 in human epithelial cells and TNFα in macrophages, compared to bare SiO_2 particles, despite the increase of cellular uptake [102]. Another study reports the dependence on the environment in which PC was formed [103]. Poly(methacrylic acid) (PMA) hollow capsules (CAPs) and core–shell particles (CSPs) were incubated with a cell-conditioned medium or medium supplemented with specific proteins (FBS, human serum, or human plasma) to form PC. Upon incubation with the PC-NP combinations, the production of pro-inflammatory cytokines in macrophages or monocytes changed in either direction compared to PC-free NPs, depending on the source of PC, i.e., the type of proteins bound to the NPs [103].

4. Strategies to avoid protein corona formation

Given the aberrant effects of PC on nanoparticle performance, drug delivery scientists have made diverse efforts to manage protein corona formation. One of the approaches is to prevent the formation of PC on NPs. A common method is to modify the NP surface by grafting hydrophilic polymers [104].

PEG is most widely used for modifying the NP surface due to its hydrophilicity and low toxicity [105]. PEG chains grafted on the NP surface provide a hydrated layer to prevent protein adsorption [106], a phenomenon so-called the "stealth" effect. The surface density, molecular weight, and chain architecture of the polymer affect the PEG conformation on the NP surface, hence the effectiveness of the stealth effect [107]. It was shown that PEG density determines the extent of PC formation on gold NPs and the composition of PC [108]. With the fixed PEG grafting density, relatively small NPs form greater PC formation due to the high curvature that leaves more room for each PEG to spread out and lowers the thermodynamic barrier to protein adsorption [108]. The examples and the effects of PEGylated NPs have been thoroughly reviewed in recent literature [109].

Poly(2-oxazoline)s (POx) is a potential alternative to PEG. POx is synthesized by cationic ring-opening polymerization of 2-oxazolines, amenable to variations in architecture and hydrophilic-lipophilic balance [110]. Due to the versatile synthesis, POx has been applied to various formulations, including drug-polymer conjugates, polymeric micelles, complexes, and hydrogels [111–113]. In a head-to-head comparison with PEG (2000 Da), poly (2-ethyl-2-oxazoline) was comparable to PEG in reducing protein adsorption to poly(organosiloxane) NPs in serum and non-specific uptake of the NPs by macrophage-like cells and endothelial cells [114].

Another alternative stealth polymer is zwitterionic polymers, represented by polybetaines such as poly(sulfobetaine) or poly(carboxybetaine) [115]. As zwitterionic molecules, the polymers bind to water molecules via electrostatic interactions, more strongly than other hydrophilic polymers relying on hydrogen bonding [115]. When grafted on hydrophobic substrates, zwitterionic polymers form a well-hydrated layer, which resists protein adsorption [116].

Polyglycerols are nonionic aliphatic polyether polyols with high protein resistance and have been used as stealth coating [117,118]. In a recent study, polyglycerol was compared with PEG as stealth coating to prevent serum protein binding to supraparamagnetic IONPs [119]. At the same weight content, polyglycerol reduced protein adsorption to the NPs in serum and NP uptake by macrophages more efficiently than PEG [119].

Polymers of natural origin, such as polysaccharides, have also been explored as potential stealth polymers [120]. For example, hyaluronic acid, a glycosaminoglycan consisting of $(1 \rightarrow 4)$-β-D-glucuronic acid and $(1 \rightarrow 3)$-β-N-acetyl-D-glucosamine, was used for coating chitosan NPs to reduce PC formation in comparison with alginic acid [121]. Hyaluronic acid coating reduced the extent of protein adsorption to chitosan NPs upon incubation in serum solution. Despite the overall low protein binding, the hyaluronic acid coating allowed the binding of anti-inflammatory proteins, suggesting the potential to reduce the immunogenicity of NPs [121]. Similarly, polyacrylamide-grafted guar gum (PAm-g-GG) was used to mitigate PC formation on ZnO NPs [122]. The PAm-g-GG-coated ZnO NPs reduced the binding of complement protein C3 and IgG compared to bare ZnO NPs. Consequently, PAm-g-GG-coated ZnO NPs experienced lower immune cell recognition and caused less liver inflammation than bare ZnO NPs, resulting in an extended circulation half-life and systemic exposure [122]. Chitosan, especially low molecular weight chitosan or water-soluble derivatives, is another natural polymer used for stealth function [120]. Coated on PLGA NPs, low molecular weight chitosan reduced protein binding to the NPs and macrophage uptake [123]. In a recent study, chitosan coating, together with albumin, prevented a negative effect of PC on the interaction of sLe^A-modified PLGA NPs with the target, selectin-expressing endothelium [124]. Chitosan or albumin alone was not as effective as their combination (or not effective at all) in counteracting the PC effect. It is postulated that the chitosan coating may have enhanced the binding of albumin, which helps interact with endothelium via albumin-specific receptors, such as glycoprotein 60 (gp60). On the other hand, the analysis of PCs on chitosan/albumin-dual coated NPs showed the enrichment of histidine-rich glycoprotein, which has a dysopsonin function. This study suggests that the stealth function of chitosan coating may be ascribed to promoting the albumin binding followed by dysopsonin binding, which is in line with Section 6 – the piggyback strategy.

Another approach that has gained significant interest in the last decade is to coat NPs with cell membranes ("cloaking") [125]. The rationale of the cloaking approach is that the cell membrane-coated NPs may simulate the cell's interactions with the physiological environment, including blood proteins, other cells, and tissues. Therefore, this method was mainly adopted to promote the delivery of NPs to target tissues [126–129] but has also proven to be effective in reducing PC formation [130]. A study with inorganic NPs for cancer imaging demonstrated that coating with red blood

cell membrane protected the NPs from protein adsorption in 100 % human plasma, showing no change in size or surface property, unlike the uncoated counterpart [130].

The examples shown here are only a limited subset of diverse approaches employed to prevent PC formation. Interested readers are referred to more comprehensive reviews dedicated to stealth modification of NP surfaces [131–133].

5. Pre-functionalization: Strategies to override protein corona

While the stealth polymers help reduce protein adsorption to the NP surface, they do not completely prevent it. Major efforts have been made to modify the NP surface with antibodies, ligands, and other functional proteins that may override protein corona and facilitate NP distribution to specific organs or tissues.

5.1. Functionalization with antibodies or ligands

Recent efforts for functionalizing NP surfaces with cell-interactive ligands have been thoroughly reviewed elsewhere [134]. These approaches help retain the NPs in target tissues and have achieved a varying degree of success in improving target-specific drug delivery with preclinical models. However, PC may shield the ligands and interfere with the intended cell-ligand interactions, as mentioned earlier. For example, silica NPs modified with a model ligand bicyclononyne, which undergoes click reaction with an azide counterpart, did not react with the corresponding substrate after incubation with serum solution [135]. Similarly, Tf-functionalized silica NPs, covered with PC, lost the specificity for TfR [84]. The protein binding was reduced by PEG linkers between the NP surface and Tf but not completely prevented [84]. The extent of ligand-receptor binding interference varies with the type of ligands and the origin of serum [136,137]. Nevertheless, due to the prevalence, PC is often considered one of the reasons for the lack of clinical success in the so-called "active targeting.".

Accordingly, efforts have been made to overcome the interference of PC with the ligand/antibody recognition of the target receptors. One approach is to "backfill" the NP surface unoccupied by targeting ligands with extra PEG. For example, gold NPs were modified with Herceptin, an ErbB2 receptor-targeting antibody, via a 5 kDa PEG linker, and the remaining surface was saturated with methoxy-PEG (mPEG) [138]. mPEG shorter than 5 kDa (1 or 2 kDa), but not 5 kDa or 10 kDa mPEGs, allowed the antibody to retain the receptor binding ability by reducing the nonspecific protein adsorption and PC formation [138]. Another study showed the reduction of PC formation by blocking residual maleimide groups on NP surface with 2-mercaptoethanol [139]. The authors argue that the small molecular weight and neutral charge of 2-mercaptoethanol were important because other thiolated compounds with charges or larger molecular weights were less efficient in reducing PC formation. Here, the charged groups would still interact with serum proteins via electrostatic interactions, and the steric hindrance of PEG limit the number of maleimides that can be blocked [139].

As envisioned from these examples, the likelihood of PC formation depends largely on the NP surface underlying the functional layer. Unlike polystyrene NPs, hydroxyethyl starch NPs were already resistant to protein binding [140]. When the hydroxyethyl starch NPs were modified with mannose via a PEG linker, they withstood the preincubation with human plasma and retained the ability to interact with the target C-type lectin and lectin-expressing immature dendritic cells [140].

These studies illustrate that backfilling the surface with a short stealth layer or using inherently nonfouling NPs as a platform may reduce the effect of PC on the ligand/antibody-mediated recognition of target cells. Nevertheless, the effectiveness of these approaches needs to be rigorously measured since the common practice of isolating PC-bound NPs may underestimate the function of loosely bound proteins. With a similar rationale, cysteine was used as a zwitterionic blocking agent [141]. Here, silica NPs were functionalized with cysteine in tandem with a model ligand biotin. The presence of zwitterionic amino acids reduced protein adsorption to NPs, allowing the NPs preincubated in serum to retain the ability to interact with the corresponding substrate (streptavidin-modified surface) or biotin receptor-positive cells. However, the cysteine modification was not enough to overcome the effect of the soft corona, which bound to the NPs relatively weakly (and hence were removed during NP washing). Accordingly, the cysteine/biotin-modified NPs, upon simultaneous incubation with serum, did not bind to biotin receptor-positive cells as effectively as those preincubated in serum and washed [141].

### 5.2. Pre-coating with functional proteins

5.2.1. Albumin

Albumin is the most abundant plasma protein with a molecular weight of 66.5 kDa, responsible for the transport of nutrients and hydrophobic drugs in circulation [142]. Albumin has attracted significant interest as a carrier or a component of an NP carrier in recent years [143–145]. In NP formulation, albumin is employed to improve colloidal stability and drug loading, reduce nonspecific cellular uptake, and prolong the circulation half-life of the NPs [146–151]. In addition, albumin may promote NP delivery to target tissues via proteins naturally interacting with albumin, such as gly-coproteins (gp60) or secreted protein acidic and rich in cysteine (SPARC) [145,152,153], and/or by taking advantage of pathological conditions that increase albumin consumption [154]. As such, various NPs have been pre-coated with albumin [155], most commonly by incubating the NPs with albumin to let it physically adsorb to the NP surface (physisorption) [151,156].

Our group has reported that pre-coating paclitaxel nanocrystals with albumin increases the colloidal stability of the nanocrystals and their cellular uptake by SPARC+ melanoma cells compared to a non-albumin coated counterpart [157]. The albumin-coated nanocrystals took advantage of NP configuration that allowed for the EPR effect, showing greater bioavailability, tumor distribution, and antitumor efficacy than Abraxane at the same dose of pacli-taxel in a murine model of melanoma [157,158]. Similarly, albumin has been used to coat silver NPs for anticancer applications [159]. The albumin-coated silver NPs showed more selective toxicity to cancer cells and generated greater ROS than bare silver NPs. Though not explicitly explained, the difference between bare and albumin-coated silver NPs may be attributable to the changes in NP interaction with the cell membrane due to the albumin coating.

The pre-coated albumin layer is not static and may attract or be replaced by other serum proteins. In a serum-free medium, the pre-coated albumin reduced cellular uptake of gelatin-oleic NPs irrespective of cell types, suggesting the interference of albumin with cell-NP interaction [160]. However, in a serum-supplemented medium, the albumin-coated gelatin-oleic NPs showed a consistent reduction in cellular uptake by A549 cells compared to bare gelatin-oleic NPs, whereas the opposite was observed in HEK293 cells. This result suggests that the pre-coated albumin attracted or was replaced by other serum proteins, which may exert differential effects depending on the cell types [160].

A caveat of pre-coating albumin on NPs is the potential to per-turb the protein structure [155]. We have modified the surface of poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles with albumin by two methods (interfacial embedding and polydopamine-mediated physisorption) and compared albumin functionality
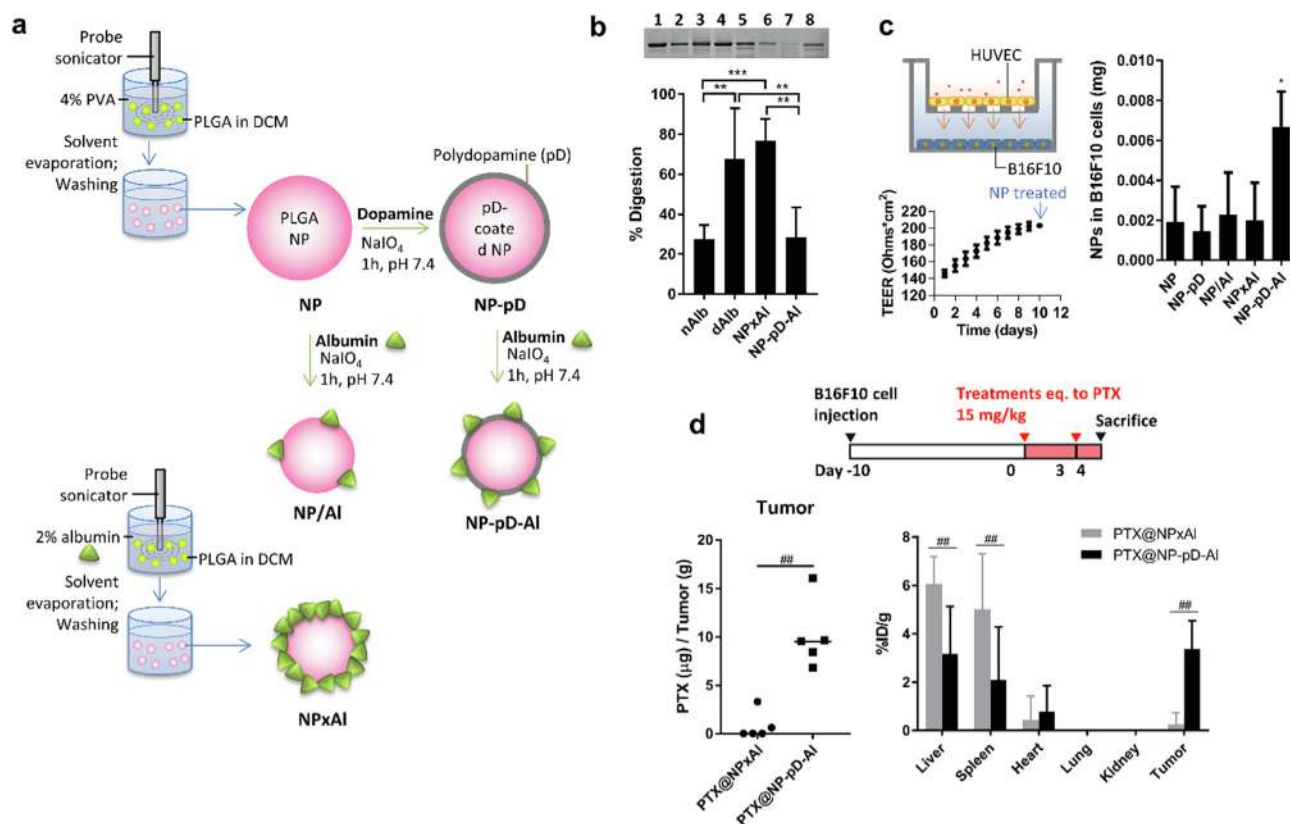
Fig. 1. **(a)** Different methods to coat PLGA NPs with albumin. NP×Al: interfacial embedding; NP-pD-Al: polydopamine-mediated physisorption. **(b)** Top: Representative SDS-PAGE gel image of albumin after pulse proteolysis. Native albumin (nAlb), denatured albumin (dAlb), NP×Al, and NP-pD-Al were treated with thermolysin for 3 min. Lane 1: nAlb; Lane 2: dAlb; Lane 3: NP×Al; Lane 4: NP-pD-Al; Lane 5: nAlb + thermolysin; Lane 6: dAlb + thermolysin; Lane 7: NP×Al + thermolysin; and Lane 8: NP-pD-Al + thermolysin. Bottom: % digestion albumin was defined as (1-albumin band intensity after proteolysis/albumin band intensity prior to proteolysis) × 100. **(c)** Schematic of a Transwell co-culture system with HUVEC in the insert and B16F10 cells in the bottom of the basolateral side (left top); Transendothelial electrical resistance (TEER) indicating the confluence of HUVEC layer at the time of NP application (left bottom); NP associated with B16F10 cells, measured at 24 h after 6 h incubation with a Transwell containing NPs and the confluent HUVEC layer. **(d)** Dosing schedule of PTX-loaded NPs (top); PTX content in B16F10 tumors treated with PTX-loaded NP×Al (PTX@NP×Al) or PTX-loaded NP-pD-Al (PTX@NP-pD-Al) (bottom left); % injected PTX dose per gram of each tissues (%ID/g) of PTX@NP×Al or PTX@NP-pD-Al in B16F10 tumor bearing mice 24 h after i.v. injection. %ID/g is defined as percentage of injected dose per gram of tissue weight. Reprinted from [161] with permission.

(Fig. 1a) [161]. The interfacial embedding method caused denaturation of surface-bound albumin, offering no particular benefit to the interaction with cancer cells but rather promoting macrophage uptake via interactions with scavenger receptor A. In contrast, albumin adsorbed to the polymerized dopamine, serving as an adhesive layer on PLGA NPs, retained the native structure, evident from the resistance to thermolysin digestion and retention of the esterase-like activity (Fig. 1b). With the native conformation, the albumin pre-coating helped PLGA NPs avoid macrophage uptake, travel across the endothelial layer, and interact with SPARC-expressing tumors (Fig. 1c) to deliver more drugs to tumors than the NPs with denatured albumin (Fig. 1d) [161]. The differential protein conformation, although often overlooked, may explain some of the conflicting reports on the effects of surface-bound albumin on NP performance (e.g., enhancement of particle uptake by phagocytes [59] vs prevention of liver accumulation [162]).

5.2.2. Apolipoproteins

Apolipoproteins are responsible for regulating plasma lipid levels [163]. As part of lipoproteins, apolipoproteins mediate the intracellular transport of the lipoproteins via LDLR or heparan sulfate proteoglycans [163]. ApoE is often identified to be one of the main components of PC that forms on NPs in human serum and affects their cellular uptake [164,165].

Apolipoproteins have been pre-coated on NPs to enhance their transport across the brain endothelium. For example, ApoE [166]

or ApoA-I [167] were covalently attached to albumin NPs, increasing endocytosis and transcytosis of the NPs by brain endothelial cells. Based on early observations of preferential ApoE binding to surfactant-stabilized NPs [168] and their brain tropism [169], ApoE4 was also pre-adsorbed on polysorbate 80-stabilized lipid NPs by simple mixing before the administration [170]. The ApoE4-bound NPs crossed the blood–brain barrier via an LDLR and reached the brain parenchyma. This approach is amenable to extemporaneous preparation; however, excess ApoE4 rather interfered with brain delivery due to the competition for the receptor [170]. Thus, a tight titration of ApoE4 would be critical to the successful delivery to the brain. An ApoE-coating on gold NPs has also been used for carrying hydrophobic sensitizer chlorin e6 (Ce6), achieving greater loading efficiency than albumin-coated gold NPs [171] and intracellular delivery of Ce6 [172].

On the other hand, ApoJ, also known as clusterin, is shown to be a PC component with a stealth effect [173,174]. Polystyrene NPs were modified with PEG or poly(ethyl ethylene phosphate) (PEEP) to reduce protein adsorption [173]. The NPs showed a difference in macrophage uptake only in the presence of serum protein, indicating that the surface-bound protein was necessary for the stealth effect. A proteomic analysis found that the PC, albeit reduced, was enriched with clusterin and it was responsible for reducing nonspecific cellular uptake of the NPs [173]. Clusterin corona is similarly credited with silver- and silica NPs [174]. Like the previous study, the silver and silica NPs showed reduced monocyte

uptake after incubation with human serum or plasma. Clusterin was identified as a protein accountable for the stealth effect [174]. These results prompted the consideration of clusterin for the stealth coating of NPs [173]. However, clusterin is also associated with microglia activation leading to inflammation and neurotoxicity [175]; therefore, its utility as a stealth coating remains to be determined.

5.2.3. Cluster of differentiation 47 (CD47)

CD47 is a highly glycosylated ~ 50 kDa plasma membrane protein, consisting of a single IgV-like domain at the *N*-terminus, a hydrophobic membrane-spanning domain, and a cytoplasmic C-terminus, broadly expressed in all tissues [176]. As a marker of "self," CD47 interacts with signal-regulatory protein alpha (SIRPα, also known as CD172a) expressed at high densities on macrophages to prevent their recognition and engulfment of host cells [177–179]. The deficiency of CD47 in red blood cells leads to lethal hemolytic anemia in nonobese diabetic mice [180]; conversely, CD47 is exploited by most human tumor cells to evade macrophage surveillance [181].

Due to its role in preventing phagocytosis, CD47 or its derivatives have been explored as a stealth (self) ligand [182,183]. For example, polystyrene NPs were surface-modified with the extracellular domain of CD47 or a small peptide ("self-peptide") with

a sequence most responsible for the interaction with SIRPα [183]. The CD47 or self-peptide-coated NPs persisted in circulation and accumulated in the tumor better than the control peptide-coated NPs [183].

6. Join them if you can't beat them: Strategies to piggyback on PC *in situ*

As the tenacity of PC formation is increasingly recognized, recent efforts have focused on designing NPs such that they attract PC specifically recognized by the target cells or tissues during circulation.

6.1. Attracting albumin

Recently, our group has reported soft polydopamine nanocapsules called Nanosac for siRNA delivery [55]. Nanosac is produced by sequential attachment of siRNA and polydopamine on sacrificial mesoporous silica NPs (MSN), followed by the removal of the MSN core (Fig. 2a). Unlike the bare MSN core, Nanosac enters cells via caveolae-mediated endocytosis, bypassing lysosomal sequestration (Fig. 2b), which occurs with traditional NPs and is detrimental to siRNA stability. Gel electrophoresis showed that the
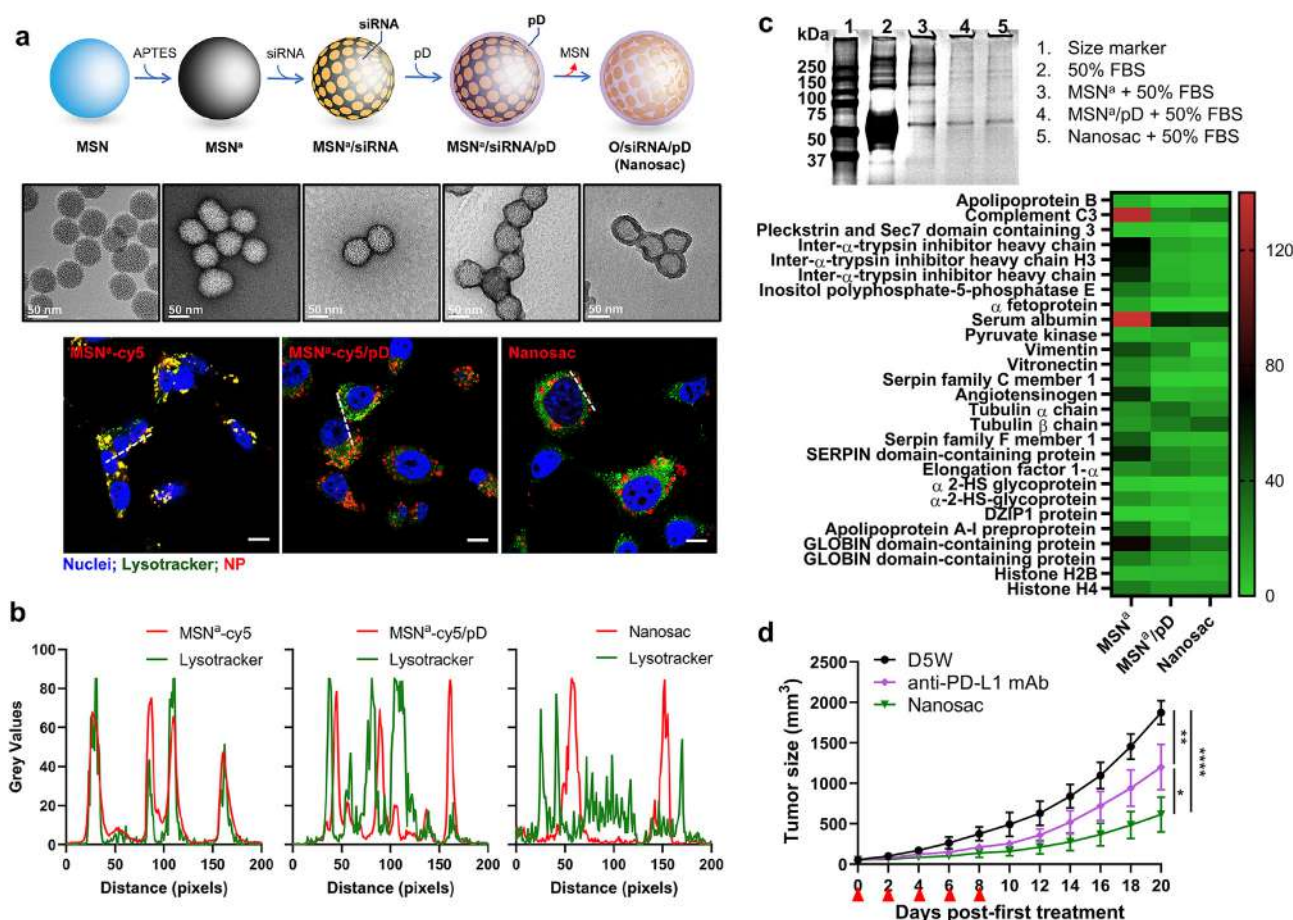
Fig. 2. (a) Schematic illustration of Nanosac (MSNᵃ/siRNA/pD) preparation and transmission electron microscopy images of Nanosac and Nanosac precursors. Nanosac is produced by sequential coating of mesoporous silica nanoparticles (MSNs) with siRNA and polydopamine, followed by removal of the sacrificial MSN core. **(b)** Confocal microscope images of cy5-labeled MSNᵃ, MSNᵃ/pD, and Nanosac relative to lysosomes in CT26 cells and fluorescence intensity profiles along the white lines in confocal images. Green: Lysotracker (lysosome); red: cy5- labeled NPs; and blue: Hoechst 33342 (nuclei). Scale bars: 10 μm. **(c)** SDS-PAGE of protein corona composition formed on MSNᵃ, MSNᵃ/pD, and Nanosac. The protein corona bound on each NPs were further analyzed by LC-MS/MS for most abundant proteins. 4 mg/mL of each NPs were incubated in 50 % FBS for 2 h and rinsed with PBS twice. **(d)** Average tumor size after treatment of anti-PD-L1 antibody and siPD-L1-Nanosac to Balb/c mice bearing CT26 tumors. (anti-PD-L1 antibody: 200 μg/mouse/time, intraperitoneal injection; siPD-L1:1.5 mg/kg/time, IV injection; q2d × 5). Reprinted from [55] with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

polydopamine surface reduced protein adsorption. Proteomics analysis identified albumin to be the dominant protein of the few proteins binding to the Nanosac (Fig. 2c), suggesting selective recruitment of albumin by polydopamine surface. Systemically administered, Nanosac delivered siRNA targeting PD-L1 to CT26 tumor, resulting in significant suppression of CT26 tumor growth compared to the monoclonal PDL1 antibody-treated group (Fig. 2d) [55]. However, it remains to be determined whether the albumin co-option occurred *in vivo* and contributed to Nanosac distribution in tumors.

In another example, PLGA NPs were deliberately decorated with maleimide for albumin binding in circulation [184]. The distance between NP surface and maleimide was varied by the length of the PEG linker (none, 500 Da, 2000 Da) to control the avidity of albumin binding. PEG 2000 Da was needed to avoid excessive protein binding, and the maleimide terminus helped attract albumin conjugating with Cys-34 residue. The albumin binding, maleimide-PEGylated PLGA NPs underwentreduced accelerated blood clearance phenomenon upon the second administration and improved tumor accumulation via interactions with SPARC and CD31 as compared to PEGylated PLGA NPs (with no maleimide) [184].

For the same purpose, NPs were prepared by molecular imprinting using albumin as a template [162]. NPs were produced by polymerizing albumin binding monomer (pyrrolidyl acrylate) and acrylamide monomers in the presence of albumin, followed by the removal of albumin by size-exclusion chromatography. The molecularly imprinted NPs captured circulating albumin *in situ*, as demonstrated by *in vivo* fluorescence resonance energy transfer microscopy, and accumulated in tumors taking advantage of the dysopsonin function of albumin [162].

6.2. Attracting apolipoproteins

As mentioned earlier, apolipoproteins bind to polysorbate-stabilized NPs and promote their delivery to the brain via the LDLR [168]. Accordingly, subsequent studies employed polysorbate 80 as a surface modifier of an NP carrier to improve drug delivery to the brain [185]. The amount of apolipoproteins binding to NPs depends on the hydrophilic-lipophilic balance of polysorbate and the corresponding NP surface: more lipophilic polysorbate attracted more ApoE to the lipid NP surface. However, this trend may not be generalized to other NPs [168].

Alternatively, there has been an attempt to control the apolipoprotein binding to LNPs by the length and amount of the surface-exposed PEG [186]. LNPs were made with PEGylated acyl chains in two different lengths (C18 vs C14) in two amounts (6 mol% vs 3 mol%). Upon incubation in mouse serum, LNPs with 3 % PEG acquired more ApoA4 than those with 6 % PEG. LNPs with C18 PEG showed greater accumulation in LDLR-expressing HepG2 than those with C14 PEG. However, there appears to be no explicit relationship between PC and biodistribution [186].

Another example shows biodegradable nonionic poly(phosphoester) (PPE)-surfactants adsorbed on polystyrene NPs helping attract apolipoproteins [187]. The PPE-surfactants consist of hydrophilic and hydrophobic blocks, where the lengths and side chains are varied to control protein adsorption and aggregation. The PPE-surfactant-coated polystyrene NPs were enriched with clusterin and ApoA-I upon incubation with human plasma. The NPs coated with the PPE surfactant and plasma showed reduced macrophage uptake, supporting the potential of the polymer surfactant to recruit "stealth" apolipoprotein in circulation [187].

A recent study uses dihydroartemisinin (DHA) to decorate PLGA NPs and attract ApoE to the NP surface [188]. DHA is a metabolite of artemisinin, an antimalarial drug known for its affinity for albumin and transferrin. When conjugated to PLGA NPs, DHA rather

recruited ApoE (than albumin or transferrin) in serum, which helped the NP uptake by LDLR⁺ 4T1 cells, and extended the NP circulation half-life and delivery to 4T1 tumors compared to plain PLGA NPs [188].

6.3. Attracting vitronectin

Vitronectin is a glycoprotein with a molecular weight of 75 kDa, abundant in blood and extracellular matrix [189]. The Arg-Gly-Asp (RGD) sequence of vitronectin binds to cell surface integrins such as $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha v\beta 1$, $\alpha IIb\beta 3$, $\alpha v\beta 6$, and $\alpha v\beta 8$, facilitating cellular adhesion, spreading, and migration [189]. Of these, $\alpha v\beta 3$ has gained particular interest in cancer therapy due to its implication in angiogenesis and metastasis [190] and has been targeted by various RGD-based peptides [191–195].

Liposome/DNA complexes (lipoplexes) comprising 1,2-dioleoyl-3- trimethylammonium propane (DOTAP) were shown to acquire a PC enriched with vitronectin and albumin upon preincubation with human plasma [196]. Similarly, LNPs containing 3β-[N-(N', N'-dimethylaminoethane)-carbamoyl]cholesterol (DC-cholesterol) showed vitronectin enrichment in PC upon incubation with mouse serum [186]. In both cases, the binding of vitronectin to the lipid particles, which is attributed to charge interaction (negatively charged vitronectin vs cationic lipids) [197], increased the particle uptake by $\alpha v\beta 3$-positive cells (but not by the $\alpha v\beta 3$-negative cells) [196]. Accordingly, cationic lipids have been incorporated in LNPs to facilitate their delivery to the $\alpha v\beta 3$-expressing tumor via vitronectin corona [198]. Nevertheless, the presence of serum was detrimental to the cellular uptake of LNPs irrespective of DOTAP inclusion [198]. *In vivo*, DOTAP-containing LNPs showed higher accumulation in the $\alpha v\beta 3$-expressing A375.S2 tumor than in the $\alpha v\beta 3$-negative HepG2 tumor. However, DOTAP LNPs did not deliver the RNA payload to the tumor cells, suggesting that the accumulation might have occurred in the $\alpha v\beta 3$-expressing endothelial cells rather than in the tumor cells [198].

6.4. Attracting other proteins

Transferrin (Tf) is a 79 kDa glycoprotein supplying irons to cells. Due to the high demand for irons, TfR is overexpressed in malignant cells, making an important target for cancer therapy [199,200]. To enable *in-situ* binding of Tf to NPs, a Tf-binding peptide was designed by iterative multiscale-modeling coupled with quantitative structure–activity relationship analysis and evolutionary algorithms [201]. Gold NPs conjugated with the Tf-binding peptide attracted serum Tf, which in turn increased the NP uptake by TfR⁺ Mia PaCa-2 cells in a Tf-specific manner [201] (Fig. 3).

Another example of PC-binding NPs is a retinol-conjugated polyethylenimine (RcP) NP, developed for the delivery of antisense oligonucleotide (ASO) [202]. The RcP NP recruited retinol-binding protein 4 (RBP) as well as albumin, where the protein binding prevented lethal aggregation of the NPs and led to the cellular uptake profile skewed to hepatic stellate cells (HSC). Controlled *in vitro* studies identified that the two proteins had distinct functions: albumin preventing macrophage uptake and RBP promoting HSC uptake of RcP NPs. Consistently, in a mouse model of liver fibrosis, the RcP NPs entered HSC in the liver, unlike free ASO that was stuck in endothelial cells and macrophages, and delivered ASO downregulating collagen I to HSC to reduce hepatic fibrosis. Of note, the retinol ligand of RcP played a significant role in controlling the functions of two proteins: as a hydrophobic compound, it helped keep the conformation of albumin, unlike cationic PEI; retinol was also critical to maintaining the functionality of RBP (uptake by HSC) [202].
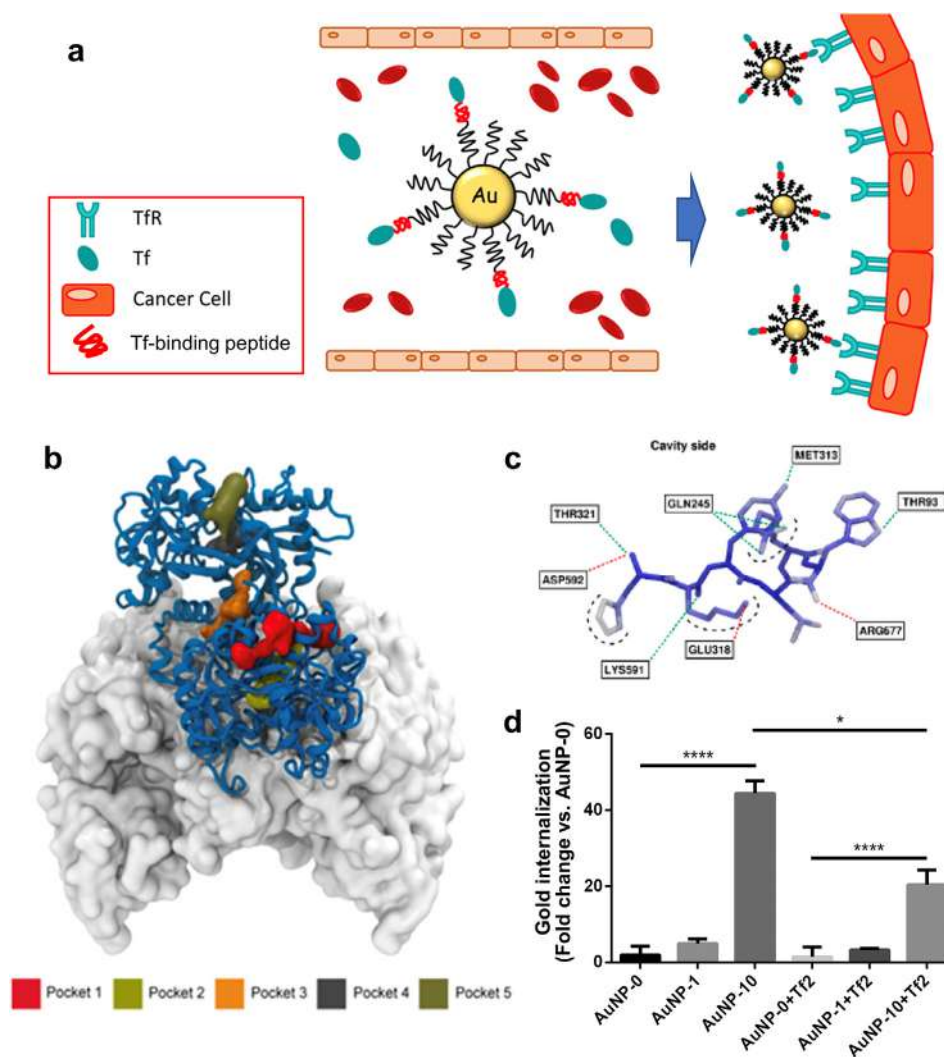
Fig. 3. (a) Schematics Illustration of gold NPs targeting TfR overexpressed on cancer cells. **(b)** Five potential binding sites, Pocket 1 through 5, identified on the human Tf predicted by Fpocket. Tf is represented with the blue-ribbon diagram, and part of the ectodomain of the transferrin receptor dimer23 is rendered by its accessible surface. Due to the adequate volume for peptide and the distance from transferrin or iron binding site, Pocket 3 (orange) is chosen to dock the peptide. **(c)** 3D docked pose of the synthesized Tf-binding peptide (Tf2) created by coarse-grained molecular dynamics simulation. Atoms are colored according to their root mean squared displacement. Blue: rigid regions; red: flexible regions; green dashed lines: hydrogen bonds; red dashed lines: salt bridges; black dashed lines: solvent exposed atoms. **(d)** Cell uptake of gold NPs conjugated with Tf2. Various gold NPs were prepared using different percentage of PepN-Tf2 (0, 1, and 10 % w/w). NPs were incubated in human plasma for 1 h at 37 °C and then with Mia PaCa-2 cells for 1 h at 37 °C in DMEM with (right, suffix +Tf2) or without (left) Tf2. The results were normalized to the amount of internalized gold in AuNP-0. Reprinted from [201] with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

## 7. Application of protein corona to organ/disease-specific nanoparticle delivery

7.1. Brain

Based on the early observation of brain tropism of apolipoprotein-coated NPs, the NP surface was deliberately engineered to co-opt apolipoproteins to enhance NP delivery to the brain [203]. Here, liposomes were decorated with a short peptide (Aβ$_{25-35}$ with amide form in the C-terminal, SP) derived from β-amyloid peptides, which captured plasma ApoA1, ApoE, and ApoJ. On the surface of liposomes (SP-sLip), SP interacted with the lipid-binding domain of the apolipoproteins, exposing their receptor-binding domains to respective receptors (SR-B1, LRP1, and LRP2) and inducing brain transport of liposomes via LRP1/LRP2/SR-B1 mediated transcytosis. As a carrier of doxorubicin (DOX), SP-sLip showed significant improvement in drug delivery to the brain and extended the survival of mice bearing intracranial tumors compared to plain liposomes [203]. A similar approach was applied to polymeric micelles, with the amide-terminated Aβ$_{25-35}$ as a ligand to bind to the lipid-binding domain of ApoE [204]. The ApoE binding increased the uptake of micelles by C6 glioma cells and human umbilical endothelial cells. The Aβ$_{25-35}$-modified micelles increased paclitaxel (PTX) delivery to the orthotopic glioma in the mouse brain, extending the survival of glioma-bearing mice, compared to the micelles without the peptide [204].

TfR is another receptor highly expressed in glioma cells and may be targeted by Tf. Since Tf is abundant in blood, NPs were designed to bind Tf in circulation for the improvement of brain delivery (Fig. 4**a**) [205]. Covalent organic framework (COF) NPs were decorated with T$_{10}$ peptide, which interacts with Tf without affecting its binding to TfR. The T$_{10}$ ligand of COF helped recruit Tf-rich PC, facilitating the NP uptake by TfR+ U87 cells (Fig. 4b). The T$_{10}$-coated COF NPs delivered more DOX to the orthotopic glioma (Fig. 4c) and extended the survival of mice than unmodified COF NPs [205].

A recent study reported that exosome mimetics (EMs) decorated with angiopep-2 (Ang) peptide, a ligand specifically
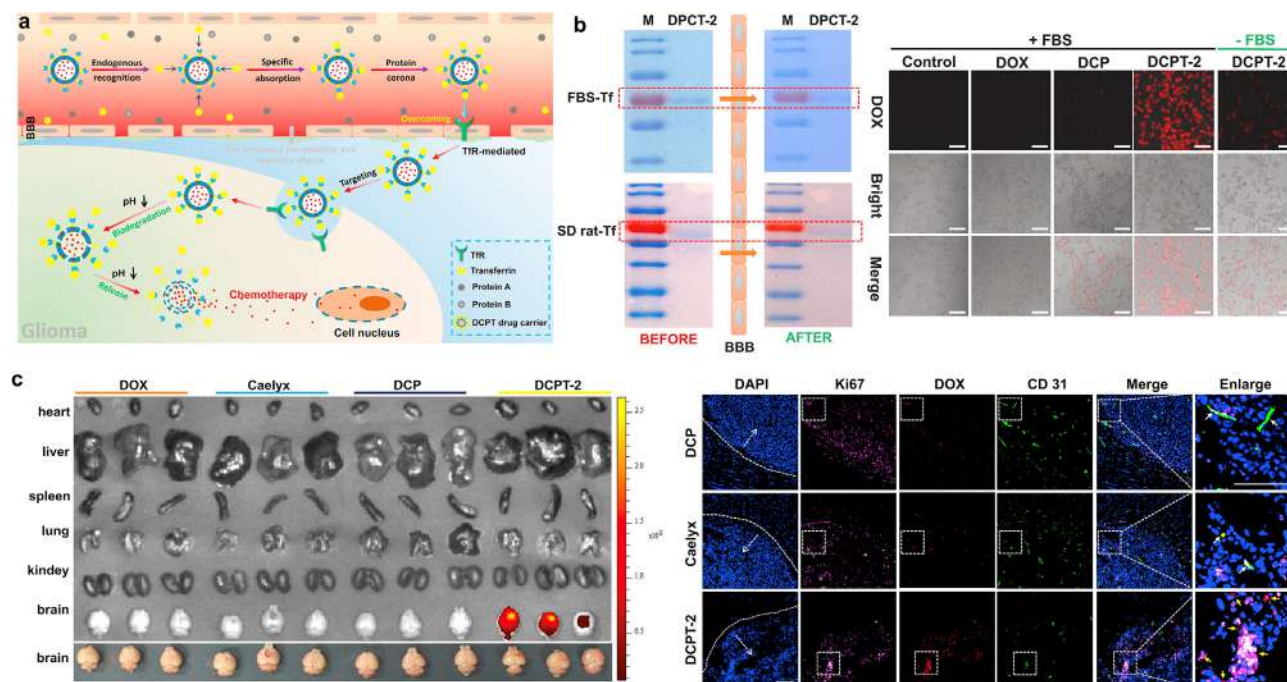
Fig. 4. Tf targeting in glioma by DOX-loaded, T$_{10}$-coated COF NPs (DCPT) NPs. (**a**) Schematic illustration of endogenous Tf corona-mediated DCPT delivery across the BBB. (**b**) SDS-PAGE analysis of PC on DCPT-2 before and after passage through the in vitro BBB model (left). FBS-Tf: Formation of Tf corona on the surface of DCPT-2 mediated by Tf from the FBS. SD rat-Tf: Formation of Tf corona on the surface of DCPT-2 mediated by Tf from the SD rat serum. Cellular uptake of DOX and COF formulations incubated with U87 cells under different conditions (right). (**c**) Ex vivo imaging of DOX in main organs of glioma-bearing mice after intravenous injection of DOX, Caelyx, DCP (DOX-loaded COF, no T$_{10}$) and DCPT-2 at 12 h (left). Immunofluorescence images of brain sections from orthotopic glioma mice after 12 h post-injection of DCP, Caelyx and DCPT-2, respectively. Blue: nuclei; purple: U87 cells; red: DOX; green: anti-CD31 labeled blood vessels. White arrows: co-localization of DOX and blood vessels; Yellow arrows: co-localization of DOX and glioma cells. Bar: 200 μm. Reprinted from [205] with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

interacting with lipoprotein receptor-related protein 1 (LRP1) to facilitate BBB transport, can retain the ligand function despite PC and deliver docetaxel (DTX) to the glioblastoma (GBM) in mice [206]. Here, Ang peptide was integrated into EM as DSPE-PEG-Ang. The Ang-decorated EM (Ang-EM) showed relatively low protein binding compared to Ang-liposomes and enhanced DTX delivery to orthotopic GBM compared to Ang-liposomes. However, due to the lack of comparison with the unmodified EM, it is unclear whether the improved brain delivery is due to the ligand effect of Ang or other attributes of EMs, such as CD47 [206].

7.2. Tumor

In controlling PC for enhancing NP delivery to tumors, the focus has been to increase the circulation time for the EPR-based tumor accumulation and/or to improve the interaction with tumor cells. The former may be achieved by decreasing opsonin binding or promoting the binding of dysopsonin, whereas the latter depends on the binding to specific proteins interactive with tumor-specific receptors.

Surface components are the primary variable to control the PC profile. For example, DNA coating on cationic liposome/DNA complexes (lipoplexes) formed opsonin-deficient PC in low concentration (5 %) plasma, which helped the lipoplexes to avoid immune cell uptake [207]. The DNA-coated lipoplexes, then coated with plasma proteins before injection, outperformed traditional PEGylated lipoplexes in avoiding RES uptake in mice [207]. When PEG is used as a surface stabilizer, its molecular weight plays a key role [208]. For example, 2.4 nm gold particles were modified with 350, 550, and 1000 Da PEG, forming 100–200 nm NP assemblies. The PC profile varied with the PEG size, thereby hydrophilicity of the surface. The NPs with 550 Da PEG had more Tf in PC than those with

350 or 1000 Da PEG. Conjugated with DOX, the 550 Da PEG-bound gold NPs delivered more drugs to TfR$^+$ HepG2 tumors than the other two NPs [208]. Albumin was another protein enriched on the 500 Da PEG-covered surface; though the increased albumin binding did not explicitly increase the circulation, it may have contributed to tumor accumulation via interactions with albumin-binding proteins (Section 5.2.1). A study with cabazitaxel nanocrystals also shows that a surface stabilizer alters the pharmacokinetics/biodistribution profiles and antitumor effect of the drug via PC [209]. Here, the nanocrystals were stabilized with D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS), which formed a PC enriched with albumin, ApoA-IV, ApoE, and Tf upon incubation with mouse plasma. The TPGS-stabilized nanocrystals showed a longer circulation half-life and greater tumor accumulation in 4T1 orthotopic tumor-bearing mice than those covered with an additional layer of lipid. The prolonged circulation was attributed to the reduced binding to IgM, and the enhanced tumor distribution to Tf, ApoA-IV, and ApoE in the PC [209].

NP components have also been varied to control the PC. With carbonate apatite NPs, a pH-sensitive drug carrier consisting of Ca^{2+}, PO$_4^{3-}$, and CO$_3^{2-}$, it was found that partial replacement of Ca^{2+} with Mg^{2+} and Fe^{3+} changes the PC formation in both quantity and components [210]. The PC change resulted in reduced NP aggregation in serum-containing medium, increased cancer cell uptake, and changes in biodistribution profile [210]. Alternatively, the variation of NP components may help recruit specific proteins that interact with cancer cells via overexpressed receptors. For example, NPs were produced with pheophytin carbon dots (PCD), a lipoid compound derived from natural chlorophyll, to impart the affinity for apolipoproteins [211]. Coated with an optimal amount of DSPE-mPEG, the PCD NPs attracted major apolipoproteins (ApoA-I, ApoC-III, and ApoE) better than those without a
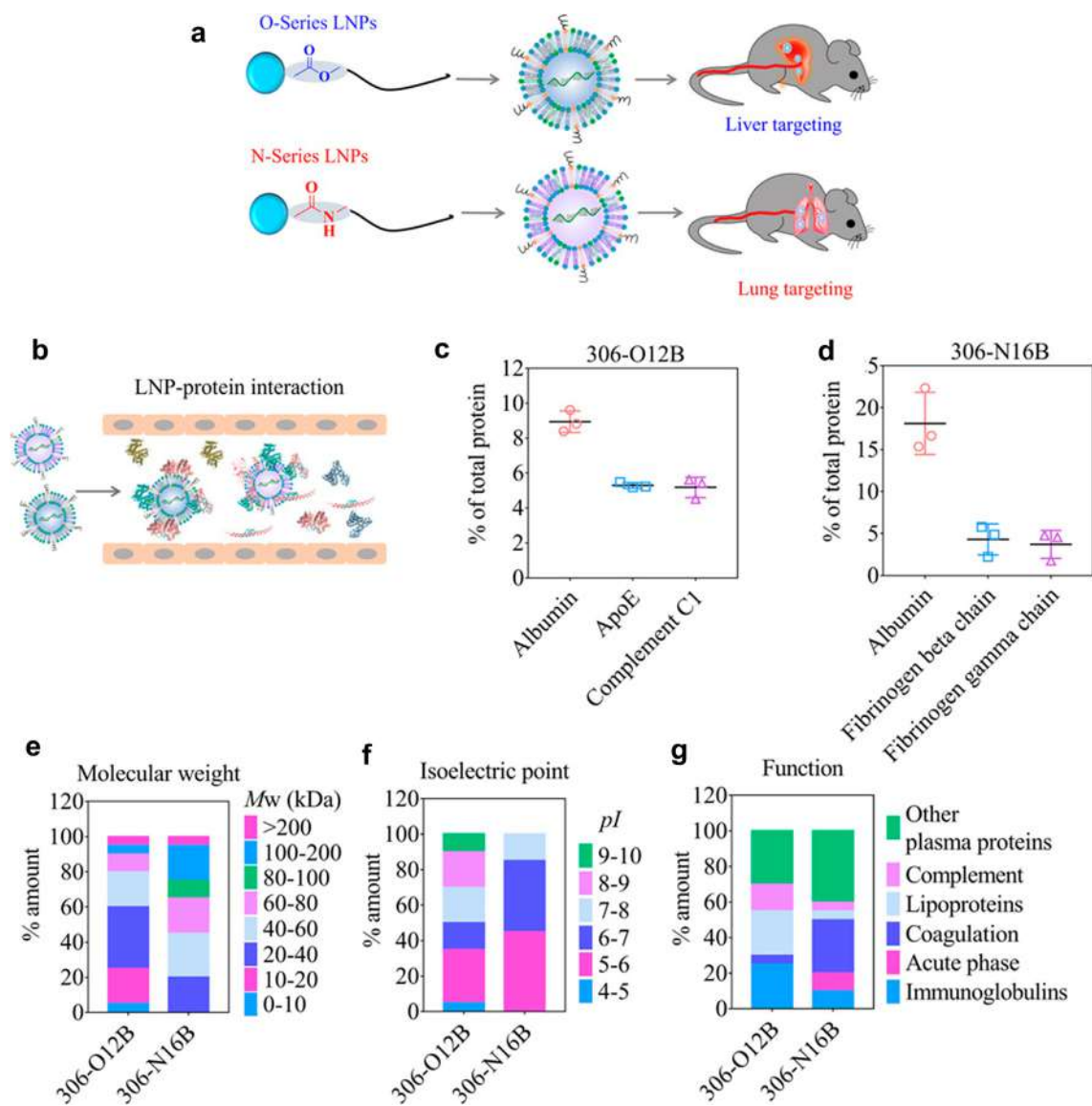
Fig. 5. Schematic illustrations of **(a)** differential organ distribution of O- and N-series LNPs and **(b)** interaction of LNPs with proteins in the blood vessel. Quantification of the percentage of total proteins of the top three protein components in the protein corona of **(c)** the O-series LNPs (306-O12B) and **(d)** the N-series LNPs (306-N16B). Top 20 most abundant corona proteins based on **(e)** their calculated molecular weight, **(f)** isoelectric point, and **(g)** biological function. Reprinted from [215] with permission.

lipoid component, showed enhanced uptake by LDLR⁺ cancer cells, and distributed more in the lungs with metastatic LDLR⁺ MDA-MB-231 tumors than in normal lungs [211].

7.3. MPS organs

The FDA-approved LNP products deliver siRNA mainly to the liver due to the binding of ApoE, which interacts with LDLR of hepatocytes [88,89]. A similar principle was applied to DNA tetrahedrons, which, upon conjugation with trivalent cholesterol, bound to various apolipoproteins and showed liver-selective delivery, achieving comparable activity to a trivalent *N*-acetylgalactosamine-conjugated system in a liver fibrosis model [212]. Meanwhile, a series of recent studies inform that the structure of a lipid or a lipidoid (lipid-like) component of NPs resulted in the variation of the PC profile and altered the organ tropism: LNPs containing imidazole-based lipidoids target the spleen [213], LNPs containing lipidoids with an ester bond in the tail (O-series LNPs) tend to go to the liver [214], whereas those with an amide bond

in the tail (N-series LNPs) showed predominant deposition in the lung [215]. The analysis of PC on O-series and N-series LNPs revealed a difference that may be responsible for the differential distribution (Fig. 5): following albumin (the most abundant protein for both LNPs), ApoE and complement C1 constituted dominant PC components in O-series LNPs, whereas N-series LNPs were enriched with fibrinogen beta and gamma chains, which enhance endothelial cell adhesion [215].

7.4. Inflammation

While opsonin binding followed by immune cell engagement is traditionally considered an undesirable event, it may be exploited to deliver drugs to active immune cells and control inflammation. For example, dextran-coated ferrous NPs (DEX-NPs), which activate the lectin complement pathway, resulting in the binding of C3b and its cleavage products, can target B cells in the spleen via the interaction of C3b with CR1/2 [94]. As such, DEX-NPs delivered a model antigen ovalbumin (OVA) and immunostimulant CpG to

splenic B cells by systemic administration, eliciting OVA-specific IgG$_{2a}$ production better than soluble OVA/CpG mixture and preventing anaphylactic shock and asthma in mice [94]. Similarly, liposomes made of 2-((2,3-bis(oleoyloxy)propyl)dimethylammo nio)ethyl hydrogen phosphate (DOCP), an anionic lipid, were shown to target active neutrophils by binding to C3 fragment iC3b, which interacts with CR3 of the cells. The neutrophils took up DOCP liposomes (but not the control DOPC liposomes), extravasated in the inflamed lungs, and delivered drugs intracellularly or to neutrophil extracellular traps [216].

Other anionic liposomes comprising 1,2-distearoyl-*sn-glycero*-3-phosphoglycerol (DSPG) are shown to recruit C1q, which facilitates their uptake by BMDCs via the scavenger receptor, leading to the induction of immunosuppressive regulatory T cells (Tregs) [217]. The DSPG liposomes were superior to another anionic liposomes based on phosphatidylserine or cationic liposomes in inducing antigen-specific Tregs. As a carrier of atherosclerosis-related antigen (p3500), DSPG liposomes suppressed plaque formation in a mouse model compared to PBS or free antigen, indicating the potential utility in Treg-mediated treatment of atherosclerosis [217].

PC has also been used to guide IONPs, a magnetic resonance imaging agent, to plaques in the inflamed arteries for the diagnosis of atherosclerosis [218]. Here, iron oxide magnetites were clustered in a phosphatidylcholine coat, forming 75 nm NP. The phosphatidylcholine coat binds to ApoB-100, which takes the NPs to the plaque, where the polar head of the coat is cleaved by phosphatidylcholine-specific phospholipase C upregulated in the plaque endothelium. The cleavage induces the aggregation of NPs, increasing T$_2$ contrast in the plaque sites [218].

7.5. Eyes

PC can affect the activity of NPs in the ocular application. Gold NPs have been explored as an antiangiogenic agent in treating ocular neovascularization based on the affinity for vascular endothelial growth factor (VEGF). Bare NPs nonspecifically bind to proteins in the vitreous, losing the ability to bind to VEGF. Pre-functionalizing the gold NPs with the top five vitreous PC proteins helped gold NPs to maintain the VEGF-binding properties in the vitreous compared to bare gold NPs [219]. In a recent application of PC to ocular delivery, cationic lipoplexes were pre-functionalized with artificial PCs, such as fibronectin or Val-Gly-Asp (VGA) tripeptide, to improve the uptake by corneal epithelial cells [220]. Bare lipoplexes bound to mucin, losing the ability to enter corneal epithelial cells, whereas fibronectin or VGA peptide-coated lipoplexes were taken up by the cells via epithelial receptors. However, it remains to be seen whether the artificial PCs retain such ligand functions despite mucin [220].

8. Future perspectives

There are numerous cases where uncontrolled PC interferes with the intended function of NPs, leading to MPS accumulation, immunological responses, and loss of target-specific interactions. Meanwhile, emerging evidence indicates that specific proteins in the blood, such as albumin, transferrin, and apolipoproteins, can enhance NP delivery to particular organs, as shown with ApoE-bound LNPs trafficking to hepatocytes [87–91]. Therefore, it is reasonable to envision pre-functionalizing NPs with desirable serum proteins or engineering the surface to co-opt those proteins preferentially *in situ*. Preclinical studies reviewed in this article demonstrate the feasibility of this approach in different disease models. At the same time, one must be aware of the remaining challenges that may complicate the maneuver of PC formation.

First, there is a considerable variation in specific protein content according to the medical conditions and diseases [221]. The inter-patient variability generates an opportunity to develop a personalized diagnostic tool based on the protein fingerprint [222–224]. On the other hand, the variability may undermine the utility of PC identified by population-based studies. A potential alternative is to couple with a computer-assisted prediction of PC-NP interaction [225] and tailor the NP design to each patient's condition.

Second, there is a limited understanding of the roles non-protein biomolecules play in NP performance [92]. For example, lipid corona can be highly relevant when the NPs are introduced via the lungs, where pulmonary surfactants form the first layer that inhaled NPs encounter [226]. Therefore, future studies are needed to understand the functions of non-protein corona and the interplay of corona components.

Third, while PC profiling has become a common practice in the characterization of NPs, most studies rely on *in vitro* incubation of NPs in sera of animal origin. The current method is limited in many ways. (i) Blood protein composition varies with the species; thus, the information obtained with animal serum may not be extrapolated to humans. (ii) The *in vitro* studies are performed in static conditions and do not involve shear stress in blood flow that may affect the NP-PC interactions [227]. (iii) Moreover, the typical protocol of PC analysis [20] focuses on hard corona and does not reflect the contribution of soft corona that is constantly remodeled in circulation [228]. A recent review elaborates on additional limitations of the current methodology [229]. Robust *in vitro* methodologies reflecting dynamic *in vivo* conditions are critical to accurate prediction of NP-PC interactions and corresponding design of NPs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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