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REVIEW

Tuning protein corona on nucleic acid nanodrugs for targeted delivery

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Abstract Nanoparticle-based delivery systems hold transformative potential for nucleic acid therapeutics. However, the fate of nucleic acid nanodrugs (NANDs) *in vivo* differs significantly from that observed *in vitro*, directly impacting their therapeutic efficacy. Upon introduction into biological fluids, NANDs rapidly adsorb proteins onto their surfaces, forming an assembled adsorption layer known as the protein corona (PC). This PC critically influences the physicochemical properties of NANDs and consequently governs their subsequent biological interactions. This review comprehensively introduces the mechanisms underlying PC formation, including dynamic adsorption kinetics and influential physicochemical and environmental factors. We further discuss how the PC modulates key *in vivo* processes, including penetration of gastrointestinal mucus and epithelial barriers, stability during systemic circulation, biodistribution and cellular tropism, as well as cellular uptake and endolysosome escape of nucleic acid therapeutics. While the PC may obscure engineered ligands and accelerate off-target clearance, it also offers opportunities to harness endogenous proteins for targeting. We therefore highlight emerging design strategies aimed at actively steering PC composition to achieve targeted nucleic acid delivery and enhanced therapeutic outcomes. Finally, we present prospects for translating fundamental knowledge of PC formation and function into the rational design of next-generation engineered nanocarriers for targeted NANDs applications.

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1. Introduction

Nucleic acid therapeutics, such as small interfering RNA (siRNA), messenger RNA (mRNA), antisense oligonucleotides (ASOs), plasmid DNA (pDNA), and clustered regularly interspaced short palindromic repeats (CRISPR)/associated protein 9 (Cas9) systems, hold great potential for treating diverse diseases through direct gene modulation[1−5]. However, their clinical translation faces major challenges due to inherent molecular instability and inefficient delivery. Unmodified or naked nucleic acids are highly susceptible to enzymatic degradation by nucleases, exhibit short plasma half-life, and suffer from inefficient cellular uptake owing to their hydrophilic and anionic nature[6]. Additionally, upon systemic administration, they are often subject to rapid renal clearance or sequestration by the reticuloendothelial system, significantly reducing their therapeutic efficacy[7].

To overcome these challenges, nanoparticle (NP)-based delivery systems have been developed to improve the stability, bioavailability, and cellular delivery of nucleic acid therapeutics. Through encapsulationwithin lipid-based NPs, polymeric carriers, or inorganic nanocarriers, nucleic acids can be protected from degradation, while also facilitating cellular internalization and enabling targeted delivery[8−10]. Notably, nucleic acid nanodrugs (NANDs) can be engineered to prolong circulation, minimize off-target effects, and promote endosomal escape, thereby optimizing their therapeutic outcomes[11,12].

Despite these advancements, NANDs inevitably encounter biological fluids upon administration, leading to the formation of protein coronas (PCs) -an adsorbed layer of biomolecules, predominantly proteins, on the NP surface[13,14]. These PCs play a crucial role in shaping the biological identity of the NPs, thereby influencing their biodistribution, cellular uptake, and immunogenicity[15−17]. As dynamic and compositionally complex entities, PCs can either facilitate or hinder NANDs delivery by altering their stability, modulating receptor interactions, and triggering immune responses[18−20].

Given the profound impact of the PC, a thorough understanding of its formation mechanisms and biological consequences is essential for the rational design of effective nucleic acid nanomedicines. This review comprehensively outlines the mechanisms underlying PC formation, key factors influencing its composition, and its critical implications for the *in vivo* fate of NANDs. Furthermore, we emphasize emerging strategies to rationally modulate the PC to advance targeted nucleic acid delivery.

2. The formation of PC

Due to their high surface free energy and large specific surface area, NP-based delivery systems carrying nucleic acid inevitably adsorb proteins, lipids, and other biomolecules when exposed to biological environments, forming a protein-rich layer onto their surfaces known as the PC. This process substantially alters key physicochemical properties of the NPs, such as size, shape, surface charge, hydrophilicity, etc. Consequently, the PC confers a new biological identity that dictates the NPs' subsequent functionality and ultimately determines their *in vivo* fate[21,22].

While the mechanisms governing PC formation are not yet fully elucidated, a consensus has emerged regarding its dynamic process and hierarchical nature. In biological fluids such as blood, plasma proteins adsorb onto NP surfaces through various physicochemical interactions. These proteins, characterized by exposed amino acid residues that present diverse functional groups and complex surface charges, interact with NPs *via* covalent bonding, hydrophobic effects, electrostatic attractions, and hydrogen bonding, ultimately generating a coronated nanostructure[23]. This process follows distinct temporal and hierarchical stages (Fig. 1). Initially, within seconds to minutes, highly abundant proteins in biological fluids (*e.g.*, albumin) rapidly coat the NP surface, forming a loosely associated and readily exchangeable "soft corona", driven primarily by their high concentration. The system then enters a transitional phase dominated by competitive displacement, following the Vroman effect: initially adsorbed proteins with lower affinity are gradually replaced by those with higher affinity from the surrounding biological fluid, such as immunoglobulins and complement components. This dynamic exchange is governed by the adsorption and desorption rate constants (K_a and K_d, respectively). The equilibrium constant K ($=K_a/K_d$) directly reflects a protein's affinity for the NP surface, with higher values indicating stronger adsorption[24]. Over a period of hours, the process reaches a stable stage in which high-affinity proteins firmly occupy key sites on the NP surface, forming a tightly bound "hard corona" that is resistant to displacement. Furthermore, proteins already bound to the NP can recruit additional plasma proteins *via* protein-protein interactions, forming secondary "soft corona" layers that significantly increase the hierarchical complexity of the PC structure[25]. The soft and hard corona exhibit distinct biological fates due to their differential binding affinities. The soft corona, with its weaker and dynamic associations, continuously exchanges with endogenous proteins in the systemic circulation. In contrast, the hard corona remains structurally stable on the NP surface for extended periods, significantly influencing the NP's subsequent biological journey[26].

Although the soft corona demonstrates weaker interfacial interactions, its dynamic exchange capability likely governs the initial interplay between NPs and biological systems. Traditional separation methods, which rely on high-speed centrifugation and repeated washing to remove unbound proteins, tend to dislodge the loosely bound soft corona due to fluid shear forces. Consequently, most previous studies have been largely limited to analyzing the hard corona. To address this bottleneck, Baimanov et al.[27] innovatively developed a "Fishing" strategy based on biolayer interferometry. By immobilizing NPs on biolayer interferometry sensor surface, centrifugal disturbance was avoided, and protein adsorption could be monitored in real time through optical interference signals. Subsequent gradient elution followed by liquid chromatography-tandem mass spectrometry enabled the separate capture and analysis of soft and hard CPs. This strategy preserved the soft corona in a near-physiological state for the first time, providing a dynamic paradigm for studying the spatiotemporal evolution of the

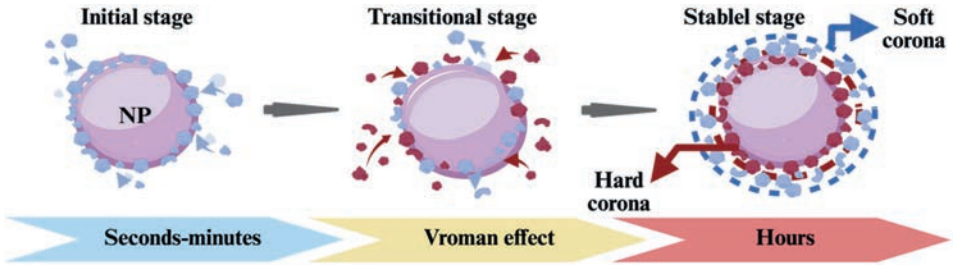

Figure 1 The dynamic formation of the protein corona (PC). The illustration depicts the dynamic adsorption process of plasma proteins onto nanoparticle (NP) surfaces: initial rapid adsorption of abundant proteins forming a loosely bound and exchangeable soft corona; competitive displacement where lower-affinity proteins are gradually replaced by higher-affinity proteins, following the Vroman effect; and establishment of a stable hard corona consisting of tightly bound proteins after several hours.

PC. Furthermore, proteins adsorption onto NPs can occur on submicrosecond timescales (<1 μs), necessitating continuous advancement in temporal resolution to unravel the ultrafast formation mechanisms and dynamic architectures of the PC[28,29]. Notably, Zhang et al.[30] developed a photocatalytic proximity labeling technique for NPs. Using 660 nm laser irradiation to activate biotin-phenol probes *via* radical transfer, this method enabled rapid and precise *in situ* labeling of corona proteins. It bypassed the dead time required for centrifugal sedimentation, improving the temporal resolution of nano-protein interactions from >30 s (with classical centrifugation) to approximately 5 s.

These dynamic processes underscore the intricate nature of bio-nano interactions at the molecular interface. Although current research has preliminarily elucidated the dynamic adsorption mechanisms and hierarchical structural features, it should be emphasized that the formation of this bio-nano interface is perpetually governed by multifactorial synergies. Subtle variations in any parameter, ranging from the intrinsic physicochemical properties of NPs to the ever-changing bio-microenvironmental conditions, can profoundly influence the composition and function of the PC. Besides, it must be acknowledged that the current understanding of the mechanism of PC formation remains constrained by available isolation and characterization techniques. Conventional separation methods based on centrifugation and washing tend to retain tightly bound proteins while losing weakly associated and dynamically exchanged components. This leads to an overrepresentation of the hard corona and introduces methodological bias that affects subsequent interpretation of PC-mediated cell interactions, biodistribution, and biological effects. Therefore, achieving an accurate and physiologically relevant characterization of the PC requires the development of complementary, low-interference, and time-resolved analytical technologies. This is a key prerequisite for reliably correlating corona composition with biological outcomes. Future investigations should prioritize rigorous control of experimental variables while advancing high-resolution spatiotemporal characterization technologies. These approaches will help disentangle the complex factors driving PC formation and provide deeper insight into its dynamic biological role.

3. Factors affecting PC composition

NANDs typically consist of a nucleic acid core encapsulated within a nanocarrier shell. Commonly used carriers of NANDs fall into three main categories: lipid nanoparticles (LNPs), polymeric carriers, and inorganic nanocarriers[31–33]. The PC is not randomly formed, and its composition is finely regulated by the inherent properties of the carrier and the surrounding microenvironment conditions.

Studies have demonstrated that key factors influencing PC formation can be systematically summarized into two categories, including the intrinsic properties of NPs (*e.g.*, shape, size, elasticity, and surface characteristics), and external environmental conditions (*e.g.*, incubation parameters, hemodynamic shear stress, administration routes, and physiological/pathological states) (Fig. 2).

3.1. Physicochemical properties of NPs

The formation and composition of the PC are fundamentally governed by the intrinsic physicochemical properties of the nanocarrier, which define its initial interface for protein binding. Key properties such as shape, size, elasticity, and surface chemistry collectively influence protein adsorption kinetics, affinity, and selectivity. This, in turn, establishes the biological identity that governs the subsequent fate and function of NANDs.

3.1.1. Shape

The shape of NPs is a critical factor influencing PC formation[34,35]. Variations in surface curvature, area, and geometry among differently shaped NPs significantly affect protein adsorption in terms of binding sites, protein identity, and corona thickness[36]. Spherical NPs, with uniform curvature and symmetry, typically exhibit homogeneous protein adsorption patterns[37]. In contrast, NPs with complex surface structures and varying curvatures show non-uniform protein localization and layer thickness. For instance, Tukova et al.[38] utilized surface-enhanced Raman spectroscopy to demonstrate that star-shaped gold nanoparticles (AuNPs) incubated with bovine serum albumin (BSA) form a heterogeneous PC, leaving regions at the tips and high-curvature edges uncovered compared to spherical and rod-shaped AuNPs. Molecular dynamics simulations further revealed a marked decrease in adsorption energy with increasing curvature, which indicates BSA's preferential adsorption onto low-curvature surfaces (such as planar regions) over high-curvature areas (like spherical tips).

Notably, incubation systems using BSA alone cannot fully replicate the complexity of biological fluids. When NPs are exposed to human plasma or serum, which contains diverse proteins, shape-dependent adsorption specificity becomes evident. For instance, Nandakumar et al.[39] compared three AuNP shapes (spiky, intermediate-spiky, and spherical) using label-free mass spectrometry (MS). They found that small globular and

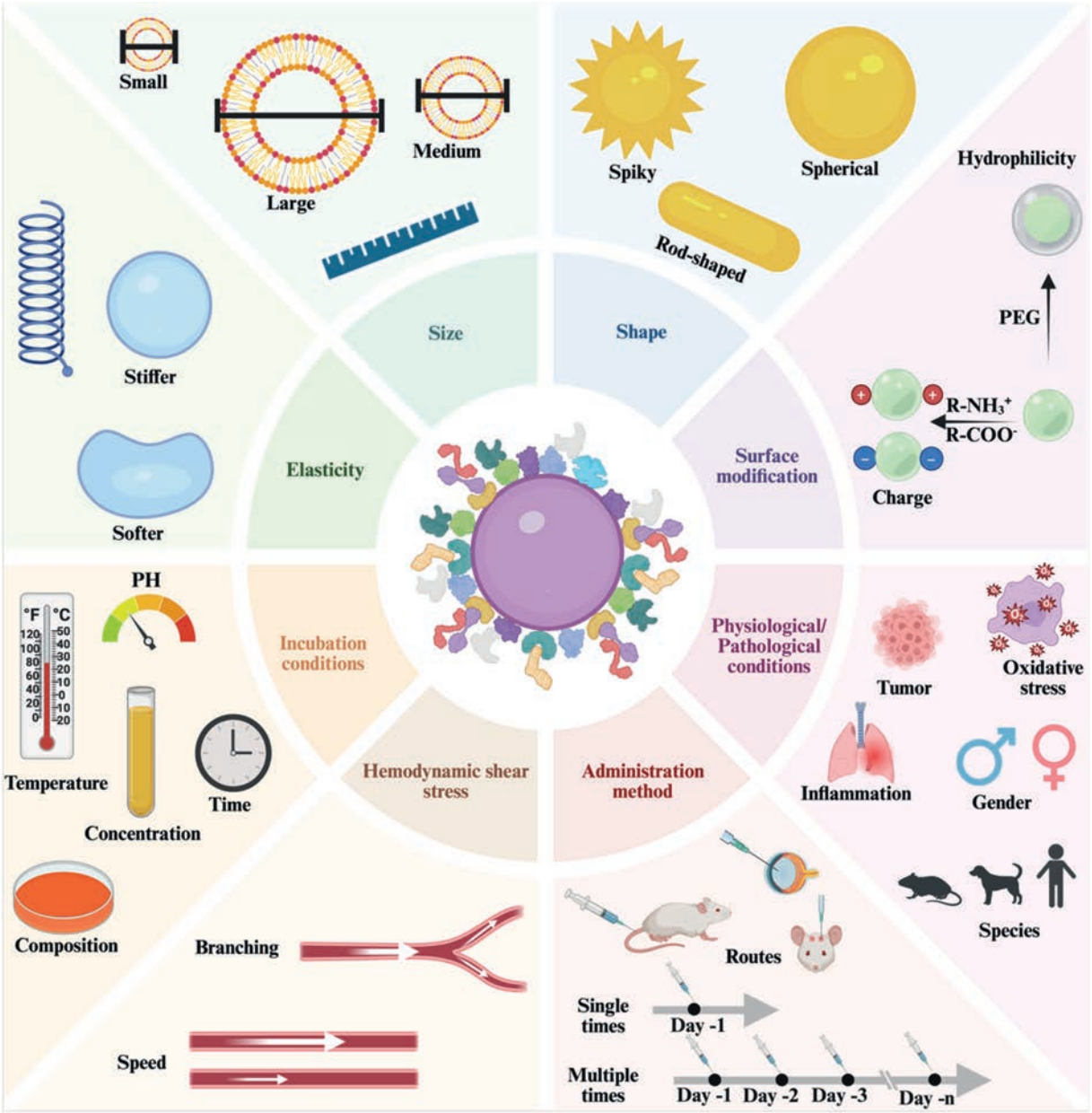

Figure 2 Factors governing protein corona (PC) composition. The composition of PC on nanoparticle (NP) surfaces is influenced by both the intrinsic properties of the NPs (*e.g.*, shape, size, elasticity, and surface characteristics) and external environmental conditions (*e.g.*, incubation parameters, hemodynamic shear stress, administration routes, and physiological/pathological states).

large fibrillar proteins preferentially adsorbed onto spiky AuNPs, whereas large proteins such as serum albumin and immunoglobulins dominated the corona on spherical AuNPs. Madathiparambil Visalakshan et al.[40] further corroborated these findings by studying mesoporous silica nanoparticles (MSNs) with spherical and rod-like morphologies. Rod-shaped MSNs adsorbed threefold more proteins from plasma and fourfold more from serum than their spherical counterparts. Immunoglobulins (Ig) showed higher abundance on rod-shaped particles, while albumin preferentially adsorbed onto spherical particles. These studies show that NP shape profoundly affects PC composition through geometric features such as curvature and surface area. However, these effects are highly system-dependent. Weakening of adsorption in high-curvature regions, observed in single protein systems like BSA, may be masked or even reversed by competitive adsorption and protein-protein interactions in complex biological fluids such as plasma. This highlights the importance of characterizing the PC under physiologically relevant conditions. In addition, it should be noted that current mechanistic studies of shape effects mostly rely on inorganic model NPs, such as gold and silica, which have fixed shapes and rigid surfaces. In contrast, clinically relevant NANDs, including LNPs and polymeric NPs, typically possess dynamic and softer interfaces. Therefore, extrapolating findings from inorganic NPs to organic systems requires caution. Future work should focus on developing libraries of soft-matter NPs with precisely controllable shapes to elucidate shape effects in conditions more representative of actual delivery systems.

3.1.2. Size

Beyond geometric shape, nanoparticle size critically modulates protein adsorption behavior, influencing both the quantity and identity of PCs by altering surface area, curvature, and the relative scale compared to biomolecules. Larger NPs typically adsorb more proteins due to their expanded surface area. For example, Wang et al.[41] reported that in a solid lipid nanoparticles (SLNs) system, the adsorption of BSA rose significantly as particle size increased from 120 to 480 nm at equivalent mass concentrations. However, the relationship between size and protein adsorption is not always monotonic. Lima et al.[42] found that when polystyrene NPs were incubated in mouse serum, both the total amount and the diversity of adsorbed proteins peaked at 80 nm, rather than on the largest 200 nm particles.

More importantly, reported size-dependent effects in the literature can appear inconsistent, underscoring the context-sensitive nature of protein adsorption. For instance, Huang et al.[43] exposed two sizes of silica NPs to A549 human lung carcinoma cells and found that protein adsorption per unit surface area did not differ significantly. However, when normalized by NPs mass, the smaller particles showed higher protein adsorption in results. Such discrepancies may stem from several key factors: first, the use of cell culture medium introduces a more complex protein microenvironment where competitive binding could mask simple size-adsorption trends; second, potential concentration-dependent NP aggregation in their experimental system could significantly alter the effective surface area available for binding, thereby interfering with direct size-adsorption correlations; and third, the method of data normalization (by mass or surface area) reflects different research priorities, with the former more relevant to dosing and the latter to interfacial interaction mechanisms.

NP size regulates PC composition not only through absolute dimensions but also *via* the relative scale between NPs and proteins. When NPs are sufficiently small compared to proteins, adsorption dynamics may reverse. Using all-atom simulations, Yin et al.[44] found that for irregularly shaped human serum albumin (HSA, about 8 nm × 8 nm × 3 nm) with distinct surface grooves, Au NPs as small as 4 nm in diameter could lodge firmly within these grooves as ligands, significantly enhancing binding strength[45]. Therefore, the influence of NP size on PC composition is a result of intertwined multifactorial regulation. It should not be examined in isolation but interpreted within the specific experimental context, characterization approach, and relative scale between NPs and biomolecules. Besides, it should be pointed out that NP size in biological environments is dynamic and often undergoes significant alterations upon the adsorption of PC. More importantly, such corona-mediated size changes do not occur in isolation; they act in concert with other interfacial properties such as surface charge and hydrophilicity/hydrophobicity to collectively regulate the ultimate biological behavior of NPs. Therefore, considering size as an independent determinant separate from other interfacial characteristics risks over-simplifying these complex bio-nano interactions. Moving forward, studies should systematically report both core size and hydrodynamic size before and after protein incubation. These metrics should be integrated with data on PC composition, dynamic changes, and functional indicators such as circulation half-life and organ distribution. By establishing a multidimensional framework that correlates size, corona properties, and biological effects, we can better elucidate the comprehensive role of NP size in determining *in vivo* fate.

3.1.3. Elasticity

While the shape and size of NPs define their static architecture, mechanical properties such as elasticity introduce a dynamic dimension to protein−NP interactions, influencing adsorption patterns through deformability and stress responses at the interface. Although the underlying mechanisms are not fully understood, NP elasticity has been shown to significantly modulate PC formation[46]. Lin et al.[47] developed liposome-sodium alginate hydrogel NPs (LSHNPs) with enhanced elasticity by incorporating an alginate network into the core of liposome-sodium alginate polymer nanoparticles (LSPNPs). After incubation in rat serum, the more elastic LSHNPs (59.39 ± 2.64 MPa) preferentially enriched apolipoprotein E (APOE) and albumin on their surfaces, whereas the less elastic LSPNPs (22.86 ± 3.61 MPa) selectively adsorbed fibrinogen α chains. In another study, Li et al.[48] proved that PC composition varies non-monotonically with NP elasticity. Using polystyrene-polyethylene glycol NPs of similar size, shape, and surface chemistry but tunable core elasticity (45 kPa−760 MPa), they found that adsorption of apolipoprotein A-I (APOA1) peaked at intermediate elasticity (75−700 kPa), compared to softer (45 kPa) or harder NPs (760 MPa). In summary, NP elasticity has been confirmed as a critical physical parameter regulating PC composition. However, current studies typically measure NP elasticity under static, simplified conditions, such as by nanoindentation-derived Young's modulus, which may not reflect the dynamic mechanical behavior of NPs in physiological environments. Whether static elasticity accurately represents NP response during protein interactions in the bloodstream remains unclear. Therefore, future efforts should focus on developing techniques for *in situ* characterization of NP-protein interfacial mechanical behavior within biomimetic fluid environments. This will help establish quantitative links between dynamic mechanical properties and specific protein adsorption, ultimately enabling elasticity to be used as a predictable and programmable design parameter in nanocarrier engineering.

3.1.4. Surface modification

Beyond the inherent properties of nanomaterials, surface modification offers a proactive strategy to engineer NP−protein interactions. Through deliberate chemical functionalization, researchers can modulate surface charge, hydrophilicity, and molecular recognition motifs, thereby steering the adsorption of specific proteins and reshaping the biological destiny of NANDs. Surface modification alters interfacial forces, such as electrostatic interaction, hydrogen bonding, hydrophobic interaction, van der Waals force, and other forces, between NPs and proteins, ultimately shaping protein adsorption and corona composition[49].

Villacorta et al.[26] compared two surface modifiers using polyethyleneimine (PEI) and BSA for poly (lactic-*co*-glycolic acid) NPs (PLGA NPs). After serum incubation, PEI- modified PLGA NPs adsorbed significantly more protein than BSA-modified NPs. This difference is closely related to surface charge-mediated electrostatic interaction: under physiological pH conditions, the main proteins in serum (such as albumin) are negatively charged due to their low isoelectric point (pI). PEI, with its branched structure and high amine density, confers a strong positive charge (+40 mV) to the PLGA NPs, promoting electrostatic attraction and enhanced protein adsorption. However, BSA-coated PLGA NPs exhibited a near-neutral or slightly negative surface, leading to electrostatic repulsion with serum proteins and reduced PC formation. Similarly, Xiao et al.[50] realized charge regulation by using block copolymers

functionalized with different chemical groups: cationic dimethylaminoethyl methacrylate (DMAEMA), anionic carboxyl groups from hydrolyzed poly (styrene-alt-maleic anhydride) (PSMA), and neutral polyethylene glycol (PEG). This approach yielded polystyrene NPs of similar size but with cationic, anionic, or neutral surfaces. Among them, cationic NPs had the highest total amount of protein adsorption, while anionic NPs and neutral NPs showed similar, lower adsorption levels.

However, surface charge is not the sole determinant of protein adsorption. Wen et al.[51] demonstrated that MSNs with similar surface charges, such as positively charged PEI-modified and amino-modified particles, could form markedly different protein coronas. PEI-modified particles preferentially enriched complement C3 and Ig, while amino-modified particles mainly adsorbed apolipoproteins (APOs). This finding underscores that specific chemical groups exert independent control over protein adsorption through their molecular recognition properties. This view is further supported by Hulugalla et al.[52], who compared glycosylated and PEGylated NPs. Poly (2-diisopropylaminoethyl methacrylate) core NPs modified with poly (methacrylamide) glucose adsorbed significantly less immunoglobulin G (IgG) and complement protein than PEG-modified counterparts, while selectively enriching clusterin. The possible reason for this difference is the interaction between surface glucose moieties and sugar-recognition domains on proteins[52].

Hydrophilic surfaces reduce protein adsorption *via* hydration shell formation, whereas hydrophobic surfaces promote interactions with protein hydrophobic domains[53,54]. Dridi et al.[55] investigated serum protein interactions using gold NPs functionalized with a series of ligands derived from dihydrolipoic acid (DHLA). They found that small DHLA ligands promoted the formation of thick and complex PCs rich in abundant proteins such as albumin and Igs, primarily *via* hydrophobic interactions. In contrast, three DHLA derivatives (whether neutral, positively, or negatively charged) modified by macromolecular PEG significantly suppressed PCs formation, an effect attributed to PEG-induced hydrophilicity and steric shielding. It is worth noting that zwitterionic DHLA ligands almost completely prevented protein adsorption through electrically neutral surfaces and strong hydration capacity. Surface modification thus represents a pivotal means to modulate the PC. In contrast to the passive stealth strategy epitomized by PEG modification (PEGylation), emerging strategies aim to actively recruit beneficial endogenous proteins, such as apolipoproteins, through precisely designed surfaces, including zwitterionic polymers, specific glycosylation patterns, or biomimetic ligands. This shifts the PC from a passive obstacle into an active driving force for targeted delivery. The core of future research lies in understanding the synergistic effects of multiple modification parameters and developing methods to validate these strategies in dynamic physiological and pathological microenvironments. Such work is essential to bridge the gap between *in vitro* design and predictable *in vivo* therapeutic efficacy.

3.2. Extrinsic environmental conditions

While NP properties underlie protein adsorption, the ultimate composition and function of the PC are dynamically shaped by various extrinsic environmental factors. Incubation conditions, hemodynamic shear stress, administration route, and the physiological or pathological state collectively modulate protein interactions, govern the spatiotemporal evolution of the PC, and ultimately determine the biological fate of NANDs.

3.2.1. Incubation conditions

The composition of the incubation medium, such as culture media or plasma, critically determines PC formation. Studies have demonstrated that small molecules in culture media, including amino acids and vitamins, can significantly influence protein adsorption onto NP surfaces. Tomak et al.[56] compared PC formation on silver NPs in two serum-supplemented media (Dulbecco's modified Eagle's medium and Minimum Essential Medium). Although Dulbecco's modified Eagle's medium contains fourfold higher concentrations of certain vitamins and amino acids than MEM, liquid chromatography−tandem mass spectrometry revealed similar protein profiles in both. However, the band intensity of loosely bound proteins was lower in MEM. Ashkarran et al.[57] reported that the addition of small molecules such as glucose, triglycerides, or phosphatidylcholine to human plasma markedly altered the PC composition on polystyrene NPs. For instance, phosphatidylcholine interacted with albumin *via* hydrophobic interactions, hydrogen bonding, and water bridges, which consequently reduced the incorporation of albumin into the corona.

pH regulates PC formation by regulating the type and strength of the interactive force[58]. In a study by Wang et al.[41], fluorescence quenching, isothermal titration calorimetry, and spectroscopic analyses revealed that the interaction between SLNs and BSA was dominated by van der Waals forces and hydrogen bonds at pH 7.4, while electrostatic attraction prevailed at pH 6.0. Correspondingly, the BSA adsorption capacity of SLNs was significantly higher at pH 6.0 than at pH 7.4. This difference arises because pH alters the surface charge of BSA, which has a pI of 4.7. At pH 6.0, BSA carries a net positive charge, leading to strong electrostatic attraction with the negatively charged SLNs. At pH 7.4, BSA becomes more negatively charged, resulting in electrostatic repulsion that weakens the adsorption. In a separate study, Shan et al.[59] studied the interaction between TiO_2 NPs and whey protein under different pH conditions. Dynamic light scattering and ζ-potential analysis showed that the TiO_2-whey protein complex reached its largest particle size at pH 5.0, the p*I* of whey protein. At this pH, the net surface charge of whey protein is near 0, and Fourier transform infrared spectroscopy analysis indicated that hydrogen bonding and hydrophobic interactions dominated the protein−NP binding.

PC formation is a dynamic process in which incubation duration significantly impacts its composition[14,27]. Baimanov et al.[27] found that when Cu_2S NPs were incubated in mouse serum, high-abundance but low-affinity proteins such as serum albumin predominated in the PC at early stages (3 min). In the later stage (30 min), competitive adsorption of proteins led to a shift toward high-affinity proteins like IgG and complement components, while albumin abundance decreased further. In time-dependent experiments (1, 12, and 24 h), Lima et al.[42] observed temporal changes in the APO profile on polystyrene NPs of varying sizes. On 200 and 80 nm particles, APOE abundance decreased over time, while APOA1 increased. Additionally, clusterin levels rose specifically on the 80 nm particles.

Temperature is another critical environmental factor influencing PC formation[60]. Extreme temperatures may alter protein structure and activity, which in turn affects adsorption behavior and corona stability[61]. Halder et al.[62] reported that gold NPs formed a soft corona through slower kinetics at lower temperatures (18−25 °C), whereas a hard corona assembled rapidly at elevated temperatures (37−42 °C). Oberländer et al.[63] investigated temperature-dependent compositional shifts in the corona of polystyrene NPs: at 4 °C, the corona was enriched with

coagulation-related proteins, while incubation at 37 °C favored the incorporation of lipoproteins and albumin. Moreover, they found that different plasma concentrations could affect specific proteins in the PC: higher concentrations increased proportions of clusterin and APOs, whereas lower concentrations elevated fibrinogen levels. This effect of plasma concentration was further confirmed by Pourali et al.[64], who showed that in mice, higher plasma concentrations led to the formation of a thicker, more complex corona on AuNPs after 24 h, containing increased amounts of proteins such as fibrinogen and hemoglobin. The aforementioned studies reveal the significant impacts of key incubation variables, such as pH, duration, and temperature, on the formation of the PC. It is important to note, however, that these factors are typically examined in isolation under simplified *in vitro* conditions. *In vivo*, they intertwined dynamically and simultaneously within the complex milieu of circulating blood. This complexity implies that the PC composition obtained in simplified static incubation systems may not accurately predict its final form and function within the dynamic blood circulation. Consequently, shifting future research paradigms from static to dynamic models that integrate these interrelated variables will be essential for more accurately approximating physiological reality.

3.2.2. *Hemodynamic shear stress*

While *in vitro* studies elucidate how the environment affects corona formation, static conditions fail to replicate the complex dynamics of living systems. *In vivo*, hemodynamic shear stress significantly modulates PC characteristics[65−67]. Jayaram et al.[68] found that within a physiologically relevant flow range (0.0085−8.5 cm/s), the total amount of serum protein adsorbed onto polystyrene NPs increased markedly. The adsorption amount of plasminogen increased in a flow-dependent manner (increasing by 144 ± 6% at 0.85 cm/s and by 175 ± 5% at 8.5 cm/s), while the adsorption of BSA was not significantly different between static and dynamic conditions. This selective adsorption may be related to the partial unfolding of plasminogen's secondary structure under shear flow. Moreover, there are hierarchical differences in the influence of dynamic conditions on PC stability. Using a dual-wavelength laser differential resonance light scattering correlation spectroscopy system combined with a microfluidic plaTForm, Zhang et al.[69] found that as the flow rate in the microchannel increased from 0 to 0.21 mm/s, the hydrodynamic diameter of gold nanospheres incubated in 10% fetal bovine serum progressively decreased. This reduction likely results from the weak affinity of some proteins with NPs, allowing the loosely associated soft corona to be more readily shed under flow.

The complexity of vascular structure further regulates PC composition. By comparing the non-bifurcation loop model with the vascular bifurcation model (including a 70° branch angle and a diameter reduction), Conjeevaram et al.[70] found that the disturbed flow at the bifurcation increased the total amount of protein adsorbed onto NPs by 75%. The number of complement system proteins identified increased from 5 to 10 (with notable enrichment of C1q and C3), while the abundance of coagulation-related proteins, such as fibrinogen chains (alpha, beta, and gamma), decreased by 50%. In summary, the studies discussed above establish hemodynamic shear stress as an independent and potent environmental variable that regulates the composition and stability of the PC. It not only selectively enriches specific proteins like plasminogen through direct hydrodynamic effects but also remodels the hierarchical structure of the PC by stripping away weakly bound proteins. The introduction of complex vascular geometries, such as bifurcations, better simulates the spatially and temporally heterogeneous microenvironment encountered *in vivo*. However, current *in vitro* models remain vastly simplified compared to real vascular physiology. Future research should advance toward more complex, multiscale vascular network models and integrate the vascular endothelial cell interface. This will help elucidate the final evolution of the PC under the combined influence of dynamic blood flow and biological interfaces, enabling more accurate predictions of NP transport efficiency *in vivo*.

3.2.3. *Administration method*

Beyond the universal mechanical forces encountered during circulation, the specific route and strategy by which NPs are introduced into the body, the administration method, fundamentally determines the initial biological fluid environment they encounter, thereby shaping the resulting PC. The composition and abundance of adsorbed proteins differ significantly depending on whether NPs are exposed to plasma, cerebrospinal fluid (CSF), vitreous humor, or other physiological fluids[71]. van Straten et al.[72] compared LNPs incubated in CSFversus plasma to simulate intracranial and intravenous delivery. CSF-incubated LNPs (C-LNPs) exhibited a 5.7-fold higher content of APOE (0.74%) compared to those incubated in plasma (0.13%). Kari et al.[73] analyzed hyaluronic acid-coated liposomes incubated in plasma versus vitreous humor. They found that the PC formed in plasma was significantly thicker, with hard and soft corona layers measuring 5.4 and 9.3 nm, respectively, compared to 1.6 and 2.7 nm in vitreous humor. Additionally, MS analysis revealed distinct protein profiles: plasma-derived coronas were enriched with complement proteins and fibrinogen, whereas those from vitreous humor predominantly contained structural proteins such as crystallins and GAPDH.

Interestingly, Tang et al.[74] found that the frequency of administration can also change the PC composition. Specifically, a-mangostin-loaded poly (ethylene glycol)-poly (L-lactide) (PEG-PLA) NPs were incubated with untreated mouse plasma (0 day-plasma) and mouse plasma after 7 days of administration (7 day-plasma) to simulate single and repeated administrations. MS analysis showed significant enrichment of complement proteins and Igs in the PC formed in 7 day-plasma compared to those in 0 day-plasma. This change may be related to the immune response induced by repeated administration, which elevates the circulating levels of these proteins in plasma. In summary, existing evidence confirms that the administration route and strategy, by exposing NPs to biochemically distinct biological fluids, predetermine the compositional profile of the PC, thereby influencing subsequent biological fate. These findings underscore the high degree of context-dependency and path-dependency inherent in PC formation. However, current understanding is primarily derived from *in vitro* simulations using isolated fluids. The future challenge lies in developing more sophisticated models capable of integrating sequential exposure to multiple biological compartments, dynamic fluid mixing, and adaptive changes in the host proteome induced by repeated administration. This will enable a more authentic understanding of the dynamic construction and functional evolution of the PC throughout the entire administration process.

3.2.4. *Physiological/pathological conditions*

The physiological or pathological state of the recipient fundamentally shapes the biomolecular pool available for PC formation, extending beyond controllable administration parameters. Variations in species, gender, health status, and disease progression can

dramatically alter protein abundance, conformation, and interaction kinetics. These differences generate patient- or condition-specific corona profiles that may either impede or facilitate targeted delivery. Under healthy physiological conditions, the formation of PC is mainly regulated by the types, concentrations, and physicochemical properties of proteins in biological fluids like plasma. Notably, these biomolecular characteristics can vary significantly across species and between sexes, directly determining the molecular makeup of the PC. For the first time, Ashkarran et al.[75] provided systematic evidence for sex-based regulation of the PC. By comparing PCs formed on silica NPs of different sizes (50 and 100 nm) and porosities (non-porous Stober and mesoporous) in plasma from male and female BALB/c mice, their MS analysis showed distinct protein patterns: mesoporous NPs specifically enriched 17 differential proteins, such as complement C8 family and resistin Retn in males, while Stober NPs bound 4 gender-dependent proteins, such as male urinary protein Mup1.

Li et al.[76] systematically studied how different species (humans, dogs, rats, mice) and strain differences affect complement C3 deposition on superparamagnetic iron oxide NPs, revealing fundamental differences in PC composition between species. Studies have found that C3 deposition in human serum is completely dependent on the alternative pathway, while in dogs, rats, and mice it relies significantly on the calcium-dependent lectin/classical pathway. This species-specific activation mechanism directly results in differing complement profiles in the PC: C3 deposition is significantly lower in human serum than in animal serum. Baimanov et al.[77] found that the hard PC of LNP in human plasma was rich in IgG/IgM and complement components (C3, C4a, C5), where anti-PEG antibodies (primarily IgG) constituted over 60% of the total hard-corona protein. In contrast, the corona formed in mouse plasma showed no significant enrichment of Ig or complement proteins; instead, it was mainly composed of transferrin (TF) and hemoglobin-related proteins. This difference likely stems from the lack of significant complement activation and anti-PEG antibody-mediated phagocytosis in humans.

Under pathological conditions, the physiological environment undergoes a series of changes, including inflammatory response, tumor microenvironment acidification, hypoxia, and dysregulated expression of specific proteins. These changes directly modify the composition and properties of proteins in biological fluids, which in turn affect the formation and properties of the PC on NP surfaces[78,79]. For example, the plasma abundance of certain proteins of cancer patients may be significantly increased or decreased, resulting in a PC composition that differs significantly from that in healthy individuals[80]. Xu et al.[81] identified distinct corona profiles in patients with non-small cell lung cancer (NSCLC) and type 2 diabetes, showing elevated levels of fibrin and clusterin but reduced TF compared to patients with NSCLC alone. Tang et al.[82] demonstrated that hypercholesterolemia remodels the corona on silica NPs, increasing APOE binding by 20-fold and decreasing complement C1QB binding 9-fold in under high-cholesterol conditions. In summary, PC formation is highly dependent on the organism's physiological or pathological context, including factors such as sex, species, and specific disease states. This dependency reveals the challenges of personalization and disease heterogeneity in clinical nanomedicine. The future frontier lies in proactively leveraging this dependency. One direction is to explore disease-specific PC profiles as potential diagnostic biomarkers. Another is to rationally design nanocarriers capable of responding to specific pathological microenvironmental cues (*e.g.*, pH, enzymes, redox status). This would enable an intelligent transformation of their PC composition and function at the target site, thereby achieving truly precise delivery and therapy.

4. Effects of PC on *in vivo* fate of NANDs

The PC fundamentally reshapes the biological identity of NANDs, determining their journey from administration to intracellular activity. It critically influences gastrointestinal mucus penetration, circulatory stability, biodistribution, and cellular tropism, as well as cellular uptake and endolysosomal escape. Although the PC may obscure engineered targeting ligands, it also introduces new biological identities *via* adsorbed proteins, ultimately dictating organ accumulation and intracellular processing pathways.

4.1. Penetration of gastrointestinal mucus and epithelial barriers

When administered orally or by inhalation, NANDs encounter an additional barrier: the gastrointestinal or respiratory mucus layer. Mucus is a complex, viscoelastic gel composed of water, electrolytes, lipids, and various proteins, whose three-dimensional network imposes steric hindrance on drug delivery systems[83]. Negatively charged mucins are key structural components of this mesh[84]. Commonly used nucleic acid nanocarriers typically possess a positive surface charge, which facilitates the adsorption of a mucin corona and consequently hinders their mobility within mucosal environments[25]. Reducing interactions between NANDs and mucins leads to a thinner, smaller mucin corona, thereby enhancing particle diffusion through mucus and improving mucosal penetration[85,86].

For orally administered NANDs, mucin corona formation may mask surface functionalization or affect their *in vivo* physicochemical properties, leading to unexpected changes in oral absorption. Yang et al.[87] observed that mucus proteins masked, displaced, and dampened the active targeting effects of TF-modified nanocarriers, thereby weakening their endocytosis and transcellular transport in enterocytes (Fig. 3). Similarly, mucin corona aggregation on the surface of mesoporous silica nanocarriers decorated with a large IgG Fc fragment interfered with neonatal Fc receptor-mediated transintestinal transport[88]. In another study, the mucin corona induced clustering of PEGylated gold nanocarriers[89], which increased their endocytosis but decreased transcytosis across the epithelial monolayer, potentially hindering entry into the bloodstream (Fig. 3). Notably, these seemingly adverse effects of PCs are not universal and may be profoundly altered under pathological conditions. In diseases such as diabetes or colitis, disease-specific intestinal protein coronas (IPCs) have been shown to act as "alternative ligands" on nanocarriers, facilitating intracellular trafficking *via* early endosomes, recycling endosomes, and the endoplasmic reticulum (ER-Golgi) pathways. This enhances transepithelial transport and oral absorption even when the original targeting ligands are masked[78]. In contrast, sulfhydryl-rich nanocarriers follow a different mechanism. After endocytosis by intestinal epithelial cells, they form disulfide bonds with apolipoprotein B48 (APOB48), the primary structural protein of chylomicrons[90,91]. This enables them to hijack the chylomicron transport pathway, traversing the ER−Golgi apparatus route and ultimately entering systemic circulation *via* the lymphatic system.

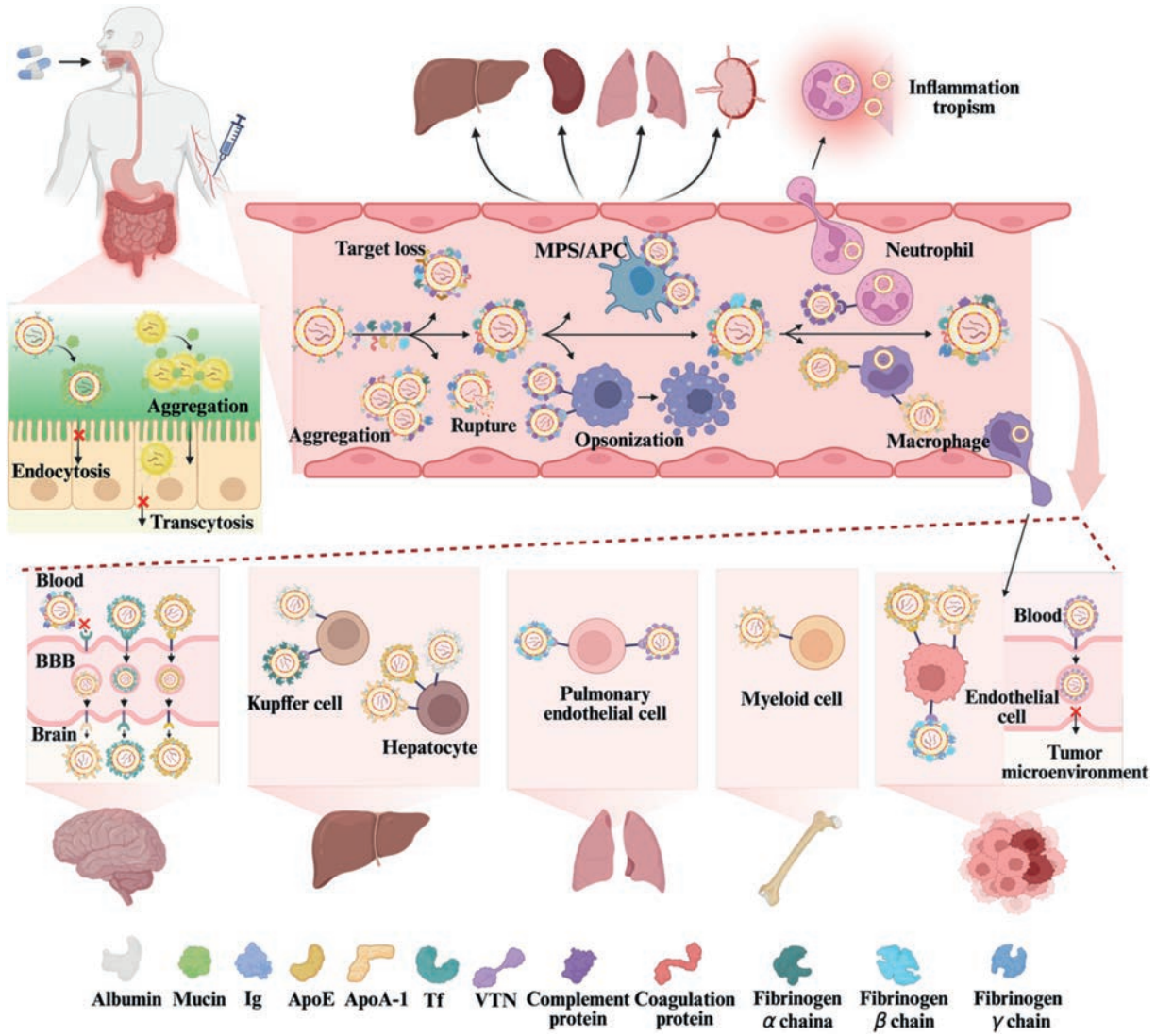

Figure 3 Effects of the protein corona (PC) on the *in vivo* fate of nucleic acid nanodrugs (NANDs). The PC affects the *in vivo* fate of nucleic acid nanodrugs by modulating gastrointestinal mucus penetration through mucin interactions, stabilizing systemic circulation *via* opsonin/dysopsonin balance, and directing biodistribution *via* receptor-specific protein components. Although the PC may obscure engineered targeting ligands and lead to unintended accumulation in tissues rich in mononuclear phagocyte system or cells expressing endogenous receptors, it also contributes to prolonged circulation and organ-specific targeting through dynamic, protein-mediated recognition mechanisms.

4.2. Stability in blood circulation

Upon intravenous injection, NANDs enter the systemic circulation. Their ability to reach target tissues depends largely on prolonged circulation, which increases opportunities for contact with target tissues or cells and improves nucleic acid delivery efficiency. However, adsorption of the PC can alter surface properties, resulting in aggregation, degradation, or clearance by the mononuclear phagocyte system (MPS) before the NPs reach their target sites[92,93] (Fig. 3). It has been shown that NPs lacking a fully formed corona tend to aggregate[94]. Transmission electron microscopy observations by Lorents et al.[95] revealed that the PC formed on splice-correcting oligonucleotide NPs appeared as a diffuse layer of loosely associated proteins, facilitating the formation of aggregates several hundred nanometers in size[95]. The effect of protein concentration is also critical: at low concentrations, protein adsorption induces NP aggregation through electrostatic and hydrophobic interactions, whereas at higher concentrations, an intact PC substantially suppresses aggregation *via* steric hindrance and surface charge shielding[96]. Additionally, the specific proteins involved modulate aggregation differently: serum albumin necessitates salts to promote electrostatic-driven aggregation, whereas immunoglobulin G (IgG)-owing to its substantial molecular size and distinct structural properties-induces more pronounced NP aggregation through hydrophobic interactions.

A further key constraint on the *in vivo* circulation stability of NANDs lies in opsonin-mediated nonspecific phagocytosis (Fig. 3). Generally, opsonins (Igs, complement proteins, and coagulation proteins) typically induce MPS to capture and eliminate NANDs, whereas dysopsonins (albumin, APOs) tend to promote prolonged circulation[97−100]. Molecular dynamics simulations reveal that HSA can competitively displace IgG from nanocarrier surfaces due to its higher lateral mobility, thereby effectively reducing opsonin-mediated clearance and prolonging blood circulation, providing a theoretical basis for designing long-circulating NANDs[13,101−103]. Moreover, highly hydrophilic surface layers, which markedly limit

protein adsorption, provide a novel strategy for designing nucleic acid nanocarriers with tailored pharmacokinetics[104]. PEGylation has long been regarded as the gold standard for reducing nonspecific protein adsorption and prolonging nanocarrier circulation[105]. However, this stealth effect may be compromised by increasing levels of anti-PEG antibodies in the bloodstream, potentially leading to accelerated blood clearance and undesirable adverse effects[106]. To address these limitations, a series of optimization strategies and alternative materials have been developed to extend circulation while maintaining biocompatibility[100,107−109]. Promising approaches can be categorized into three main directions: (1) structural redesign of PEG-LNPs using, for example brush-shaped polymer lipids to evade recognition by anti-PEG antibody[110]; (2) complete replacement of PEG with alternative hydrophilic materials, such as zwitterionic lipids, glycolipids, or synthetic polymers like poly (2-(methylsulfinyl)ethyl glycidyl ether), which provide effective hydration and steric shielding with minimal immunogenicity[111−113]; (3) leveraging endogenous proteins, such as through albumin-binding lipids, to improve circulation kinetics and avoid hepatic clearance[114]. However, corona-coated nanocarriers with comparable opsonin/dysopsonin content exhibited distinct circulation times, suggesting that these biomolecules are not the sole determinants of *in vivo* fate[115].

4.3. Biodistribution and cellular tropism

Organ-, tissue-, or cell-specific delivery of NANDs is essential for maximizing the therapeutic efficacy and minimizing the adverse effects of nucleic acid therapeutics. In this regard, surface functionalization with targeting ligands is the most extensively employed strategy. However, despite ingenious design, numerous ligand-mediated actively targeted NANDs are still unable to function effectively *in vivo*. The PCs have been identified as the culprit, as their formation can compromise or shield the surface-targeting ligands of NANDs from binding to cognate receptors[22] (Fig. 3). Furthermore, the PCs themselves can also directly influence the biodistribution of NANDs. Since many adsorbed plasma proteins possess endogenous receptors, their presence can redirect NANDs to tissues or cells expressing those specific receptors[22].

When NANDs are opsonized by opsonins, they are readily directed to tissues enriched with MPS or antigen-presenting cells (APCs), such as the liver, spleen, lungs, and lymph nodes. Uptake is often most pronounced in the liver due to interactions between opsonins and receptors on phagocytic cells[116−118]. However, this form of accumulation may also lead to rapid clearance[118].

APOA1 binds the class B type I scavenger receptor (SRB1) *via* its unique helical structure, enabling it to target macrophages, hepatocytes, myeloid cells, and tumor cells[119,120]. Therefore, NANDs enriched with APOA1 in their corona tend to accumulate in the liver, bone marrow, and tumors[121−123]. Inhibition of hepatocyte SRB1 leads to reduced hepatic uptake of siRNA-LNP, shifting their accumulation instead to myeloid immune cells in circulation and the liver[124]. In addition to SRB1, macrophages also highly express other apolipoprotein-specific receptors such as low-density lipoprotein receptor (LDLR) and LDLR-related protein 1, which can also be engaged byapolipoprotein-NP complexes[125]. Given the critical role of macrophages in the tumor microenvironment, modulating their natural tumor-homing ability offers a promising strategy to overcome the typically low targeting efficiency of NANDs for cancer treatment, thereby harnessing these cells to combat tumors[90,125].

Additionally, APOE adsorption onto NANDs promotes hepatic uptake by targeting the LDLRs that are highly expressed on hepatocytes (including hepatocellular carcinoma cells), thereby enabling efficient nucleic acid delivery to the liver[126,127]. Johnson et al.[128] discovered that NPs with albumin-enriched surfaces but deficient in APOE may redirect delivery to Kupffer cells rather than hepatocytes, compromising the therapeutic outcomes of loaded siRNA. However, albumin binding to LNPs may facilitate an APOE-independent pathway (*via* albumin-associated macropinocytosis and endocytosis) for mRNA delivery to hepatocytes[129], reducing the relative importance of APOE in this context. This could be attributed to either saturation of hepatocyte-secreted APOE, which masks LNP-mediated APOE uptake, or to intrinsic differences between mRNA and siRNA LNP formulations. Vitronectin (VTN) is frequently identified in the PC of cationic NPs and directs them toward cells with high $\alpha_v\beta_3$ integrin expression, such as pulmonary endothelial cells and certain tumor cells[130−132]. The fibrinogen β and γ chains also contribute significantly to NP-mediated nucleic acid delivery to pulmonary endothelial cells[133,134], while the fibrinogen α chain facilitates NANDs delivery to Kupffer cells[135].

The blood−brain barrier (BBB), playing a central role in maintaining brain homeostasis, is the primary barrier to drug−brain delivery[136]. This complicates the delivery of NANDs and the treatment of related neurological diseases. Both the transferrin receptor (TFR) and the LDLR are highly expressed in brain endothelial cells and have been extensively investigated for NP-mediated drug transport across the BBB[137,138]. Consequently, their ligands, TF and APOE, are frequently recognized as beneficial PC components that facilitate NAND transport across the BBB and subsequent accumulation in the brain[139,140].

Overall, PC formation confers NANDs with a new biological identity that fundamentally determines their *in vivo* biodistribution (Fig. 3). Nevertheless, their ultimate spatial distribution and cellular localization are further refined by organ-specific physiological factors. These factors, such as hemodynamic shear stress, endothelial permeability, vascular architecture, and local receptor density, refine targeting outcomes. Consequently, even identical PC-mediated ligand−receptor interactions (*e.g.*, APOE-LDLR) can result in divergent accumulation patterns between organs like the liver and brain.

4.4. Cell uptake and endolysosome escape

The entry of NANDs into target cells is a prerequisite for nucleic acids to exert their biological functions. Generally, PC formation modifies NP−cell interactions, which in turn alter the pathways and efficiency of NAND cellular uptake. Although PC may obscure specific ligands on the surface of NANDs and potentially block their corresponding internalization routes, certain PC components can act as endogenous ligands that facilitate target cell recognition and uptake. Additionally, for certain positively charged NANDs such as DC-cholesterol LNPs, the PC layer masks their surface charge, compromising their ability for direct penetration of negatively charged cell membranes[141]. VTN, an abundant adhesive glycoprotein present in plasma and tissues, facilitates the adhesion of mRNA-LNPs to the cell membrane of HepG2 but subsequently hinders their internalization[142]. But for APOs, the primary abundant lipophilic proteins in the corona, are capable of facilitating NAND incorporation into cytomembranes through insertion of their amphiphilic α-helices into the lipid bilayer, implying a potential mechanism for direct transmembrane delivery of nucleic acid[48,143].

NPs are typically internalized by non-phagocytic cells through macropinocytosis, clathrin-mediated endocytosis, or caveolae-mediated endocytosis[144]. Faiad et al.[145] found that serum albumin induces the dissociation of spherical nucleic acids (SNAs). While intact SNAs are internalized through both clathrin-dependent and independent processes, dissociated SNAs primarily utilize clathrin-independent uptake pathways at similar levels. Given that most NANDs enter the endosomal−lysosomal pathway after cellular uptake-an acidic, enzyme-rich environment that promotes degradation-efficient endolysosomal escape is critical for successful delivery. In this regard, the caveolin-mediated uptake pathway offers a distinct advantage by largely bypassing the degradative endosomal/lysosomal compartment[146]. Caracciolo et al.[147] reported that serum proteins competed for binding sites on cationic surface of cholesterol-1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE)/DNA lipoplexes, inducing their aggregation and shifting cellular entry from clathrin-dependent to caveolae-mediated entry pathway, which correlates with enhanced transfection efficiency. In contrast, PC formation on multicomponent lipoplexes can shift the balance from caveolae-mediated endocytosis toward macropinocytosis, favoring delivery to degradative lysosomal compartments[148]. Even upon entry into endosomes, NANDs can evade lysosomal degradation by destabilizing the endosomal membrane[146]. A critical component enabling this escape in LNP is the cationic ionizable lipid (CIL), which remains neutral at physiological pH but becomes positively charged in acidic endosomes[149]. This property minimizes nonspecific adsorption of LNPs in the bloodstream while facilitating their escape from endosomes by fusing with the negatively charged endosomal membrane[150,151]. Voke et al.[142] reported that although APOE significantly enhanced hepatocyte uptake of LNPs, it concomitantly induced greater lysosomal retention, ultimately limiting mRNA expression. Sebastiani et al.[152] indicated that APOE binding may redistribute CILs from the LNP shell to the core, potentially limiting LNP endosomal escape. Aliakbarinodehi et al.[153] developed LNPs using a pH-sensitive ionizable lipid DLin-MC3-DMA (MC3). MC3 became protonated and positively charged as the pH decreased during endosome maturation, which promoted the LNP binding to and stepwise large-scale collapsing onto the endosomal membrane, enabling mRNA release. However, PC (particularly by lipoproteins) formation can shift this binding and subsequent disintegration process to a lower pH, reducing interaction with endosomal membranes and thus decreasing functional mRNA delivery.

Membrane fusion is a fundamental biological process in living organisms that enables cellular membranes to merge and their internal contents to mix[154]. Inspired by this natural phenomenon, fusogenic liposomes have been engineered to merge directly with cellular membranes through structural integration, delivering nucleic acid payloads (*e.g.*, CRISPR/Cas9, mRNA, siRNA, pDNA) into the cytoplasm without requiring endocytosis or lysosomal trafficking[155,156]. However, the PC formed on the fusogenic liposome surface during systemic circulation converts its membrane-fusion performance, redirecting uptake toward lysosome-dependent endocytosis and consequently substantially impairing the efficacy of nucleic acid delivery *in vivo*[104].

5. PC modulation strategies for targeted delivery of NANDs

Given that PC formation critically reshapes the *in vivo* identity and fate of NANDs, PC modulation has emerged as a central strategy for achieving organ-selective nucleic acid delivery. Conceptually, these approaches can be categorized into three overarching design principles based on the core intervention mode: surface chemistry modification-driven PC recruitment, surface ligand modification for active PC engineering, and pre-coating PC *in vitro* for controlled *in vivo* identity. Each principle leverages distinct mechanisms to tailor the PC, thereby guiding NANDs toward target tissues/cells while minimizing off-target effects. Collectively, these strategies cover the full spectrum of PC modulation, from indirect guidance of endogenous protein adsorption to directly engineering corona components, providing flexible solutions for targeted delivery across multiple organs.

5.1. Surface chemistry codification-criven PC recruitment

Modulating the PC through surface chemistry modification represents the most extensively investigated and practically validated strategy for guiding NAND biodistribution. Upon systemic administration, NANDs immediately encounter complex biological milieus, where spontaneously adsorbed endogenous proteins define their biological identity and downstream fate. Owing to the dominant role of the MPS, NANDs intrinsically accumulate in clearance organs such as the liver and spleen, often resulting in rapid sequestration and limited therapeutic efficiency. Rather than attempting to eliminate PC formation, this strategy leverages rational surface chemical design to bias the composition of the PC, thereby redirecting NAND biodistribution through endogenous protein-mediated recognition pathways without the need for exogenous targeting ligands.

At the molecular level, surface chemistry governs protein recruitment by modulating electrostatic interactions, hydration, steric accessibility, and interfacial free energy. Variations in ionizable lipid headgroups, hydrophobic tail architecture, linker chemistry, helper lipid composition, and polymer coatings collectively reshape the competitive adsorption landscape among plasma proteins. Such modulation not only alters the quantity of adsorbed proteins but critically determines the functional identity of the hard corona, which in turn dominates receptor engagement, cellular uptake, and organ tropism *in vivo*.

5.1.1. Liver

Given its central role in NP clearance and lipid metabolism, the liver serves as the most thoroughly characterized organ for surface chemistry-driven PC modulation[157]. LNPs represent the most advanced plaTForm for nucleic acid delivery. Following intravenous administration, conventional LNPs are typically directed to the liver *via* APOE adsorption (Table 1[121,129,135,158−161]). This mechanism underpins the hepatocyte targeting of Onpattro (Patisiran), an siRNA-LNP therapy approved by the FDA in 2018 for transthyretin-mediated amyloidosis[158]. Studies demonstrate that the preferential hepatic targeting of Onpattro is mediated by APOE adsorbed onto the surface of NANDs post-intravenous administration. Conventional LNPs comprise four essential components: cationic/ionizable amino lipids, a helper lipid, cholesterol, and a PEG-lipid. The structural versatility of these lipids allows extensive formulation screening to identify candidates capable of engaging endogenous targeting pathways (Table 1[121,129,135,158−161]). Miao et al.[129] developed biodegradable LNPs by introducing alkyne and ester groups into the lipid tails of MC3. These formulations could enter hepatocytes *via* an albumin-dependent pathway rather than through APOE-mediated uptake. Relevant studies showed that precise modulation of the

Table 1 PC-based strategies for targeted liver delivery of NANDs.

Utilized strategy	Protein	Protein receptor	Target cell	Ref.
Conventional LNPs	APOE	LDLR	Hepatocyte	158
LNPs with modification of the backbone structure of Dlin-MC3-DMA by introducing alkyne and ester groups into the lipid tails.	Albumin	The glycoprotein scavenger receptors gp30 and gp18	Hepatocyte	129
Changes in the hydrophobic tail length of diketopiperazine-based lipids	APOE-independent	LDLR-independent	Hon-hepatocytes	159
Onizable lipid PPZ-A10-formulated LNPs	APO A-I, VTN, and complement proteins	SRB1 and $\alpha_v\beta_3$ integrin	Macrophage	121
Ionizable polymeric micelles formed by ionizable oligomers and polylactide-polyethylene glycol	Proteins functionally related to binding.	–	Hepatic stellate cell	161
DNA tetrahedron with trivalent cholesterol conjugation	Lipoprotein-associated protein	SRB1 and LDLR	Hepatocyte in healthy mice and myofibroblast in fibrotic mice	160
Zwitterionic polymer LNPs assembled with the zwitterionic polymer polycarboxybetaine modified 1,2-dimyristoylglycerol ($pK_a = 6.34$)	Fibrinogen α chain	–	Kupffer cell	135

LNP, lipid nanoparticle; APOE, apolipoprotein E; LDLR, low-density lipoprotein receptor; VTN, Vitronectin; APO A-I, apolipoprotein A-I; SRB1, class B type I scavenger receptor.

ionizable lipid structure of LNPs enabled efficient delivery into other cell types independent of APOE involvement[159]. This observation was further supported by Yang et al.[121], who reported that LNPs containing the ionizable lipid PPZ-A10 recruited APOA1, complement proteins, and VTN to the surface, enabling selective mRNA delivery to macrophages in hepatocellular carcinoma[121]. Alternatively, such as high-density PEGylation coupled with mannose decoration can further redirect LNPs from hepatocytes to liver sinusoidal endothelial cells[161]. Collectively, these findings expand the potential of LNPs for extrahepatic and cell-type-specific nucleic acid delivery in systemic applications.

Beyond lipid-based systems, polymeric nanocarriers further expand the scope of chemistry-driven PC engineering in the liver (Table 1). For instance, Zhou et al.[162] designed ionizable polymeric micelles that uniquely adsorb proteins involved in cellular adhesion while avoiding APOs and complement proteins from their corona. This distinct adsorption profile minimizes rapid clearance and redirects delivery to non-hepatocytic cell types, such as activated hepatic stellate cells (HSCs) in fibrotic liver, underscoring the potential of polymeric systems to transcend limitations of conventional LNPs.

5.1.2. Lung

In recent years, LNP formulations have been engineered to achieve extrahepatic targeted delivery of nucleic acids, particularly to the lung (Table 2[131–133,135,163–172]). He et al.[163] explored a structure-function relationship for ionizable lipids, showing that lipids featuring *N*-methyl and secondary amine headgroups with three tails originated from epoxy alkanes exhibited superior pulmonary selectivity and transfection efficiency. Proteomic analysis revealed that the PC of these mRNA-LNPs was enriched in arginine-glycine-aspartic acid-rich proteins, including VTN, fibrinogen, fibronectin, and dentin-saliva-phosphoprotein proprotein. Lung-specific mRNA delivery has also been achieved by substituting the amine-containing ionizable lipid with positively charged sulfonium lipids, with certain protein species commonly shared across different lung-targeting LNPs[164]. Qiu et al.[133] designed phospholipid with different amine headgroups and acrylate tails, finding that simply changing the tail linkage from an ester bond to an amide bond (N-series) shifted LNP accumulation from the liver to the lungs. And minor tuning of the headgroup structure of these N-series lipids further altered their selectivity among pulmonary cell types. Lung-targeting LNPs adsorbed large amounts of albumin and fibrinogen β/γ chains, while liver-targeting counterparts predominantly bound APOE. Zhang et al.[132] replaced conventional PEG-lipids with the zwitterionic polymer poly (2-methyacryloyloxyethyl phosphorylcholine), creating polyzwitterionic LNPs that accumulated in the lungs mediated *via* VTN. Li et al.[135] replaced PEG with polycarboxybetaine (PCB) to synthesize DMG-PCBn with varying degrees of polymerization, which were then assembled into zwitterionic polymer LNPs (ZP-LNPs)[135]. By adjusting the PCB degree of polymerization, lipid ratios, and lipids-to-siRNA mass ratios, they designed various ZP-LNPs with distinct targeting profiles: B4-3@siRNA (higher pK_a) accumulated in the liver, likely through fibrinogen α chain adsorption and Kupffer cell interaction, while B5-1@siRNA (lower pK_a) preferentially targeted the lungs *via* enhanced binding to vitronectin, complement factor D, and fibrinogen α chain. LNP-mediated high potency and specificity of the lung was achieved by incorporating the quaternary ammonium lipids of trimethylammonium propane series when VTN, clusterin, albumin, and prothrombin were enriched, and complement component C1q and Ig were reduced, suggesting an ensemble of multiple proteins may help determine the lung selectivity[165]. However, the propensity of positively charged surfaces to induce thrombotic complications warrants careful consideration, as cationic NPs may inadvertently activate coagulation cascades and platelet aggregation[173].

A promising strategy to address the challenges associated with multi-component LNPs-including inconsistent assembly, limited

stability, and potential toxicity-is to simplify formulations while retaining organ-targeting capabilities (Table 2). This principle has been effectively demonstrated by the development of three-component (3-Comp) LNPs consisting of an ionizable cationic lipid, a permanently cationic lipid, and a PEG-lipid[166]. By omitting cholesterol, these 3-Comp LNPs reduced lipoprotein coating and outperformed their 4-Comp and 5-Comp counterparts in both pulmonary mRNA accumulation and translation, while also maintaining remarkable stability.

Polymeric nanomaterials have emerged as equally formidable players for lung targeted nucleic acid delivery (Table 2). Le et al.[167] developed cationic poly (β-amino ester) NPs that preferentially transfected pulmonary endothelial cells, guided by distinct PC profiles enriched in proteins with molecular weights below 200 kDa and p*I* between 5 and 7. This enabled localized bevacizumab mRNA expression and enhanced anti-angiogenic therapy in lung cancer models. Similarly, Pu et al.[168] engineered bioreducible polyamidoamine complexes that, following subcutaneous administration, spontaneously adsorbed lung-targeting proteins like VTN and fibronectins. Through deliberate surface-charge modulation and albumin coating, these complexes achieved 10-fold higher pulmonary mRNA expression compared to other organs.

5.1.3. Spleen

The RES-based strategy facilitates splenic targeting of NAND through a mechanism analogous to that underlying hepatic targeting. Compared to SNAs composed of poly-thymine oligonucleotides, G-rich SNAs adsorb more complement proteins, particularly complement C3b, onto their surface. These proteins are recognized by complement receptors expressed on macrophages, facilitating cellular uptake and preferential accumulation

Table 2 PC-based strategies for targeted lung delivery of NANDs.

Utilized strategy	Protein	Protein receptor	Target cell	Ref.
LNPs with nonpermanently charged ionizable lipids carrying *N*-methyl and secondary amine groups in the heads, and three tails originated from epoxyalkanes	Arginine-glycine-aspartic acid -rich proteins (includes VTN, fibrinogen, fibronectin, and dentin-saliva-phosphoprotein proprotein)	–	–	163
Sulfonium LNPs constructed from sulfonium lipids	Fibrinogens, apolipoproteins, fibronectin, vitronectin, complement proteins and alpha-1-antitrypsin	–	Endothelial cell, epithelial cell and immune cell	164
LNPs with the changed linker from ester bond to amide bond	Albumin, fibrinogen β and γ chains	–	Endothelial cell, macrophage and epithelium	133
Polyzwitterionic LNPs with zwitterionic polymer poly (2-methyacryloyloxyethyl phosphorylcholine) modified 1,2-dimyristoyl-*sn*-glycerol lipid	VTN	–	Macrophage	132
Zwitterionic polymer LNPs assembled with the zwitterionic polymer polycarboxybetaine modified 1,2-dimyristoylglycerol ($pK_a = 7.04$)	VTN, complement factor D, and fibrinogen α chain	Complement receptor and integrin receptor	Macrophage	135
LNPs incorporated with the SORT molecule quaternary ammonium lipid	VTN, prothrombin, clusterin, serum paraoxonase 1, fibrinogen, and albumin	–	–	165
The three-component ionizable cationic lipid/permanently cationic lipid/PEG-lipid LNPs	Reduced lipoproteins	–	Endothelial cell	166
Poly (β-amino esters)-lipid hybrid NPs	Proteins that were less than 200 kDa and which isoelectric point values fell within the range of 5 and 7	–	Endothelial cell	167
Polyamidoamine polymers	VTN and fibronectin	–	–	168
LNPs modified with CD47 and anti-CD31 antibody	Albumin, APOC3 and APOC4	–	Endothelial cell	169
LNPs modified in the polar-head group	VTN and prothrombin	–	–	170
LNPs with siloxane-incorporated lipidoids	VTN	$\alpha_v\beta_3$	Endothelium	171
LNPs incorporated with the SORT molecule 1,2-dioleoyl-3-trimethylammonium-propane	VTN	$\alpha_v\beta_3$	Endothelium	131
LNPs incorporated with the higher fifth component ionizable cholesterol analogs	Large-sized protein	–	–	172

LNP, lipid nanoparticle; VTN, Vitronectin; SORT, selective organ targeting; NP, nanoparticle.

in the liver and spleen[14]. However, this opsonin-mediated splenic delivery often entails faster clearance and lower targeting efficiency than hepatic uptake. By modulating nanocarrier cholesterol content, serum opsonins may exhibit selective recognition of macrophages residing in either the liver or spleen[174]. Beta-2-Glycoprotein 1 (B2GP1), a highly abundant plasma protein with strong affinity for anionic phospholipid membranes such as phosphatidylserine exposed on senescent erythrocytes, directs their splenic sequestration and macrophage-mediated clearance[175,176]. Dilliard et al.[131] incorporated achieved effective spleen targeting by the anionic lipid 1,2-dioleoyl-*sn*-glycero-3-phosphate (18 PA) into conventional LNPs, promoting B2GP1 adsorption and enhancing functional mRNA delivery to splenic THP-1 macrophages. Subsequently, Xue et al.[177] constructed a library of dendron-like degradable ionizable lipids by altering amine headgroups and multiarmed tails. One dendritic LNP formulation, 18-2-9b2, exhibited superior specificity for splenic red-pulp and marginal-zone macrophages over 18 PA LNPs. Its PC was enriched with proteins closely associated with cellular activity, notably Integrin Subunit Alpha 2b (ITGA2B), which is predominantly expressed on platelets and megakaryocytes. Interaction with ITGA2B likely directs NANDs to the spleen *via* its abundant platelet reservoir. Therefore, differences in the functional microenvironments of hepatic and splenic macrophages, as reflected in the composition of PCs, may represent a viable avenue for enhancing spleen-targeted delivery (Table 3[14,127,131,169,170,172,177–180]).

Ideal spleen-targeted nucleic acid nanocarriers should also be designed to minimize unintended hepatic uptake. Zhang et al.[127] reported that the helper lipid 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC) induced weaker APOE binding to LNPs than does DOPE, redirecting siRNA and mRNA delivery from the liver to the spleen. Suzuki et al.[178] developed a novel ionizable lipid library based on ionizable tri-oleoyl-tris scaffolds. By modulating the relative proportions of lipid components, they found that 15% DSPC-LNPs, compared to 3% DSPC-LNPs, exhibited a rigid, hydrophobic, and charge-neutral surface, which minimized APOE-dependent hepatic uptake while maximizing complement receptor-mediated splenic B cell targeting. In addition to the reduced APOE affinity conferred by DSPC, the lower cholesterol content in 15% DSPC-LNPs may further diminish APOE adsorption[82]. However, for 1,2-dioleoyl-3-dimethylammonium propane (DODAP), typically classified as inefficient, it enabled complement C3-mediated delivery of pDNA to splenic immune cells only when co-formulated with DOPE[179]. Liu et al.[180] formulated simplified lipid-polymer nanoparticles (LPNs) using an esterase-responsive quaternized lipidoid and PEG-*block*-polylactide, achieving complement C3-dependent, spleen-specific Fc gamma receptor 2B mRNA delivery to B cells. Although immune cell-associated opsonin binding is generally considered an undesirable event, it can be leveraged for nucleic acid delivery to active immune cells for immunomodulation (Table 3). Most spleen-focused nanomedicine systems exploitthe organ's role as a secondary lymphoid organ and can be classified into two categories: immune activation

Table 3 PC-based strategies for targeted spleen delivery of NANDs.

Utilized strategy	Protein	Protein receptor	Target cell	Ref.
LNPs incorporated with the SORT molecule, anionic lipid 1,2-dioleoyl-*sn*-glycero-3-phosphate	β2-GPI	–	Macrophage	131
Dendron-like LNPs formulated by dendron-like degradable ionizable lipids with tailed dendron-like architectures	ITGA2B	–	Red pulp macrophage and marginal metallophilic macrophage	177
LNPs containing the helper lipid 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC)	Reduced APOE	–	–	127
LNPs based on ionizable tri-oleoyl-tris compounds which contained 15 mol% 1,2-distearoyl-*sn*-glycero-3-phosphocholine	Complement C3b	Complement receptor	B Cell	178
LNPs formed by certain 1,2-dioleoyl-3-dimethylammo-nium propane and 1,2-dioleyoxy-*N*,*N*-dimethyl-3-aminopropane ratios	Complement C3b	Complement receptor	Immune cell	179
LPNs formulated with AMB-POC18 lipidoid and poly (ethylene glycol)-*block*-polylactide	Complement C3b	Complement receptor	B Cell	180
LNPs modified with CD47 and anti-CD4 antibody	Albumin, APOC3 and APOC4	–	T Cells	169
LNPs with branched hydrophobic chains	Actin, myosin, and the immunoglobulin lambda-like protein	–	–	170
LNPs incorporated with the lower fifth component ionizable cholesterol analogs	Medium-sized protein	–	–	172
SNAs composed of guanine-rich oligonucleotides	Complement C3b	Complement receptor	Macrophage	14

LNP, lipid nanoparticle; SORT, selective organ targeting; β2-GPI, β2-Glycoprotein I; APOE, apolipoprotein E; SNA, spherical nucleic acids.

or suppression. Immune enhancement aims to stimulate both T- and B-cell zones in the spleen, promoting subsequent migration to disease sites for enhanced antitumor immunity[179]. Conversely, immune suppression strategies focus on mitigating excessive immune responses, such as in rheumatoid arthritis, to maintain systemic homeostasis[180].

5.1.4. Brain

The BBB poses a major challenge for delivering nucleic acids to the brain parenchyma following systemic administration[181]. Despite advances in delivery technologies, traversing the BBB remains an extraordinary challenge for nanotherapeutics[182]. Although successful instances of brain-targeted nucleic acid delivery are still limited, strategies that engage endothelial receptors on the luminal BBB surface are paving the way (Table 4[139,140,183]). Kim et al.[139] screened a set of DNA nanostructures and revealed that a cube-shaped DNA nanostructure functionalized with TF-binding efficiently penetrated the BBB and delivered ASOs to treat glioblastoma multiforme (GBM).

5.1.5. Bone marrow

Despite reports of NANDs being delivered to the bone marrow (BM), effective therapeutic delivery remains severely limited by multiple barriers. These include the low frequency and quiescence of hematopoietic stem cells, limited blood perfusion, the vascular endothelial barrier, and the inherently low targeting specificity of nanocarriers[22,184]. Yet strategies harnessing apolipoproteins show emerging promise. Lian et al.[185] achieved successful delivery of mRNA, genome, and base editors to the BM using LNPs containing covalent-bond-forming lipid species (Table 5[122,185]). This BM delivery was dependent on the surface enrichment of APOE, indicating a previously unknown role for APOE.

5.1.6. Tumor

PC formation generally increases NP size and restricts their tumor extravasation and penetration, thereby posing challenges for antitumor delivery[23]. Nevertheless, the PC can also function as a source of endogenous targeting ligands when tumors express cognate receptors (Table 6[90,130]). For instance, NANDs enriched with APOE in their PC accumulate in LDLR-expressing HepG2 tumors *in vivo*[131]. The $\alpha_v\beta_3$ receptor is expressed in various tumor cell types, including glioblastoma, breast cancer, and melanoma cells. siRNA-LNPs formulated with DOTAP as the primary cationic lipid recruit VTN and preferentially transfect $\alpha_v\beta_3$-expressing HepG2 and A375. S2 cells[130]. However, following systemic administration, these NPs were sequestered by $\alpha_v\beta_3$-expressing endothelial cells lining tumor vessels before reaching tumor cells, resulting in minimal gene silencing within tumors. Highly thiolated trimethyl chitosan-cysteine (TC) NPs were engineered to achieve effective oral pDNA delivery by *in situ* adsorption of APOB48 in intestinal tissues, enabling macrophage targeting and leveraging macrophages' intrinsic tumor-homing capability[90]. This approach holds promise as macrophages autonomously penetrate vascular endothelial interstitium and migrate through dense, highly cross-linked extracellular matrix. Utilizing macrophages as nanocarrier vehicles inherently circumvents PC-related interference during these processes, potentially simplifying the design of the NPs themselves.

5.1.7. Tunable organ-selective targeting across different organs

Recent studies have focused on tuning and redirecting NAND organ tropism by modulating nanocarrier composition and the associated PCs, thereby enabling preferential delivery to different organs under defined formulation contexts. In LNP systems, single-organ targeting strategies can be extended to multi-organ

Table 4 PC-based strategies for targeted brain delivery of NANDs.

Utilized strategy	Protein	Protein receptor	Target cell	Ref.
Cube-shaped DNA nanostructure	TF and APOE	Transferrin receptor 1, lipoprotein receptor-related protein 1, and 2, and LDLR	Endothelial cell and GBM cell	139
LNPs modified with APOE	APOE	LDLR	Endothelial cell, neural stem cell, and/or neural progenitor cell	183
Nanocapsules modified with APOE	APOE	LDLR	Endothelial cell and GBM cell	140

TF, transferrin; APOE, apolipoprotein E; LDLR, low-density lipoprotein receptor; GBM, glioblastoma multiforme.

Table 5 PC-based strategies for targeted bone marrow delivery of NANDs.

Utilized strategy	Protein	Protein receptor	Target cell	Ref.
Prototype apolipoprotein NPs	APOA1	SRB1	Myeloid cells and their progenitors	122
LNPs incorporated with the SORT molecule covalent-bond-forming lipid species	APOE	–	Haematopoietic stem cells	185

NP, nanoparticle; LNP, lipid nanoparticle; APO A-I, apolipoprotein A-I; SRB1, class B type I scavenger receptor; APOE, apolipoprotein E; SORT, selective organ targeting.

Table 6 PC-based strategies for targeted tumor delivery of NANDs.

Utilized strategy	Protein	Protein receptor	Target cell	Ref.
LNPs with 1,2-dioleoyl-3-trimethylammonium-propane as the main cationic lipid	VTN	$\alpha_v\beta_3$ integrin	Endothelium, HepG2, and A375. S2 cell	130
Trimethyl chitosan−cysteine NPs with high thiolation	APOB48	APOB48 receptor	Macrophage	90

LNP, lipid nanoparticles; NP, nanoparticle; VTN, vitronectin; APOB48, apolipoprotein B48.

targeting by introducing or modulating specific components. This approach alters the adsorbed PC, enabling selective delivery from the liver to the lung or spleen and potentiating gene expression or editing in relevant target cells. Endogenous mRNA trafficking can also be tuned *via* modifying ionizable lipid chemistry to engage pathways independent of APOE, and the LDLR[159]. Branched hydrophobic tails exhibit enhanced spleen-targeting propensity, while polar headgroup modifications can markedly shift biodistribution from the lung to the spleen, a mechanism influenced by PC formation in extrahepatic tissues[170]. Similarly, Xue et al.[171] systematically demonstrated that combinatorial structural changes in siloxane-based ionizable lipids could precisely redirect mRNA-LNPs to liver, lung, or spleen through minor alterations in siloxane core architecture (Si_2−Si_{12}) and tail linkages (epoxide/ester *versus* amide). Notably, lung-targeted Si_5-N14 LNPs selectively enriched VTN through their cyclic siloxane-amine headgroups, which facilitated $\alpha_v\beta_3$ integrin-mediated pulmonary endothelial targeting.

A novel strategy has recently been developed by integrating a fifth component, termed a selective organ targeting (SORT) molecule, into conventional LNP formulations[131]. Upon administration, SORT molecules are exposed following the desorption of PEG lipids from the LNP surface. This allows specific recognition and adsorption of serum proteins onto the LNP. The adsorbed proteins subsequently interact with cognate receptors expressed on target organ cells, thereby facilitating mRNA delivery to specific tissues. Therefore, SORT molecules effectively dictate the bio destination of mRNA. For instance, the anionic SORT molecule 18 PA promoted B2GP1 adsorption, directing LNPs to splenic macrophages, whereas the cationic SORT molecule DOTAP enhanced VTN adsorption, mediating uptake by pulmonary endothelial cells[131]. To address potential biocompatibility and toxicity concerns associated with SORT technology, Liu et al.[172] introduced ionizable cholesterol analogs as a fifth component. Simply modulating their proportion enabled organ-selective mRNA delivery: lower ratios yielded medium-sized PCs for spleen targeting, while higher ratios formed large-sized PCs for lung targeting. Beyond electrostatic tuning, the recently developed peptide-encoded organ-selective targeting (POST) plaTForm achieves precise extrahepatic delivery by modularly tuning peptide codes on the LNP surface. This strategy exploits amino-acid-sequence-dependent PC affinities rather than simple charge effects, enabling precise mRNA delivery to multiple extrahepatic organs such as the placenta, bone marrow, adipose tissue, and testis. The POST approach substantially expands both the design flexibility and the range of tissues accessible for mRNA therapeutics[186].

Surface chemistry-driven PC recruitment represents a broadly applicable yet highly context-dependent strategy for directing nanocarriers to diverse organs, including the liver, lungs, spleen, and beyond. Its generality stems from leveraging endogenous protein adsorption, allowing a scalable and formulation-tunable route to control organ tropism. However, current advances rely predominantly on empirical screening, and a quantitative understanding of how specific chemical features dictate PC composition and downstream biological fate remains limited. Consequently, subtle physicochemical modifications can produce divergent corona profiles across species, disease states, or dosing conditions, undermining predictability. Furthermore, intentional enrichment of opsonins or apolipoproteins often improves targeting at the expense of accelerated clearance or unintended immune engagement. Together, despite striking preclinical demonstrations of organ redirection, the field faces two major barriers to rational design and robust clinical translation: a persistent reliance on trial-and-error optimization and an incomplete mechanistic map linking surface chemistry to PC formation and receptor engagement. Encouragingly, the convergence of multi-omics profiling, high-throughput screening, and data-driven frameworks integrating machine learning and molecular modeling is beginning to transform PC modulation from empirical optimization toward predictive, mechanism-informed design[187].

5.2. *Surface ligand modification for active PC engineering*

Beyond passively biasing protein adsorption through surface chemistry, an increasingly sophisticated strategy involves actively engineering the PC *via* surface ligand modification. Here, exogenous ligands are deliberately introduced not primarily to engage cellular receptors directly, but to deliberately program the composition and function of the subsequently formed protein corona. In this paradigm, surface ligands act as molecular recruiters or regulators of endogenous proteins, effectively transforming the PC into a secondary, biologically evolved targeting interface. A prominent example is the modification of the "don't eat me" signal CD47 on LNPs. Papp et al.[169] demonstrated that antibody-targeted LNPs engineered with CD47 underwent substantial corona remodeling: APOE content was reduced, while levels of hepatic-uptake inhibitors such as apolipoproteins C3 and C4 and albumin were elevated. This reconstituted corona enhanced blood retention, reduced liver accumulation, and improved mRNA delivery efficiency to target cells, including pulmonary endothelial cells and splenic T cells. This case illustrates how a strategically chosen surface ligand can actively orchestrate complex shifts in corona composition, overriding default tropisms to achieve precise, cell-specific targeting.

The principle of ligand-driven corona engineering also extends to chemically defined motifs that hijack endogenous transport systems. For instance, Kim et al.[161] engineered a DNA tetrahedron conjugated with trivalent cholesterol, which leveraged an *in situ*-formed lipoprotein-associated PC to enable liver delivery of a transforming growth factor beta targeting ASO, reducing liver fibrosis in a murine model. Hepatic stellate cells store the majority of the body's vitamin A and overexpress retinol-binding protein receptors, which mediate uptake of circulating retinol-binding protein (RBP)/VA complexes. Based on this biology, Huang et al.[188] developed VA-modified nanopolyplexes that hijacked endogenous RBP, enabling selective platelet-derived growth factor receptor beta siRNA delivery to HSCs and effectively alleviating liver fibrosis. These strategies illustrate a shift from merely minimizing non-specific adsorption toward the intelligent acquisition of a targeting-competent biological identity.

Active PC engineering *via* surface ligands represents an emerging evolution from passive modulation to intentional biological reprogramming. Yet this strategy introduces new tensions: ligand density, orientation, and stability critically shape corona remodeling while raising concerns regarding immunogenicity, manufacturing complexity, and batch-to-batch reproducibility. Importantly, whether ligand-driven PCs remain stable under dynamic *in vivo* exchange remains debated, highlighting a key gap between elegant design and physiological robustness.

5.3. *Pre-coating PC in vitro for controlled in vivo identity*

In vitro pre-coating of NPs with defined PC components has emerged as an effective strategy to impose a controlled *in vivo*

biological identity, thereby enhancing targeted delivery of NANDs.

As early as 2014, APOE-modified LNPs were applied as delivery vehicles for DNA and nucleic acids to the brain[183]. Zhang et al.[140] further developed an APOE-modified temozolomide nanocapsule (APOE-MT/siPKM2 NC) that leverages APOE to achieve both BBB penetration and GBM targeting. Inspired by the natural affinity of APOA1 for myeloid cell surface receptors, Hofstraat et al.[122] developed APO NPs (aNPs) that use endogenous trafficking pathways to deliver siRNA, ASO, and mRNA to myeloid cells and their progenitors in the BM (Table 5,[122,185]). By fine-tuning aNP properties, tunable biodistribution and efficient RNA delivery across diverse immune-cell subsets can be achieved.

Despite their targeting benefits, pre-defined protein coronas may adversely affect intracellular trafficking by limiting endosomal escape and nucleic acid release. Thus, *in vitro* PC design must address not only receptor engagement but also post-internalization barriers. Dual-protein camouflage using HSA and APOA1 exemplifies this principle, as it redirects cellular uptake toward caveolae-mediated pathways, reduces lysosomal degradation, and enhances cytoplasmic siRNA availability under serum-containing conditions[189]. These findings highlight the necessity of integrating extracellular targeting with intracellular fate in PC engineering to maximize the therapeutic efficacy of NANDs.

In vitro PC pre-coating offers the highest control over the initial biological identity of NPs, minimizing the variability associated with *in situ* corona formation. This approach is particularly attractive for hard-to-target tissues such as the brain and bone marrow. Nonetheless, its limitations are equally evident: pre-defined coronas may be rapidly remodeled *in vivo* or inadvertently impair endosomal escape and intracellular trafficking[142]. Thus, while pre-coating reduces uncertainty at the systemic level, it shifts the translational bottleneck toward maintaining functional stability and balancing extracellular targeting with intracellular efficacy, underscoring the need for integrated, multi-stage PC design principles.

6. Conclusions and perspectives

The inevitable formation of a PC fundamentally dictates the *in vivo* fate and therapeutic efficacy of NANDs, often obscuring engineered targeting ligands and diverting biodistribution. Rather than merely presenting a barrier, however, the PC offers a rich source of endogenous targeting signals that can be actively harnessed. This review has detailed how the physicochemical properties of nanocarriers and the environmental factors dynamically shape the PC, which subsequently governs key delivery processes, from mucosal penetration and circulatory stability to cellular tropism and intracellular trafficking. Critically, emerging design strategies now enable rational modulation of PC composition to steer NANDs to specific tissues and cells. Future advancements will rely on elucidating PC formation using high-resolution spatiotemporal techniques, developing predictive multi-scale models, and expanding an organ-specific PC atlas. Together, these advances will support the design of next-generation NANDs with more predictable *in vivo* performance.

In addition to these conceptual and technological advances, the clinical translation of actively tunable PC systems is inevitably constrained by regulatory and practical considerations. From a regulatory perspective, the dynamic and adaptive nature of corona engineering poses challenges in standardization, reproducibility, and quality control, as subtle variations in material composition, surface chemistry, or manufacturing processes may lead to divergent *in vivo* corona profiles and biological outcomes. Such complexity complicates batch-to-batch consistency and hinders the establishment of clear structure−function relationships required for regulatory approval. Moreover, key translational hurdles include scalable manufacturing, long-term physicochemical stability, and the lack of predictive *in vitro* models that faithfully recapitulate patient-specific proteomic environments. Therefore, the future development of actively tunable NANDs must integrate regulatory thinking at early stages. Emphasis should be placed on robust, simplified principles, standardized corona characterization frameworks, and clinically relevant validation models. By bridging mechanistic insight with practical application, such an integrated approach will accelerate the translation of PC-engineered nanomedicines into real-world therapies.

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Author contributions

Wenyan Yu, Yang Zhou, Jinjin Shi, Xiaoqing Yu and Ming Li designed and wrote the manuscript. Xiaoqing Yu and Ming Li investigated references. All the authors have revised the manuscript and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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