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(REVIEW ARTICLE)

THE PROTEIN CORONA AT THE NANO-BIO INTERFACE: MECHANISMS, BIOLOGICAL CONSEQUENCES, AND TRANSLATIONAL HURDLES IN NANOMEDICINE

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ABSTRACT

When nanoparticles enter biological fluids, they are immediately enveloped by a dynamic layer of proteins and other biomolecules, forming what is known as the protein corona. This corona fundamentally alters the nanoparticle's physicochemical properties, confers a new biological identity, and critically determines its in vivo fate—from cellular uptake and biodistribution to immune recognition and clearance. Despite two decades of intensive research, the protein corona remains a formidable barrier to the clinical translation of nanomedicines. This review provides a comprehensive overview of the fundamental mechanisms governing protein corona formation, including the Vroman effect, the distinction between hard and soft corona, and the influence of nanoparticle physicochemical properties such as size, charge, surface chemistry, and hydrophobicity. We critically examine how the corona modulates cellular interactions, endocytic pathways, immune responses, and targeting efficiency. The translational barriers posed by the corona—including loss of targeting functionality, batch-to-batch variability, and patient-specific corona compositions—are discussed in depth. Emerging strategies to overcome these barriers, including rational surface engineering, biomimetic coatings, and pre-coating approaches, are evaluated. We further highlight the potential of artificial intelligence and machine learning to predict corona composition and biological outcomes. Finally, we outline future directions, including the need for standardized methodologies, the exploration of the personalized protein corona, and the integration of multi-omics approaches to accelerate the safe and effective translation of nanoparticle-based therapeutics.

Keywords: Protein corona, Nano-bio interface, Nanomedicine, Translational barriers, Oopsonization, Surface engineering, Personalized nanomedicine

1 INTRODUCTION

The advent of nanotechnology has ushered in unprecedented opportunities for the diagnosis, treatment, and monitoring of human diseases. Nanoparticles—materials with at least one dimension in the 1–100 nm range—possess unique physicochemical properties that enable the design of sophisticated drug delivery systems, imaging agents, and

theranostic platforms. Their high surface-area-to-volume ratio, tunable surface chemistry, and ability to encapsulate both hydrophilic and hydrophobic therapeutics have made them particularly attractive for biomedical applications.

However, the journey from benchtop to bedside for nanomedicines has been fraught with challenges. A critical, often underappreciated, obstacle arises the moment a nanoparticle encounters a biological fluid. Upon systemic administration, nanoparticles are immediately exposed to a complex milieu of proteins, lipids, metabolites, and other biomolecules. Within seconds to minutes, a dynamic layer of proteins adsorbs onto the nanoparticle surface, forming what is known as the protein corona. As described by Cedervall et al. (2007), this corona is not a static entity but a constantly evolving structure whose composition changes over time as proteins with higher affinity displace those with lower affinity—a phenomenon governed by the Vroman effect.

The protein corona has profound implications for nanomedicine. It masks the intended surface functionalities of nanoparticles, alters their hydrodynamic size and surface charge, and determines how they are recognized by cells and the immune system. In many cases, the corona—rather than the nanoparticle itself—dictates the biological fate of the nanocarrier, including its circulation time, biodistribution, cellular uptake, and clearance. This has led Monopoli et al. (2012) to recognize that the protein corona provides the "biological identity" of nanoparticles, often superseding the synthetic identity engineered by researchers.

The significance of the protein corona extends beyond fundamental nanoscience. It represents one of the most formidable barriers to the clinical translation of nanomedicines. Corona formation can abrogate active targeting strategies, trigger unintended immune responses, cause premature drug release, and introduce variability that undermines the reproducibility and predictivity of preclinical studies. Moreover, as highlighted by Hadjidemetriou and Kostarelos (2017), the composition of the corona is influenced by patient-specific factors such as age, sex, disease state, and genetic background, raising concerns about the generalizability of nanomedicine efficacy across diverse patient populations.

This review aims to provide a comprehensive and critical overview of the protein corona at the nano-bio interface. We begin by examining the fundamental mechanisms of corona formation, including the thermodynamic and kinetic principles that govern protein adsorption. We then discuss how nanoparticle physicochemical properties and biological environment factors shape corona composition. The biological consequences of corona formation—particularly its effects on cellular uptake, immune recognition, and targeting—are critically evaluated. We next address the translational barriers posed by the protein corona and review emerging strategies to overcome them. Finally, we offer future perspectives on how advances in artificial intelligence, standardized methodologies, and personalized medicine approaches may help unlock the full potential of nanomedicine.

2 FUNDAMENTAL MECHANISMS OF PROTEIN CORONA FORMATION

2.1 The Vroman Effect and Corona Dynamics

The formation of the protein corona is governed by principles first described for protein adsorption on macroscopic surfaces, collectively known as the Vroman effect. As initially characterized by early surface science studies, in a mixture of proteins, those with the highest concentration and fastest diffusion rates adsorb first to the nanoparticle surface. However, these initially adsorbed proteins are gradually displaced by proteins with higher affinity for the surface, even if they are present at lower concentrations. Tenzer et al. (2013) demonstrated that this exchange process continues until a quasi-equilibrium state is reached, typically within minutes to hours. The time-dependent nature of corona formation has significant implications for nanomedicine, as nanoparticles circulating through the body encounter different biological compartments—blood, interstitial fluid, and cellular environments—each with distinct protein compositions.

2.2 Hard Corona versus Soft Corona

The protein corona is conventionally divided into two layers based on the strength and exchangeability of protein binding. The hard corona consists of proteins that bind directly to the nanoparticle surface with high affinity (dissociation constants typically in the nanomolar to micromolar range). These proteins are irreversibly adsorbed and remain associated with the nanoparticle even after extensive washing. The hard corona forms rapidly and its composition is largely determined by the physicochemical properties of the nanoparticle surface. The soft corona, in contrast, comprises proteins that associate with the nanoparticle through weaker interactions—either by binding to the hard corona proteins or through transient interactions with the nanoparticle surface. Walkey and Chan (2012) emphasized that these proteins are exchangeable and their composition is more sensitive to the surrounding biological environment. The distinction between hard and soft corona is operational rather than absolute, as there is continuous exchange between the two layers.

2.3 Thermodynamic and Kinetic Considerations

Understanding protein corona formation requires consideration of both thermodynamic and kinetic factors. Thermodynamically, protein adsorption is driven by a combination of hydrophobic interactions, electrostatic forces, hydrogen bonding, and van der Waals interactions. The overall free energy change determines the equilibrium binding affinity. Kinetic factors are equally important, particularly given the non-equilibrium nature of biological systems. As noted by Lima and Sousa (2023), the rate of protein adsorption depends on protein concentration, diffusion coefficient, and the frequency of protein-nanoparticle collisions. The dissociation rate determines how long proteins remain bound. Importantly, the in vivo environment is an open system with constantly changing protein concentrations, meaning that equilibrium descriptions of corona composition are insufficient to predict nanoparticle behavior.

3 FACTORS INFLUENCING PROTEIN CORONA COMPOSITION

3.1 Nanoparticle Physicochemical Properties

The composition of the protein corona is profoundly influenced by the intrinsic properties of the nanoparticle.

Size affects the surface curvature and the available binding area. Bilardo et al. (2022) reported that smaller nanoparticles (under 50 nm) exhibit higher curvature, which may restrict the binding of larger proteins due to steric constraints, whereas larger nanoparticles provide flatter surfaces that accommodate a wider range of proteins.

Surface charge is a major determinant of corona composition. Positively charged nanoparticles tend to adsorb negatively charged proteins such as albumin, while negatively charged nanoparticles preferentially bind positively charged proteins such as apolipoproteins. Charge also influences the kinetics of adsorption, with charged surfaces generally promoting faster protein binding.

Surface chemistry and hydrophobicity play equally critical roles. Hydrophobic surfaces tend to adsorb proteins through hydrophobic interactions, often leading to protein denaturation and exposure of cryptic epitopes. Hydrophilic surfaces, in contrast, typically adsorb proteins through hydrogen bonding and electrostatic interactions, resulting in less conformational change. Ke et al. (2017) emphasized that surface functional groups—such as carboxyl, amine, or thiol moieties—also influence the specific proteins recruited to the corona.

Shape has emerged as an additional factor influencing corona formation, though it remains less studied than size and surface chemistry. Rod-shaped and star-shaped nanoparticles exhibit different protein adsorption patterns compared to spherical particles of equivalent composition, likely due to differences in surface curvature and hydrodynamic behavior.

3.2 Biological Environment Factors

The composition of the biological fluid in which nanoparticles are introduced dramatically affects corona formation. Plasma, serum, interstitial fluid, and cerebrospinal fluid each have unique protein profiles that yield distinct coronas. Protein concentration and the relative abundance of different proteins are primary determinants of corona composition. High-abundance proteins such as albumin and immunoglobulins often dominate the corona, even if they have relatively low affinity for the nanoparticle surface.

Disease states significantly alter the protein corona through changes in the systemic proteome. Inflammatory conditions, cancer, and metabolic disorders all produce characteristic alterations in plasma protein composition that are reflected in the corona. This has given rise to the concept of the "personalized protein corona" as discussed by Mahmoudi (2018), wherein the same nanoparticle acquires different coronas when incubated with plasma from different patients. Patient-specific variables including age, sex, genetic ancestry, and environmental factors further modulate corona composition.

Table 1: Key Factors Influencing Protein Corona Composition and Their Biological Consequences

Factor	Influence on Corona Composition	Biological Consequence
Nanoparticle Size	Smaller NPs (<50 nm) restrict large protein binding; larger NPs accommodate diverse proteins	Altered cellular uptake pathways; size-dependent biodistribution
Surface Charge	Positive charge attracts negatively charged proteins (e.g., albumin); negative charge attracts positively charged proteins (e.g., apolipoproteins)	Charge-dependent opsonization and immune recognition
Surface Hydrophobicity	Hydrophobic surfaces promote strong protein adsorption and denaturation	Increased immune recognition; potential immunogenicity
Surface Chemistry	Functional groups (carboxyl, amine, thiol) selectively recruit specific protein classes	Modulated cell interactions and targeting efficiency
Biological Fluid Source	Plasma vs. serum vs. interstitial fluid yield distinct coronas	Poor correlation between in vitro and in vivo performance
Disease State	Inflammatory and malignant conditions alter systemic proteome	Personalized corona; variable efficacy across patient populations
Protein Concentration	High-abundance proteins dominate corona initially; lower-abundance high-affinity proteins displace them over time	Time-dependent biological identity; Vroman effect dynamics
Nanoparticle Shape	Rods, stars, and spheres exhibit different protein adsorption patterns	Shape-dependent cellular uptake and circulation time

3.3 Biological Consequences of Protein Corona Formation

3.3.1 Cellular Uptake and Intracellular Trafficking

The protein corona fundamentally alters how nanoparticles interact with cells. While naked nanoparticles may be taken up through specific receptor-mediated pathways, corona-coated nanoparticles engage cells through interactions between corona proteins and cell surface receptors. The corona can shift the mechanism of cellular uptake from one endocytic pathway to another. Salvati et al. (2013) showed that corona formation on liposomes changed internalization from clathrin-dependent endocytosis to caveolae-mediated endocytosis, with consequent effects on intracellular trafficking and drug release. The specific proteins in the corona—particularly opsonins such as immunoglobulins and complement components—can trigger phagocytic uptake by macrophages and other professional phagocytes. The corona also influences the intracellular fate of nanoparticles, affecting endosomal escape, lysosomal degradation, and the eventual release of therapeutic payloads.

3.3.2 Immune Recognition and Clearance

Perhaps the most clinically significant consequence of protein corona formation is its role in immune recognition. The corona determines whether a nanoparticle is recognized as "self" or "non-self" by the immune system. Opsonins—proteins that promote phagocytosis—include immunoglobulins (IgG), complement components (C3b, C4b), and certain acute-phase proteins. When the corona is rich in opsonins, nanoparticles are rapidly cleared by macrophages of the mononuclear phagocyte system, particularly in the liver and spleen. Conversely, dysopsonins—proteins that reduce phagocytic uptake—include albumin, apolipoprotein A-I, and clusterin. A corona enriched in dysopsonins can prolong nanoparticle circulation time by conferring a "stealth" property. The corona also affects complement activation, which can trigger inflammatory responses and anaphylactic reactions, as noted by Tenzer et al. (2013), who found that protein denaturation within the corona can expose cryptic epitopes not normally accessible to the immune system.

3.3.3 Impact on Targeting and Drug Delivery

Active targeting—the decoration of nanoparticles with ligands that bind to receptors overexpressed on target cells—is a cornerstone of modern nanomedicine. However, the protein corona poses a serious challenge to this approach. The corona can mask targeting ligands, preventing them from engaging their intended receptors. Even when ligands remain accessible, the corona may create steric hindrance that reduces binding affinity. In some cases, the corona can redirect nanoparticles to unintended cell types through the interactions of corona proteins with off-target receptors. The corona also affects drug release kinetics, as proteins can form a barrier that slows drug diffusion or interact with the drug itself, altering its release profile.

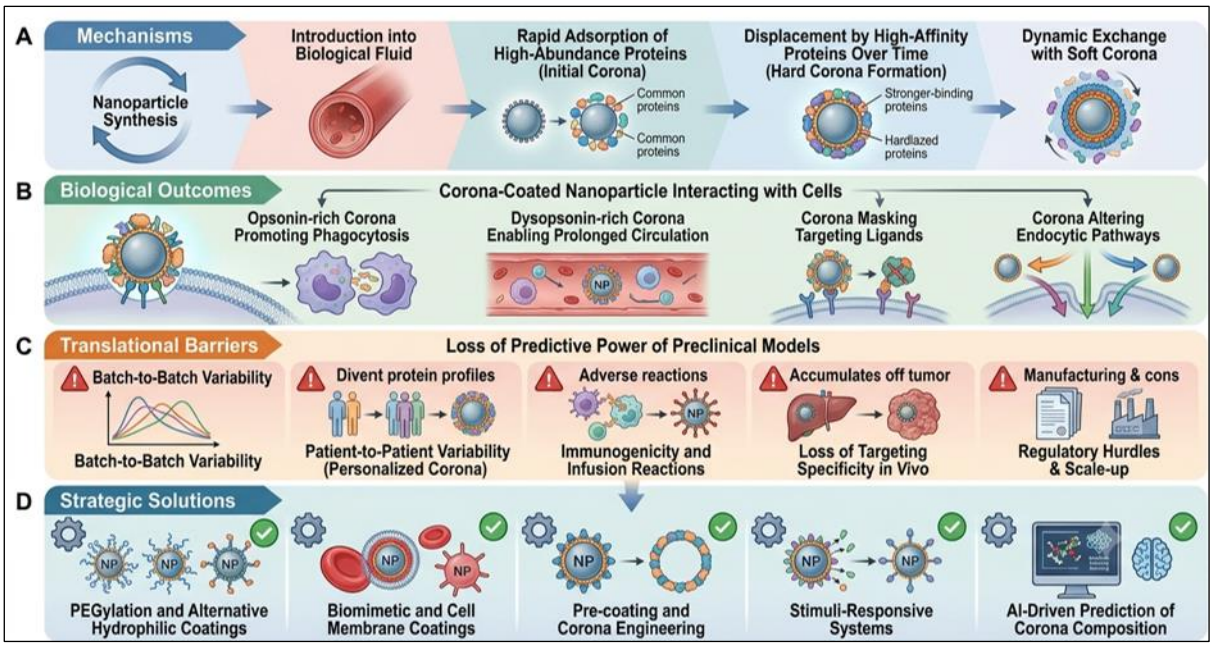

Figure 1: Schematic Representation of Protein Corona Formation, Biological Consequences, and Translational Barriers

3.4 Translational Barriers Posed by the Protein Corona

Despite decades of research and substantial investment, the clinical translation of nanomedicines has been slower than anticipated. The protein corona is a significant contributor to this translational gap. Loss of predictive power of preclinical models is a major concern, as most preclinical studies use nanoparticles in idealized conditions with fetal bovine serum that does not replicate human plasma. Batch-to-batch variability in corona composition complicates the production of consistent nanomedicines. Even nanoparticles with identical physicochemical properties can acquire different coronas due to minor variations in biological fluids. Patient-to-patient variability is perhaps the most daunting challenge, as the personalized protein corona means the same nanomedicine may perform differently in different patients. Immunogenicity and hypersensitivity reactions have been observed with several nanomedicines, and the protein corona is increasingly implicated in these adverse events. Finally, loss of targeting specificity in vivo persists, with nanoparticles often losing their targeting ability upon systemic administration.

3.5 Strategies to Overcome Protein Corona Barriers

The most widely adopted strategy to minimize protein corona formation is PEGylation—the covalent attachment of polyethylene glycol (PEG) chains to the nanoparticle surface. PEG creates a hydrophilic, sterically hindered layer that reduces protein adsorption. However, as discussed by Walkey and Chan (2012), PEGylation has limitations, including immunogenicity and accelerated blood clearance upon repeated administration. Alternative hydrophilic polymers such as poly(2-oxazoline)s and zwitterionic polymers are being explored. An emerging paradigm is to engineer the protein corona rather than prevent it. Cell membrane coatings—where nanoparticles are enveloped in membranes derived from red blood cells or platelets—provide a "self" signature that reduces immune recognition. Pre-coating strategies (corona engineering) involve pre-forming a corona of known composition before administration, reducing the variability introduced by the host environment.

4 FUTURE PERSPECTIVES

Several emerging trends and unresolved questions promise to shape the future of protein corona research and its translation to clinical medicine.

Artificial intelligence and machine learning are poised to revolutionize the field. Predictive models that correlate nanoparticle physicochemical properties with corona composition and biological outcomes could dramatically accelerate the design of nanomedicines with predictable in vivo behavior. Machine learning approaches may also enable the identification of corona signatures that predict therapeutic efficacy or toxicity.

Standardization of methodologies is urgently needed. The lack of standardized protocols for corona preparation, characterization, and data reporting hampers reproducibility and cross-study comparisons. Consensus guidelines—similar to those developed for other areas of nanomedicine—would accelerate progress.

The personalized protein corona represents both a challenge and an opportunity. While patient-to-patient variability complicates drug development, it also offers the potential for personalized nanomedicine. Corona profiling could serve as a diagnostic tool to predict which patients are most likely to benefit from a given nanotherapy. Conversely, nanomedicines could be designed to exploit the unique corona composition of specific patient populations.

Integration of multi-omics approaches—combining proteomics, lipidomics, and metabolomics—will provide a more complete picture of the biomolecular corona. Zhang et al. (2022) highlighted that top-down proteomics offers the ability to identify proteoforms in the corona, providing deeper mechanistic insights.

In vivo corona characterization remains a major technical challenge. Most studies characterize the corona after isolating nanoparticles from biological fluids, a process that may alter corona composition. Advances in in situ characterization techniques will be essential to understand corona dynamics in real time. The role of non-protein corona components—including lipids, metabolites, and nucleic acids—is increasingly recognized. Lima et al. (2020) demonstrated that the "lipid corona" may be as important as the protein corona in determining nanoparticle fate. Regulatory considerations will need to evolve, with agencies potentially requiring characterization of corona composition as part of product release specifications for nanomedicines.

5 CONCLUSION

The protein corona is an inevitable consequence of nanoparticle exposure to biological fluids, and it fundamentally determines the biological fate of nanomedicines. This review has demonstrated that corona formation is governed by complex interplay between nanoparticle physicochemical properties and the composition of the surrounding biological environment. The corona confers a new biological identity upon nanoparticles, profoundly influencing cellular uptake, immune recognition, targeting efficiency, and ultimately therapeutic efficacy.

Despite significant advances in understanding the mechanisms of corona formation and its biological consequences, the protein corona remains a major barrier to the clinical translation of nanomedicines. Loss of predictive power from preclinical models, batch-to-batch and patient-to-patient variability, immunogenicity concerns, and loss of targeting specificity in vivo all stem, at least in part, from the protein corona.

Emerging strategies to overcome these barriers—including advanced surface engineering, biomimetic coatings, pre-coating approaches, and AI-driven prediction—offer hope for the next generation of nanomedicines. However, realizing this potential will require continued investment in fundamental research, standardization of methodologies, and a shift toward more physiologically relevant models that capture the complexity of the in vivo environment. The protein corona, once viewed solely as an obstacle, is increasingly recognized as a tunable interface that can be harnessed for therapeutic benefit. By understanding and ultimately controlling the corona, we may transform it from a translational barrier into a tool for precision nanomedicine.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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