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REVIEW

Protein–Nanoparticle Interaction: Corona Formation and Conformational Changes in Proteins on Nanoparticles

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Abstract: Nanoparticles (NPs) are highly potent tools for the diagnosis of diseases and specific delivery of therapeutic agents. Their development and application are scientifically and industrially important. The engineering of NPs and the modulation of their in vivo behavior have been extensively studied, and significant achievements have been made in the past decades. However, in vivo applications of NPs are often limited by several difficulties, including inflammatory responses and cellular toxicity, unexpected distribution and clearance from the body, and insufficient delivery to a specific target. These unfavorable phenomena may largely be related to the in vivo protein–NP interaction, termed "protein corona." The layer of adsorbed proteins on the surface of NPs affects the biological behavior of NPs and changes their functionality, occasionally resulting in loss-of-function or gain-of-function. The formation of a protein corona is an intricate process involving complex kinetics and dynamics between the two interacting entities. Structural changes in corona proteins have been reported in many cases after their adsorption on the surfaces of NPs that strongly influence the functions of NPs. Thus, understanding of the conformational changes and unfolding process of proteins is very important to accelerate the biomedical applications of NPs. Here, we describe several protein corona characteristics and specifically focus on the conformational fluctuations in corona proteins induced by NPs.

Keywords: nanoparticle, protein corona, structure, surface characteristic, conformational change

Introduction

Understanding the interaction between nanoparticles (NPs) and proteins is imperative to the application of NPs as nanomedicines or nanocarriers and to control NP-associated environmental biohazards.[1–3] Various types of NPs are currently being used in clinical research.[4] Aside from metal and inorganic NPs, different organic NPs have been successfully used in the medical field. The largest economic value-added sectors are magnetic resonance imaging (MRI) and drug delivery, and several NPs have received FDA approval or are currently in clinical trials.[5–7]

Drug delivery systems are generally designed to control the release and absorption of the carrier drug or to deliver it to a specific part of the body.[8,9] Drug delivery systems reduce the side effects of the drug while maximizing its efficacy by delivering effective amounts to the target site for a specific period of time. NPs have been actively studied as effective drug delivery systems.[8] They have a large surface area to volume ratio, allowing excellent drug adsorption and controlled drug

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release kinetics according to the adsorption method.[10] NPs have been developed as carriers for the delivery of various molecules such as growth factors, genes, antibacterial agents, anti-inflammatory agents, and antibodies.[2,11,12]

The use of nanomaterials and carbon nanotubes (CNTs) as drug carriers has increased greatly but their use faces some technical limitations. Nanomaterials may cause immune reactions in vivo and side-effects such as inflammation.[13,14] Toxicity is reported after their in vivo administration and long-term retention.[15] Further, problems such as biological signal disturbances caused by their unexpected interactions and binding with various biomolecules such as proteins in vivo have been reported. Therefore, to use these particles as general-purpose drug carriers, the biophysical and biochemical characteristics of the starting material must be investigated.[16]

In addition to their use as small drug carriers, NPs have recently been used as immunomodulators, enzyme inhibitors, and transporters of therapeutic proteins. These new applications are associated with the protein–nanoparticle interaction, a phenomenon termed as "protein corona." The layer of proteins adsorbed on NPs functions as a biological module in vivo and is difficult to understand at the level of a single protein. The process underlying corona formation is complicated and involves complex kinetics and dynamics. Thus, the in vivo behavior of NPs relies on protein corona formation, which defines the biological activity or toxicity of NPs. Protein corona formation is highly diverse depending on the sources and/or production methods of NP systems, including metals, metal oxides, polymers, composites, and CNTs. For example, gold nanoparticles affected albumin in the circulating system,[17] while those produced by enzymatic method showed binding to cellular RNAs and proteins.[18] Casein-coated gold NP can translocate across the blood-brain barrier (BBB), resulting in corona formation with Abeta42.[19] Magnesium oxide (MgO) NPs spontaneously form an albumin complex upon introduction,[20] while MgO NPs produced through green synthesis can also interact with cellular proteins such as superoxide dismutase 1 (Sod1) and p53 after internalization into cells.[21]

Regarding protein corona formation, the structural changes in proteins on NPs should be noted and studied to enhance the in vivo availability of NPs. The correct structure of the protein is necessary for its proper function. Various biological systems, including chaperons, proteasome, autophagy, and ER-associated degradation monitor the quality of the protein structure and tightly regulate the fate of proteins in cells depending on their conformational state.[22] Uncontrolled disruption of the folding pathway can lead to disease onset. For example, the unfolding or misfolding of proteins is directly related to amyloid-associated diseases, such as Alzheimer's disease,[23–25] Parkinson's disease,[26,27] type 2 diabetes,[28] and familial amyloidosis.[29,30] The immunoglobulin light-chain in the blood stream occasionally forms aggregates, accumulates at various sites, and causes a significant problem in the body, which may be due to protein unfolding.[31] Thus, the unfolding or structural disruption of corona proteins by NPs could be linked to unexpected abnormalities in vivo. A recent study highlighted that quantum dots composed of CdSe/ZnS could disrupt the secondary structure of insulin and induce aggregation and fibrillation, depending on the specific size and surface charge of NPs.[32]

To overcome the potential problems of NP application, recent studies have focused on how the protein corona can be used to produce beneficial effects in vivo. Pre-incubation or artificial coating of NPs with a corona protein can enhance the NPs function.[33] The designed corona formation with NPs can be helpful for evading the host immunity.[34] To obtain successful results with these approaches, a better understanding of the structural changes in corona proteins on NPs may be helpful. In this regard, we initially described the general aspects of protein coronas, including physicochemical factors affecting corona formation, and explored the structural details of corona proteins in various NPs.

Factors Influencing Protein Binding and Corona Formation

The physical characteristics of NPs, such as their size and surface properties, serve as the basic determinants of their biochemical, physiological, and pharmacological applications. The details of the basic properties of NPs affecting corona formation have been well reviewed in other articles.[35] Thus we briefly summarized the influential parameters. Protein adsorption and binding are governed by several factors such as the size, shape, surface area, and surface charge of NPs. This binding is dependent on the source of nanomaterials such as metals,[36–38] organic polymers,[39,40] and CNTs.[41,42]

Surface Area

In general, NPs have a large surface area, which may be advantageous for their nonspecific interactions with serum proteins.[42, 43] Platelet aggregation was recently shown to

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be dependent on the surface area of NPs and not on NP size.[44] Further, the high ratio of the total available surface area of NPs and the protein concentration does not always result in high adsorption and binding of plasma proteins. For instance, silica NPs bound more plasma proteins than polystyrene NPs of the same size in the presence of low concentrations of plasma proteins, but their binding capacity was lower in the presence of high concentrations of plasma proteins. The polystyrene NPs showed the opposite behavior.[40] Moreover, the protein species bound to silica and polystyrene NPs were quite different,[40] indicating that not only the density but also the species of NP is important for selective protein binding. The solvent-accessible surface area of a protein is a counterpart determinant of selective corona formation. Plasma proteins such as bovine fibrinogen, gamma globulin, and serum albumin were found to be adsorbed onto CNTs through the π-π stacking of the exposed aromatic residues (Trp, Phe, Tyr) of proteins.[45] The amount of protein adsorbed onto CNTs was proportional to the exposed surface area of the CNTs.[45]

Radius of Curvature

The radius of curvature of NPs is another factor that affects the binding and unfolding of proteins.[46] The curvature of NPs is directly related to their size and shape. A large radius of curvature results in a planar surface, and small-sized NPs possess a small radius of curvature. The planar surface may provide a wide contact area for protein binding, resulting in stronger interactions between proteins and NPs.[47,48] As many proteins are smaller than NPs such as CNTs, a bulk of proteins could be adsorbed and may accumulate on the surface of NPs. The effect of NP size on blood protein binding was well explained in a study using gold NPs;[49] the smaller the gold NP size, the lower the amount of human serum albumin (HSA) bound. Consistent with the size effect, the association constant of plasma proteins, as determined by a fluorescence quenching assay, was found to increase with an increase in the size of gold NPs.[49] However, high molecular weight proteins, such as immunoglobulin G (150 kDa), have molecular diameters (10–15 nm) comparable to NPs and may bind to small NPs at a 1-to-1 ratio. Figure 1 compares the sizes of several proteins to NPs.[50] The binding stoichiometry between proteins and NPs may affect the conformational state and the functionality of the bound protein. Boselli et al used 2–5 nm gold NPs and found that smaller NPs did not form a conventional "protein corona" and that the layers comprised plasma proteins bound around NPs.[51] Thus, the specific interaction between NPs and proteins may be regulated by controlling the size of NPs. In terms of the effect of NP size on protein binding, the influence of single-walled and multi-walled carbon nanotubes (SWCNTs and MWCNTs) on corona formation is interesting. Several reports have shown their toxicity to cells and different effects on protein structures. SWCNTs were more toxic to macrophages than MWCNTs.[52] Tau protein strongly bound to SWCNTs and underwent significant structural changes, while the interaction between the MWCNT and Tau protein was negligible.[53]

Shape

The effects of NP shape as well as size, curvature, and surface area on protein binding cannot be excluded.[54] The binding affinity of HSA to spherical-shaped gold NPs was three times higher than that of branched-shaped gold NPs of similar size (50–70 nm). Furthermore, the thickness of the protein corona adsorbed on gold NPs differed depending on their shape and was smaller for spherical-shaped gold NPs, as measured from the hydrodynamic radius of the NP and protein complex.[55] Small zinc oxide (ZnO) NPs showed different activity for β-galactosidase (GAL) depending on the shape of the NPs, such as pyramids, plates, and spheres. The strongest inhibition was observed with pyramid-shaped ZnO NPs.[56] These authors suggested that GAL has a long groove at the active site on the surface and that the pyramidal-shaped NPs could bind well to this region as compared to plates or spheres.

Biofluid

The main driving force for protein corona formation may be the noncovalent, nonspecific, and hydrophobic interactions between proteins and NPs. The hydrophobic aggregation of molecules is largely affected by the solution being examined. Biological systems, especially human body fluids, contain various electrolytes, small metabolites, peptide hormones, lipids, sugars, and nucleotides, all of which may significantly affect the hydrophobic strength of the interaction.[40] Thus, protein binding to NPs in biological fluids may be different from that in culture media or buffers.[57] Immune activation by the NP–immune protein complex in cellular systems does not always correlate with the immune activation reported under in vivo conditions.[58] Gold NPs incubated in Dulbecco's modified Eagle's medium showed greater adsorption of proteins than those incubated in Roswell Park Memorial Institute medium.[59]

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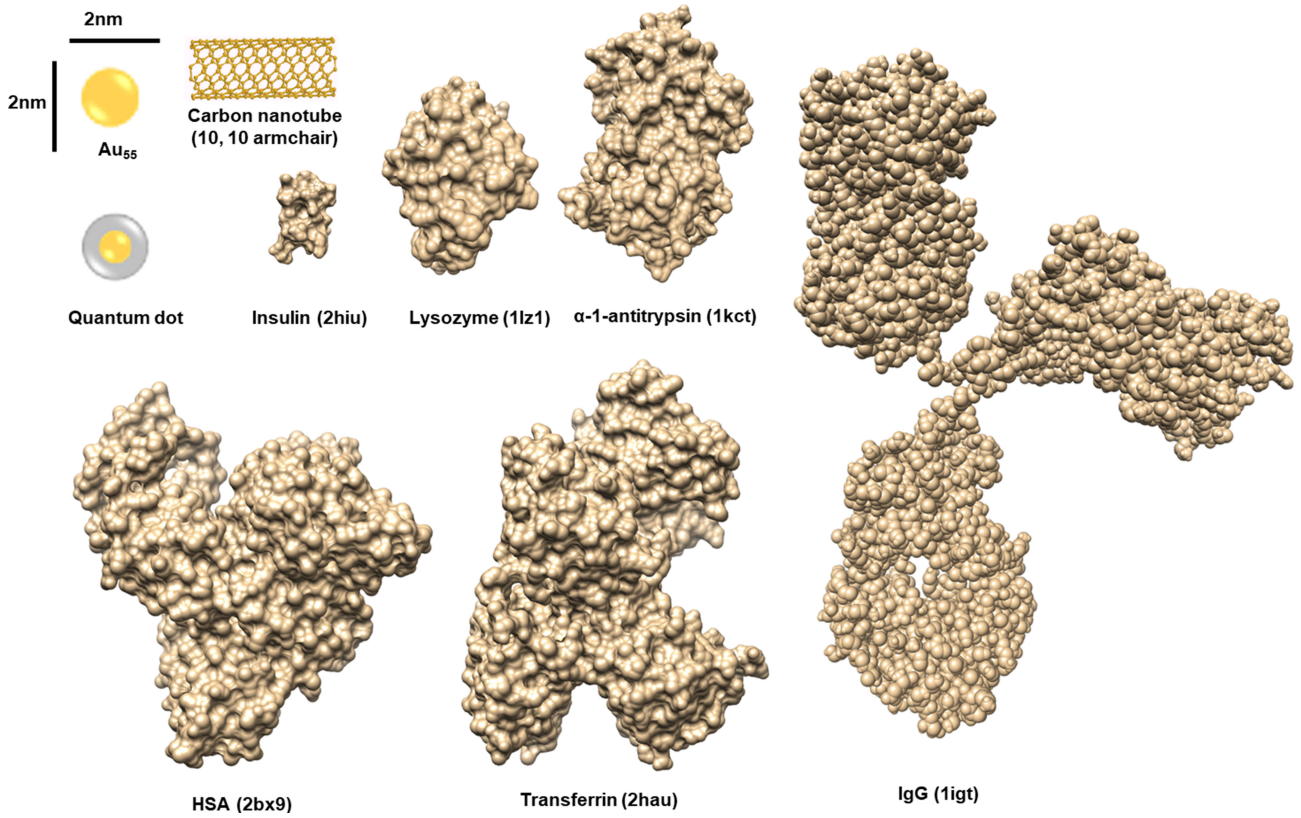

Figure 1 Size comparison between proteins and NPs.
Notes: The sizes of NPs are compared to those of various proteins. The codes in brackets are those from the PDB database. Adapted with permission from Kopp M, Kollenda S, Epple M. Nanoparticle-Protein Interactions: Therapeutic Approaches and Supramolecular Chemistry. *Acc Chem Res*. 2017; 50(6):1383–1390. Copyright (2019) American Chemical Society.[50]
Abbreviations: HSA, human serum albumin; IgG, immunoglobulin G.

Affinity and Exposure Time

Many in vitro studies on the interaction between proteins and NPs have mainly focused on specific protein binding; however, the behavior of NPs in biological systems should be understood with respect to protein corona formation. NPs can aggregate with other biomolecules such as organic compounds, carbohydrates, and lipids. However, the majority of bio-coronas are protein coronas,[60,61] which are dynamically formed in vivo and undergo changes in composition over time.[1,15,57] Time-dependent corona formation is defined by the Vroman effect,[62,63] which explains how fibrinogen at the surface of materials may be replaced by other high-affinity proteins. That is, abundant proteins are nonspecifically adsorbed on the surface of NPs immediately after their in vivo administration. Most of these proteins may have low affinity for NPs and may be released from the complex and replaced by those with higher affinity after a long exposure time.[64] This weakly bound layer is called a "soft" corona, while the strongly bound layer is called a "hard" corona.[64–66] The composition of soft and hard corona is affected by many factors, such as the surface characteristics, biological environment around NPs, times of exposure, and physiochemical properties of NPs.

Protein corona formation is highly related to the functionality and activity of NPs in either a positive or negative manner.[13] Which of the strongly or weakly bound proteins influences the biological functions of NPs is still unclear. Weber et al have suggested the role of hard corona proteins, such as immunoglobulin G and clusterin, in the internalization of NPs into cells.[67]

Synthetic Methods

Due to ethical and environmental reasons, various production methods of NPs, so called green synthesis, have been introduced in consideration of the environment and human health. In particular, there are many studies on the production of metal and metal oxide nanomaterials.[68,69] Interestingly, the different synthetic methods could result in different biocompatibility and toxicity of NPs as well as

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different binding property to cellular proteins. The green-synthesized MgO NPs showed different mortality, biocompatibility, and toxicity in zebrafish compared to the commercially synthesized MgO NPs: authors suggested that the different toxicity may be related to different protein binding property in the ROS cascade even though the size and charge characteristics of both NP systems were similar.[21] The green-synthesized gold NPs also showed reduced toxicity with reduced ROS, resulting in reduced apoptosis.[18]

Conformational Changes of Proteins in the Protein Corona

NPs have different chemical environments on their surfaces, which drive structural changes in the bound proteins. Physical properties such as size, shape, curvature, and surface area affect the structural characteristics of the bound proteins. The surface characteristics of proteins are important factors that induce structural changes upon binding. Structural changes in corona proteins are biologically meaningful, as the loss-of-function after structural changes may provoke the destruction of physiological homeostasis and unwanted immune responses.[70] In addition, bulk conformational changes may trigger protein aggregation and amyloid fiber formation.[71,72] Hydrogenated NPs promote β-sheet structures and aggregation through a reduction in zeta potential, which may enhance the collision between intact Aβ40 peptides.[73] Hen egg white lysozyme was unfolded by silica NPs, resulting in the formation of β-sheet-rich fiber-like protein aggregates.[74] Thus, the knowledge of the functionality of NPs demands an understanding of the conformational changes in the protein corona of each NP system (Figure 2).

Detection Methods

Tertiary structural changes in proteins are difficult to monitor owing to methodological limitations. The most frequently used method is circular dichroism (CD) spectroscopy, which highlights secondary structural changes as well as alterations in protein melting temperatures. For instance, the serum protein fibrinogen was studied by CD, and a reduction in the α-helical content and an increase in the β-strand content of fibrinogen were reported depending on the surface characteristics and density of nanotubes.[75] Immunoglobulin G was highly unfolded in MWCNTs, while polyethylene glycol (PEG)-modified nanotubes maintained its structure.[76] CD spectroscopy is widely used for corona protein studies, although it suffers from low sensitivity. The combined use of CD with a highly sensitive photothermal detection system was recently described as photothermal CD, which enhanced the sensitivity of CD spectroscopy.[77] Dynamic light scattering (DLS) may be used to observe alterations in particle size after protein binding. Through DLS, the thickness and aggregation of the corona on NPs can be probed. The hydrodynamic radii of bovine serum albumin (BSA) and lysozyme were measured with DLS, and the relationship between the aggregation of NPs and the radius was highlighted with anionic silica NPs.[78] Electron microscopy methods such as transmission electron microscopy (TEM) and atomic force microscopy (AFM) are useful for obtaining information on a single NP. The size and shape of a single NP with/without protein corona can be determined using these techniques. A study described tau protein aggregation on the surface of titanium NPs, and suggested that the early-stage tau aggregates were unordered and amorphous.[79] Nuclear magnetic resonance (NMR) is not commonly used in NP studies, as the molecular weight of NP systems is usually over the detection limitation of NMR. However, the TROSY technique[80] was successfully used to quantify GB3, a small immunoglobulin-binding domain from *Staphylococcus aureus* adsorbed onto various sizes of gold NPs, and to describe the molecular mechanism of the interaction between them.[81]

Cases

Many studies on the conformational changes in proteins caused by NPs have revealed that α-helices typically decrease in number and/or β-sheet formation typically increases.[47,82] However, the same protein may exhibit different changes upon binding to different NPs. Furthermore, the same NPs with different surface characteristics, such as charges or length of aliphatic branches may exert different effects on protein structures. Capomaccio et al revealed secondary structural changes in HSA following binding to gold NPs (~20 nm).[83] Native HSA is an α-helical protein and its helicity decreased following interaction with gold NPs with an increase in β-structure. The decrease in helicity was proportional to the increase in the concentration of gold NPs. The molecular dynamic simulation between HSA and gold NPs (large crystalline shape) showed that the domain III (lipid-binding site) of HSA mainly interacted with the NP surface through a loop carrying Lys_{464}, Thr_{504}, Phe_{505}, and Leu_{581}.[84] This study also highlighted the significant decrease in α-helicity from 68% to 45%. However, citrate-coated

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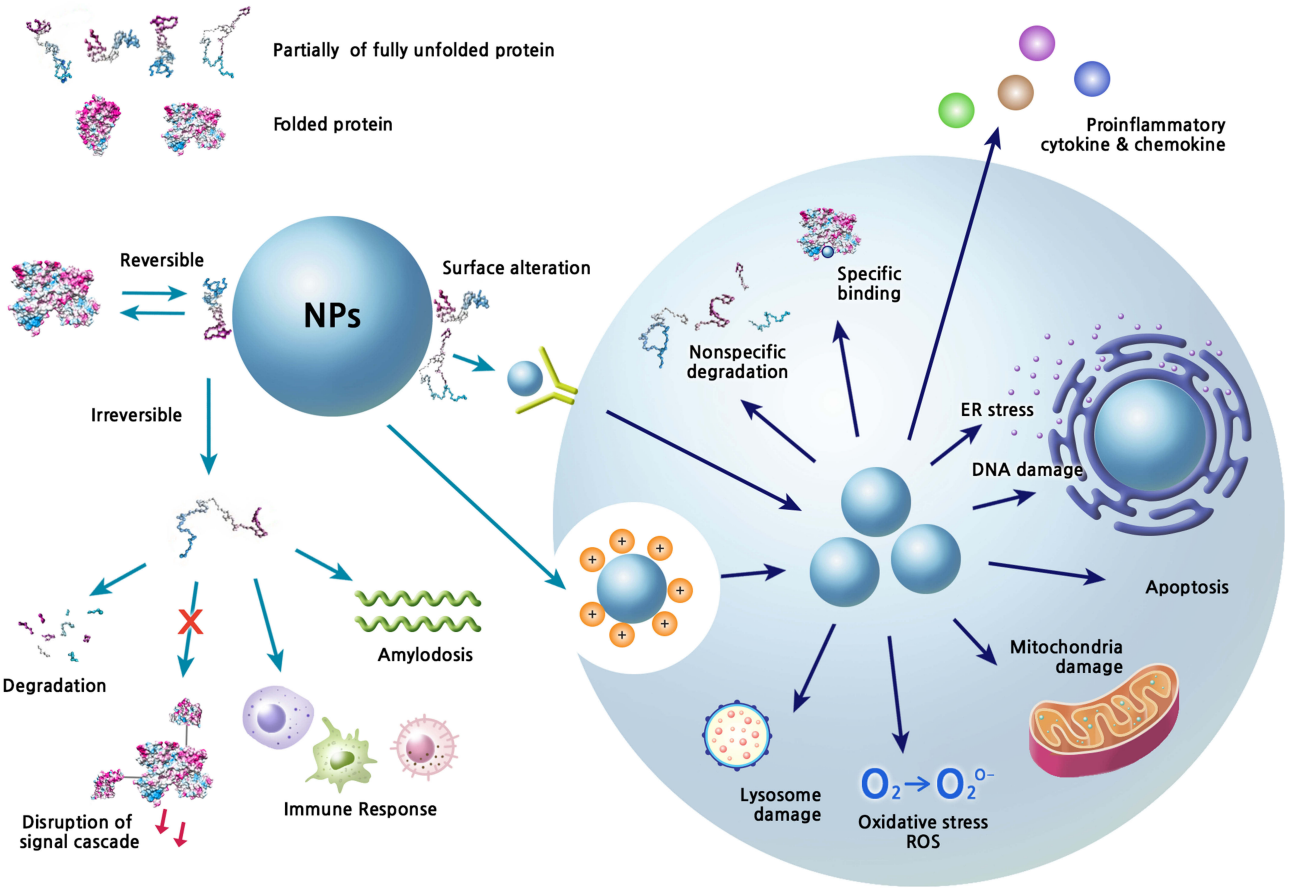

Figure 2 Extracellular and intracellular events caused by the structural changes of corona proteins.
Notes: The interaction of NPs with proteins can induce variety of signal modulations and toxic effects in biofluids and in cells. Various physicochemical properties of NP systems basically contribute to the corona formation and structural changes of proteins. The conformational change is a dynamic process and the composition of corona proteins on NPs can be changed according to the surrounding environment. The reversible or irreversible changes of protein structures can perturb the downstream signaling, which may consequently be harmful to the host. The characteristics of corona formation may be expected to be different between extracellular and intracellular spaces. The internalized NPs by various ways such as receptor mediated internalization and endocytosis by charge can produce many toxic situations directly through their own chemical characteristics and/or indirectly through corona formation.
Abbreviations: ER, endoplasmic reticulum; ROS, reactive oxygen species.

silver NPs failed to induce significant structural changes in HSA;[85] the smallest silver NPs (~16 nm) induced only a 4% reduction in α-helicity, while an increased size of ~40 nm resulted in less than 1% reduction in helicity.

Table 1 shows several proteins studied with NPs and their effects on protein structure upon NP binding. The heterogeneous changes in the protein corona can be identified.

Cellular Proteins

Besides the corona formation in the circulating system, the corona formation with cellular protein is also related to the toxic effects of NPs (Figure 2). The cellular responses by NPs appear as oxidative stress, inflammatory responses, DNA damage, apoptosis, ER stress, and etc., which were widely studied while the direct complexation of cellular proteins with NPs was less studied. The SWCNTs and MWCNTs bind to adhesive proteins such as extracellular fibronectin probably by the nonspecific manner, which subsequently results in integrin-mediated cell attachment.[86] Cai et al showed the over 750 proteins from human HeLa cell lysate could bind MWCNTs by quantitative proteomics:[87] among the potential corona proteins, secondary structural characteristics of 269 proteins were analyzed and the α-helical content of those proteins notably seems to be important for complexation with NPs (Figure 3). The skeletal proteins such as actin may be affected by SWCNTs through changing the filament assembly.[88] The in silico docking studies described the protein-metal NPs complexes such as the transcription factor Oct4-AgNPs,[89] the enzyme Sod1-AgNPs,[90] the apoptotic factor p53-AgNPs,[90] and the transmembrane lipoprotein VLDLR-titanium oxide NPs.[38] These studies showed specific binding of NPs to the pockets in the

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Table 1 Representative Conformational Changes in Proteins Following Complexation with NPs

NPs	Surface Functional Group	Interacting Protein	Conformational Changes	Detection Method	Ref
SW CNT	None	Protein-G	The α-helicity diminished through hydrogen bond breakage.	Molecular dynamics (MD)	128
	None	Carbonic anhydrase (CA)	The CA-NP complex exhibited increased total α-helix content and decreased β-sheet content.	Circular dichroism (CD)	129
	None	Lysozyme	The α-helix to β-sheet transition was reported.	MD	130
	None, -COOH	Bovine serum albumin (BSA)	BSA interacted less strongly with pristine SWCNT than with carboxylated SWCNT. BSA lost more of its α-helix content upon binding to the carboxylated SWCNT.	CD	131
	None	Estrogen receptor α (ER)	ER binding to NPs triggered signal transduction by changing the structure of ER from the free form to the agonist-bound form.	Fluorescence MD	132
	-COOH	HRP, subtilisin, lysozyme	HRP maintained only 68% of the native α-helical structure after complexation. Subtilisin maintained only 76% of the native β-structure after complexation. Lysozyme retained 63% of the native structure.	CD	133
	-COOH	Human IgG, HSA, fibrinogen (FG)	The adsorption capacity to NPs was as follows: FG > HSA > IgG	Fluorescence MD	134
	None	Tau protein	The random coil structure → β-sheet transition	CD	53
MW CNT	None	Tau protein	No change in secondary structure was reported.	CD	
	-COOH	Porcine trypsin (pTry)	The enzymatic activity of pTry reduced. The α-helical content reduced and unfolding started.	MD, UV, CD	135
	-OH	Amylase	The loss of the α-helical structure occurred, decreasing from 41.1% to 21.9%	CD	136
	None	BSA	The β-sheet content decreased from 33.3% to 29.8%; The β-turn content increased from 2% to 5%.	CD	137
	-COOH	HSA, FG, IgG, histone H1 (H1)	HAS, FG, and IgG showed a red shift in fluorescence, indicative of conformational changes in the hydrophobic core open, while H1 showed a blue shift.	TEM, CD, Fluorescence	138
	None, -COOH -PEG	BSA, IgG	The α-helicity diminished and the β-structure slightly increased for BSA. The effect was greater in COOH-NP and pristine-NP. The α-helicity greatly decreased and the β-structure was elevated for IgG. The overall folding moved to the unfolding state especially in COOH-NP and pristine-NP.	CD, TEM, DLS	76

(*Continued*)

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Table 1 (Continued).

NPs	Surface Functional Group	Interacting Protein	Conformational Changes	Detection Method	Ref
AuNP	-MUA -TCOOH	Cytochrome-c	Reductions in the α-helical content and highly denatured form were observed.	CD	139
	-COOH	Cytochrome-c (CC), chymotrypsin (ChT)	CC: No change ChT: Complete denaturation upon binding	CD	140
	-COOH	Factor VIII IgG	Factor VIII, IgG: The extent of α-helical structure of both the proteins was reduced and structural transition occurred from α-helix to β-sheets.	Fluorescence CD	141
	-COOH	BSA	Reduction in the α-helical content	CD	142
	-COOH	BSA	Loss of α-helical content	CD	143
	-COOH	BSA	Loss of α-helical content and formation of more open structures.	ATR-FTIR fluorescence	144
	-Chloride -CTAB (GNR)	HSA	Reduction in α-helical content and an increase in random coil content were observed. The effects were greater in GNR.	CD, ITC	17
	-COOH, -CTAB TGNP GNR	BSA	Significant secondary structural changes were found in CTAB gold NP, TGNP, and GNR. The unfolding ability of citrate (-COOH) gold NP was weak.	CD	145
	-Chloride -CTAB (GNR)	BSA	The α-helical content was diminished.	FT-IR	146
	MHDA-GNR	Lysozyme, α-chymotrypsin (ChT)	Lysozyme: Ellipticity at 222 nm reduced by 15% for lysozyme. ChT: Ellipticity at 222 nm reduced by 10% for ChT.	CD	147
	MHDA-GNS	Lysozyme ChT	11% of ellipticity of lysozyme at 222 nm was reduced, while the structure of ChT was unchanged.	CD	
AgNP	$-BH_4^-$	α-A-Crystallin	The protein was partially unfolded with the exposure of two cysteine residues that could form coordinate bonds with AgNP.	FRET, FT-IR	148
	-COOH	BSA	The α-helix content decreased by up to 7% with the addition of AgNPs.	FT-IR, CD	149

Abbreviations: HRP, horseradish peroxidase; PEG, polyethylene glycol; MUA, mercaptoundecanoic acid; TCOOH, thioalkylated tetraethylene glycol; CTAB, cetyltrimethylammonium bromide; GNR, gold nanorods; TGNP, triangular gold nanoplates; MHDA, 16-mercaptohexadecanoic acid, anionic, nontoxic; GNS, gold nanosphere.

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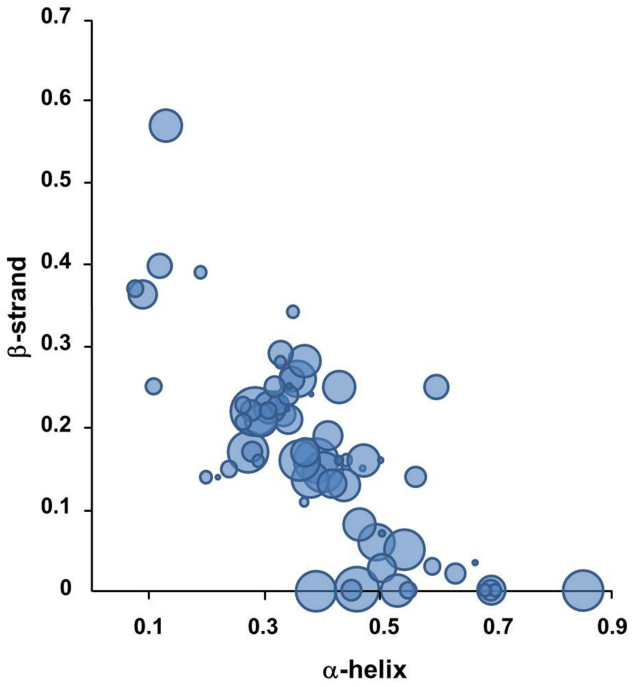

Figure 3 The preference of secondary structural elements for MWCNT binding.
Notes: About 750 cellular proteins were monitored for binding to MWCNT by mass spectrometry-based proteomics. The secondary structures of the bound proteins were analyzed using the 3D structures deposited in the Protein Data Bank. 269 proteins out of identified 778 proteins were used for the analysis. The proportion of α-helix and β-sheet for each protein was quantified. The protein classes among the CNT-binding proteins are represented with bubbles. The most abundant protein classes contained cytoskeletal proteins, endosomal proteins, and heat shock proteins. The bubble size represents the relative binding affinity to MWCNTs. Adapted from Nanomedicine: Nanotechnology, Biology and Medicine, 9(5), Cai X, Ramalingam R, Wong HS, Cheng J, Ajuh P, Cheng SH, Lam YW. Characterization of carbon nanotube protein corona by using quantitative proteomics. *Nanomedicine*. 583–593, Copyright (2013), with permission from Elsevier.[87]
Abbreviation: MWCNT, multi-walled carbon nanotube.

target proteins without disruption of folded state. The silica NPs (SiO_2) might interact with the nucleoplasmic proteins such as topoisomerase I clusters and induce the large aggregates in the cell nucleus.[91] Various cellular proteins may be directly affected by the internalized NPs, resulting in numerous disruption of cellular events such as transcription, proliferation, signal transduction, cell cycle regulation, metabolism, apoptosis, and etc. However, structural studies on the interaction between these proteins and NPs at the atomic level are currently limited.

Effects of Surface Modification on Protein Conformation

The surface chemistry of NPs is inevitable for their stabilization and to prevent coagulation and agglomeration. Thus, surface modification of NPs is generally required to maintain them in a well-dispersed colloidal state. Agglomerated NPs exert different effects on protein conformation; i.e., the characteristics of protein coronas of agglomerated NPs are quite different from those of coronas formed on normal NPs.[92,93] This observation may be associated with alterations in available surface area, modified exposure of chemical motifs, changes in shape, and loss of charge balance. Studies have shown that agglomeration could be controlled by the formation of protein corona on polystyrene NPs.[94,95] In this case, proteins may serve as a protective shield against the accumulating NPs. Thus, it is important to properly design the surface modification of NPs to control protein corona formation and achieve NP stability for clinical applications.

Surface modification can be performed in two major ways, namely, by controlling the hydrophobicity and by controlling the charge property. Polymers such as PEG and poly ethyl ethylene phosphate (PEEP) are widely used to control hydrophobicity.[96] NPs coated with polymers have extended half-lives in circulation in vivo.[97] PEG has been used to recover the ability of herceptin-conjugated NPs to specifically bind to targeted receptors by "backfilling" the surface of NPs.[98] In this system, protein corona formation was suppressed by PEG, resulting in the retention of specific-targeting ability. PEEP-coated polystyrene NPs also showed decreased protein corona formation, but weak and nonspecific binding was still observed at their surfaces.[99] The structures of corona proteins on PEG-NPs have not been extensively studied, and whether conformational changes are highly affected by PEG is unclear. A study using different lengths of PEG reported that the effect on the secondary structure of lysozyme was not significant, but fluctuations in melting temperatures were obvious.[100] It seems that the contact of PEG-coated gold NPs with lysozyme may occur within a limited range, but further studies are warranted.

The hydrophobic contact between NPs and proteins may induce large structural changes, as the inner hydrophobic core of proteins may be exposed to the polar solvent environment through hydrophobic interactions. However, it is difficult to predict the effect of hydrophobicity of NPs on protein binding and conformational changes. Chakraborti et al suggested that the conformational change in α-lactalbumin, a highly hydrophobic protein, may be mainly attributed to its hydrophobic interaction with zinc NPs.[101] Neutral gold NPs were bound by only a few plasma proteins, while charged gold NPs attracted several proteins, including fibrinogen.[102] Several model proteins, including BSA, transferrin, and apolipoprotein, showed high binding affinity to

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neutral hydrophobic polystyrene NPs, but not to charged NPs.[103]

Surface charge characteristics may highly influence the conformation of bound proteins[104] and regulate protein adsorption, binding affinity, and structural changes, all of which may induce alterations in the protein-protein (ligands) interaction and biological functions of NPs. For instance, the positively charged model NPs prepared with polylactide showed two-fold higher uptake in HeLa cells. Interestingly, the positively charged NPs, but not the negatively charged NPs, were internalized via the clathrin pathway, which indicated a different corona protein interaction in the latter case.[105] In the case of quantum dot NPs, negatively charged NPs were more efficiently transported into HEK cells via the lipid raft/caveolae pathway but not the clathrin pathway.[106] Polystyrene NPs modified with carboxyl (-COOH) and amine (-NH_2) groups showed differential cellular uptake. The carboxylated NPs were better internalized by macrophages, while the positively charged NPs preferred monocyte THP-1 cells.[107] Positively charged residues such as lysine and arginine of lysozyme may be exposed to the solvent following binding to gold NPs, thereby facilitating NP aggregation owing to the interaction between these exposed residues of lysozyme and other proteins.[108] The species of surface charge may determine the protein types bound to NPs. Positively charged polystyrene NPs showed high affinity to albumin, which has an isoelectric point (PI) below 5.5, but negative NPs preferred to form corona with IgG with a PI above 5.5.[109] In addition to charged species, charge density may also affect corona formation. The increase in the surface charge density of polystyrene NPs was accompanied by an increase in the adsorbed amount of proteins without any change in protein species.[110]

To compare the effect of charge on corona formation and conformational change, model proteins with different surface charge properties were monitored in the presence of differently charged CNTs (unpublished data). The selected model proteins were as follows: albumin and α-1-antitrypsin with a negative surface or local negative patch; lysozyme and transferrin that carry a positive surface or local positive patch; and fibrinogen composed of three different subunits (α, β, γ) with different charge properties. The PI values and calculated net charges are listed in Table 2. The surface of the model CNTs was modified into –COOH, –OH, and –NH_2. The –OH modification was intended to monitor the effect of the hydrogen bonding donor or acceptor.

The effect on conformational changes would be expected to follow the charge profiles of proteins, with the exception of fibrinogen, as the electrostatic interaction between oppositely charged proteins and NPs may govern this complexation process. However, the order of secondary structure changes in proteins was not consistent with the expectation, while the changes in the Tm values of proteins matched well with the theoretical effect (Table 2). Figures 4 and 5 show the CD spectra for secondary structural changes and Tm value changes. The reference CD spectra of each protein were obtained without CNT (labeled as PBS in the figures) to compare with the spectra of protein-NP complexes. All spectra were measured in phosphate-buffered saline (PBS, pH 7.4). The changes in the secondary structures of the five proteins were analyzed with the corresponding CD analysis software, CDNN,[111] and the estimated contents of each secondary structure in the total structure are summarized in Table 3.

Albumin possesses highly negatively charged patches on its surface (Figure 4). Interestingly, the secondary structural changes were most significant in the negatively charged COOH surface, although the difference in changes with other surface-modified CNTs was not large. Generally,

Table 2 Structural Changes in Model Proteins on Various Surfaces of Carbon Nanotubes

Protein	PI[a]	Net Charge[a]	Theoretical Effect[b]	Secondary Structure Change[c]	Melting Temperature (Tm) Change[c]
Albumin	5.92	−11	NH_2>OH>COOH	COOH>OH=NH_2	Tm increase NH_2>OH>COOH
α-1-Antitrypsin	5.37	−15	NH_2>OH>COOH	OH>COOH>NH_2	Tm decrease NH_2>OH=COOH
Transferrin	6.81	−2	NH_2>OH>COOH	NH_2=OH=COOH	Tm decrease OH≥NH_2≥COOH
Lysozyme	9.28	8	COOH>OH>NH_2	COOH>OH>NH_2	Tm decrease COOH>OH>NH_2
Fibrinogen (α, β, r)	8.23, 8.54, 5.61	3, 6,−10	COOH=OH=NH_2	COOH>NH_2>OH	Tm increase COOH>NH_2>OH

Notes: [a]The expected charge properties were calculated using the amino acid sequences of each protein at a pH of 7.4. [b]The expected amount of changes in the NP solution considering the net charge of proteins. [c]All results were obtained using CD spectroscopy in phosphate buffer (pH 7.4).

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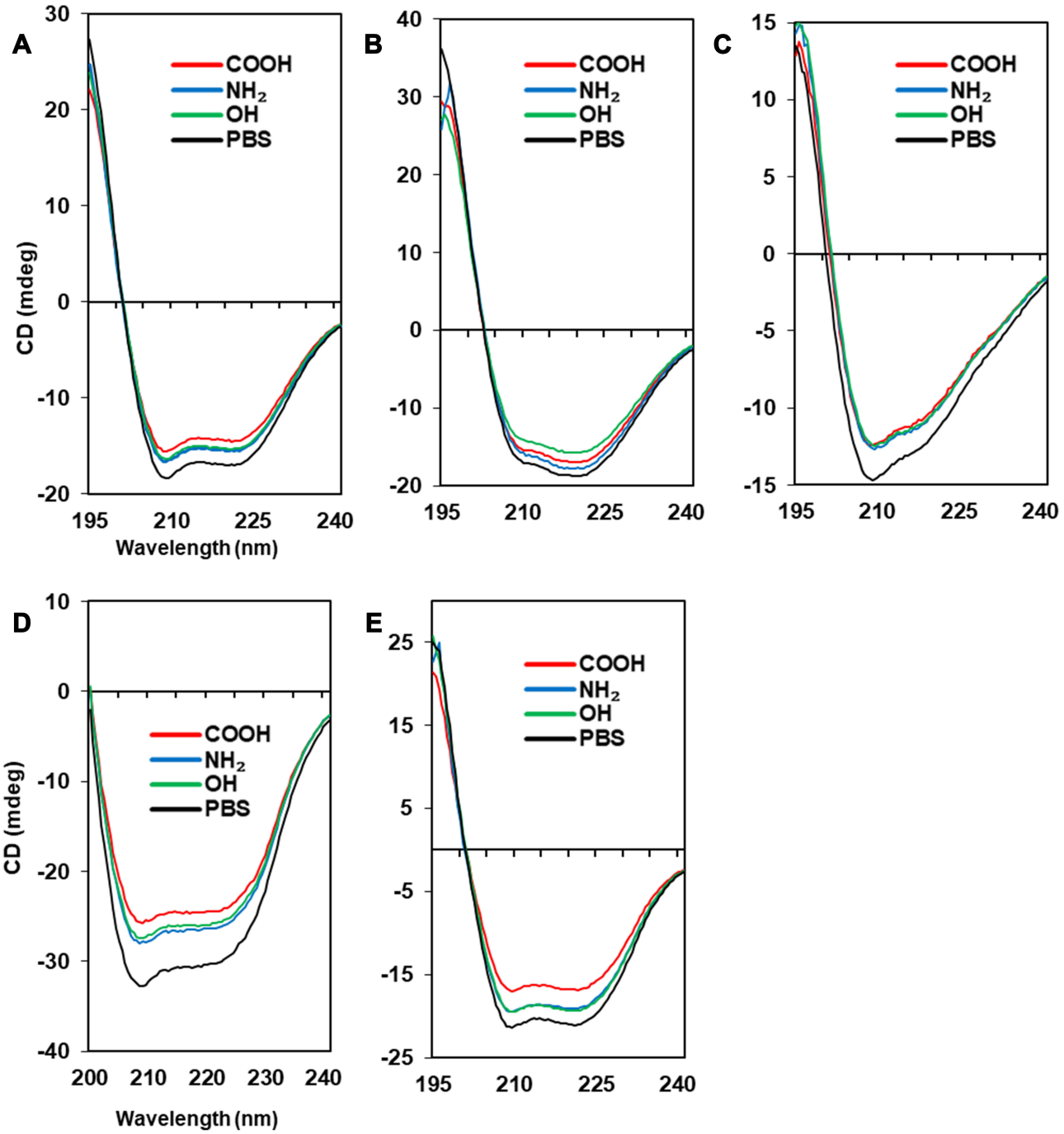

Figure 4 Secondary structures of protein-NP complexes (unpublished data).
Notes: PBS represents the reference CD curve without NPs, measured only in phosphate-buffered saline (pH 7.4). All other curves were measured with NPs in phosphate-buffered saline (pH 7.4). (**A**) Human serum albumin, (**B**) α-1-antitrypsin, (**C**) transferrin, (**D**) lysozyme, (**E**) fibrinogen (α, β, r).
Abbreviations: CD, circular dichroism; NP, nanoparticle.

the amounts of α-helical content decreased in all NPs, while the amount of β-sheets and random coils increased. The increase in β-sheets or random coils may imply partial unfolding or aggregation of the protein. The surface charge of α-1-antitrypsin was similar to that of albumin (Table 2 and Figure 4), while the most significant changes were unexpectedly found in the OH-modified surface, as shown in Table 3. The decrease in α-helicity and increase in β-sheet and random coil were identified in all proteins. Since the p*K*a of the terminal α-amino group ($–NH_2$) is known to be around 8.0, the charge strength of the surface $–NH_2$ of CNTs seems to be weak at pH 7.4. This may weaken the

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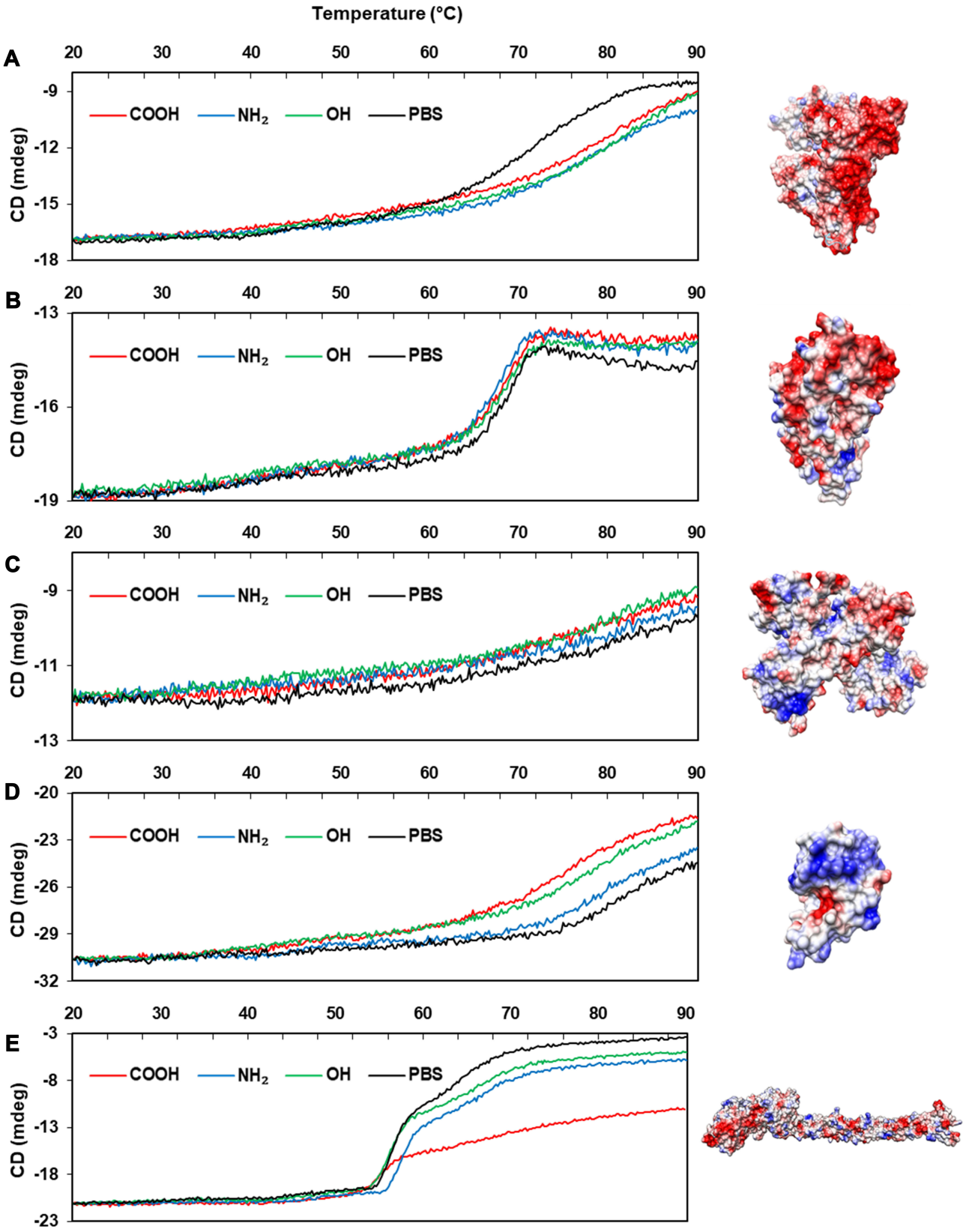

Figure 5 The Tm curves of protein-NP complexes.
Notes: PBS represents the reference Tm curve without NPs. (**A**) Albumin (PDB code: 2bx8), (**B**) α-1-antitrypsin (PDB code: 1kct), (**C**) transferrin (PDB code: 2hau), (**D**) lysozyme (PDB code: 1lz1), (**E**) fibrinogen (α, β, r, PDB code: 3ghg). The structure of each protein was obtained from PDB database (http://www.rcsb.org). The Coulumb parameters were ε = 4r and thresholds ± 5.93 kcal/mol·e. Negative charge is indicated in red, positive in blue, and neutral in white. Surface charge was calculated using UCSF Chimera.
Abbreviations: CD, circular dichroism; NP, nanoparticle; Tm, melting temperature.

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Table 3 Secondary Structural Changes Depending on the Surface Characteristics

Proteins	Contents	Surfaces			
		PBS	COOH	NH_2	OH
Albumin	α-helix	**40.7***	**34.8**	35.1	35.1
	β-sheet	**13.7**	**16.2**	16.0	16.0
	β-turn	**15.6**	**16.4**	16.4	16.4
	Random coil	**30.0**	**32.6**	32.5	32.5
α-1-Antitrypsin	α-helix	**32.2**	30.1	31.5	**28.2**
	β-sheet	**17.5**	18.6	17.9	**19.8**
	β-turn	**16.8**	17.2	16.9	**17.5**
	Random coil	**33.5**	34.1	33.7	**34.5**
Transferrin	α-helix	**32.8**	29.3	30.0	29.5
	β-sheet	**17.3**	19.2	18.8	19.1
	β-turn	**16.9**	17.4	17.3	17.4
	Random coil	**33.0**	34.1	33.9	34.0
Lysozyme	α-helix	**59.9**	**48.1**	52.8	51.3
	β-sheet	**7.9**	**11.0**	9.7	10.1
	β-turn	**13.1**	**14.5**	13.9	14.1
	Random coil	**19.1**	**26.4**	23.6	24.5
Fibrinogen (α, β, r)	α-helix	**33.9**	**27.6**	30.2	31.1
	β-sheet	**16.6**	**20.2**	18.6	18.1
	β-turn	**16.6**	**17.7**	17.2	17.0
	Random coil	**32.9**	**34.5**	34.0	33.8

Notes: *The calculated value is the percentage of each secondary structural element in the total structure. The percentages of structural elements obtained from the reference spectra (PBS) and those obtained from the most highly changed condition were represented by bold numbers.

interaction between CNT-NH_2 and α-1-antitrypsin. Transferrin does not possess a highly charged surface on its structure and shows the similar effect in the CD spectra. All CNTs slightly reduced the α-helicity and slightly elevated the β-sheet content, which may imply that the hydrophobic interactions with the CNTs are important for α-1-antitrypsin. Lysozyme was highly affected by the surface of –COOH due to its positively charged surface. Notably, the change in the Tm value due to the surface of –OH was also significant, as shown in Figure 5, as was the change in the secondary structure. This may suggest that not only the surface charge but also the hydrogen bonding through the surface oxygen of CNTs may affect the conformational change in lysozyme. The largest model protein, fibrinogen, showed a similar pattern of change to those of albumin and lysozyme.

The changes in fibrinogen would be caused by a very complex event since it is composed of three different subunits: α, β, and r. Free fibrinogen without NPs showed two distinct transitions in the Tm curve around 50°C and 60°C (Figure 5). However, the second transition was highly altered with COOH-CNT, and the protein seemed to be less denatured, possibly because each subunit of fibrinogen may be differently affected by NPs.

These results may support the hypothesis that charge profiles of proteins and NPs are highly linked to the conformational changes in proteins. The correlation between charge profiles of proteins and NPs may be reflected by the overall conformation characteristics such as Tm value, while local structural changes (secondary structure) in bound proteins may be difficult to predict based on only charge profiles; i.e., not only surface charge but also the local structural aspect of NPs should be considered to control the secondary structures of corona proteins.

The previous molecular dynamics study showed that the partial denaturation of albumin can be induced by electrostatics and affects the self-assembly of albumin. Through counter-ion association with albumin, hydrophobic aggregation was promoted.[112] The partial unfolding of albumin could affect the drug- or toxin-binding properties or amyloid formation. It has been suggested that misfolded albumin contributes to the pathogenesis of aging-related dementia and Alzheimer's disease.[113] α-1 antitrypsin is prevalent in human serum, plays important roles in anti-inflammation, and reduces the damage to the lungs caused by proteases and inflammatory responses.[114] The malfunction of α-1antitrypsin can be induced through protein misfolding and could be linked to liver and lung disease. The mutational variant of α-1antitrypsin occasionally partially unfolded with opening of the main β-sheet of the protein, resulting in amyloid-like fiber formation.[115] The unfolding of lysozyme is also related to amyloidosis in the body. For the amyloid formation of lysozyme, the structural stability between the folded and the unfolded states was suggested to be an important factor.[116] Figure 5 clearly shows that the folding stability was significantly lowered by the various NPs. Forming the transferrin corona with NPs may be beneficial to enhance drug delivery to the brain[117] as transferrin-conjugated carbon dots (C-Dots) easily penetrate the BBB through receptor-mediated transport. Interestingly, binding to C-Dots did not induce a large conformational change in transferrin. It was shown that small C-Dots may prevent unfolding of proteins and suppress fibrillation of proteins: the mixture of insulin

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and C-Dots inhibited the secondary structural changes in insulin and fiber formation.[118] In addition, our CD data revealed that the degree of structural changes in transferrin was relatively small compared to other proteins, which may imply that folding stability of transferrin is higher than that of other model proteins. Fibrinogen is essential for the formation of fibrin clots, and the molecular mechanism of clot formation was suggested to begin with the unfolding of the fibrinogen γ-chain.[119] The unfolding curves of fibrinogen shown in Figure 5E revealed that a unique unfolding process exists in the presence of COOH-CNT. It is unclear whether this unique unfolding process initially follows the known γ-chain unfolding process or if a completely different unfolding pathway was adopted by the fibrinogen corona state.

Perspectives: Application of the Protein Corona

The formation of the protein corona may be disadvantageous for most in vivo applications of NPs. Corona proteins can eliminate the targeting ability of NPs, as the bound proteins may sterically mask the pre-coupled targeting ligands that recognize specific receptors or target molecules on cells. The surface protein ligand of NPs may lose its structure upon interaction with corona proteins. The corona may provoke unintended distribution of NPs in the body and immune responses through conformational changes of bound proteins.

Various trials have focused on the affirmative use of corona formation. NPs pre-incubated and pre-coated with proteins may gain a new biological identity. This may allow alterations in immunogenic responses against NPs by stealth effects, improvement in targeting of NPs, and stabilization of NPs against agglomeration. The PEG NPs coated with clusterin showed reduced uptake by macrophages.[99] The agglomeration rate of silver NPs was reduced by the formation of an HSA corona depending on the concentration of HSA as compared to bare NPs.[120] Antibody-conjugated NPs used for targeting cancer cells showed improved association with the human ovarian cancer cell line SK-OV-3 through HSA corona formation.[33] Protein coronas made from high concentrations of fetal bovine serum could reduce the cytotoxicity of graphene oxide nanomaterials, suggestive of an approach to improve safety.[121] Serum corona formation of hyaluronic acid (HA)-based capsules significantly enhanced the targeting specificity of capsules to human mammary gland cancer cell lines by reducing nonspecific capsule-cell interaction.[122] A similar effect was also observed with antibody-labeled gold NPs for hard corona.[123] Gamma-globulin-coated silica NPs could recruit and accumulate serum immunoglobulins on their corona layer, indicative of a potential tool for the regulation of serum immune proteins.[34] PEG-conjugated polymer NPs were proposed as capturing agents for serum Aβ42 in the circulating system, as the corona of these NPs could preferentially bind to Aβ42.[124] Casein-coated gold NPs also showed the

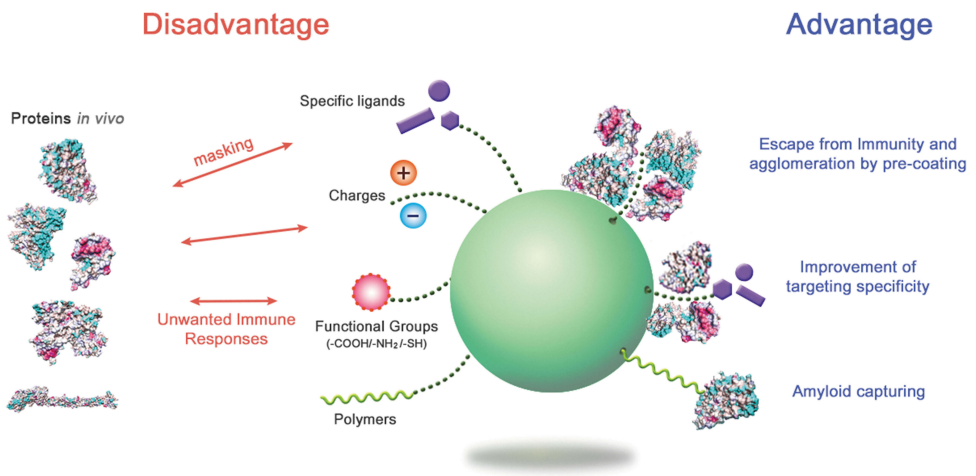

Figure 6 The advantages and disadvantages of protein corona formation.
Notes: By regulating the protein coronas through appropriate surface modification and NP selection, the biological behavior of NPs in the body could be improved. Structural studies on the corona proteins in NP systems may provide insight into how to handle the NPs.
Abbreviation: NPs, nanoparticles.

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elimination of Aβ42 in a nonspecific-binding manner.[19] These NPs may improve the condition of Alzheimer's disease. A modified version of liposome assembled with phospholipid and membrane proteins from leukocytes (leukosome) absorbed specific corona proteins on its surface and showed reduced protein corona-mediated uptake by immune cells.[125] The acute toxicity of silica NPs was shown to be reduced by the pre-formation of a serum corona complex.[126] In addition, metal oxide NPs, Fe_3O_4-PEG was saturated with protein corona, resulting in the reduction of ROS toxicity and inflammatory response in human macrophages.[127]

Extensive studies on the protein corona of NPs have improved our knowledge on the behavior of NPs in biological systems. As described above, several proposals have been suggested to control the biological behavior of NPs, and many applications have focused on how to recruit specific proteins on and unload specific proteins from NP surfaces (Figure 6).

Concluding Remarks

To enhance the safety and efficiency of NP application, it is necessary to understand how protein coronas can affect and regulate the functionality of given NP systems. The conformational characteristics of corona proteins recruited by various NPs should be a critical determinant of their functionality and safety. However, the current findings on the structural features of corona proteins at the atomic level are still insufficient to fully evaluate and understand the corona-NP system. In-depth studies on the structural changes of each corona protein on NPs would bridge the gap between "applications" and "basics" of NPs, as the behavior of NPs in vivo is definitely related to the orientation and unfolding of certain proteins within the corona environment.

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Disclosure

The author reports no conflicts of interest in this work.

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