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Nanoparticle personalized biomolecular corona: implications of pre-existing conditions for immunomodulation and cancer

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Nanoparticles (NPs) have demonstrated great promise as immunotherapies for applications ranging from cancer, autoimmunity, and infectious disease. Upon encountering biological fluids, NPs rapidly adsorb biomolecules, forming the "biomolecular corona" (BC), and the altered character of NPs due to their newly acquired biological identity can impact their *in vivo* fate. Recently, it has been shown that the NP–BC is person-specific, and even minute differences in the biomolecule composition can give rise to altered immune recognition, cellular interactions, pharmacokinetics, and biodistribution. Given the current rise in the development of NP-based therapeutics, it is of utmost importance to better understand how pre-existing conditions, that result in the formation of a personalized BC, can be leveraged to aid in the prediction of the therapeutic outcomes of NPs. In this minireview, we will discuss the formation of the BC, implications of the BC for NP-biological interactions, and its clinical importance in the context of immunomodulation and cancer therapeutics.

1. Introduction

Nanotechnology has cemented itself in the field of medicine as a robust platform for improving diagnostic and therapeutic systems. In the past decade, sixteen nanoparticle (NP) formulations have gained Food and Drug Administration (FDA) approval and over 1000 new clinical trials have begun.[1,2] Among the FDA approved nanoformulations, eight are clinically used for cancer imaging or therapy. Despite the extensive literature on characterizing NP formulations, several biological barriers exist that collectively pose a challenge to their clinical translation.[3,4] A meta-analysis showed a potential reason for the lack of success in the field of cancer nanomedicine was that an estimated 0.7% of injected NPs reach solid tumor tissue, whereas the vast majority accumulated in non-tumor sites including the liver and spleen.[5] One aspect that has been identified as a confounding variable is the interaction between synthetic materials and biological media. When NPs are exposed to biological fluids, such as plasma, opsonins and other biomolecules rapidly adsorb to the surface.[6–8] This coating, mainly consisting of proteins, lesser amounts of lipids, and other biomolecules, is referred to as the "biomolecular corona" (BC). The formation of the BC represents a transformation of the NP by altering its "synthetic identity" away from design features such as composition, charge, topology, and surface functionalization as it acquires a new "biological identity".[7] Accordingly, NP biological identity has been linked to a number of deleterious biological effects including altered immune cell activation, increased blood clearance, and altered tumor biodistribution.[9] The adsorption of opsonins (such as immunoglobulins, complement factors, and lectins) to NPs has been well understood to promote phagocytic clearance, but the effects of additional endogenous biomolecule adsorption on nano-bio interactions is a promising new field of research.

Recently, it has been shown that the BC fingerprint is not only unique to specific NP formulations, but also the individuals' disease-state and plasma composition can give rise to alterations in BCs independent of the NP's synthetic identify. The term "personalized protein corona" or "personalized biomolecular corona" (PBC) has been developed to account for these disease state-dependent effects of BC formation on NPs (Fig. 1).[10] Different disease-states have significant effects on the concentration and composition of biomolecules in the bloodstream. Furthermore, genetic background, lifestyle, and geographical origin play important roles in PBC changes between healthy individuals. These unique differences between individuals can directly affect the BC composition and subsequent NP biological fate. Given the recent advances

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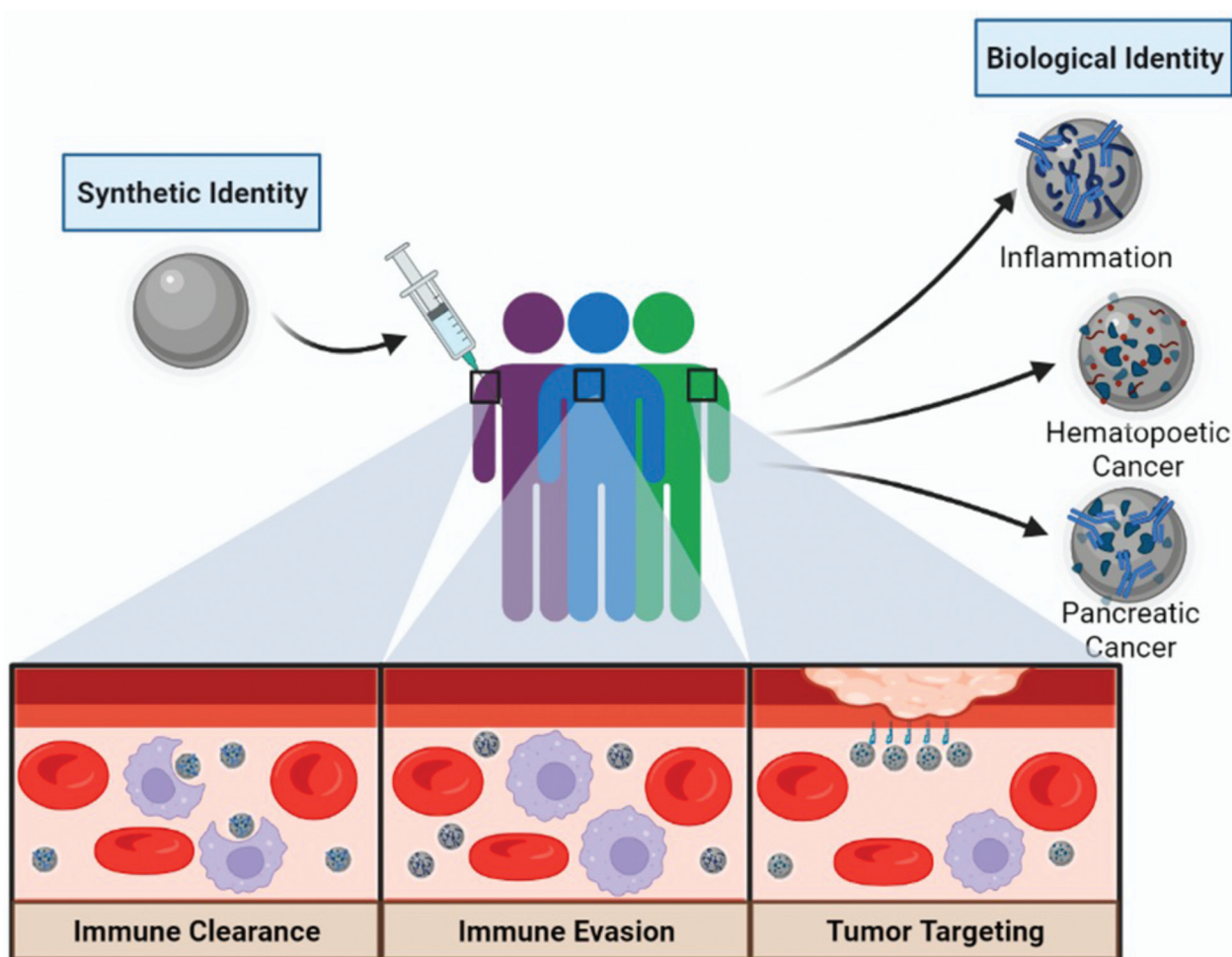
Fig. 1 Concept of the personalized biomolecular corona and the implications of pre-existing conditions on nanoparticle treatments. Distinct patient populations and co-morbidities potentially affect the PBC composition through differences in biomolecule compositions and concentrations in the blood. The PBC affects the nano-bio interface, which can result in increased immune recognition (or clearance), aid in immune avoidance (or evasion), or act as inherent targeting ligands to enhance tumor targeting. Created with Biorender.com.

in characterizing the PBC, the notion that synthetically identical nanomaterials would elicit similar effects in all patient populations should be reconsidered. Understanding the PBC's impact on NP-driven therapeutic outcomes is imperative to the development and clinical translation of personalized medicines. This minireview will highlight recent examples of the implications of the BC on NP cancer therapeutics, including commonly identified biomolecules in the corona and their receptors, BC-dependent immune cell activation, recent advances in understanding disease-specific BC innate immune and cancer cell targeting, and its clinical relevance in cancer nanomedicine.

2. Personalized biomolecular corona

An often-overlooked factor when it comes to discussions about BC formation is patient plasma composition and the respect-

ive concentration of biomolecules. Biomolecule binding to nanomaterials is determined by a variety of factors including, NP size, hydrophobicity, charge, topology, shape, and the biological media composition it is exposed to. Historically, BC formation is understood to be driven by the ability of the NP's physicochemical properties to draw in molecules through non-covalent forces such as van der Waals, hydrophobic interactions, and hydrogen bonding.[11] These interactions leading to BC formation are ubiquitous among NPs formulations, although some groups have developed coatings such as hydrophilic and zwitterionic coatings to diminish this phenomena.[12,13] Conjugation of poly(ethylene glycol) (PEG) chains on the surface of NPs has long been considered an efficient strategy to limit corona formation and promote immune evasion, but recent proteomic profiling suggests that while PEGylation diminishes total protein abundance, it has only been shown to have a minor effect on altering total BC composition.[14] Furthermore, anti-PEG antibodies have been

shown to opsonize NPs to further promote phagocytic clearance. These findings are contrary to the so-called "stealth effect" where PEGylation was thought to impart improved NP pharmacokinetic properties leading researchers to develop PEG alternatives and anti-PEG antibody accommodations.[15,16] Given this, there is a need to characterize the BC influence in both pristine and sterically-coated NP formulations. In addition to NP physicochemical properties, several parameters have a significant influence on the composition of the BC, including biomolecule binding affinities, relative concentration, and exposure time.[17] According to the Vroman effect, the most abundant biomolecules in the media are readily adsorbed to the surface at the early stages of BC formation, but they are dynamically replaced by higher affinity species as time proceeds.[18] Thus, disease-specific alterations in plasma biomolecule compositions and concentrations influence BC formation and subsequent nano-bio interactions.

Extensive research has gone into understanding the impact of NP modifications on BC formation, but the role of blood composition as a function of interindividual and disease state variations has only recently been evaluated. Hajipour *et al.* documented differences in the protein corona fingerprint of polystyrene NPs incubated with plasmas from varying individuals, diseases, and disorders.[10] Whole protein analysis using SDS-PAGE identified patient-specific BC compositions; these differences were elevated in the cases of hematological conditions (such as hypercholesterolemia, hemophilia, hyperfibrinogenemia). Interestingly, differences in protein fingerprints were observed between healthy individuals as well. Furthermore, BC composition may be dependent on the type, period, and severity of the disease. Table 1 lists commonly adsorbed BC molecules, their prospective receptor interactions, impact on NP therapeutics, and examples comorbidities associated with respective biomolecule upregulation in

Table 1 Commonly adsorbed biomolecules identified in the biomolecular corona and their implications on biological function

Protein	Biological function	Receptor targeting	Impact on nanoparticles	Associated comorbidities	Ref.
Alpha-2-macroglobulin	Humoral defense by binding foreign peptides and particles	Alpha2-macroglobulin receptor and low-density lipoprotein receptor-related protein	Immune activation, MPS clearance	Diabetes, nephrosis, infection	55, 61 and 62
Anti-thrombin	Inhibits thrombin and regulates the blood coagulation cascade	Heparin receptors and glycosaminoglycans	MPS clearance	Diabetes	54 and 63
Apolipoprotein A-I, A-II, A-IV, A-V, B-100, C-I, C-II, C-III, C-IV, D, E, L1	Lipid transport and metabolism	Low density lipoprotein receptors (LDLR), low-density lipoprotein-associated receptors	Immune evasion, liver sequestration, blood–brain barrier penetration	Cardiovascular disease, various cancers	52 and 60
Complement, C1, C3, C4, C8	Complement cascade for innate immune surveillance	Complement receptors	Immune activation, MPS clearance	Infection, various cancers	56 and 67
Fibrinogen	Cleaved into fibrin to polymerize and stimulate blood clotting	Glycoprotein (gp) IIb/IIIa integrin, MAC-1	Immune activation, MPS clearance, coagulation induction	Infection, inflammation	53 and 64
Fibronectin	Extracellular matrix glycoprotein that binds integrins	Integrins	MPS clearance	Cardiovascular disease, various cancers	50 and 63–66
Hemoglobin	Oxygen transport	CD163	Immune evasion	Cardiovascular disease, pulmonary fibrosis	57 and 68
Immunoglobulin	Humoral immunity elimination of foreign pathogens	Fc receptors and complement binding	Immune activation, MPS clearance	Infection, inflammation, various cancers	59 and 69
Prothrombin	Component of the blood coagulation cascade	Protease-activated receptor 1	MPS clearance, coagulation induction	Cardiovascular disease, liver cirrhosis	51, 64 and 70
Serine protease	Moieties in the lectin pathway of complement	Protease-activated receptor 2	MPS clearance	Pulmonary fibrosis	31 and 71
Serum albumin	Most abundant component of plasma necessary for homeostasis	Gp18, gp30, p60, SPARC	Immune evasion, vasculature targeting	Inflammation, malnutrition	45 and 72
Vitronectin	Cell adhesion and spreading factor	$\alpha v \beta 3$ integrin	Immune activation, MPS clearance	Cardiovascular disease, various cancers	42, 73 and 74
Von Willebrand factor	Component of the blood coagulation cascade	GpIbα and gpIIb/IIIa integrin	Immune activation, MPS clearance, coagulation induction	Cardiovascular disease, anemia	58, 64 and 75–77

the blood. Given the BC composition has been implicated in NP biological fate, it is essential to understand the role of the BC on NP-based therapeutics.

3. Biomolecular corona-mediated immune activation

The adsorption of proteins on the NP surface can induce alterations in the structures of adsorbed proteins, which can affect immune responses. Apart from the nanotoxicological implications associated with opsonization and complement-mediated MPS clearance, NPs may induce additional adverse effects by inducing conformational changes, unfolding, and fibrillation (the process of misfolded proteins forming large linear aggregates) of the adsorbed proteins. The misfolding or denaturation of the protein tertiary structure may lead to exposure of new potentially immunogenic, cryptic epitopes that can cause self-protein immunogenicity and subsequent autoimmune reactions. The phenomenon of plasma proteins unfolding upon interaction with NP surfaces has been well reported. Generally, it has been observed that NPs with high hydrophobicity or surface charge density can more readily denature protein conformations. It is important to understand not just the BC fingerprint, but also the conformational statuses of the proteins themselves in order to fully understand how the BC affects NP-immune recognition.

Designing NP physicochemical properties to modulate BC denaturation can allow for the fine tuning of immune phenotypes. Recently, Deng et al. showed that fibrinogen bound to poly(acrylic acid)-conjugated gold NPs undergoes denaturation, activates the integrin receptor Mac-1, and stimulates downstream NF-κB expression of inflammatory cytokines IL-8 and TNFα.[19] Fibrinogen binding was observed to be dependent on NP surface charge, indicating an avenue for modulating this immune response. In another study, Park et al. characterized the protein structure and immune responses of PEGylated carbon nanotubes pre-coated with common plasma proteins.[20] Interestingly, they observed an elevation in reactive oxygen species levels and proinflammatory cytokine release in IgG and α-1-acid glycoprotein (AGP) coronas, but not for fibronectin or vitronectin in human macrophage cell lines. Structural analysis of these coronas indicated denaturation in the IgG and AGP proteins, which were associated with proinflammatory phenotypes. Additionally, in vivo intravenous administration confirmed immune stimulation through the elevation of splenic neutrophils, natural killer (NK) cells, and CD8^{+} T cells in the nanotube protein corona treatment groups compared to soluble protein controls. It was hypothesized that modulating this immune stimulation could be favorable in the treatment of solid tumors because of the increased infiltration of NK cells and CD8^{+} T cells associated with the innate and adaptive immune clearance of tumor tissue, respectively. Thus, designing NPs to leverage plasma protein alterations could be used to promote immune cell infiltration into the tumor microenvironment. Although there is a deficit in the lit-

erature describing the impact of the PBC on immune regulation, this is a promising opportunity to evaluate if altered serum protein abundances can be used to modulate this phenomenon.

4. Leveraging innate immune cell interactions

A major hurdle that alters nanomedicine effectiveness is MPS clearance. Intravenously injected NPs are generally recognized as foreign materials and processed as such. This manifests as the adsorption of opsonins, activation of the complement system, and subsequent macrophage clearance, resulting in undesirable nanotoxicity. Interestingly, Tavares et al. evaluated the effect of depleting liver macrophages (Kupffer cells) on NP delivery efficiency to the tumor by avoiding sequestration, but this strategy was unable to increase delivery efficiency above 2%, providing evidence that other factors were major contributors.[21] Depending on patient co-morbidities and cancer pathology, elevations in plasma opsonin levels can influence BC-dependent immune cell targeting.[22] Many researchers have investigated the role of physicochemical modifications to reduce NP opsonization to achieve immune evasion; however, selectively targeting immune cells by leveraging the PBC is an attractive opportunity for immunomodulation. Administration of NPs in an opsonin-rich environment may allow for the specific targeting of phagocytic immune cells and delivery of immunomodulatory therapies. Ultimately, a better understanding of the PBC and its composition is necessary for researchers to achieve specific targeting or evasion of immune cells. Within this section, we will highlight examples of BC components and their impact on innate immune cell interactions and immunomodulation.

(a) Classical complement

Complement proteins have long been identified as elevated markers that play a dual role in cancer immunosurveillance and enhanced tumor proliferation.[23] Recently, Ren et al. demonstrated that gadolinium metallofullerenol NPs, previously shown to promote tumor clearance through inducing a proinflammatory phenotype of M1 macrophages and Th1 T cells, bound to systemically upregulated complement 1q (C1q) proteins in lung cancer patient plasma. The classical complement pathway is activated when the complement protein complex C1q binds to IgG molecules that have recognized and bound to a foreign surface leading to enhanced MPS clearance. Understandably, elevated C1q corona content was associated with increased macrophage targeting, phagocytosis, and a subsequent increase in proinflammatory cytokines TNFα and IL-1β (Fig. 2).[24] Further, the enhancement in cytokine secretion was higher for C1q-coated compared to C1q alone. A follow-up investigation examined the influence of healthy patient PBC on immune cell uptake of PEGylated liposomal doxorubicin (Doxil/Caelyx), the first FDA approved liposomal nanomedicine for various solid tumors. Twenty-three healthy
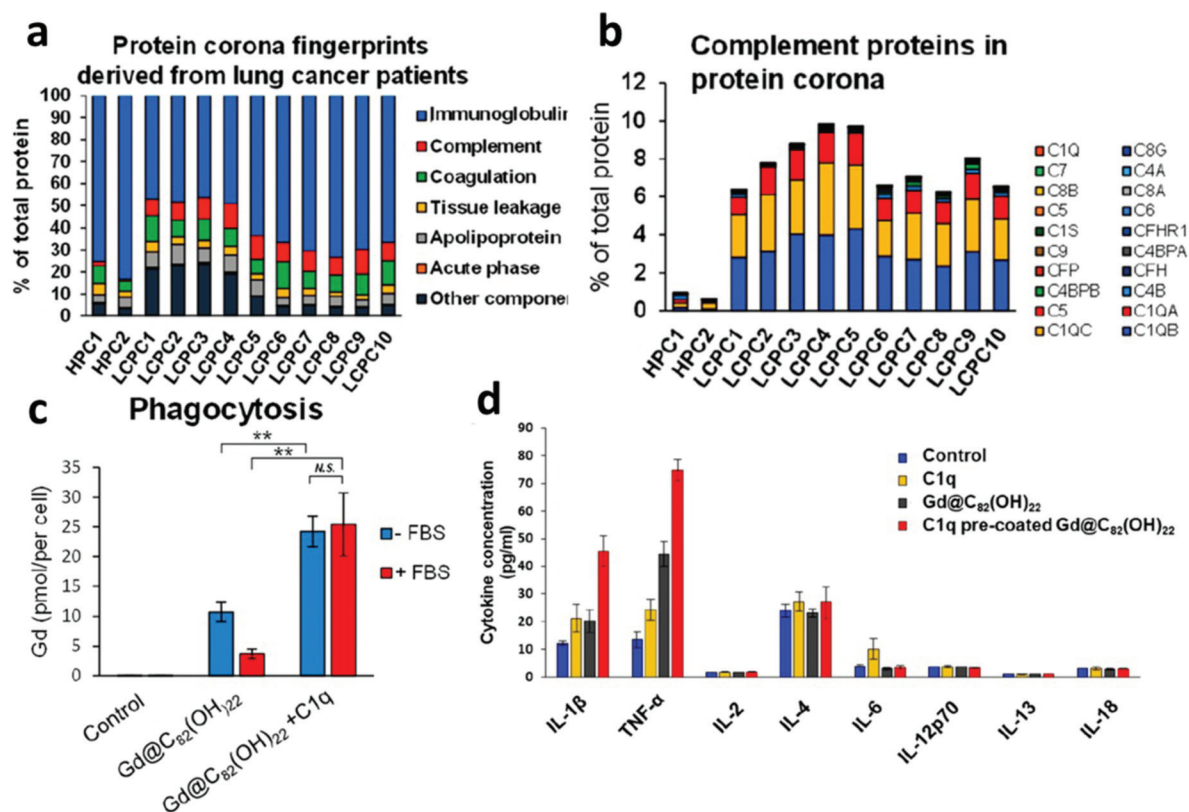
Fig. 2 Personalized complement factor corona in lung cancer patients. (a) Classification of the personalized protein corona of healthy human patient corona (HPC), lung cancer patient corona (LCPC). (b) Relative abundance of complement factors are specific to lung cancer coronas. (c) NP uptake by human macrophages is elevated in C1q precoated samples. (d) Cytokine expression modulation with C1q precoated NPs. Adapted with permission from ref. 24. Copyright 2019 American Chemical Society.

patient-derived PBCs were evaluated and identified to have unique uptake profiles by both macrophages and B cells.[25] Given these results, leveraging elevated complement factors in relevant cancer patient plasmas, in addition to appropriate NP choice, can not only allow for macrophage targeting immunotherapies but also has implications in B cell targeting for influencing immune cell phenotypes or the delivery of vaccines.

(b) Immunoglobulin

Among opsonins, immunoglobulins play an important role in foreign material clearance through phagocyte targeting of Fc receptors. In the process of characterizing the PBC of Doxil/ Caelyx in murine lung and melanoma cancers, Hadjidemetriou *et al.* observed an elevation in BC-associated pathogen clearance proteins, immunoglobulin fragments, and mucin.[26] Similarly, Colapicchioni *et al.* examined the protein corona fingerprint of the NP formulation Ambisome, in breast, gastric and pancreatic cancers by SDS-PAGE.[27] Ambisome consists of liposome encapsulated antifungal amphotericin B, clinically administered prophylactically before chemotherapy to prevent infections. An increased abundance of 37 kDa proteins associated with immunoglobulin alpha (IgA) and immunoglobulin gamma (IgG) heavy chains were identified in

pancreatic cancers patients but not others. It is thought that IgG binding to phosphatidylcholine/phosphatidylglycerol-based liposomes, like Ambisome, is primarily controlled by non-specific adsorption. It has been observed that many different cancer types induce an elevated production of IgG and IgA autoantibodies as immune-defenses against tumors.[28] Elevated concentrations of IgG in cancer patients have been linked to a proportional elevation in BC-bound IgG.[29] These findings are of particular interest because elevated adsorption of antibodies is correlated with complement system clearance of NPs, reduced systemic circulations, innate immune activation, and nanotoxicity.

(c) Lectins

The lectin pathway of the complement system, similar to the classical pathway, is an integral component of the innate immune system recognizing and neutralizing pathogens through patterns of carbohydrates on their surfaces. Although not all NPs contain surface-exposed sugar moieties, many engineered NPs have been observed to provoke lectin pathway complement clearance.[30] Digiacomo *et al.* observed an elevations in mannan-binding lectin serine protease 1 (MASP1) and ficolin-3 liposomal corona adsorption.[31] MASP1 and ficolin-family proteins are known to be important com-

ponents of the lectin complement pathway for targeted pathogen clearance.[32] The phenomena of BC-driven targeting to innate immune cell populations is important in understanding nanotoxicity and may open up new therapeutic opportunities for immunotherapeutics by developing nanomaterials that preferentially adsorb opsonins for active immune cell targeting (Fig. 3).[33,34] Ultimately, it is crucial to characterize the PBC influence on NPs biological outcomes in order to improve therapeutic efficiency and nanotoxicity profiles in downstream clinical applications.

5. Inherent cancer cell targeting

The inherent heterogeneity in the physiological effects of cancer can cause variations in PBC composition and NP cancer cell uptake mechanism and specificity.[35,36] Cancer cells often have elevated consumption of plasma proteins such as apolipoproteins (Apo), vitronectin, serum albumin, and fibrinogen. The presence of these plasma proteins in the BC can function as pseudo-active targeting ligands to specific cell types. A succeeding study from Hajipour et al.'s 2014 paper examined the effect of PBC on graphene oxide (GO) sheet uptake in MCF-7 and MDA-MB-231 breast cancer cell lines.[35] GO sheets were opsonized with plasma from a broad range of patient backgrounds (healthy, pregnancy, diabetes, hypercholesterolemia, leukemia, hypofibrinogenemia, thalassemia, rheumatism) and their differential cellular responses were studied in vitro. Interestingly, GO sheet uptake and toxicity were determined to be both BC-dependent and cell line-dependent. Current evidence suggests that PBC formation can enhance cancer cell targeting through the adsorption of endogenous molecules. Here, we will discuss how changes in the disease-specific plasma components and the resulting BCs

promote cancer cell targeting of NPs in the absence of other engineered targeting ligands.

(a) Apolipoprotein

Previously, researchers have exploited NP targeting strategies utilizing the protein corona by binding specific plasma proteins (albumin, apolipoproteins, and fibrinogen) to the surface of NPs. In particular, apolipoprotein E (ApoE) is a glycoprotein associated with cholesterol metabolism, cellular proliferation, angiogenesis and metastasis of cancers (e.g. gastric, lung, prostate, thyroid, ovarian, endometrial cancer and glioblastoma).[37] Furthermore, liposomal NP formulations are found to preferentially recruit ApoE in their BCs and apolipoprotein-enriched BCs shifted their cellular uptake mechanism from micropinocytosis to clathrin-dependent endocytosis.[38] Chen et al. demonstrated the recruitment of ApoE in their liposomal BC significantly enhanced NPs transfection efficiency of hepatocellular carcinoma HepG2 cells compared to ApoE absent NPs.[39] Furthermore, work from Akinc et al. demonstrated ApoE-dependent cellular uptake of GalNAc lipid nanoparticles in HeLa cells through the low-density lipoprotein receptor (LDLR).[40] These results were further recapitulated in ApoE$^{-/-}$ knockout mice that demonstrated reduced NP efficacy. Taken together, these findings demonstrate that the systemic elevation of ApoE in cancers and BC recruitment can allow researchers to target LDLR overexpressing cancer types. That being said, precaution must be taken given the endogenous expression of LDLR in hepatocyte tissue, which can lead to off-target toxicity.

(b) Vitronectin

In a thorough proteomic analysis of cationic liposomes opsonized with healthy human plasma, Palchetti et al. identified
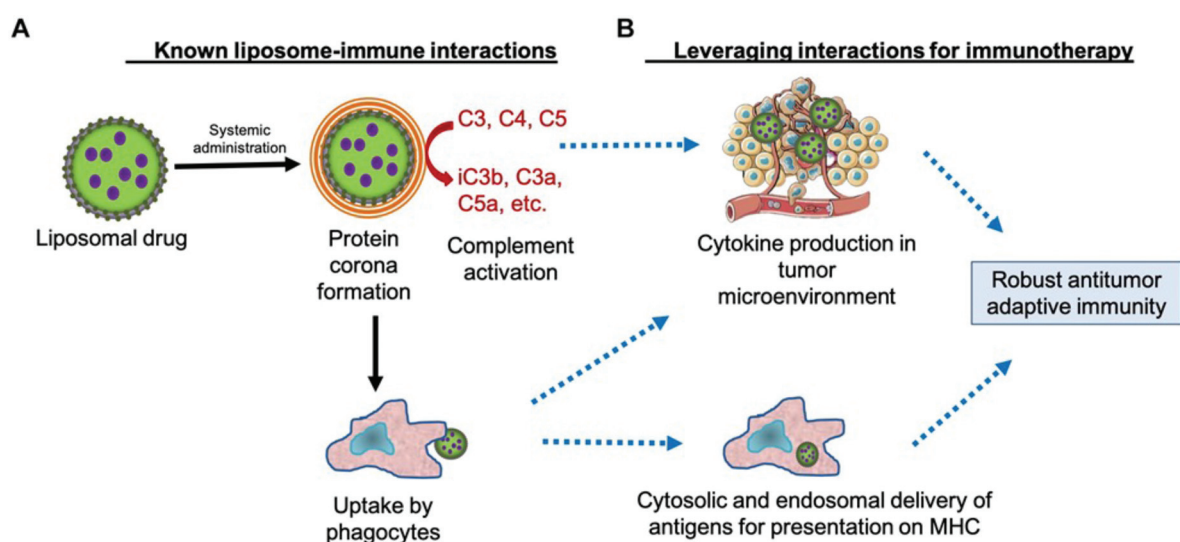

Fig. 3 Leveraging the complement protein biomolecular corona for immune system targeting in cancer. A. Known mechanism of NP clearance by complement-induced phagocyte uptake. B. Potential utilization of complement activation to deliver tumor antigens and inducing a proinflammatory phenotype in tumor resident immune cells. Adapted with permission from ref. 33. Copyright 2019 Frontiers in Pharmacology.

key proteins associated with NP uptake in HeLa cells. Correlations between the BC's relative protein abundance and cellular uptake allowed the identification of eight key proteins (vitronectin, ApoA1, ApoA2, ApoB, ApoC2, immunoglobulin heavy chain V-III region BRO, vitamin K-dependent protein, and integrin β3) associated with NP increased uptake.[41] Apolipoproteins are known to bind apolipoprotein receptors and LDLRs (Table 1), which are often upregulated in certain cancers. Vitronectin is one of the major cell adhesion glycoproteins in plasma and was found to be abundant in the liposomal BC. Vitronectin is specifically recognized by ανβ3 integrins, which are overexpressed on many solid tumors and tumor vasculature.[42] These results support previous findings that the preferential BC recruitment of vitronectin may promote tumor cell targeting through elevated ανβ3 integrin expression.[43]

(c) Albumin

Among BC proteins, albumin is the most abundant serum proteins and is associated with dysopsonin-mediated immune evasion, prolonged systemic circulation, and tumor vascular endothelium targeting. Tumor targeting is mediated by binding to the receptor gp60 on vascular endothelium and the reliance of poor lymphatic drainage in susceptible tumor tissues.[44] Tumor albumin accumulation has been demonstrated in several solid tumor models (such as sarcoma, ovarian carcinoma, and Novikoff hepatoma).[45] To leverage albumin's utility, researchers have coated paclitaxel NPs with albumin and observed an enhancement in tumor targeting of B16F10 melanoma cells expressing secreted protein acidic and rich in cysteine (SPARC).[46] Given this, disease-specific elevations in PBC albumin levels may lead to the specific targeting of tumor vasculature. BC formed from pancreatic patient plasma was identified to have a minor elevation in serum albumin adsorbed to cationic liposomes.[47] Interestingly, Caputo et al. observed a statistically significant decrease in serum albumin adsorption in pancreatic patient compared to health control in GO sheets.[48] These findings are exemplary to how different nanoformulations can recruit unique proteomic fingerprints in the same disease condition. Although NP-bound albumin has been demonstrated to allow for the increased targeting of therapies to tumor tissues, further research is required to examine if personalized upregulation of serum albumin can allow for the targeting of NPs to tumor vasculature.

6. Clinical implications and future directions

Recent advances in NP-based therapeutics have resulted in a surge of research in the field. Despite the extensive research, the clinical translation of cancer nanotherapeutics has been bottlenecked by the failure to recapitulate in vivo findings. Recent work suggests that an important aspect underlying this lack of translatability is due to our insufficient understanding of the nano-bio interface. The BC around NPs has been identified as a fundamental factor in defining NPs' biological fate.

Although the nano-bio interface poses several challenges for nanomaterials beyond the BC, an increased understanding of PBC interactions may provide an opportunity to refine our drug delivery strategy. Further research in identifying patient populations that have increased affinity for particular BC fingerprints of interest would enable increased control over biomolecule binding, thereby providing potential for development of inherently immune-targeted cancer therapies with improved tumor tissue accumulation, reduced nanotoxicity, and increased NP therapeutic efficacy. Importantly, progress is being made around machine learning and meta-analysis with respect to predicting NP–BC compositions and biological implications. For example, Ban et al. developed a computational methodology to predict with high certainty the protein corona composition and cell recognition associated with NP–BC.[49] More accurate prediction models in concert with characterizing NPs in environments that replicate in vivo conditions is expected to yield significant advancements in NP therapeutics. With the advances in the understanding of the PBC, the view that synthetically identical nanomaterials will elicit identical biological effects on all patient populations should be reconsidered. Thus, characterizing the PBC in heterogeneous diseases such as cancer, among others, may help in the prediction of the nano-bio interactions of NPs, speed up clinical translation, and improve therapeutic efficacy.

7. Conclusion

The PBC has been demonstrated to play an important role in determining the biological fate of NPs. Systemically, the BC has been shown to impact NP toxicity, immune recognition, targeting capability, biodistribution, intracellular uptake and drug release. To date, the majority of investigations characterizing the BC formation have overlooked the contribution of the physiological environment, instead focusing on the effects of the NPs' physicochemical properties. Differences in plasma biomolecule concentration and composition may be responsible for conflicting NP therapeutic results obtained between cancer cell lines, patient populations, varying disease-states, and unsuccessful clinical translation of promising formulations. Although there has been an increase in studies understanding the PBC, information on the corona-dependent cellular interactions is still limited. We envision that a better understanding of the relationship between the PBC and NP physicochemical properties will act to guide the design of future experiments and potentially leverage the heterogeneous corona composition in cancers for active cell targeting applications and immunotherapies.

Author contributions

Conceptualization, J. S. and R. M. P.; methodology, J. S. and R. M. P.; investigation, J. S.; writing—original draft preparation, J. S.; writing—review and editing, J. S. and R. M. P.; visualization,

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Conflicts of interest

There are no conflicts to declare.

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