Colloids and Surfaces B: Biointerfaces 179 (2019) 505–516

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

journal homepage: www.elsevier.com/locate/colsurfb

Protein corona variation in nanoparticles revisited: A dynamic grouping strategy

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ARTICLE INFO

Keywords:
Corona
Biological fluid
Bio-nano interface
Grouping strategy
Protein
RADAR

ABSTRACT

Bio-nano interface investigation models are mainly based on the type of proteins present on corona, bio-nano interaction responses and the evaluation of final outcomes. Due to the extensive diversity in correlative models for investigation of nanoparticles biological responses, a comprehensive model considering different aspects of bio-nano interface from nanoparticles properties to protein corona fingerprints appeared to be essential and cannot be ignored. In order to minimize divergence in studies in the era of bio-nano interface and protein corona with following therapeutic implications, a useful investigation model on the basis of *RADAR* concept is suggested. The contents of *RADAR* concept consist of five modules: 1- **R**eshape of our strategy for synthesis of nanoparticles (NPs), 2- **A**pplication of NPs selected based on human fluid, 3- **D**elivery strategy of NPs selected based on target tissue, 4- **A**nalysis of proteins present on corona using correct procedures and 5- **R**isk assessment and risk reduction upon the collection and analysis of results to increase drug delivery efficiency and drug efficacy. *RADAR* grouping strategy for revisiting protein corona phenomenon as a key of success will be discussed with respect to the current state of knowledge.

1. Introduction

Increased exploitation of nanotechnology in industrial applications has led to a significant progress in the field of nanomedicine, mirroring the potential of nanostructure biomaterials in personalized/customized medicine [1–3]. However, there are several disadvantages associated with the use of NPs including significant discrepancies in bio-information and the large gap between *in-vivo* and *in-vitro* results [1,4]. One reason for this discrepancy may be due to the manners in which protein corona is recognized in bio-nano interface and biosystem dynamics [5]. Therefore, current knowledge about the behavior of NPs in biological environments, particularly mediated by plasma proteins, is relatively unclear and it can disrupt the progress in understanding and integrating bio-information in nanomedicine [6].

Although behavior of NPs in biological environments is complex, the development of a comprehensive and biocompatible NPs that can orchestrate the results of different techniques may beneficially improve our understanding of the NPs behavior [7]. This behavior is due to the exposure of NPs to the human fluid and the reciprocal effects of the biomilieu on NPs [8]. The largest proportion of FDA-approved NPs (51 NPs) belongs to the polymeric, nanocrystal and liposomal NPs [9,10]. Currently, the proportions of protein-based NPs, metal and micellar NPs in the clinical trials are increasing in which they will be commercial after approval of *in-vitro/in-vivo* results and the clinical trials [9]. Perhaps in order to make such FDA-regulated commercial products, the crosstalk of NPs with biological fluid needs to be determined and considered as hidden factor components, despite the improvement of analytical techniques.

Another reason for the variations in the results of NP protein corona is related to the use of non-commercial NPs, non-comprehensive and

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https://doi.org/10.1016/j.colsurfb.2019.04.003
Received 18 November 2018; Received in revised form 31 March 2019; Accepted 2 April 2019
Available online 03 April 2019
0927-7765/

not so-called “excellent” protocols for protein corona identification [6]. Interlaboratory in-house physicochemical factors of non-commercial NPs and various developed protocols of protein corona appeared to generate different results even with commercial NPs [6,11]. Recently, the investigation models showed different *in-vitro* results than clinical outcomes. For example, *in-vitro* evaluation of blood flow effect on protein adsorption showed a clear diversity between the obtained patterns from static and dynamic corona [12,13]. However, nano-strategy have decreased the challenges of traditional drug delivery such as low-solubility and instability [14]. The limitations associated with NP biodistribution, toxicity and immune responsesas well as the evaluation of *in-vitro* and *in-vivo* correlations requires standard operation protocols (SOP) linked to the hidden factors such as protein corona [15]. Thus, using an optimized strategy for protein corona characterization is necessary to reduce the variations among the experimental results and to fill up the gaps in our knowledge [6].

Upon the exposure of NPs to the bio-fluid, the protein coverage of corona in NPs appeared to be dependent on many factors, which as follows: 1- the type of NPs, 2- the size of NPs, 3- the surface area of NPs, 4- the structure of NPs, 5- the charge of NPs, 6- the highly abundant proteins in human blood occupied the NPs surface at the expense of low abundant proteins, 7- human blood source-dependent and 8- interspecific and intraspecific competition between high-affinity/low affinity and high abundancy/low abundancy [16]. Replacement of fast exchange and low affinity plasma protein such as albumin with slow exchange and high affinity proteins, reflects the importance of NP surface chemistry and physical characteristic in biological NPs identity [16–18]. On the other hand, the NP biological identity is related to the protein content of the human plasma, which itself is associated with a variety of exogenous and endogenous factors including medical and biological history [19–28]. In other words, a high efficient crosstalk between NPs and human blood are NPs physicochemistry- and human blood source-dependent. With respect to the separate components of the overall bio-nano interface systems and their interactions, the factors based on changes in the engineered NPs [11], the hidden factors within experimented protein source [7], as well as the emergence of changes in the bio-nano interface relative to the pristine characteristics of proteins-NPs [7], affect the adsorption profile of proteins and determine the interaction of NPs with biological systems [18,19,29]. In this regards, little information is available on the mechanisms by which proteins are unfolded after adsorption into the NPs, suggesting that altered spatial conformation of proteins is linked to the physical nature of the NP surfaces and also the events following protein binding [30]. Nevertheless, this protein shell of native-like biomarkers undergoes a “*Look-and-Read*” process by the living cells and causes biological consequences [17].

In a number of studies, the systematic definition of the influence of overlooked factors in distinct parts of an investigation is not considered [31–33]. Moreover, correlation between *in-vitro* and *in*-vivo knowledge can be considered as important factor in the development of reliable tests for identifying the compatibility of NPs. Several investigations have stated good correlations between *in-vitro* and *in-vivo* toxicity [34]. For example, toxicity induced by metal oxide NPs on erythrocytes indicates that the *in-vitro* toxicity data is strongly in line with the results of *in-vivo* toxicity [35]. Similarly, the immuno-response to poly(ethylenimine) and poly(ethylenimine)-graft-poly (ethylene glycol) block copolymer NPs, showed good similarity between *in-vitro* and *in-vivo* complement activation assays [36]. These results help us to reshape our vision and can provide a large gap between desired theoretical and practical results in terms of therapeutic efficacy if overlooked factors are also considered.

With respect to the models proposed for explaining the protein corona effects, a grouping strategy model (Fig.1) on the basis of *RADAR* concept for introducing dynamic process of corona formation on NP surfaces in bio-nano interface is presented. The outputs of the dynamic *RADAR* logic may be used to conduct the investigation in more efficient NP developments by refining studies direction based on the hidden factor, protein corona. In this model, the concept of protein corona is divided into 5 modules including 1- **R**eshape of our strategy for NPs synthesis, 2- **A**pplication of NPs selected based on human fluid, 3- **D**elivery strategy of NPs selected based on target tissue, 4- **A**nalysis and characterization of proteins present on corona using correct procedures and 5- **R**isk assessment and risk reduction upon the collection and analysis of results to increase drug delivery efficiency and drug efficacy.

2. Reshape of our strategy

The goal of most studies in the area of nanobiomedicine is to design more efficient clinical nanostructures compare to the current clinical therapies. The desired clinical outcome can be achieved through a combination of promising previous results and clarifying foregoing approaches. Attempts to adopt these approaches in the development of NPs and accurate assessing behavior of *in-vivo* bio-nano interactions resulted in a reduction of gap between the theoretical and practical efficiency.

A possible reason of the emergence of these inconsistencies is the overlooked factors that have been ignored. Most of these hidden factors are related to the protein corona, which precise recognition of the phenomena associated with protein corona, can be used for development, assessment, and refinement of appropriate approaches to induce more efficient responses [6]. Considering the achievements in the field of protein corona, a need to link capillaries between *RADAR* sections is inevitable, so that the data of both *in-vivo* and *in-vitro* studies can be more reliable and repeatable. The capillary connection between the *RADAR* modules leads to an emergence of more efficient and safe nanocarriers. However, *in-vivo* fate of NPs and the convenient efficacy are related to the design of NPs, since corona formation can result in mistargeting, aberrant distribution and reduced therapeutic efficacy along with undesirable toxicity [37–41]. NP design along with a reshaped strategy for synthesis of NPs can also govern the protein affinity and conform to NP surfaces by non-covalent bond interactions [18,42]. The protein corona compositions are influenced by the surface chemistry factors, size, shape and targeting ligands. On the other side, the corona is affected by medical and biological factors, governing the gap between the hypothetical and observed therapeutic efficacy [19,43–46]. The significant role of these indicators refers to the synthesis strategy of NPs as a result of previous researches and the main source of future investigations in multi-stage translational projects. Premeditated functionalization of NPs for biomolecules delivery to target sites can be influenced by the corona despite the appropriate *in-vitro* (even in low-protein medium) or *in-vivo* poor efficacy results [47–49].

With respect to the corona formation at various concentrations of blood plasma with static and dynamic conditions, Salvati et al. studied protective role of protein corona in transferrin-functionalized silica NPs. The theoretical efficacy of NPs designed with biological reality varies significantly and the wrapped proteins significantly reduce the mediated cellular uptake by the transferrin-epithelial receptors of the A549 lung cell [40]. This finding reveals the diversity between the hypothetic and practical efficacy of targeted NPs in both *in-vivo* and *in-vitro* results.

It is important to note that pre-coating approaches of protein and non-protein compounds such as polysorbates may be used to derive a synthetic identity to an effective biological identity which significantly enhance the targeting efficacy [50,51]. According to the findings of different studies, fabricating NPs with specific targeting efficacy, know-how to accessibility and conformational orientation of the corona functional motifs can lead to a more efficient NP design [52,53].

The interplay of NPs with a man-made identity with proteins as well as the modified identity of pristine NP when is introduced into the biological milieu are necessary to be explored in order to design biocompatible and efficacious NPs for therapeutic purposes. Although these factors can improve outcomes in experimental models, this may

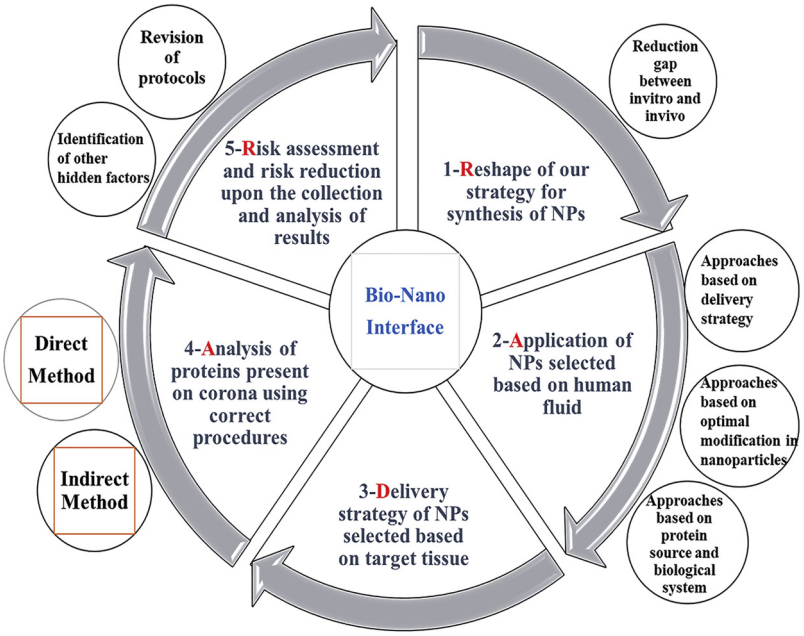

Fig. 1. Modules of dynamic circular logic: **R**eshape of our strategy, **A**pplication of NPs, **D**elivery strategy of NPs, **A**nalysis techniques and **R**isk assessment.

be more feasible through redefining the approaches in association with NP toxicity, immunological recognition, targeting capability, bioavailability, drug release and intracellular uptake [38].

3. Applications of NP

In principle the hypothesis of NP applications involve the development of NPs with an improved performance and monitoring protocols to achieve the predefined efficiency and safety vision. The most common approaches have been used to modify the efficacy of NPs, based on three perspectives outlined in Fig. 2. However, this approach has a number of steps which influences the NP biological identity and it's therapeutic efficacy [54–58].

The selected approaches are divided into one of the following three categories: a) approaches based on an optimal NPs surface modification, b) approaches based on delivery strategy and c) approaches based on protein source in biological systems. Approaches based on surface modification are characterized by administration of specific protein or non-protein compounds directing anti-fouling and zwitterionic effects.

Approaches based on delivery strategy are strategies to be assessed after hard corona formation in the investigation methods. The variations in NP bio-identity in comparison to the results of pristine NP when the corona is not considered, alter the drug targeting/release profiles and the intensity of the immune responses [8,38,59].

The third section, involves the approaches based on personalized/customized protein corona in the biological systems. This category is essential for developing NP designs from laboratory towards predictable translational settings. Therefore, special individual-design NPs should be formulated for the specific disease, since each individual with a definite medical and biological biography can change the NPs biological identity in accordance with the induced biological system identity [19,60].

3.1. Approaches based on optimal surface modification

Ideally, the surface modification of NPs through the targeting strategy improves the stability, systemic absorption and therapeutic efficacy of the NPs as a powerful vehicle for drug delivery [61]. Targeting strategies for therapeutic objectives such as cancer therapy and Alzheimer's diseases [61–63], include active and passive targeting in

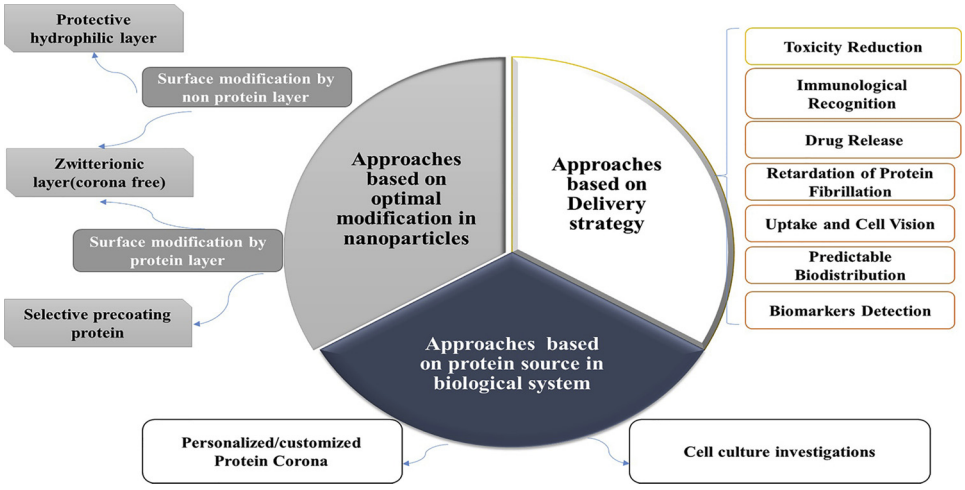

Fig. 2. Grouping strategy of approaches in bio-nano interface field.

which the latter one deals with the physiological change of the tissues. For instance, the passive targeting strategy increases the vascular permeability in order to facilitate the transmission of the drug-loaded NPs to the target tissue. Active targeting includes grafting of polymers [11], small molecules (Folic acid, Biotin) [64,65], nucleic acids (Aptamers) [66], proteins (Transferrin, Anti amyloid β) [67,68], peptides (RGD) [69] and antibodies (IgG) [70] onto the surface of NPs. Active targeting approaches can also be categorized as conventional targeting (such as 1- ligand-receptor interaction [71], 2- antigen-antibody interaction [61], 3- aptamer-mediated targeting [72]) and targeting of plasma proteins (such as tuning the surface functionality and pre-coating NPs surface [8,60]). In this regard, recent studies have indicated that abundant proportion of clusterin protein, C4BPA (complement component 4 binding protein alpha), IGLC2 (immunoglobulin lambda constant 2), apolipoproteins, complement system and coagulation proteins into corona composition perfectly directs NPs towards macrophages [60].

3.1.1. Surface modification by protein layer

The pre-coating strategy has been used to control the NPs biological identity which may have significant effects on targeting features of the nanostructures [73,74]. It is evident that in addition to the composition of specific protein layer used as pre-coating technique, the conformational arrangement plays a critical role for the further proteins adsorption during the hard corona phase [60,75].

Another strategy is using the zwitterion proteins such as cysteine to hinder corona formation. A recent study reported that in cancer cells the higher targeting efficacy of silica NPs containing zwitterion-cysteine coating with the biotin-targeting agent is due to the inhibitory effects on protein adsorption and the concealed target agent [76].

3.1.2. Surface modification by non-protein layer

Modification of NP surfaces by non-protein layer is one of the strategies to inhibit non-specific protein adsorption. For instance, NPs coated with hydrophilic and anti-fouling materials such as polyethylene glycol (PEG) are designed to prevent non-specific protein adsorption [77–80]. Nevertheless, this approach initially seemed to be a good choice as the conformational hinder for the protein adsorption in order to make NPs free of corona. However, the evaluation of formed corona on the PEGylated surfaces indicated that it contains opsonin protein, which is significantly depended on the density, thickness and conformation of PEG layer [81,82].

A recent study employed an interesting strategy to modify NPs using non-protein ingredients with zwitterion properties which increases the NPs biocompatibility and resident time. Moreover, the benefits of this approach have been reported by inhibiting the protein corona formation and masking effects on target agents in which the caused effect is negligible. Other characteristics of these excipients are the cationization capability leading to the strong cell-surface interactions in acidic pH-microenvironment and intensify the NP uptake [60].

3.2. Approaches based on delivery strategy

3.2.1. Toxicity reduction

The safety assessment of nanomaterials is one of the most important information on the cellular and biological environments [83–85]. The protein modification of biological source during the formation of corona around NPs, can trigger cytotoxic processes due to NP-induced protein misfolding and conformational changes [75,86].

Contrary to toxicity scenarios, protein corona can mitigate NP-induced cytotoxicity [87,88]. One aspect of the toxicity responses is associated with the cell membrane damage due to the lack of nutritional and pH balance. This determines how pre-coating approaches can be applied to mitigate the cellular damage and protein-induced interactions in the bio-milieu [89]. Consequently, protein corona can decrease the overall toxicity of NPs, but the conformational change of protein and pH changes caused by the imbalance of essential nutrients in cell culture medium should not be ignored after corona formation.

3.2.2. Immunological recognition

The process of immunological recognition deals with three factors, non-stealth NPs, opsonin proteins and reticuloendothelial system [80,90]. Opsonins, such as immunoglobulins, are rapidly adsorbed to the non-stealth NPs and counteract exogenous factors by Fc receptor expressed at the surface of cells like macrophages, neutrophil and dendritic cells [80,91–94].

Repetitive units of protein structures found on the surface of stealth NPs and the conformational changes of the corona layer such as complement epitopes are at progressive risk for recognition of the immunity and the subsequent complement activation [94,95]. In many instances, hydrophilic antifouling ingredients such as PEG are required to bypass the immunological recognition. In this respect, the density of the antifouling agent and type of conformation or grafted-PEG chain govern the protein corona patterns [96,97].

3.2.3. Drug release

Drug release rate from nano-carries including mesoporous silica NPs [98], liposomes [99,100] and polymer nanocapsules [101] can be significantly altered upon the interactions of proteins with NP surfaces. The efficiency of protein corona, which is relatively low for solid polymer nanocapsules may be is due to the thicker polymer shell compared to the corona. Alternatively, comparison of drug release profile from liposomes and porous silica NPs in medium containing proteins revealed that the shrinkage of liposomes and blockage of pores on porous silicon NPs lead to burst and delay release respectively. In addition to physicochemical characterization of NPs that can control the overall rate of drug release, biological identity derived by factors such as serum concentration, concentration of surfactants and the buffering capacity may affect the amount of passive diffusion of drug into the NPs (Fig. 3) [102].

3.2.4. Retardation of protein fibrillation

The variation of the conformation structure of adsorbed proteins on the surface of NPs can be reversible or irreversible which influences the protein stability. Protein instabilities have been reported in the self-assembly cluster [103,104] and linear amyloid forms in which the latter is resulted from the accumulation of insoluble protein Beta strand [38].

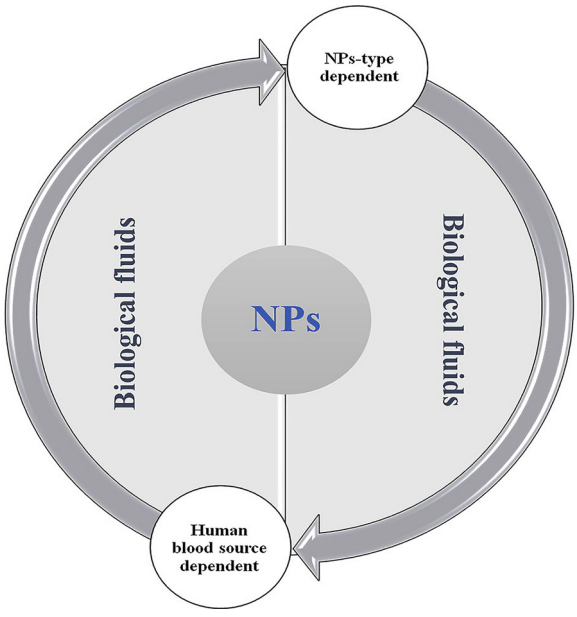

Fig. 3. Crosstalk between synthetic and biological identities.

The misfolding kinetic rate occurs much faster than unfolded type with human serum albumin [105] and Amyloid Beta (Aβ) [106,107].

Studies on corona coated NPs (e.g. Silica (100–200 nm), polystyrene (100 nm) and carbon nanotubes (CNTs)) except bare gold NPs and polymeric Mannan Nanogel [108], have reported that the plasma concentration, NP biological identity, incubation time [109] and the type of corona have inhibitory effects on protein fibrillation [109,110]. Mahmoudi et al. suggested that protein corona is an important factor for investigating the inhibitory effect of protein fibrillation on corona-coated compared to bare NPs [111]. It is concluded that the phenomenon occurs beyond the size, shape and surface chemistry of NPs [109]. A recent investigation reported that in both nanospheres/nanorods forms of gold NP, the accelerated or inhibitory proceeding of Aβ fibrillation is related to the type of amino acid residue attached to the NP surface [112]. The influence of protein fibrillation has become more important as this approach has led to a significant potential in the treatment of neurodegenerative diseases such as *Alzheimer's* and *Parkinson's* [104,110,112].

3.2.5. Uptake and cell vision

Physicochemical properties of NPs and different types of coating around it, generally govern the entity and intensity of the protein adsorption on NP surfaces. Finger adsorption of complement proteins, apolipoproteins, fibrinogen and immunoglobulins, refers to the localization, tracking, and NP distribution into the different organs [113–115].

NP uptake occurs in a two-stage process in which the NP initially attaches to the cell membrane and then internalizes into energy-dependent pathways [116]. The best known is that what the cell sees before membrane-NP interaction is a NP with a biological identity and not a man-made one, which is referred to as cell vision [113]. Due to the cell vision, the uptake of PH-sensitive NPs in both Hela and HEMC-1 cell lines, indicated that cell type provides different responses towards NPs [117,118]. The type of cell lines, the stage of cell cycle and protein interactions make changes to the cellular uptake pathways, providing different results for the bare and corona-coated NPs [42,119]. In certain investigations, low cellular uptake has been reported due to decreased adhesion of corona coated NPs to the cell membranes [87,120]. Conversely, other studies have reported an increased uptake of crowned protein nano-carriers [121,122]. This is a strategy for cellular detoxification which is exploited by the cells in response to the active pharmaceutical ingredients (APIs), such as API-loaded NPs, toxins and drugs [123].

The conformational rearrangement of adsorbed protein on NP surfaces, considered as the new epitope for cell surface-expressed receptors, can further enhance or inhibit uptake [42,113]. When adsorbed protein containing hidden epitopes conformationally is revealed on a particle surface, the exposure of new epitope sites may initiate an immune response and alters the cellular uptake process [113].

Time factor causes time-dependent of biological-identity changes, which as a result of dynamic modifications of protein hard corona, may have an impact on the cellular uptake. Due to the dynamic shift of high-affinity proteins instead of low-affinity proteins with time, NP size and the type of adsorbed proteins will be altered [124].

3.2.6. Predictable biodistribution

The distribution and accumulation of NPs are affected by the type and amount of the conformational adsorption of proteins on the NP surface. Adsorbed proteins on the surface of NPs are physiologically classified into different groups such as opsonins, dysopsonins, apolipoproteins and coagulation factors [50,125]. For instance, adsorbed opsonins enhance the liver-spleen accumulation whereas apolopoproteins provoke the brain targeting. Some dysopsonins such as albumin prolong the residence time and decrease the accumulation of NPs in liver [125].

Anatomical difference between normal and abnormal (such as the tumor) tissues can be effective in the distribution and accumulation of NPs as therapeutic agents. The vascular anatomical difference and the extravasation level can affect the efficiency and efficacy of nanoscale-based therapies. The vascularity and permeability of tissue are also effective in the biodistribution, where the impact of size may influence the accumulation of NPs in the tissue [61,126]. It should also be noticed that the amount of protein adsorbed on NP surfaces alters NP pristine size so that the new biological size plays an important role in tissue localization/accumulation [126,127].

3.2.7. Biomarkers detection

Biomarkers detection is a necessary need for the development of non-invasive diagnosis tests through the identification of proteins in the composition of the protein corona. The abundance and structure of vital plasma proteins conformation and other protein sources are altered by the clinical manifestations that are themselves influenced by the biomedical factors [19,128,129]. The new interface formed around the NP surfaces changes its synthetic identity [130]. Hard corona as *nano-concentrator* or *nano-accumulation* is a finger printwhich is very much dependent on the surface characterization of NPs, protein source and concentration, temperature and incubation time [12,56,128,131,132].

According to the costly and invasive screening test methods with low sensitivity, extensive investigations aimed at developing very fast, inexpensive, highly sensitive and non-invasive tests by perceptions of the protein corona which seems to be the easiest for early detection of cancers. In very early stages of cancer patients, minor changes in the concentration and functional structure of proteins [133] are not detectable by routine tests. In this area, citrate-capped gold NPs and *NanoDLSay* technique were used to measure the level of produced autoantibodies in prostate cancer patients in response to tumor. Zheng and colleagues reported that the level of IgG increases as an immunological response in the early stages of prostate cancer. By electrophoretic and electrostatic binding of immunoglobulins to citrate coated NP surfaces, the results showed a higher specificity and selectivity compare to the Prostate-Specific Antigen (PSA) test [134]. In other studies, spiking of tumorous prostate lysates in both benignand malignant tissue into human serum samples, resulted in a significant reverse correlation between the malignancy degree and the mean biological size of the citrate-capped gold NPs [135].

In addition to the specific autoantibodies of tumor antigens, apolipoproteins have been used for diagnosis, prognosis and progression of various cancers[129]. The incubation of liposomal NPs formulations with blood samples of 20 pancreatic cancer patients and 5 non-malignant samples resulted in four molecular weight regions between 25 and 120 kDa extracted from Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) gels. The results show that the four selective protein bands are a powerful tool for differentiating pancreatic cancer patients from healthy individuals [133].

3.3. Approaches based on protein source in biological system

3.3.1. Personalized/customized protein corona

The concept of personalized/customized protein corona (P/CPC) depicts the biological identity of NPs affected by the biological systems specialty such as medical background and lifestyle factors [19,128].

The concept relevance of P/CPC with the biomarker detection approach provide a relationship between diseases and detectable concentrated biomarkers on NP corona that is not possible to be detected by conventional methods. NPs could be designed and customized to tailored disease, gender, age, lifestyle and other factors. Besides of multiple diseases with variously plasma protein composition, some diseases (such as Alzheimer, Parkinson, Huntington, Lafora [136], Amyotrophic Lateral Sclerosis (ALS) [137] and frontotemporal dementia linked to chromosome 3 (FTD3) [138]) known as *proteinopathies* could trigger conformational changes in the plasma proteins [86,128,138–140]. For instance, fibrinogen with an affinity to the

Table 1
Analysis techniques of key parameter of protein corona.

Analysis techniques of key parameter of protein corona			
Key parameter	Relative changes to pristine nanomaterials	Method	Techniques
Thickness/Density	Impact on hydrodynamic size of NPs	Indirect	DLS,TEM,SEC,DCS
Affinity and kinetic of protein binding	Impact on the dynamic interface of bio-nano	Indirect	SEC,SPR,ITC,QCM,FCS, Zeta potential, AFM,UV-vis
		Direct	Fluorescence Quenching
Conformational information	Impact on the spatial rearrangement and presented epitope of adsorbed proteins	Indirect	DSC,FCS
		Direct	CD,FTIR,NMR,AFM,SERS
Qualitative assessment	Impact on the type of bio-identity	Direct	1D,2D SDS-PAGE, MS(in-gel, non-gel)
Quantitative assessment	Impact on relative protein abundance	Direct	Thermogravimetric Analysis, Bradford assay, BCA assay, nLC-MS/MS,ICP-MS

MAC-1 leukocyte receptor could be triggered by a series of inflammatory cascade due to the resulting conformational changes [141]. According to the studies in P/CPC, finding capillary relevance between this approach and other *RADAR* logic modules may result in translational, safe and efficient therapies [140,142,143].

3.3.2. Cell culture investigations

Other approaches that should be considered in the cellular investigation models include overlooked factors such as cell properties (shape, type, sex, size, origin and the number of the cell passages) [117,144–148]. The shape of native cells can be different due to the stiffness of the surrounding scaffolds. Two-dimensional media can affect the shape of the cells compared to the 3D media, considering the pressure of surrounding tissues and scaffolds [149,150].

Accordingly, many of NPs-cell responses with respect to the toxicity and cellular uptake can be affected by cellular diversity. The size of cells may be affected by the cell cycles, which plays a key role in NPs uptake quantity [151]. Another important factor in toxicity and intracellular trafficking of NPs is the cells sex. In focus-based studies of the cell sex due to the sex differences and the type of proteins and hormones, different uptake were reported in male and female cells [119,145]. Due to changes in the cell signaling pathways in different stages of the cell passages, the number of cell passage may affect the type of cellular responses [148,152,153].

4. Delivery strategy of NPs selected based on target tissue

The desired aim of efficient nano-based drug delivery systems is to enhance the *in-vivo* stability, cellular uptake and optimal therapeutic effect in the target tissue [154,155]. This aim is achieved by the drug controlled release, heightens the therapeutic index and diminished side effects [61]. This part of the *RADAR* modules is dedicated to the preparation method for NPs development. NP-based biomedical products based on a safe therapeutic intention have not been much progressive [60,156], most likely because of the challenges related to the hidden factors like protein corona. Different nano-carrier with various compositions such as inorganic NPs, polymer NPs, solid lipid NPs, liposomes, nanocrystals, nanotubes and dendrimers are used for biomedical applications and diagnostic imaging [156]. For example, various methods are applied to synthesize polymeric NPs [157,158].

NPs surface modification is the most common strategy in order to improve nanomaterial resident time in the bloodstream through the non-specific bio-distribution reduction and targeting at tissues and cell-surface receptors using targeting ligands such as aptamers, peptides, and small molecules [159]. Along with modification approaches, NPs could be engineered by hydrophilic protecting compounds such as PEG (anti-fouling agent) [160], Zwitterion (protein and non-protein) compounds [76,161] and selective pre-coating protein [74]. The development of different methods for selectively adsorbing proteins could intensify the efficacy and efficiency of NPs to increase the resident time, non-specific biodistribution reduction due to immunologically-protective coatings [159]. Surface coatings with hydrophilic excipients that do not provoke immunological responses, are the potential approaches to escape the invisible NPs from the immune system, known as the *Trojan horse* or stealthing method [162–164]. Using this method, NPs (with a size less than 100 nm) hydrophilic surfaces modified by human serum albumin, PEG, polyvinylpyrrolidone (PVP) and polysaccharides have the greatest capability to bypassing the molecular phagocytic system [162].

There are two strategies for active and passive targeting in the design of drug delivery systems. In passive targeting, anatomical discrepancies between normal and overtaken tissue are exploited for drug delivery [165]. Active targeting is achieved by identifying the ligand-receptor through the antigen-antibody interaction as well as targeting by aptamers [166]. As noted by some studies, poorly *in-vivo* targeting NP might be due to the biomolecules and ligands masking on NP surfaces by protein layer [61]. For example, using NP albumin bound (*Nab*) technology by the mediation of the 60-kDa endothelial cell surface glycoproteins is an effective opportunity for intensifying drug targeting to the target site and toxicity reduction [18]. Therefore, the factors modifying development of nanostructure formulation with impact on the corona pattern may affect the efficacy, biocompatibility and safety [8].

5. Analysis and characterization of proteins present on corona

Various classifications have been suggested for recapitulation of techniques in studying and evaluating protein corona [167–170]. Only by using different analytical techniques (Table 1) it may be possible to evaluate the changes in NP physicochemical features or changes in native proteins (due to structural or conformational changes) as well as change of corona coating into primary NP (e.g. changes in size, density, mass, drug release and bio-stability) [8,18,167,169,171]. Methods of direct protein corona evaluations investigate adsorbed protein on the NP surfaces and provide data about the structure, identification and quantification of proteins (Fig. 4A). Some of the direct methods such as Gel Electrophoresis (GE) [76,112,172,173], Mass Spectrometry (MS) [174] and Inductively Coupled Plasma Mass Spectrometry (ICP-MS) [175], can determine loose proteins after digestion, but in some there is no need for destructive digestion such as Nuclear Magnetic Resonance (NMR) [176], Circular Dichroism (CD) [177], Fourier Transformed Infrared Spectrometry (FT-IR) [178], Atomic Force Microscopy (AFM) [75,179] and Surface Enhanced Raman Scattering (SERS) [180]. The latter techniques investigate the structural and conformational changes of adsorbed proteins on the NP surfaces. However, nano Liquid Chromatography-Mass Spectrometry (nLC-MS) and ICP-MS determines the adsorbed proteins and for total protein evaluations the bicinchoninic acid assay (BCA) Bradford has been used. In GE, qualitative and semi-qualitative data on proteins are provided based on the molecular weight of standard proteins [167].

Imaging techniques for evaluation of protein corona such as fluorescence quenching are based on the inherent fluorescence characteristic of proteins that contain amino acids (tryptophan, tyrosine and phenylalanine) or dye labelled protein. Formation of NP-protein complex may

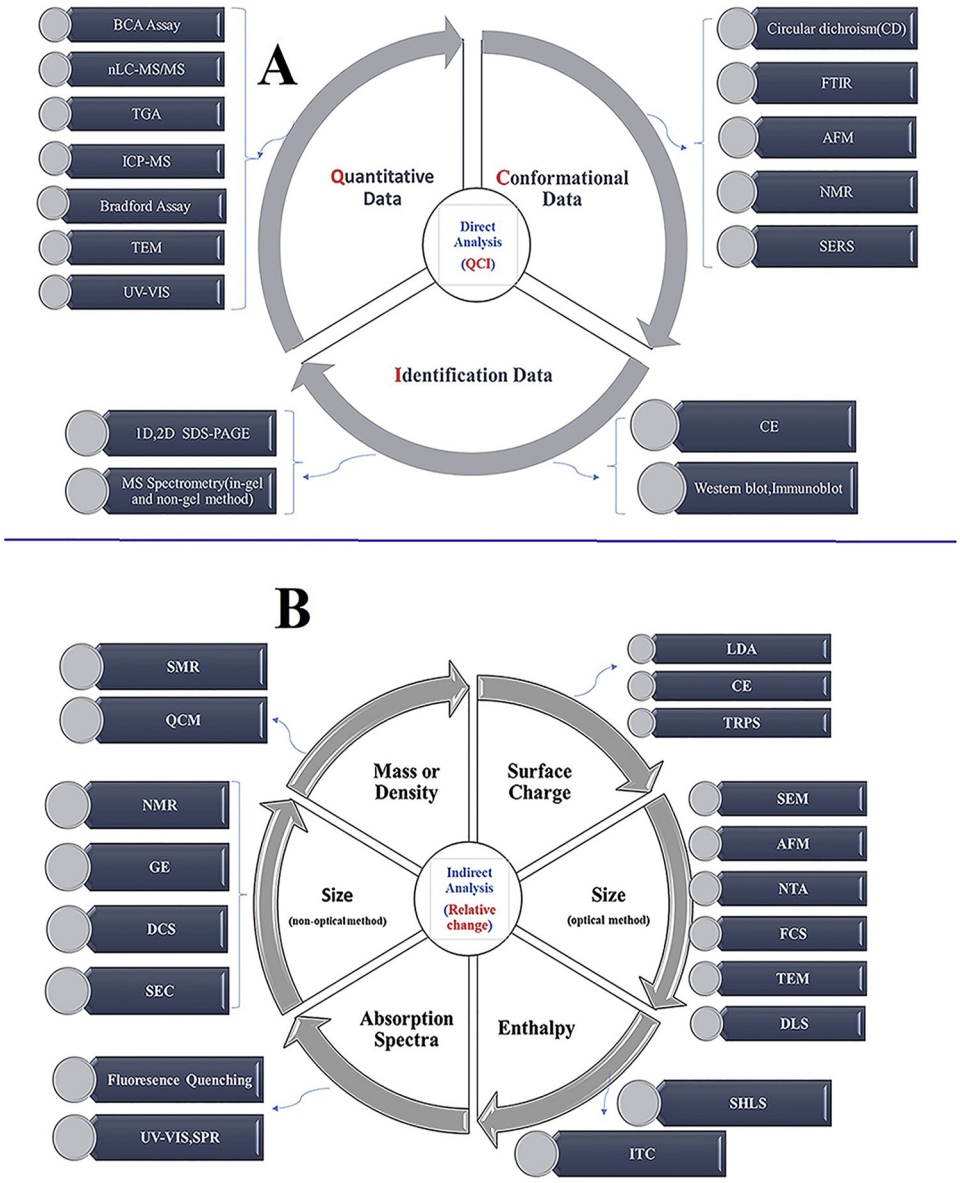

Fig. 4. Direct (A) and indirect (B) methods for protein corona analysis.

lead to quench protein fluorescence [181]. By interaction of the quencher molecules with fluorophores, the intensity of the fluorophore may be decreased, due to direct quenching of the inherent fluorescence proteins or as a consequence of the conformational changes on adsorbed proteins [182].

Alteration of NPspristine characteristic is another view point to study protein corona, which could complete the visual puzzle of the protein impact by indirect methods. In indirect methods (Fig. 4B), protein corona is investigated through the comparison of a biological identity versus synthetic identity [167]. Modification of NPs pristine characterizations such as the synthetic size, charge and density, fluorescence properties, mass and plasmonic properties may alter the biological identity and needs to be investigated by analyzing the protein corona [167,169,171].

Several techniques have been used to measure the NP increased size in biological environments such as serum, plasma, vitreous and cerebrospinal fluid. NP Tracking Analysis (NTA) [183], Transmission Electron Microscopy (TEM) [184], Scanning Electron Microscopy (SEM) [185], Dynamic Light Scattering (DLS) [186] and Fluorescence Correlation Spectroscopy (FCS) [187] are optical-based techniques. Non-optical techniques such as Nuclear Magnetic Resonance (NMR), Size Exclusion Chromatography (SEC) [188]and Differential Centrifugal Sedimentation (DCS) [189] provide proper information on the size of protein-coated NPs. Surface charge that may be affected by the biological systems could be analyzed by Laser Doppler Anemometry (LDA) [114], Tunable Resistive Pulse Sensing (TRPS) [190] and Capillary Electrophoresis (CE) which are the strong techniques for measuring the electrophoretic mobility of NPs in non-filler columns [191]. Quenching or enhancing NP fluorescence and ultraviolet–visible (UV–vis) absorption spectra shift to the red zone by plasmonic NPs as well as the plasmonic peaks expansion provide the other investigation evidence of indirect methods [167].

Surface Plasmon Resonant (SPR) [192] and Multiplexed SPR techniques [193] are used for lacking plasmonic effect of NPs. The second harmonic light scattering (SHLS) technique [194] is used to measure the number of adsorbed protein molecules on the NP surface. An index of NPs that could be affected by protein corona is the mass variation that is measurable with Quartz Crystal Microbalance (QCM) [195] and Suspended Microchannel Resonator (SMR) [196] methods. In addition to the SHLS, the Isothermal Titration Calorimetry (ITC) has been used

to determine the thermodynamic parameters of the corona protein formation, such as constant binding affinity and the enthalpy variations [167,168,171].

6. Risk assessment and risk reduction upon the collection and analysis of results to increase drug delivery efficiency and drug efficacy

In this part of the *RADAR* grouping strategy model, improvements of the protocols on the basis of corona extraction and toxicological effects will be discussed. A clear understanding of non-formulation factors such as temperature [197], time [198], osmolality [199] of the biological environments and the blood flow speed [12] (bio-fluid rheology) should be dedicated to surveying dynamic factors in protein corona measurements [6]. In order to obtain repeatable data in *in-vitro* and *in-vivo* bio-nano interface, the revision of the protein corona protocols could minimize the major challenges in this field and will be debugged the discrepancies in various studies. The different strategies applied for protein adsorption on NPs are reported differently in terms of bio-fluid type and concentration of proteins [174,200]. One particularly important factor of discrepancies in the protein corona investigation is the incubation time with plasma. For instance, in some studies the incubation time is reported to be varied from 30 min to 12 h [29,90]. Additionally, in some studies the interactions of NPs with plasma proteins have been carried out at ambient temperature [12] or at 37 °C [174], which indicates the difference between operational protocols. Therefore, the prerequisite for more reliable and repeatable *in-vitro/in-vivo* data is the provision of SOP for different NPs. The reported protocols in a series of conducted studies on biocompatible Poly(lactic-co-glycolic acid (PLGA)-based NPs, protein adsorption vary in terms of the quantity of NP mass, incubation time, centrifuge speed, and the protein digestion techniques [6,29,90,201]. Consequently, integrating these variables into man-made NPs dedicated to the laboratories and various protein sources causes conflicting reports in protein corona data. The uniformity absence of dedicated protocols means that the toxicological rules should be reassessed, due to revised toxicological protocols focused on the bio-nano interface could mitigate the bottlenecks [202] in the toxicology method whereby a unifying protocol is deployed between various labs for reliable and realistic toxicity investigations [203]. Therefore, identifying the hidden factors and updating of toxicological protocols by overlooked factors is essential in nano-toxicology fields. However, during the toxicological investigation, the conformational shift of proteins hidden motifs to the presented active site as well as the pH changes may decrease or increase [56] the overall toxicity of NPs, which should not be ignored after corona formation [89].

7. Conclusion

Many factors called as hidden factors may cause the major discrepancy in the investigation results of bio-nano interface. The main objective of bio-nano investigation models (e.g., challenge-opportunity or approach-oriented), is the development of safe, efficient and custom-designed nano-systems. In the present review, we proposed a new model in five modules related to the protein corona that remarks the impress of the corona issue on NP efficiency, biodistribution, cell uptake, toxicity, immunological recognition, targeting capability and drug release. The *RADAR* model is the dynamic and 360-degree outlook that represents grouping strategy of key factors in the bio-nano interface. This model can be related to the adoption of appropriate approaches along with the design of bio-nano assessment techniques. The complete account of the impressible factors in bio-nano interface requires a revised corona protocol to ensure that the consequences of *in-vitro* and *in-vivo* investigations are repeatable and reliable.

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