International Journal of Pharmaceutics 552 (2018) 328–339

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

The impact of protein corona on the behavior and targeting capability of nanoparticle-based delivery system

Wei Xiao, Huile Gao*

Key Laboratory of Drug Targeting and Drug Delivery System of the Education Ministry, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China

ARTICLE INFO

Keywords:
Nanoparticles
Protein corona
Protein adsorption
Targeting capability
Biodistribution

ABSTRACT

Once introduced into physiological environment, nanoparticles (NPs) are immediately coated with proteins, resulting in formation of what is known as protein corona. The formation of protein corona can be affected by many factors. Likewise, the addition of protein corona can alter the physicochemical properties and biodistribution of NPs. NPs with the coating protein corona can be considered as a biological identity that recognized by cells in biological system. Thus, to understand and regulate the effect of protein corona on targeting capability of NPs in vivo, it is necessary to elucidate the interaction between the NPs and the biological fluid. In this review, we first elucidate the factors influencing the formation of protein corona, including NPs physicochemical factors, such as NPs composition, size, shape, surface chemistry, etc., and environmental factors, such as environmental temperature, protein origins, etc. Then, we focus on the effect of protein corona on the passive targeting and active targeting, and discuss the probable reasons that causing the discrepant results. Finally, we review the strategies for tuning the protein corona to promote targeting, including reducing protein adsorption and recruiting specific proteins.

1. Introduction

As nanotechnology progresses these decades, many types of carriers have been developed for drug delivery, including liposomes, micelles, dendrimers, and polymeric and organic nanoparticles (NPs). Encapsulation of therapeutics in NPs can increase their solubility and stability, alter their bio-distribution, minimize side effects, and also improve targeting efficiency. Tumor targeted delivery strategies are usually divided into two types: passive targeting and active targeting. Passive targeting is based on the accumulation of NPs in specific tissues via the enhanced permeability and retention (EPR) effect (Fang et al., 2011; Ngoune et al., 2016). While active targeting can build on the effects of passive targeting, and often involves utilizing ligands on the surface of NPs for specific binding to receptors that overexpress on target cells by receptor-mediated mechanism (Choi et al., 2010; Yu et al., 2010). Despite recent advances in targeted therapy for cancer, only 15 passively targeted NPs have been clinically approved and none of the actively targeted NPs has advanced past clinical trials (Rosenblum et al., 2018). What are the potential reasons for their limited clinical translation? Is protein corona the missing link?

In biological environments (e.g., blood), proteins adsorb onto the surface of NPs and form the protein corona. The interaction between proteins and NPs is critically determined by intrinsic NPs properties (i.e. NPs composition, size, shape, and surface characteristics) and environmental factors (i.e. gradients of plasma, kinetic equilibrium constants, circulation time and temperature) (Charbgoo et al., 2018; Neagu et al., 2017). As a result, the adsorbed proteins create a unique biological identity of NPs, regulating their interactions with cells and barriers in biological system and determining their biological fate and pharmacokinetics (Caracciolo et al., 2017; Monopoli et al., 2012).

Ideal blood clearance and tissue selection is the ultimate aim of targeted therapy. However, according recent meta-analysis, less than 1% of the injected NPs reached the solid tumor site (Wilhelm et al., 2016). To achieve optimal targeting, more attention has been paid on the corresponding mechanistic studies (Cox et al., 2018; Guan et al., 2018). So far, increasing studies describe the impact of protein corona on NPs targeting (Corbo et al., 2015; Gaspar, 2013). Intravenously administered NPs can bind to opsonins which can be recognized by the mononuclear phagocyte system (MPS). It is regarded as a limit step for long-circulating and targeting (Gao and He, 2014). While adsorption of dysopsonins can improve the blood circulation and is good for targeted delivery (Gao and He, 2014). As for actively targeted NPs, some work reported that its targeting ability can be lost or maintained in the presence of plasma proteins (Kang et al., 2015; Salvati et al., 2013).

* Corresponding author.
E-mail address: gaohuile@scu.edu.cn (H. Gao).

https://doi.org/10.1016/j.ijpharm.2018.10.011
Received 8 September 2018; Received in revised form 4 October 2018; Accepted 6 October 2018
Available online 09 October 2018
0378-5173/

Therefore, the protein corona is not always detrimental. In-depth understanding these influences is important to improve targeting effect.

To minimize the adverse effects by protein corona and promote NPs targeting, many strategies were developed, such as reducing protein adsorption or recruiting specific proteins with specific targeting ability, etc (Dai et al., 2015b; Moyano et al., 2014). As our understanding is increasing, it is hopeful to rationally design drug delivery carriers with highly efficient targeting capability.

In this review, we focus on the effect of protein corona on NPs targeting. The factors affecting the formation of protein corona and the strategies for tuning the protein corona to promote targeting are discussed as well.

2. Protein corona formation and influencing factors

Biological media comprise a variety of active biomolecules, including proteins, lipids, nucleic acids, metabolites, etc. As the most important biological media, blood plasma carries roughly 3700 identified proteins at protein concentration typically 60–80 g/L (Chen et al., 2017a). Clearly, NPs injected in the blood fluids are immediately (< 30 s) coated with proteins resulting in formation of protein corona (Tenzer et al., 2013). Varied forces contributing to this NPs-protein interaction include H-bonds, van der Waals interactions, electrostatic interactions, hydrophobic interactions, and π-π stacking interactions, etc (Yang et al., 2013). According to the 'Vroman effect', high abundant, low-affinity proteins are dynamically replaced by lower abundant, higher-affinity proteins over time during the nano-bio interaction (Dell'Orco et al., 2010; Vroman et al., 1980). The 'hard corona' represents the tight-binding, non-exchangeable layer of proteins whereas the 'soft corona' represents the loose-binding, highly exchangeable layer (Milani et al., 2012). As a dynamic process, these complicated interactions are not only highly dependent on the NPs properties, but also on the biological environment (Charbgoo et al., 2018). These adsorbed proteins with NPs together form a unique biological identity that really interacts with barriers encountered and render their in vivo targeted behavior. Thus, the study of the nano-bio interaction can help to investigate the unpredictable behavior of NPs.

2.1. NPs physicochemical factors

NPs composition is a critical factor in determining the affinities and species of proteins that adsorb on NPs. Caracciolo and co-workers showed that species of lipid that used for liposome preparation significantly influence the liposome-protein corona composition (Caracciolo et al., 2015). The authors revealed that DOTAP specially promotes the adsorption of apolipoproteins and vitronectin, whereas DOPE selectively induces the adsorption of apolipoproteins and serum albumin. In particular, Both DC-Chol and cholesterol elevates the binding of opsonins, including immunoglobulins and complement proteins. Lai and co-workers have studied the binding of human plasma proteins to 20 nm gold and silver NPs with the same surface modification (Fig. 1) (Lai et al., 2017). They demonstrated that the core material of NPs significantly determines the qualification and quantification of corona proteins on NPs.

Particle size, which is associated to the surface curvature of NPs, plays a vital role on the formation of protein corona. Due to surface curvature effect, proteins tend to adopt varied conformations on the surface of NPs compared to flat surfaces, resulting in different protein binding affinities (Hill et al., 2009). Previous researches have demonstrated that binding constant depends on the NPs size. Yin and co-workers also showed that binding constants of human serum albumin (HSA) were gradually increased with the increase of Au nanoclusters size, which may be attributed to the different binding ways of HSA to NPs of different surface curvature (Yin et al., 2017). Therefore, the effect of particle size on binding constant may further affect the formation of protein corona. Lundqvist and co-workers demonstrated that the particle size influences the type of absorbed proteins around NPs (Lundqvist et al., 2008). Our group identified that smaller size of gold NPs could reduce plasma protein adsorption (Xiao et al., 2018). Clearly, particle size significantly affects the composition of protein corona. Piella and co-workers investigated the in vitro formation of protein corona on highly monodisperse citrate-stabilized gold NPs with size ranging from 3.5 to 150 nm. They observed that the thickness and density of the protein corona were strongly dependent on the particle size: the smaller the particle, the thinner the protein layer. In addition, they further revealed the key role that size plays in the kinetics of this adsorption process, in which the protein coating came more quickly for smaller NPs (Piella et al., 2017). Another researcher showed the adsorption of lysozyme reached saturation within 10–15 min for 100 nm nanodiamonds (NDs), whereas 30–40 min were demanded for 5 nm NDs (Perevedentseva et al., 2011). Remarkably, the size of NPs is a key determinant governing the adsorption kinetics. Although many in vitro studies have identified that particle size plays a vital role in protein corona formation, specific relationships under realistic in vivo conditions still remain elusive. Researchers have presented a study of in vivo protein corona formation after systemic injection of gold nanostars (AuNSs) with two sizes of 40 and 70 nm (Garcia-Alvarez et al., 2018). A significant larger amount of protein was found to adsorb onto 70 nm AuNSs than the corresponding 40 nm AuNSs, whereas a higher number of protein types was significantly higher in the case of 40 nm AuNSs, which means smaller AuNSs showed a more complex protein corona. Above results also demonstrated that the total amount of absorbed protein does not necessarily reflect the complexity of the protein corona composition.

The geography or shape has a great impact on the structure and composition of protein corona. The helicity of hemoglobin and HAS that binds to NPs was reduced after the shape of NPs was changed from spherical to triangle through TEM and CD analysis, as described by Chaudhary and co-workers (Chaudhary et al., 2016). A in vivo study showed that 40 nm gold nanostars (AuNSs) displayed a significantly higher number of protein types than 40 nm gold nanorods (AuNRs). However, there was an opposite behavior for 70 nm NPs, where AuNRs presented a more complex protein corona than AuNSs of a similar size (Garcia-Alvarez et al., 2018). The different adsorption behaviors between above two sizes suggest that protein corona formation is governed by multi-factors.

Surface chemistry of NPs includes surface modification, charge, and hydrophobicity/hydrophilicity, etc. In this section, surface modification that is another crucial factor influencing the formation and evolution of protein corona on NPs, will be mainly discussed. Protein adsorption can be tuned by modifying the surface properties of NPs (Fig. 2). Covalently linking, adsorbing or entrapping polyethylene glycol (PEG) onto the surface of NPs that have become the gold standard for controlling the surface properties of NPs. The use of PEG can endow NPs with the so-called "stealth" properties to reduce the protein adsorption (Pelaz et al., 2015). A study reported by Benetti and co-workers showed that 60 nm PEG-coated gold NPs presented a significantly lower protein adsorption compared to the 60 nm citrated-coated gold NPs. However, there were no significant differences for 10 and 200 nm sized NPs (Benetti et al., 2013). Thus, both the surface modification and the size of NPs were indeed important determinants governing the complex process of protein adsorption. Importantly, different ligand modification will induce different effects on protein corona formation. Our group recently demonstrated that the larger molecular weight of transferrin (Tf) showed a greater influence on the adsorption of plasma proteins than the smaller molecular weight of RGD peptide, which may show different influences on targeting ability (Xiao et al., 2018). In addition, another study reported by our group recently identified that different size and conformation significantly affect the in vitro and in vivo protein corona formation by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and Nano-LC-ESI-MS/MS methods (Zhang et al., 2018). In this study, three types of Tf receptor (TfR)-targeting ligands