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Review article

Gold nanoparticle should understand protein corona for being a clinical nanomaterial

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ABSTRACT

Gold nanoparticles (AuNPs) have attracted great attention in biomedical fields due to their unique properties. However, there are few reports on clinical trial of these nanoparticles. In vivo, AuNPs face complex biological fluids containing abundant proteins, which challenge the prediction of their fate that is known as “bio-identity”. These proteins attach onto the AuNPs surface forming protein corona that makes the first step of nano-bio interface and dictates the subsequent AuNPs fate. Protein corona formation even stealth active targeting effect of AuNPs. Manipulating the protein corona identity based on the researcher goal is the way to employ corona to achieve maximum effect in therapy or other applications. In this review, we provide details on the biological identity of AuNPs under various environmental- and/or physiological conditions. We also highlight how the particular corona can direct the biodistribution of AuNPs. We further discuss the strategies available for controlling or reducing corona formation on AuNPs surface and achieving desired effects using AuNPs in vivo by engineering protein corona on their surface.

1. Introduction

Emerging field of nanotechnology had introduced different nanomaterials with diversity in shape, size and properties [1,2]. Among them, researchers paid specific attention to gold nanoparticles owing to the significant progress made in their highly efficient and easy-to-make synthesis processes, surface functionalization, and promising biomedical applications [3–7]. These include bio-imaging [8], analytical sensing [9], gene diagnostics [10], photothermal treatment of tumors [11], and targeted delivery of various biomolecular and chemical cargos [12–14]. To date, there are six clinical trial studies based on AuNPs demonstrating the increased willing to use them in clinics [15–20], but there is still no drug based on AuNPs in clinics.

In vivo, AuNPs would be intravenously injected or enter through oral ingestion causing their exposure to a very complex environment of blood and digestive tract. There, high levels of metabolites, lipids, sugars, ions [21] and specifically proteins would be adsorbed onto the AuNPs surface due to high surface energy [22–24] forming so called biomolecule corona which first introduced by Owens [25]. It is now accepted that protein corona (PC) is the most important class of corona formed in vivo. It is known that proteins are complex macromolecules with diversity in weights, charge and hydrophilicity that can be adsorbed onto all NPs surface during first few minutes when being exposed to blood or biological fluids [26]. The adsorption of proteins on AuNPs surface can be organized through irreversible interactions, i.e. producing the so-called hard corona, or through weak “protein–protein” interactions, that provides soft corona [3,5,22]. Formation of a PC critically affects interactions, cellular recognition, uptake and intracellular location of AuNPs in biological media and alters their bio-identity, which differs from their synthetic identity. It is demonstrated that three different surface modified-AuNPs after coating with one identical blood protein like hemoglobin as PC show similar biological effect independent of surface modified agent [27]. The reason is that the cells could only see PC not the modified-AuNPs.

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For a decade, considerable studies have been made on the effect of PC on AuNPs in vivo [28,29] since untangling the AuNPs fate while facing biological milieu is crucial for their future use in the biomedical and clinical studies. To date, several reviews have been published which discussed different aspects of PC formation on nanomaterials [22,30–39]. However, here for the first time, we reviewed particularly the bio-identity of gold nanoparticles while enter the body regarding protein corona formation and the points shall be considered for engineering corona composition on AuNPs and methods of their analysis. We also investigated the current inconsistency facing PC impacts on AuNPs bio-identity and different approaches to avoid PC formation on AuNPs in order to have effective targeting, long circulation time and predictable therapy.

2. Untangling protein corona on AuNPs surface

As AuNPs found elevated applications in both diagnostic and therapeutic approaches, their "nano–bio" interface and potential to adsorb proteins has attracted great attention in recent years. Using different techniques, it is now clarified that some proteins could more abundantly bind to the surface of AuNPs through specific interactions that are all mentioned below (Chart 1).

2.1. Molecules involved in protein corona formation on AuNPs surface

It is demonstrated that > 70 different serum proteins are heterogeneously formed corona on AuNPs surface [40,41]. Regarding the molecular scale, it is believed that proteins that are more abundant can extensively interact with AuNPs surface. This leads to dynamic competition between the species already exist on the surface and the additional molecules, which bind to AuNPs, surface via slower association rates, but eventually higher affinity [42]. The four most common serum proteins, human serum albumin (HSA), fibrinogen, apolipoprotein A1 (ApoA1) and immunoglobulin G (IgG), were reported to form hard corona on AuNPs [43]. Among these proteins, ApoA1 had the highest affinity for the surface of AuNP. After that, fibrinogen and HSA had high affinity, respectively while the lowest affinity was exhibited for IgG [42,44]. Other proteins such as hemoglobin fetal subunit beta, α-2-HS-glycoprotein, α-1-antiproteinase, hemoglobin and apolipoprotein C − III were respectively demonstrated to attend in corona formation on Au-based nanomaterials [44,45]. Moreover, comparing fibrinogen and insulin as two abundant proteins of plasma accurately demonstrated that single layer of proteins surrounded the AuNPs constitute up to 20 insulin and only 3 fibrinogens [46]. This fact is a critical point in the field of diabetes research. It is worth mentioning that fibrinogen triggered a rapid and irreversible agglomeration with AuNPs [43] which makes sense because upon entry into the interstitial spaces it encounter a space rich in fibrinogen. Currently, significant data has been collected considering the structure and activity of the PC in blood, plasma of human and mouse. For example, findings from the experiments in mouse indicated that the two proteins alpha-1-antitrypsin 1-1 and kininogen-1 had important role in AuNPs binding to the cells as promoter and inhibitor, respectively [47].

However, it is now known that PC identity is naturally dynamic and alters over time, environment and NP physicochemical properties [48].

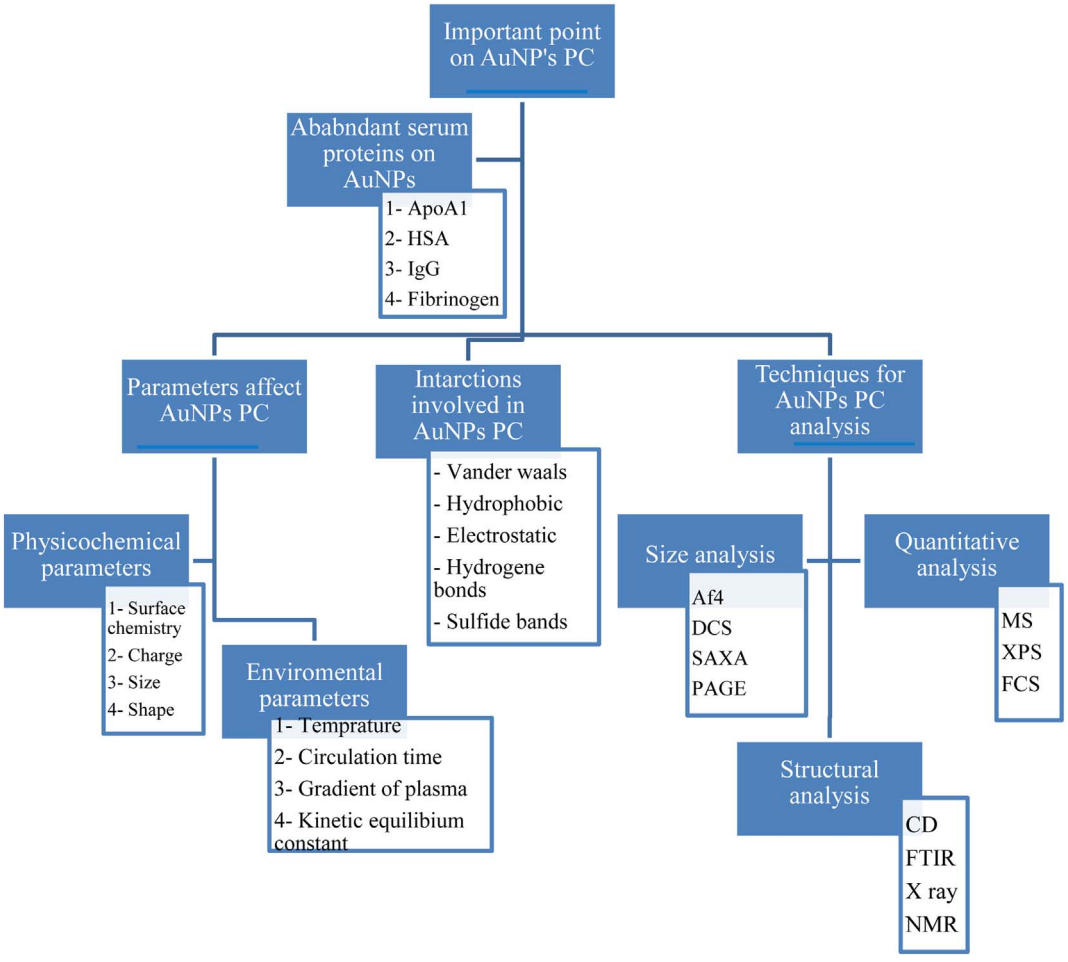

Chart 1. Summarizing all-important point related to PC formation on AuNPs surface.