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A review on Nanoparticle and Protein interaction in biomedical applications

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Abstract

Nanoparticles are molecules with size depended chemical and pyhsical characteristics, enabling interesting and correlated approaches while dealing with fundamental biological questions. Nanoparticles are capable of strong and important interaction with other molecules. Many different nanoparticles are produced, with variety of different roles, but Gold nanoparticle as metal based beads, have specific importance due to their attractive physical and chemical properties, biocompatibility, and facile surface modification. In general, nanoparticles have the ability to interact with whole physiological surrounding once when they enter human body. In most of the cases, first molecule they interact with are proteins, which are the main constituens of human body and the driving force of most of the biological processes. This understanding of interaction between nanoparticles and proteins represents an important essence for secure and efficient application of nanoparticles. In this regards, several methods for nanoparticle-protein interaction were developed and analysed in this review.Further, this paper reviews the current scientific development in nanoparticle-protein interactions.

Keyword:Nanoparticles (NPs), Goldnanoparticles (GNPs), Nanomedicine, Protein corona

1. Nanoscience and Nanomedicine

Nanoscience technology had outstanding developments in the past decades that enables usage of micro-scale and nano-scale materials in different areas of technology and medicine. Nanoscience depends on exact organization of nanoparticles in the order to get unique functionality [1].Nanoscientists aim to build new materials with ultimate properties, miniaturize existing products and of course provide us with deeper understanding of nature and life [2] . Nanoparticles, especially due to their size (100nm), have specific features that are ideal for manipulating biological interactions. In this regards, it is very important to understand nanoparticle interaction at cellular, sub-cellular and bio molecule level [3,4,5].Nanoparticles can be used as drug or drug carrier, acting like double-edged sword, they can be toxic agents or platform for therapy. Scientists are working hard to find nanoparticles that have most suitable properties for therapeutic applications [6], mostly for purposes of transporting small molecules as well as bio-macro - molecules to diseased cells or tissues [7].Furthermore, nanoparticles are being used to probe biological processes that are critical for diagnostics, but still there is no enough knowledge about potential risks from nanoparticles therapeutics applications [8].

Nanomedicine, based on application of nanoparticles in medicine has great capacity to treat viral or genetic diseases and even cancer, since smaller objects are more practical for the cell manipulation and disease treatment in humans. The national Cancer Institute and National Aeronautics and Space Administration, USA is working to develop nano sized technologies that can detect, diagnose and treat disease.Nanoscience and Nanomedicine could lead to next generation of products, diagnostics, and medical device, and enhanced gene therapy, tissue engineering procedures, medicine and medicine delivery techniques. On the other hand, knowledge about bio-compatibility and risk of exposure to nanoparticles is limited and there is a great need of comprehension the molecular mechanisms of interactions between nanoparticles and biological systems [6,9,10].

Understanding the protein-nanoparticles interactions is essential to stabilize and deliver protein-based therapeutic drugs and vaccines. In this regards, the purpose of this paper is to review the importance of nanoparticles-proteins interaction and to explain the basics of most important analytical methods responsible for characterization of nanoparticle-protein interaction. Furthermore, this review will focus on interaction of nanoparticles with bio molecules, with special emphasis on interaction of gold nanoparticles and proteins.

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2. Nanoparticlesand Protein corona

Size of nanoparticles makes them able to enter in almost all parts of human body, including cells and organelles, while flat surfaces can only affect biological processes via cell surface receptors such as integrins[9, 11].When nanoparticles enter biological fluid, the first molecule that will react with nanoparticles, are proteins in more than 95% of all cases. The result of protein coating on nanoparticles surface is protein corona [10]. Protein corona may influence cellular uptake, inflammation, accumulation, degradation and clearance of nanoparticles[12]. Proteins of protein corona can change their native conformation, influencing the downstream regulation of protein-protein interactions, cellular signal transduction and transcription of DNA. For a better understanding of interactions between nanoparticles and proteins, we acquire information on binding affinities and stoichioetries for different combinations of proteins and nanoparticles. Adsorption of protein on nanoparticle surface is aided by hydrogen bonds, solvation forces, Van der Waals interactions, etc. [13,14]. Since different nanoparticles have distinct properties, the composition of protein corona is unique to each kind of nanoparticles and depends on many parameters [11].

The proteins corona can be hard and soft. It is thought that hard corona proteins interact directly with nanoparticle surface with high affinity, while soft corona consists of loosely bound proteins that interact with hard corona via weak-protein interactions [11]. Scientists proposed this model for protein corona as primary binders and soft corona as secondary binders that may influence hard corona and even prevent their interaction with the surrounding environment [15].It was shown that typical lifetime of hard corona can be even eight hours which indicates that hard corona defines the biological identity of the particle. Hard corona is formed in seconds, while the time of forming soft corona varies from seconds to hours. In contrast to hard corona with lifetime of around eight hours, soft corona will probably be desorbed in ten minutes [16]. Since there are many proteins that can absorb on nanoparticles in their biological environment, it is concluded that protein corona is not a fix layer and the composition of protein corona can be determined by kinetic rate of adsorption and desorption of each protein. Dynamic of protein corona as „biological identity“ might lead to more clear classification system of nano-safety and could be used for engineering of nanomedical products [9].

2.1. Parameters affecting protein corona

Due to diverse parameters that affect protein corona the scientific community can understand why some nanomaterial’s select specific type of proteins [11]. The most important parameters are explained in the following subparagraphs.

2.1.1. Surface charge of nanoparticle

Acting as important parameter in protein interaction, surface charge of nanoparticle can also denaturate the adsorbed proteins. It was found that proteins can denaturate when they interact with positively or negatively charged ligands, whereas neutral ligands can keep the native structure of proteins. In most study cases, positively charged nanoparticles were attracting proteins with isoelectric points less than 5, 5 such as albumin, but proteins with pI higher than 5.5 adsorb negatively charged particles [11].

2.1.2. Surface functionalization and Coating

Since nanoparticles are travelling through different environment of an organism, they may get pre-coated with different proteins and that pre-coatingcan determine which new proteins will bind to nanoparticle-protein complexes[10].

2.1.3. Hydrophobicity and Hydrophilicity

Nanoparticles withcharged orhydrophobic surfaces, tend to adsorb and denaturate more proteins than neutral and hydrophilic surfaces. This action happens due to clustering of hydrophobic polymer chain that forms distinct protein-binding sites [11]. Different particle features determine protein adsorption into nanoparticles, but hydrophobic interactions tend to be dominating feature [Schaefer, 2012]. In one study done in 2007, the affinity to nanoparticles of proteins that have uniform surfaces, increases with the increasing charge density and hydrophobicity [17].

2.1.4. Nanoparticle size

Same nanoparticles with different sizes have unlike compositions of protein corona[11], where nanoparticles have different sizes, from 70-700nmand that the amount of bound plasma proteins increased with increasing available surface area at constant particle weight[13].Nanoparticles surface area, available for protein binding, increases with decreasing of particle size [18].

2.1.5. Biological environment

Many in vitro studies have been done to examine nanoparticle-protein interaction, but it was still hard to predict the behavior of nanoparticles in living biological environment. That is why scientists are trying to use different cellular media in their experiments for better prediction in vivo events. In

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most case two different cellular media are used, Dulbecco's Modified Eagle's Media (DMEM) and Roswell Park Memorial Institute medium (RPMI) with differently sized citrate coated gold nanoparticles[19].

In the case of Gold nanoparticles, it is characterized that the dynamics of protein-nanoparticle interaction, can be differently mediated by different composition of cellular media. For example, DMEM cellular media induced a more abundant and stable protein corona on different sizes of gold nanoparticles, comparing to another cellular media,as withRPMI media [20].

3. Gold Nanoparticles (GNP)

In the last several years Gold nanoparticles (GNPs) became main topic of interest for researches around the world. Interactions of inorganic particles with biomolecules, like proteins, are central field of interest to biotechnology and nanotechnology[21].GNPs have potential to be used for treatment of AIDS, tumors and Parkinson`s disease [22]. These nanoparticles have therapeutic benefits in treating cancer. It is well known that ionizing radiation does not make difference between malignant and normal cells, so healthy cells are also being damaged. When cancer targeting molecules, such as antibody, nucleic acid aptamer, oligopeptide and small targeting molecules are attached to the surface of GNPs cancer cell targeting is enhanced [4]. These appealing properties make GNPs good model particle system and standard platform for nanomedicine applications [6].

The attractive physical and chemical properties of GNP, they are most commonly used as inorganic nanoparticles for biological applications [8]. Gold nanoparticles in nanoscale size have very different physical and chemical properties than those of bulk metal [6].GNPs have been used for electron microscopy (EM) because of their size, density and electrical properties, which are ideal for accurate diagnostic properties, by enhancing the contrast of images and for electrochemical biosensors [23].

3.1. How nanoparticles enters body

Using NPs for drug delivery, imaging, labelling and visualizing applications require knowing the routes of NPs entrance in the body [2, 8], and how they affect the organism when they enter [8]. Primary interface for NPs with human body are respiratory system, gastrointestinal tract and skin. One of the most common ways of entering the NPs into the organisms is through the respiratory system. NPs less than 2.5 μm in size can pass easily, but larger particles are removed from the respiratory tract by the mucociliary escalator. NPs can also be eliminated by NP translocation into the lymphatic system via their uptake by macrophages or NPs dissolution followed by the transfer of the products into the blood. Alveolar macrophages are also involved in the elimination of inhaled NPs. Interaction of macrophages with high concentrations of NPs can cause asthma, obstructive pulmonary disease or respiratory infection.In the case of moderate concentrations of NPs, it may cause autophagy or apoptosis of lung cancer, which is actually positive effect [11]. Skin serves as strong barrier for everything that can enter human body. But, certain types of NPs use skin for entering body, for example TiO2 particles found in cosmetics. Skin wounds can make entrance of NPs easier. And the third major way of NPs entrance into the body is gastrointestinal tract (GIT). When NPs enter the GIT they have two possibilities, entering the bloodstream, and soon getting to the liver or lymphatic system that may cause immune response [2].NPs can also be injected directly into the bloodstream where competition of different biomolecules can occur in order to be adsorbing on the surface of the NPs. At the beginning, at so called early stage, most abundant proteins (mainly albumin, IgG, fibrinogen and apolipoprotein) will be the first ones to adsorb, but later on those proteins will be replaced by proteins of lower abundance, higher affinity, and slower kinetics[2]. In this regards, other immunoglobulins, apolipoproteins and components of the complement system can later be nanoparticle-bound proteins. This phenomenon of competitive adsorption of proteins onto a surface based on protein concentrations, affinities and incubation time is called Vroman`s effect [11,24]. Vroman`s effect is very important in determining how the protein corona forms as the nanoparticle is moved from one part of the body to another [24].

4. Protein Adsorption on Nanoparticle Surface

After inhalation or ingestion very small portion of NPs (1% or less) will move to the bloodstream. There is a great chance that NPs agglomeration will occur too. Bio-distribution of NPs is very important and depends on adsorption of proteins in the different body parts and liquids. A model for characterization of NPs- small organic molecules biological surface adsorption index approach (BSAI), was developed and discussed. The model can applied for characterization of interactions between NPs and biomolecules (proteins, amino acids etc.) [10,25, 26]. NP-protein interactions are changing all the time, even within the same environment. Different factors can affect the kinetics of protein adsorption on the NP surface. One of the factors that influence the nanoparticle protein corona (NP-PC) composition is amount of proteins that may interact with NP surface. Apart from the amount of proteins, affinity of the protein toward the NP surface also affects the adsorption. Different proteins can arrange

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themselves differently on the NP surface. For example, plasma proteins such as human serum albumin adsorb in a monolayer on iron-platinum NP surface. The way the proteins arrange in this situation, can affect the biological reactivity of the complex (10).

5. Effects on Protein Conformation

Proteins are complex molecules made from long chains of amino acids. Each protein type differs in the sequence which makes the protein unique. That sequence determines protein`s shape, structure, function, and protein`s three-dimensional shape which is the native conformation of the protein[27]. The native conformation is stable, but can be easily disrupted by the interactions with the surface. The function of a protein changes with changing the conformation [9].

Proteins are known as surface active molecule; they can be adsorbed and accumulated in the interactions with other molecules which can even result in protein loss and degradation [28]. Proteins that are adsorbed on NPs can be used as biosensors and in drug delivery. This is why our understanding of the effect of NPs on the protein structure is crucial for nanomedicine application [14]. When proteins bind to planar surface, it is very possible that the changes in secondary structure will occur. The curved shape of NP surface can help proteins to keep their native conformation [30].

Nevertheless, different studies on NP –protein interaction indicate that disturbance of protein structure will appear in many cases [11]. By using fluorescence spectroscopy, we can observe the misfolded proteins that lose their normal biological activity [6]. When proteins adsorb on the surface of NPs, nanoparticle protein corona formation occurs depending on the characteristics of both NP and protein, and local environment. NP surface can change the structure of the adsorbed protein thus affecting the overall bio-reactivity of the NP [2,10]. For example, Gold nanoparticles can change structure in the bovine serum albumin (BSA) but no conformational changes occur when BSA adsorb to carbon C60 fullerene NP [10]. It is discovered that some proteins can keep their native structures, like RNAse and lysozyme on silica NP[29]. Hovewerm, a differenet study discovered also irreversible structural changes in albumin and lactoperoxidase on silica NP, proving that conformational changes depend on type of the protein and nanoparticles[10]. For biological applications of nanoparticle protein corona, it is very important that labelling does not change the protein structure so the protein can stay functional and active. Its is shown that binding and dissociation parameters of protein-NP complex depend on the surface characteristic of NP as well as physiochemical properties of the protein [1]. During the stronger binding of the proteins to the NPs, it is natural that conformational changes occur.

All the parameters that affect the strength of protein-NP binding also affect relative value of the protein-NP binding equilibrium constant (K). Protein-NP binding constant (K) quantifies the relative strength of the protein-NP binding [6]. Equilibrium constant for plasma proteins and GNPs are in the range of 104 to 107 (mol/L-1).

In the study on interaction of GNPs with human blood proteins it is observed increase of binding constant where NP size was in the range between 5 and 60 nm. This is in contrary to findings that show that binding association constant can decrease when NPs size is larger than about 80 nm [6].

There are thousands of different proteins in real body fluids, and those proteins actually compete to adsorb on the NPs surface. Change in conformation lead to peptide aggregation and the formation of amyloid fibrils. This was used for tracking development of several neurodegenerative diseases. Scientist shows that some NPs can inhibit the fibrillation of the disease-associated amyloid β protein [14].It can be concluded that still there is no enough information about how NP adsorption induces the level of protein conformational changes, even under conditions where protein binding constants are rather similar [6].

6. Nanoparticle role inProtein Fibrillation

Protein fibrillation is defined as process by which misfolded proteins form large linear aggregates or amyloid fibrils [31). Nanoparticles have great potential to enhance rate of protein fibrillation. Their potential to induce protein fibrillation is a function of both the NP surface charge, which promotes adherence of the protein, and its large surface area. The observation of fibrillation, which is a specific kind of aggregation phenomenon relevant for amyloid proteins, raises the possibility that NPs could play a role in increased risk of amyloidosis and other protein-misfolding diseases [32].Depending on their physiochemical properties, nanoparticles can have various effects on kinetics of amyloid beta peptide fibrillation process. For instance, positively charged super-magnetic iron oxide nanoparticles are capable of promoting fibrillation compared to uncharged nanoparticles at same particle concentration [33]. In addition, with their enormous surface area which act as a scaffold for protein adsorptions they offer significant potential for probing the mechanisms of protein fibrillation, and in the longer term for diagnosis or even treatment of amyloidogenic diseases [32,33].

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Numerous proteins and peptides are responsible for making amyloid fibrils during specific disease formation, including amyloid beta peptide, glucagon, polyglutamine protein, but most commonly used is amyloid beta peptide. Since amyloid beta peptide is amphipathic molecule that is prone to self-association and formation of fibrils, it is used as model peptide to investigate the effects of nanoparticles on fibrillogenensis [34].

7. Methods Used For Protein-Nanoparticle Interactions

Proteins that are part of nanoparticle protein coronaare being isolated and identified in order to understand bio-reactivity of specific NPs. Methods that can be used to study NP-protein interactions are numerous, but the most common are Fourier transform infrared spectroscopy (FTIR), Circular Dichroism (CD) spectroscopy, Isothermal titration calorimetry (ITC), Surface plasmon resonance (SPR), Fluorescence spectroscopy, Nuclear magnetic resonance (NMR) spectroscopy but the most used method for studying nanoparticle protein corona is Mass spectrometry (MS). Mass spectrometry can be used for many types of NPs and is used to identify proteins and quantify amounts of proteins adsorbed on NP surface [9,10]. Combination of these methods should provide more complete picture about protein-nanoparticle interactions; protein structure and conformation upon their interaction with nanoparticles [6].

7.1. Fourier transform infrared spectroscopy (FTIR)

FTIR provides useful information on protein-nanoparticle interaction. FTIR has ability to give detailed description of bonds, their lengths, strengths, angles and conformation, chemical and physical structure, redox state, hydrogen bonding, electric fields, conformational freedom and dynamic motions [28]. The goal of any absorption spectroscopy is to measure how well a sample absorbs light at each wavelength, so that this technique.

7.2. Raman spectroscopy

It is another important method for studying protein-nanoparticle interactions. Raman spectroscopy involves interaction of light from the laser and a molecule, which results in the scattered light. After that interaction, light is scattered from the sample and the frequency shifts according to the frequency of the molecular vibrational mode [28].

Raman spectroscopy and FTIR are not so often used for studying the electrostatic interactions even though these two methods can provide important information because of the characteristics bands that many charged residues exhibit in the vibrational spectrum [28].

7.3. Circular dichroism (CD) spectroscopy

Along with the FTIR and Raman spectroscopy, CD spectroscopy is valuable method for determining protein secondary structure. It is valuable tool to study the interaction of proteins with other molecules too. CD spectroscopy involves absorption in the far (180-250 nm) and near (250 nm-visible) UV spectrum. It provides information about protein secondary and tertiary structure upon binding [6,28]. One of the most commonly used technique for analyzing secondary structure is based on far-UV CD spectroscopy [14].

7.4. Fluorescence spectroscopy

Fluorescence spectroscopy can be used for studying proteins, determining protein structure, size, shape and dynamics. It is proven to be very fruitful in the studies of the protein`s structure and conformation [6]. In its base, this method uses a beam of light that excites the electrons in the molecules of certain compounds, which makes them emitting light [28].

One of the factors that regulates the spectroscopy accuracy is Photoluminescence (PL) quenching, widely used because of its sensitivity, reproducibility and suitability. In general, decrease of fluorescence intensity by interaction of the excited state of the fluorophore with its surroundings is known as quenching. For example, Gold can efficiently quench the emission of many chromophores. Chromophores are molecules that adsorb light [6]. Furher, the emission typical for tryptophan, tyrosine and phyenyline residues in proteins are used for investigating binding and conformation changes of proteins when interacting with small molecules like nanoparticles. When protein binds to the NP, tryptophan, tyrosine and phyenyline residues become accessible to the metallic surface of the NP are then quenched. By decreasing the NP size, the surface area is increases, making smaller NPs more efficient fluorescence quenchers than larger ones.Conformational changes of a protein can, in principle, be evaluated by the measurement of changes in the peak intensity wavelength λmax in the continuous fluorescence emission intensity spectrum [6].

7.5. Nuclear magnetic resonance spectroscopy (NMR)

NMR spectroscopy provides useful information on protein structure and it was used for studying interactions

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of ubiquitin molecules with gold nanoparticle surface. For example, the information obtained with NMR spectroscopy provided possibility to distinguish the exact ubiquitin domain that bound to the NP surface [10]. In general, this methods is a powerful technique, which directly analyses the molecularscale of nanoparticle formation and morphology in situ, in both the solid and the solition phase, for the study of noble metal nanoparticles[35].

7.6. Isothemal titration calorimetry (ITC)

Isothermal titration calorimetry (ITC) is used to directly measure the thermodynamics of protein-ligand interactions [28]. In combination with other techniques can contribute to more complete understanding of NPs-biomoleculesinteraction. All these techniques provide data quickly and require minimal sample preparation [28].

8. Conclusion

The nanoparticle protein interaction represents the basis of bioreactivity of nanoparticles. These interactions results in the formation of a dynamic protein corona around nanoparticles. The protein corona is responsible for various physiologicalfunctions such as absorption. In addition,its is shown that nanoparticle surface is important factor resulting in conformational changes in the adsorbed protein molecules and, therefore, affect the overall nanoparticle bioreactivity.Due to their beneficial characteristics' gold nanoparticles (GMPs) are the most commonly used inorganic nanoparticles for biological applications. When GNPs enter a biological fluid like blood, proteins adsorb on the surface of GNPs, and GNP-protein corona formation occurs depending on the characteristics of both protein (protein corona) and local environment.A significant increase in biomedical applications of nanomaterials and their potential toxicity requires deverse analytical techniques to determine protein – nanoparticle (NP) interactions. Most important tecnhiques for the analysis of binding affinity, binding ratio, and binding mechanisms of NP-protein interaction, are based on spectroscopy. Since NP-protein binding is a dynamic event, Fourier transform infrared spectroscopy (FTIR), Nuclear magnetic resonance spectroscopy (NMR), Fluorescence spectroscopy and other methods are used. Understanding of the effect of NPs on the protein structure is crucial for nanomedicine application. Further studies on the formation and the composition of the protein corona needs to be done, including all the possible consequences that are incurred by the specific proteins.

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