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ZnO Nanoparticles: Recent Biomedical Applications and Interaction with Proteins

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Abstract

From the last decade, Nanoscience and nanotechnology have been multiple explored for vast research in medical science. Different optical and structural properties of Zinc oxide nanoparticles (ZnO NPs) are great interest in the nanoparticle based drug delivery bio-imaging, pharmaceutical applications for mankind. ZnO nanoparticles are useful for sunscreen lotion, various cosmetic products, Drug Delivery, Biomedical imaging, Gene delivery, Biosensors, MRI, and therapy. Due to the large free surface energy, nanoparticles (NPs) are highly reactive. Hence they interact with bio molecules. Before different biomedical applications of ZnO nanoparticles, it is useful to study their effect on biomolecules. This mini review discusses about the different biomedical applications of ZnO nanoparticles and the interaction of ZnO nanoparticles with protein molecules as reported by the different researchers.

Mini Review

Zinc Oxide (ZnO) is very well known multifunctional wide and direct band gap (3.37eV) semiconductor nanostructures. It's have excellent size dependent tunable optical property. ZnO has large excitonic binding energy of 60meV at room temperature [1]. It is an important optical nonlinear crystal due to noncentrosymmetric structure resulting from hexagonal wurtzite phase. ZnO nanocrystals possess large second and third order nonlinearities, resulting in the production of SHG, SFG, and electronic four wave mixing (FWM), which could be successfully applied for biological microscopy. The commonly used CdTe, CdSe nanoparticles are toxic for biological systems. Therefore, much effort has been devoted to the development of less toxic fluorescent nanoparticles such as ZnO nanoparticles and ZnO based composites.

Biomedical applications

ZnO nanoparticles are efficient for excitonic blue, near-UV emission and green luminescence related to oxygen vacancies [2]. This property of emission is important for cellular imaging. Due to the fluorescence, the penetration of ZnO nanoparticles in animal skin was imaged *in vitro* and *in vivo* [3]. The optical band gap and emission properties of ZnO nanoparticles can be tuned by doping with appropriate elements. Co, Cu, or Ni doped ZnO NPs are useful for tuning the optical properties and these materials were employed for cellular imaging studies in various cells [3]. Gd doped ZnO nanoparticles are handy for magnetic resonance and fluorescence imaging (MRI-FI) nanoprobes. ZnO NPs have been employed to fluorescence lifetime imaging in human skin. ZnO nanomaterials are versatile nanoplatforms for drug delivery applications, due to their large surface area, versatile phototoxic effect, surface chemistry, among others. *In vitro* studies have shown that ZnO nanoparticles can be highly toxic to cancer cells or leukemic T cells [4,5]. Hence, they have also been studied for cancer therapy. Fe_3O_4-ZnO core-shell nanoparticles are important for cancer imaging and therapy. Upon uptake of photosensitizers into cancer cells, irradiation with light of suitable wavelength and dosage can generate reactive oxygen species (ROS) which can induce cell death [6]. ZnO nanoparticles can induce ROS (hydroxyl radical, superoxide, hydrogen peroxide) in aqueous solutions upon absorption of UV illumination, making them good candidates for PDT [7]. ZnO nanoparticles are important for Gene Delivery. Recently Gene therapy has attracted considerable interest for cancer treatment [8]. A wide variety of nanomaterials have been investigated for gene therapy and delivery applications, including ZnO nanomaterials which have shown promise in various literature reports [9]. The different properties of ZnO nanoparticles like high catalytic efficiency, high isoelectric point (IEP; ~9.5), strong

adsorption capability, are suitable for adsorption of certain biomolecules (e.g proteins) by electrostatic interaction [10]. The high surface area, good stability, low toxicity, and high electron transfer capability also make them promising nanomaterials for biosensors [11]. The majority of reported ZnO nanocrystal-based biosensors are for the detection of various small molecule analytes such as glucose, phenol, H_2O_2, cholesterol, Enzyme, urea, etc [12-14]. Recently, several important reports appeared on ZnO-based glucose biosensors [15]. ZnO nanoparticles are used for Phenol Biosensors. Phenolic compounds are highly toxic to few animals and plants. Since they commonly exist in industrial waste, it is important to detect and measure them for environmental monitoring. Among the many analytical methods developed for detection of phenolic compounds, biosensors based on immobilization of tyrosinase were shown to be convenient, high sensitive, and effective [16]. Many of these biosensors have been fabricated on a platform of ZnO nanoparticles, because of the inherent electrostatic attraction between electropositive ZnO nanostructures and tyrosinase [17]. ZnO nanoparticles are used for H_2O_2 Biosensors. In recent report, ZnO nano flowers /chitosan composite matrix immobilized with enzyme HRP, were used to generate a biosensor with fine reproducibility and stability [18]. Different biosensors were constructed by immobilizing cholesterol oxidase, through either physical absorption or electrostatic interaction, onto ZnO nanoparticles. The first urea biosensor based on ZnO nanomaterials was reported in 2008, in which urease was immobilized onto ZnO-chitosan nanobiocomposite film on ITO coated glass by physical adsorption [19]. Recently, ZnO NW arrays fabricated on gold coated plastics were also utilized in a urea biosensor, where urease was immobilized by physical adsorption [20]. Recently 1% Pt or Mn and Co doped ZnO nanofilms are very good for sensing of H_2, CO, and ethanol vapour [21]. ZnO-based biosensors have also been reported for the detection of substances such as uric acid, lactic acid, protein, DNA [22-24]. ZnO nanoparticles are efficiently used for drug delivery nanocarriers [25,26]. Red Fluorescent Zinc Oxide Nanoparticle is novel platform for Cancer Targeting. Recent studies have shown that ZnO nanoparticle cores capped with polymethyl methacrylate are useful in the detection of low abundant biomarkers.

Interaction of nanoparticles with protein

The surface to volume ratio of nanoparticle is large than bulk material. This property leads to formation of large surface free energy. Due to the large free surface energy, nanoparticles (NPs) are highly reactive [27]. The knowledge about the effects of NPs on protein systems and their potential toxicity is very limited. Thus the interaction of NPs especially having luminescence property with proteins has come out as a key parameter in nanomedicine [28] and nanotoxicology [29] in the recent research. When nanoparticles are exposed to protein fluid systems, NPs form molecular complexes with encountered proteins and a dynamic layer (called 'protein-corona') of proteins is formed on the surface of NPs. The surface adsorption may lead to unfold, corona formation and protein aggregation [30]. Therefore, the concept of bio-safety and bio-compatibility of ZnO NPs is a key issue in favour of applications in biomedical applications.

Review on ZnO nanoparticles-protein interaction

The interaction of ZnO nanoparticles with different kind of proteins, studied by different researchers. Bardhan et al. [31-39] showed the formation of ground state complex between ZnO nanoparticles and BSA with static quenching of BSA. The interaction between ZnO nanoparticles with BSA is spontaneous and electrostatic in nature [31]. Their observation strongly indicates that the binding of ZnO to BSA induced some conformational change (the decreased from 64.51% in free BSA to 54.83%) in BSA. The interaction between ZnO nanoparticles (average size <40nm) with bovine haemoglobin (BHb) is studied by Mandal et al. [32]. Their spectroscopic studies on BHb in presence of ZnO nanomaterials showed the formation of a ground state complex via static quenching mechanism, with the number of binding sites, n being ~1. ZnO nanoparticles affect both the Soret band and the band corresponding to the tryptophan and tyrosine residues of the BHb. The CD spectra of their result showed that the content of α-helix of BHb decreases with the addition of ZnO nanoparticles though the structure of BHb remains predominantly α-helical even in the presence of maximum concentration of ZnO nanoparticles used during the experiment. The interaction between two heme proteins myoglobin (HMb) and horseradish peroxidise (HRP) with zinc oxide (ZnO) nanoparticles are investigated by using UV-VIS absorption, steady state fluorescence, FTIR, circular dichroism (CD) techniques by Mandal et al. [33]. They observed static mode in fluorescence quenching mechanism of HMb and HRP by ZnO nanoparticles due to formation of ground state complex. The process of binding of ZnO nanoparticles with the two proteins are spontaneous molecular interaction procedure. They observed that with increase in temperature there is a gradual decrease in molar ellipticity which shows the possibility of the loss of α-helix and increase in β-sheet and random structure content in HMb-ZnO and HRP-ZnO complex. Chakraborti et al. [34] studied the interaction of Polyethyleneimine-Functionalized ZnO Nanoparticles of core size of ~3-7 nm with BSA [34]. They observed static and single type of protein quenching with quenching rate constant to be 4 × 1012 M-1 s-1 by using Stern-Volmer equation. The binding between ZnO-PEI and BSA occurs via electrostatitic interactions. Their observation in UV CD spectra showed the decrease of the negative ellipticity with minor loss of helical contents of BSA after interaction with ZnO. The secondary structure of BSA remain unchanged as the shape of the peaks and their positions remain unaltered after interaction. The effect on secondary structure of BSA is also confirmed by FTIR spectroscopy. Bhogale et al.[35] studied the interaction of ~7.5nm Zinc oxide (ZnO) nanoparticles with

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BSA at the three temperatures 283K, 298K, 310K [35]. Their result showed that the binding constant (K) and number of binding sites (n) decreases with increase of temperature. The calculated thermodynamic parameters (ΔG, ΔH, and ΔS) suggest that binding occurs spontaneously involving hydrogen bond and van der Waals forces. Our research group [36-38] studies details about corona formation, emission quenching, unfolding of protein and effect of temperature on the corona of protein due to interaction with ZnO NPs. Wahab et al. [39] studied the interaction of ZnO-QDs with BSA and bovine haemoglobin (BHb) by using fluorescence quenching method and circular dichroism (CD) spectroscopy [39]. In the fluorescence spectra, quenching of fluorescence intensity of BSA with increasing concentration of ZnO-QDs is observed. The fluorescence intensity decreases by 91% at 2μM concentration of ZnO-QDs. In addition, blue shift of 3nm was observed after interacting with 2μM ZnO QDs.

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