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Gold nanoparticles applications: from artificial enzyme till drug delivery

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ABSTRACT

Today, nano-medicine promotes new therapeutics and diagnostics tools, including sensing of biomolecules as a biosensor, cancer chemotherapy and drug or gene delivery. Because of small size and biocompatibility of gold nanoparticles (GNPs), they become a good candidate for biological application. Also, thanks to their biological and chemical properties, they can mimic function of some enzymes including super oxide dismutase (SOD), esterase, etc. Also, biomaterials and bioengineering have grown so fast since the last decade for many therapeutic applications such as tissue regeneration. Among these cutting edge technology, nanomaterials find the way to becoming a very powerful tool for using in many fields of researchers including biosensing, gene therapy and chemotherapy. In this review, we focused on some biological applications of GNPs in biology and medicine.

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Introduction

Gold nanoparticles (GNPs): an overview

It is accepted that some metal-based nanoparticles (NPs) potentially mimic enzyme function [1]. Among all NPs, GNPs are so believed because of enzymatic properties and their application in biology [2]. Moreover, "hidden talents" of GNPs revealed as artificial enzymes, including ability of GNP to mimic the nuclease, esterase, silicatein, glucose oxidase, peroxidase, catalase and superoxide dismutase [3] as well as GNPs with either positive or negative surface charges show peroxidase mimicking activity [4]. These enzyme-like activities of GNPs are related to functional groups. In fact, GNPs enzyme-like activities help scientist to develop and design of biosensors, immunoassay, clinical studies, detection and photothermal activity of micro-organisms and cancer cells, targeted delivery of the drug, and as well as in bioimaging according to this potential (Figure 1) [3–7]. GNPs are biocompatible because of special properties such as non-toxicity, facile synthesis, size and shape tenability [7]. Besides, biological safety and user-friendly methods for constructing GNPs, they have no toxic material after degradation [8]. In this manner, it is possible that GNPs combined to different parts of plants, fruits, microorganisms and biomolecules [8]. For example, synthesis of GNPs from Curcuma longa root extract by 'exploiting' the reduction capabilities of varied phytochemicals present in was confirmed [9].

GNPs enzymatic potential

GNPs have enzymatic properties itself via surface-bound ligands that derived them to catalytic reactions; it is a usual method to mimic catalytic activity in synthetic aspects. However, the GNP can also be designed as the catalytic component as various enzyme mimics [10]. One of the enzymatic aspects of GNPs is to act as glucose oxidase mimic that the performance of GNPs is mentioned above (Figure 2).

Glucose oxidase (GOx) mimic

GOx is an oxide-reductase enzyme that catalyzes the oxidation of β-D-glucose to gluconic acid, by utilizing oxygen as an electron acceptor with simultaneous production of hydrogen peroxide (H_2O^-) [10]. Notably, the GOx-like activities of Au-NPs have been for simple and reliable detection of DNAs [11,12]. Although other metal nanomaterials, such as Cu, Ag, Pd and Pt, are tested, but did not show significant oxidase-like activity under similar conditions [13]. A non-enzymatic electrochemical method has been developed for the detection of glucose by using gold (Au) NPs self-assembled on a three-dimensional (3D) silicate network obtained by using sol–gel processes [14]. As well as, GNPs showed that the Au NPs catalyze the oxidation of glucose at less positive potential (0.16 V) in phosphate-buffered solution (pH 9.2) and in the absence of any enzymes or redox mediators [15,16].

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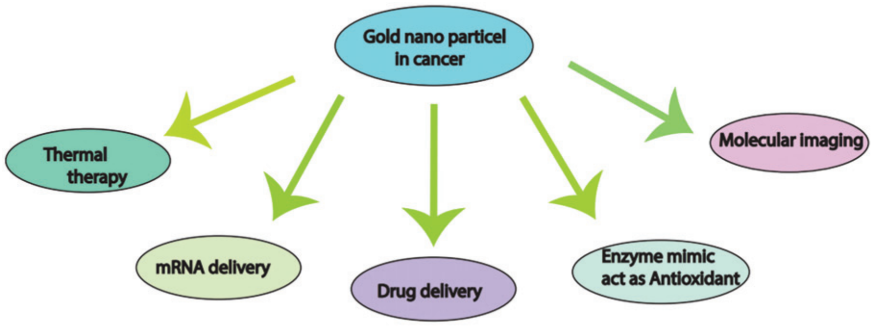

Figure 1. The schematic view of gold nanoparticles (GNPs) biological activity including gene and drug delivery, enzyme mimicking, molecular imaging and thermal therapy.

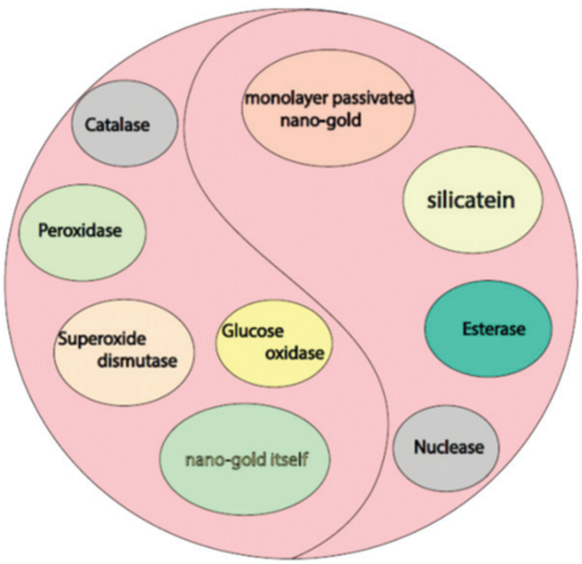

Figure 2. The schematic view of gold nanoparticles (GNPs) enzyme mimicking properties.

In addition to glucose sensing, nano-gold-aggregation (NGA) phenomenon has provided some other usages, such as solution-based immune-assays and DNA-hybridization assay [17]. In NGA reaction, two macromolecules, such as antigen–antibody, should be bounded together [18]. Notably, GNPs were used as a novel ultrasensitive multiplexed immunoassay method by combining alkaline phosphatase (ALP)-labelled antibody-functionalized GNPs (ALP-Ab/Au NPs) and GNP as an enzyme catalyzed in the presence of silver NPs at a disposable immune-sensor [19,20]. Also, Weijie et al. fabricated a self-catalyzed and self-limiting growth of glucose oxidase mimicking GNP. They showed that AuNP catalyzed glucose oxidation and produced H_2O_2. However, size-dependent activity decreases have a great impact to control enzymatic activity [21]. Self-limiting or smart nanomaterial fabricates according to shape and size, and having fewer toxicity.

Peroxidase mimic

Previously, researchers proved that ferromagnetic NPs occupy the intrinsic peroxidase-like activity. Since then, many studies have been developed to design of various GNPs with a great potential of peroxidase-like activity. Peroxidases are a large family of enzymes that typically catalyze the oxidation of horseradish peroxidase (HRP). However, GNPs are optimized in pH =3 and *in vitro* condition, but not in biological condition and pH =7.4 [22]. Glucose detection is a well-known biological activity of GNPs [23]. Colorimetric detection of H_2O_2 and glucose was performed according to intrinsic peroxidase-like activity and catalyzes the oxidation of the peroxidase substrate 3,3,5,5-tetramethylbenzidine (TMB) by [24]. GNPs as a peroxidase mimetic were first developed for the enzymatic spectrophotometric analysis of uric acid via detection H_2O_2 that was generated by uric acid [25]. Notably, GNPs are a promising method for uric acid analysis in human serum [23,24]. A novel immunoassay technique designed thanks to peroxidase-like activity and GNPs for detecting of α-fetoprotein, by enhanced ultrasensitive chemiluminescence enzyme immunoassay for the determination of α-fetoprotein [26]. The method was based on 4-(4′-iodo) phenyl-phenol (IPP) as a new potential signal enhancer and double-codified GNPs (DC-Au-NPs) that are labelled with HRP-conjugated anti-AFP which is used for further signal amplification [27]. According to the protocol, antigen in the sample was captured by the immobilized primary antibody on the surface of magnetic beads and recognized by the second antibody labelled with DC-Au-NPs consequently [28]. Also, it is possible to design peptides on GNPs to give nanomaterial with some chemical properties that are analogous to those of proteins [29].

Superoxide dismutase (SOD) mimic and catalase mimic

SOD is an important antioxidant defence against free radicals. It catalyzes the dismutation of superoxide (O^{2-}) into O_2 and H_2O_2 [30]. Also, catalase is an enzymatic group supporting the cell from oxidative damage by reactive oxygen species [29]. Markedly, GNPs have received a great deal of interest because of their unique properties of optical and in biomedical applications [31,32]. There is growing evidence that GNPs can catalyze then rapid decomposition of hydrogen peroxide that is followed by the formation of hydroxyl radicals at lower pH and oxygen at higher pH. These results strongly demonstrated that GNPs can act as SOD catalase mimetic [33,34]. However, these challenges thank to chemical synthesis of NPs that are proposed in toxicology [35]. In a study, these synthesized biocompatible GNPs (Tu-AuNPs) are used as an antioxidant against 1-methyl-2-phenyl pyridinium ion (MPP+) which induced cytotoxicity and cell death in PC-12 cells [36,37]. Incubation of PC-12 cells with Tu-AuNPs prevented

MPP+-induced loss in cell viability and enhanced LDH. In addition, reduction in the level of non-protein thiol, glutathione (GSH), activities of the antioxidant enzymes, superoxide dismutase (SOD), catalase (CAT) and glutathione-S-transferase (GST) as well as the increased MDA levels have also been found to be prevented by this NP in cancerous cells [38,39].

Esterase mimic

An esterase is a hydrolase enzyme that ruptures esters into an acid and an alcohol in a chemical reaction in water. The reaction is called hydrolysis [40]. According to evidence, the first example of peptide-functionalized GNPs is hydrolytically active against carboxylate esters. The active units are constituted by His-Phe-OH terminating thiols [41,42]. A highly sensitive and selective fluorescent assay for the detection of acetylcholine (ACh) was developed based on enzyme mimics of Au/Ag NPs [43]. This mechanism involved is the following: reacting ACh with acetylcholinesterase (AChE) to form choline that is in turn oxidized by choline oxidase (ChOx) to produce betaine and H_2O_2, which reacts with Amplex UltraRed (AUR) in the presence of bimetallic NPs catalyst to form a fluorescent product [44].

Other biological usages

Gene delivery

GNPs with synthetic microRNAs can enter cells without the aid of cationic co-carriers [45]. MicroRNAs belong to non-coding RNA family and regulate multiple proteins in interactions with the 3 prime untranslated regions of the target messenger RNA and control cell behaviour at post-translational level [46]. The GNPs–microRNA conjugation is a new tool for microRNA delivery and is candidates for the microRNA replacement delivery system [47].

It is demonstrated that polyvalent DNA-functionalized GNPs (DNA-Au NPs) selectively enhance Ribonuclease H (RNase H) activity while inhibiting most biologically relevant nucleases. Then, high RNase H activity results in rapid mRNA degradation and general nuclease inhibition results in high biological stability [48,49]. Selective RNase H activity in the high DNA density of DNA-Au-NPs is responsible for this unusual behaviour [50]. Also, polyvalent DNA-Au-NPs regulate gene expression as a new model for selectively controlling protein – NP interactions [51]. The potential of a single molecular nanoconjugate is to intersect with all RNA pathways including gene-specific down-regulation such as siRNA and miRNA pathways [52]. Gold-nano-beacons are capable of silencing gene expression and endogenous miRNAs, while yielding a quantifiable fluorescence signal directly proportional to the level of silencing [53,54]. Also, GNPs have a great role in tissue regeneration as a scaffold [53]. Human mesenchymal stem cells (hMSCs), is critical for the development of effective cellular therapies for tissue engineering [53]. Developing bioengineering as a multidisciplinary field of research helps scientists to fabricate different stem cells by GNPs. One of the main advantages of this method is the induction of immune tolerance [54].

Drug delivery

Another application is cancer-targeted drug delivery. GNPs conjugated with chemotherapeutics drugs such as doxorubicin may overcome side effect of chemotherapy like nausea or cardiac toxicity [55]. In 2009, gold nanoshells Aurora's took FDA approval in chemotherapy [56]. However, other GNPs are still using in research [57–60].

Immunoassays

Au nanorodes were employed for immunoassays. For example, sandwich ELIZA for IL-2. Integrin specific peptide was engineered by Au NP to mimic peroxidase mimics. This protein is used as a probe to detect cancer [21]. Glucose have been detected by Au-based nanomaterial. According to evidence, AuNPs mimics glucose oxidase to detect glucose.

Anti-bacterial properties

AuNPs encapsulated within mesoporous silica demonstrated antibacterial activity. AuNPs have exhibited both oxidase and peroxidase mimicking activities and end material of reactions is reactive oxygen species. Antibacterial properties proved against both Gram-negative and Gram-positive bacteria [61].

Conclusions

All in all, because of many advantages that GNPs including small size, flexible synthesis and biocompatibility, they have wide applications in biology and medicine. However, they mimic some biological effects of functional proteins such as enzymes. Also, they are used in drug delivery and gene delivery system. Thanks to the fast growing of this technology, great varieties of GNPs synthesize in different shapes and size. It is useful for promoting NPS biological applications and it is necessary to continue research on nanomaterial safety in parallel.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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