Gold Nanoclusters: Nanomedicine Potentials and Applications

Abstract

Attractive tiny gold nanoclusters (AuNCs) has opened golden gates of various applications in the world of technology. To name some of these applications we can refer to areas such as biosensor, contrast agent, drug and gene delivery system, etc. Here we will describe the potentials and applications of single and modified AuNCs for nanomedicine and theranostics.

Keywords: Gold nanoclusters; Nanomedicine; Theranostics; Cancer; Fluorescence Imaging; X-ray computed tomography; Magnetic resonance Imaging; PET Imaging; Diabetes; Nanovaccine; immunostimulatory

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Abbreviations: AuNCs: Gold Nanoclusters; BSA: Bovine Serum Albumin; GSH: Glutathione; Ab: Antibodies; DTX: Docetaxel; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; FI: Fluorescence Imaging; PET: Positron Emission Tomography; CA: Contrast Agent; NIR: Near Infrared; HSA: Serum Albumin; CpG-SH: Thiolated Cytosine-phosphate-Guanine

Introduction

Nanoscience and technology has been recognized as an attractive field of science for research groups worldwide. Efforts for development of nanoscience and technology to face clinical problems introduced nanomedicine as a new potential solution for prevention and treatment of diseases. Some nanostructures that can simultaneously be utilized for therapy and diagnostics applications are defined as Theranostics [1].

Metal nanoclusters (NCs) are a group of subnanometer structures consisting of several to ten metal atoms such as gold, silver, copper and etc. They are <2nm in size [2]. Stabilization of these tiny NCs requires protective materials. Proteins, peptides, DNA oligonucleotides and polymers are performed as ligands for reduction and stabilizing of metal ions to be formed as Metal NCs. The most important characteristic makes difference between metal NCs and nanoparticles is their molecular-like luminescence property.

Fluorescence NCs can be used for theranonstic nanomedicine. Because of their various type of stabilizers which can be functionalized for medical applications [3]. Gold nanoclusters (AuNCs) are the most attractive NCs for research studies because of their biocompatibility, low toxicity and photostability. Xie et al. [2] synthesized bovine serum albumin (BSA) stabilized AuNCs first time [2-3], hence their green synthesis method has been used for synthesis of AuNCs by another protein scaffolds such as lactoferrin, transferrin, insulin and glutathione (GSH).Recent *in vivo* studies showed comparison between GSH- and BSA-capped AuNCs for 24 hours. Renal clearance of GSH-capped AuNCs was almost 36 folds better than BSA-capped AuNCs [4]. Furthermore doping of AuNCs by radioactive elements allows them to be detected easily *in vivo* [5]. In this article AuNCs nanomedicine will be discussed Figure 1.

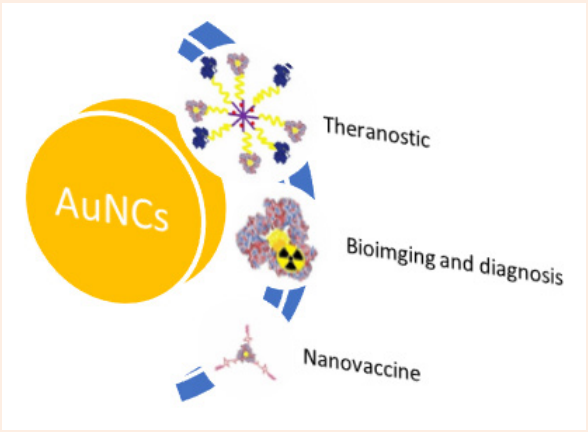

Figure 1: AuNCs nanomedicine.

Nanoconjugated NCs for cancer diagnosis and therapy

As explained before various types of scaffolds have been used for stabilizing of Au NCs. Functional groups such as carboxyl and amine are active sites in the scaffolds which can be applied for binding to active targeting agents. Over expressed receptors on the surface of cancerous cells can be targeted by nanoconjugated NCs. Conjugation of antibodies (Ab), peptides and polymers facilitate this smart selection of solid tumors *in vivo* for theranostic application [6].

Wang et al reported their findings on BSA-capped AuNCs, binded to trastuzumab Ab, for targeting and nuclear membrane localization in HER2$^+$ breast cancer cells and tumor tissues as a novel theranostic agent. They found that AuNCs-trastuzumab could be protected by endosomal escape and enter the nucleus.

This improves therapeutic effect of trastuzumab. They measured the diffusion time and condensation amounts of AuNCs in the nucleus of cancer cells. They demonstrated that the nuclear localization of AuNCs-trastuzumab increases the anticancer effect of trastuzumab by enhancement of DNA damage. They introduced a new nanostructure for fluorescence imaging and nuclear delivery of drugs. The conversion of biocompatible AuNCs to a smart anticancer delivery system decreases cell viability by apoptosis unlike non conjugated AuNCs [6].

Another study also reported the development of theranostic micelles of D-alpha-tocopheryl polyethylene glycol succinate (TPGS) .Vitamin E TPGS micelles conjugated with transferrin were designed for targeting of cancer cells with transferrin receptor over-expression. Transferrin conjugated Vitamin E TPGS micelles were utilized for co-delivery of docetaxel (DTX) and ultrabright AuNCs as a model imaging agent for simultaneous cancer therapy and fluorescence imaging. These theranostic transferrin conjugated micelles targeted transferrin receptors of MDA-MB-231-luc breast cancer cells. While NIH-3T3 fibroblast cells were employed as control cells possessing low cellular uptake. These two types of cells were studied for *in vitro* tests such as cellular uptake and cytotoxicity. MDA-MB-231-luc tumor bearing SCID mices were studied for biodistribution of AuNCs nanoconjugated micelles by Spectrum imaging system. These investigations were based on AuNCs fluorescence and luciferase bioluminescence. The IC50 results showed that the targeted and non-targeted micelles could be 71.73 and 15.31 folds more toxic than DTX after 24 hours presence in the MDA-MB-231-luc cells culture medium. Targeting transferrin receptors via theranostic micelles in xenograft model demonstrated potential of real-time tumor imaging and suppression of tumor growth [7].

Another interesting report demonstrated the opportunity of BSA-protected AuNCs assembling to form theranostic nanoparticles for delivery of doxorubicin and two photon imaging in He la as cancer cell model for *in vitro* experiments [8].

Bioimaging and diagnosis

There are many types of imaging systems for diagnosis such as X-ray computed tomography (CT), magnetic resonance imaging (MRI), fluorescence Imaging(FI), positron emission tomography (PET) and etc. The structure of AuNCs allows it to be a flexible contrast agent (CA) that can promote image quality of all mentioned devices. Diagnosis and progress monitoring of diseases such as cancer is dependent on devices that CAs improve validity of their data.

AuNCs can act as multimodal CAs. This means one structure can be CA simultaneously for two or more imaging systems. Optimized BSA-Protected AuNCs without any modification were applied for fluorescence imaging and X-ray CT *in vivo* because of high quantum yield, powerful X-ray absorption and high Hounsfield unit [9].

According to another report, decoration of GSH-protected AuNCs on the surface of magnetic nanoparticles (Fe_3O_4@AuNCs) creates a system for MRI/FI. Confocal microscopy showed that the fluorescent signal distribution was not only in the cytoplasm, but also in the nucleus sharper and this system could be utilized as a nanoprobe for real-time imaging of the cells. Also 3T MRI system demonstrated increasing of relaxation rate by increase of Fe_3O_4@ AuNCs concentration [10].

Hu and Huang introduced a novel system for PET and near infrared (NIR) imaging at the same time. Their novel idea was doping of human serum albumin template AuNCs (HSA-AuNCs) with radioactive ^{64}Cu. This radiolabeled system because of its positron emitting could be traced by PET imaging system. But the most important aspect of ^{64}Cu-doped AuNCs is self-illumination property that allows it to be monitored by NIR fluorescence imaging *in vitro* and *in vivo* [5].

Insulin-directed synthesized fluorescent AuNCs showed retention of the insulin bioactivity. Insulin- AuNCs not only are CAs for X-ray CT and FI but also regulate blood-glucose *in vivo*. This bioactive structure can be applied for diabetes medicine [11].

Nanovaccine

After decades Immunotherapy has been accepted for treatment of many type of diseases such as viral base, cancer, etc. To design a new vaccination strategy, protein antigen-based subunit modern vaccines were utilized for synthesis of novel nanovaccines. These nanovaccines are made of thiolated cytosine-phosphate-guanine (CpG-SH) and protein antigens such as ovalbumin could investigate immune responses. For example intially Tao et al [12] attached CpG-SH oligodeoxynucleotides covalently to ovalbumin and used these conjugates as template for AuNCs formation. Cytokine assays showed considerable immunostimulatory. Also *in vitro* and *in vivo* study confirmed high immunogenicity of CpG-ovalbumin-AuNCs nanovaccine. Furthermore engineered nanovaccine were synthesized by straight stabilizing of CpG-SH and antigen peptides [12-13].

Conclusion

Metal nanoclusters are recognized as missing link between atoms and nanoparticles. These fluorescence nanostructures are biocompatible and photostable. Especially gold nanoclusters are the most prominent of them because of its high quantum yield and simple synthesis methods. The various functionalized ligand and their sub-nanometer size allow them to emerge as promising materials for diagnosis and therapy. These metal nanoclusters were used in facing diseases such as cancer and diabetes. They also play role as contrast agent for multiple types of diagnosis system and immunestimulatory activity. These examples demonstrate the great potential of AuNCs nanomedicine for clinical applications.

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