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Core-satellite gold nanoparticle biosensors for monitoring cobalt ions in biological samples

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ABSTRACT

Elevated cobalt levels in the bloodstream due to wear debris from metal-on-metal hip implants can cause adverse health effects. Herein, we report a highly sensitive and specific label-free assay for cobalt detection using cysteine-linked core-satellite gold nanoparticles. We demonstrate the detection of clinically relevant concentrations of cobalt ions in biological samples down to 10 nM within 15 minutes using a standard laboratory plate reader. This method can be developed as a valuable tool for prompt monitoring of cobalt ion levels in patients with metal-on-metal hip implants.

1. Introduction

Metal-on-metal (MoM) hip replacement procedures, which replace joints that have suffered injuries or degraded due to aging, have increased steadily over the past decade [1]. Since the metal components must be corrosion resistant, these artificial joints are generally made of cobalt and chromium alloys [2]. Friction between components of MoM implants releases metal ions to the surrounding tissues and into the bloodstream. Although healthy bodily functions require such ions, elevated cobalt concentrations are toxic to the body and can lead to bone loss, severe inflammation, heart failure, or dementia [3]. Current detection techniques for cobalt poisoning include X-ray imaging, magnetic resonance imaging, and inductively coupled plasma–mass spectrometry, which are costly and are sometimes performed only after patients suffer from side effects [4]. As such, a fast, accurate, and cost-effective assay to monitor trace levels of cobalt ions in biological samples is required.

A number of electrochemical and optical sensors for the detection of heavy metals have been reported [5,6]. Electrochemical techniques typically employ a setup with three electrodes: a reference electrode, a counter electrode, and a working electrode. Bare electrodes can detect heavy metal ions without the need of modification with recognition elements. Alternatively, the working electrode, also known as the sensing electrode, can be modified with different materials for selectivity towards specific heavy metal ions. To our knowledge, electrochemical or optical sensors for cobalt ions are limited to detection in water or buffers (Table 1) [7–15], and sensors that can monitor clinically relevant nanomolar concentration of cobalt ions in biological samples do not currently exist.

Nanoparticle biosensors have the potential to improve chemical and biological sensing with enhanced sensitivity [16–19]. Gold nanoparticles (AuNPs) with diameters ranging from 1 to 100 nm offer distinct properties that make them excellent candidates for designing biosensors. They have high surface area that can be functionalized with biological ligands, and possess unique size- and shape-dependent optical properties that arise from the Localized Surface Plasmon Resonance (LSPR) phenomenon, which can be linked to the presence or absence of target analytes. AuNP-based colorimetric assays have been used to detect a wide range of analytes including DNA [20,21], bacterial toxins [22,23], enzymes [24–28], proteins [29,30], and metal ions [13–15,31–36]. These assays are primarily based on controlling the aggregation of AuNPs in solution. In previous work, ligand-functionalized AuNPs have been shown to detect cobalt ions with a limit of detection (LoD) in the micromolar range [13–15] (Table 1). While these designs are successful in their own right, they are not applicable for the detection of cobalt ions at the clinically relevant nanomolar concentration range, in particular for MoM hip replacement [37–39].

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Table 1
A comparison of the performance of the proposed method with other reported sensors for cobalt ion detection.

Detection technique	Materials	Detection limit	Detection time	Sample matrix	Ref
Electrochemical	Multiwalled carbon nanotube modified glassy carbon electrode	1.36 μM	3 min	Water	[7]
	Zn/Al-2(3-chlorophenoxy)propionate modified carbon paste electrode	0.01 μM	N/A	Water	[8]
	Benzenesulfonohydrazide modified glassy carbon electrode	0.09 nM	0.3 min	Water	[9]
Optical (fluorescence-based)	Carbon dots	0.45 μM	30 min	Water	[10]
	Phenol-ruthenium(II) tris(bipyridine) complex	0.05 μM	N/A	Water and NaOAc buffer	[11]
	1,2-dihydroxyanthraquinone/β-cyclodextrin	0.02 μM	30 min	Water	[12]
Optical (LSPR-based)	4-aminothiophenol-functionalized AuNPs	57.90 μM	N/A	Tris buffer	[13]
	Peptide-functionalized AuNPs	2.00 μM	3 min	Water	[14]
	Thiosulfate-stabilized AuNPs	0.04 μM	20 min	Water	[15]
	Cysteine-conjugated core-satellite AuNPs	10 nM	15 min	Human serum (diluted in PBS buffer + human serum albumin)	This work

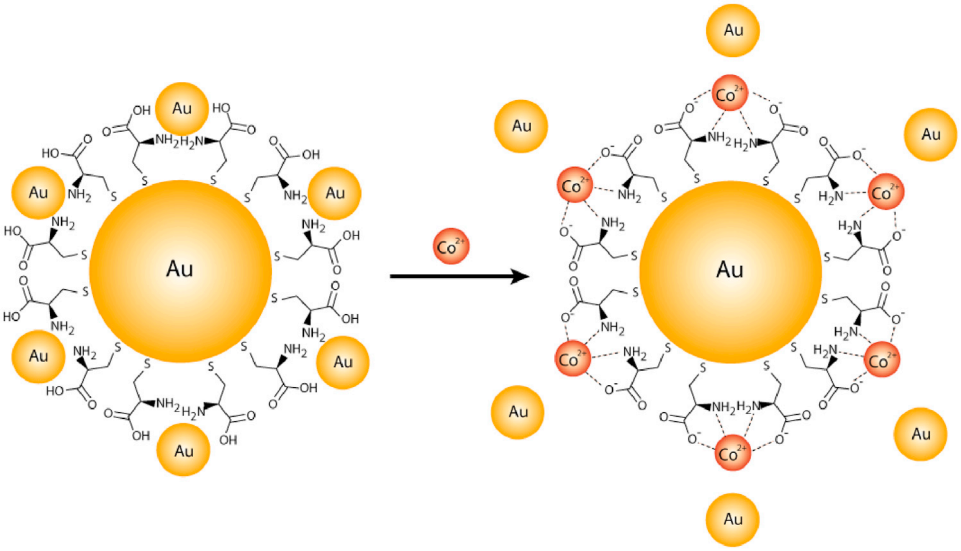

Fig. 1. Schematic illustration of cobalt ion detection based on controlled architectural changes of core-satellite gold nanoparticles (AuNPs). Core-satellite particles are formed using cysteine as a molecular linker. In the presence of cobalt ions (Co^{2+}), satellite nanoparticles are displaced causing a shift in the surface plasmon resonance (SPR) peak, which can be detected via UV–vis spectrophotometry.

Recent reports have shown that self-assembly of nanoparticles into ordered superstructures offer enhanced size-dependent properties of the building blocks [40,41]. In particular, core-satellite AuNP superstructures, which consist of a large core AuNP surrounded by smaller peripheral AuNPs, demonstrate an enhanced plasmonic coupling resonance shift relative to the single core AuNPs, induced by the close proximity between core and satellite nanoparticles [42]. This phenomenon leads to a significant shift of the SPR peak upon assembly and disassembly of the satellite particles around the core, which offers an opportunity to maximize the signal-to-noise ratio during biosensing [43,44].

To overcome the limitations of current cobalt detection techniques, in this work, we investigate core-satellite AuNPs and harness the enhanced plasmonic properties of the core-satellite particles for improving assay sensitivity, and report for the first time core-satellite AuNPs for the detection of clinically relevant concentrations of cobalt ions in biological samples. A number of biomolecules used to control the assembly architectures of AuNPs includes DNA and amino acids. DNA provides unique programmability and sequence-directed hybridization specificity [45–48], while amino acids offer a highly cost-effective approach for self-assembly of AuNPs due to their availability and ease of purification [49,50]. Specifically, single amino acids have both an amino group and a carboxyl group for conjugation to nanoparticles, and possess metal-ligating groups for specific analyte binding [51,52]. In our approach, we form core-satellite AuNP networks using amino acids, and due to the specific ligating properties of metal-coordinating amino acid residues, the presence of cobalt ions results in changes in the particle architecture, which can be followed by a significant shift of the SPR peak (Fig. 1). In particular, we: (i) use 50 nm AuNPs and 10 nm AuNPs as the building blocks for core and satellite particles, respectively; (ii) screen and examine 20 natural amino acids as molecular linkers to enable core-satellite AuNP formation; (iii) demonstrate cobalt detection based on a satellite displacement mechanism; and (iv) investigate the sensitivity and specificity of the assay for cobalt ion detection in biological samples.

2. Materials and methods

2.1. Materials

Gold nanoparticles (10 nm and 50 nm in diameter), amino acids (alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine,