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K^+ colorimetric detection in the nanomolar range based on K^+-aptamer quadruplex-NPs association

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ABSTRACT

This report presents a sensitive, proximity binding-induced DNA hybridization-based colorimetric assay for detecting K^+ in aqueous solution. The detection mechanism is based on the fact that DNA1 and DNA2 were designed to contain the two K^+ binding aptamers, the target K^+ can interact with a segments of the two different DNAs to form G-quadruplex/K^+ complexes and prompt DNA hybridization, thus the subsequently added gold nanoparticles (AuNPs) can be captured by the 5′ terminus of DNA1 and DNA2 through Au-S binding, leading to the aggregation of AuNPs. The color of the AuNPs changed from green to yellow and red under dark-field microscopy observation. By use of the dark-field images of the AuNPs, the lowest detectable concentration for K^+ was measured to be 0.18 nM according to the $3\sigma/k$ rule. This assay allowed the detection of K^+ in real serum samples. The results in detecting K^+ from serum samples via this method agreed well with those from buffer.

1. Introduction

Potassium ion (K^+), as one of the most abundant physiological metal ions in living organisms, plays key roles in biological systems, such as blood pressure control, proper digestion, nerve transmission, muscle contraction, osmoregulation, protein synthesis, electrical neutralization, photosynthesis, enzyme activation, and heartbeat [1,2]. In particular, several diseases were caused referring to the abnormal K^+ levels in living organisms, including heart disease, Addison's, rhabdomyolysis, neural dysfunction, AIDS, kidney, and cancer [3,4]. In this context, the development of effective methods to detect K^+ concentration is urgently needed and significant.

To this goal, various analytical methods have been developed, such as flame photometry [5], atomic absorption/emission spectrophotometry [6], ion-selective electrodes [7], ion chromatography [8], and electrochemical method [9]. However, these conventional methods are intricate and time-consuming and also involve cumbersome laboratory procedures, which limit the scope of their practical application [10,11]. Therefore, it is necessary to develop simple and sensitive alternatives for K^+ detection.

Colorimetric methods have recently become useful for many types of analytes without the need for advanced instruments because molecular events can be transformed into color changes [12–18]. Recently, dramatic advances have been witnessed in the development of sensitive and selective biosensors for K^+ detection based on G-quadruplex [19–23]. We herein proposed a target K^+-induced G-quadruplex/K^+ complexes and DNA hybridization-based assay for direct colorimetric detection of K^+ in aqueous solution. Different from previous G-quadruplex-based K^+ sensors, in previous G-quadruplex DNA structure, it contains only one K^+ binding aptamer. Whereas G-quadruplex counterparts in this work contain two K^+ binding aptamers (DNA1 and DNA2), which will help us to design gold nanoparticle (AuNP) oligomer-based colorimetric method. In the presence of the target K^+, binding of the two DNA strands to the same target K^+ promoted hybridization between the complementary stem segments attached to the two DNA. The subsequently added AuNPs could be captured by the two DNA and formed oligomers. The color of the aggregated AuNPs changed from green to yellow and red under dark-field microscopy.

2. Experimental section

2.1. Materials

Hydrogen tetrachloroaurate trihydrate ($HAuCl_4 \cdot 3H_2O$, 99.9%), trisodium citrate, Tris(2-carboxyethyl) phosphine hydrochloride (TCEP, 98.0%) obtained from Sigma-Aldrich. DNA oligonucleotides were synthesized by Sangon Biotechnology Inc. (Shanghai, China). Their base sequences were designed as follows: DNA1: 5′-GGT TGG TGT GGT TGG TTT TTT GGG TTT AAC ATG-$(CH_2)_6$-SH-3′, and

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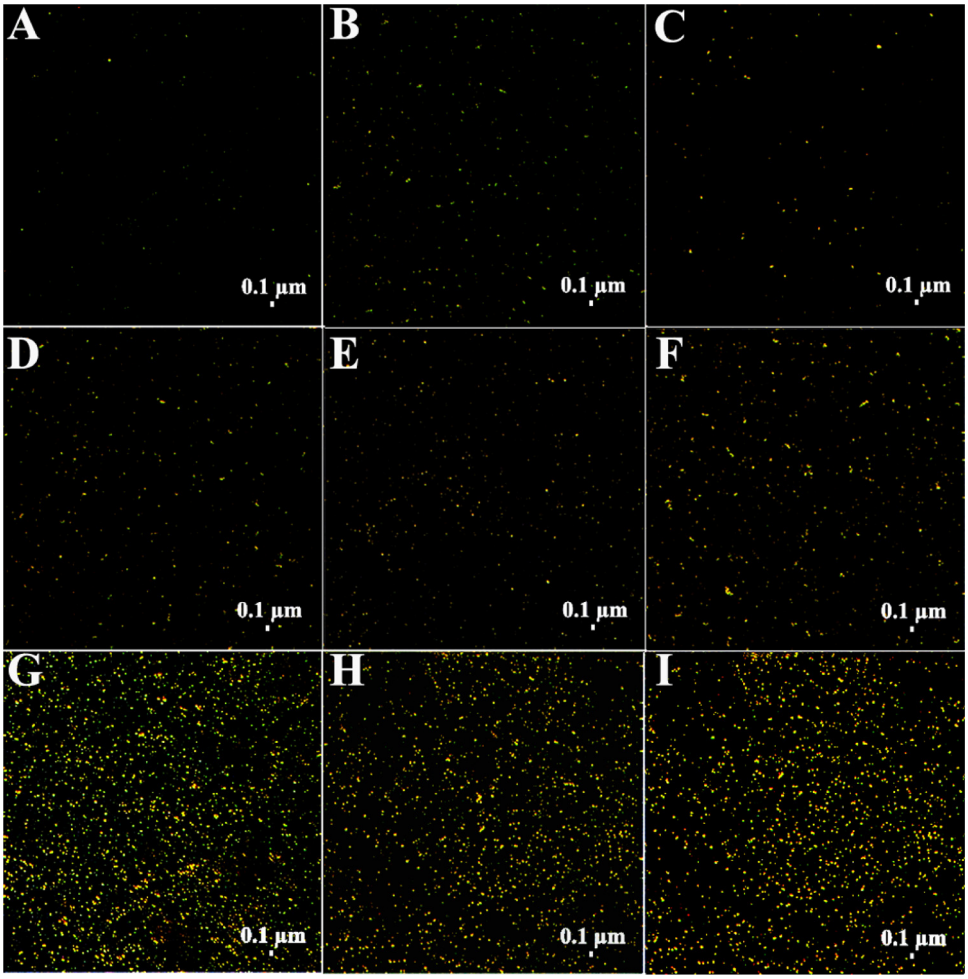

Fig. 1. Representative dark-field microscopy images of AuNPs under different target K^+ concentrations: (A) 0, (B) 1, (C) 10, (D) 20, (E) 40, (F) 60, (G) 80, (H) 100, and (I) 120 nM.

DNA2: 5′-SH-$(CH_2)_6$-CAT GTT AAA CCC TTT TTT AGT CCG TGG TAG GGC AGG TTG GGG TGA CT-3′. All other chemicals are of analytical reagent grade. Ultrapure water obtained from a Millipore water purification system (>18.2 MΩ cm, Milli-Q, Millipore) was used in all assays and solutions. 10 mM Tris-HCl (pH 7.4) buffer was employed as buffer.

2.2. Apparatus

A dark-field microscope (Eclipse TE2000-U, Nikon, Japan) was used to observe dispersed and aggregated AuNPs. Transmission electron microscope (TEM) images were obtained on a Hitachi (H-7650) transmission electron microscope.

2.3. Synthesis of AuNPs

AuNPs were synthesized through a sodium citrate reduction of an aqueous $HAuCl_4$ solution [24]. Briefly, 250 mL of 1 mM $HAuCl_4$ was brought to a boil. Next, 25 mL of 38.8 mM sodium citrate was added to the boiling $HAuCl_4$ solution with vigorous stirring. The solution was boiled for 5 min to complete the citrate reduction of the gold ions. The solution was then stirred for 15 min until the solution color changed from yellow to deep red. The solution was subsequently filtered with a 0.2 μm filter to remove aggregated particles. Finally, the AuNP solution was cooled to room temperature and stored at 4 °C for future use.

2.4. Detection of K^+

Prior to detection, DNA strands were treated with TCEP. TCEP (5 mM) was employed to reduce the possible disulfide bonds in DNA sequences to thiols. TCEP-treated DNA1 and DNA2 (final concentration: [DNA1] = [DNA2] = 10 nM) were added K^+ with various concentrations at 37 °C for an hour, respectively. Then, the DNA1 and DNA2 solutions with the same concentration were added to the two aliquots of AuNP solution with mild stirring at 37 °C for 4 h to form DNA-functionalized AuNPs via Au-S bonds. After that, 10 μL of the DNA-functionalized AuNP solution was drop-coated onto the modified glass. The prepared glass slide was mounted on a closed confocal imaging chamber, and inserted into the sample holder of a dark-field microscope. Prior to use of the glass slide, the glass slide was first cleaned in acetone by sonication for 30 min, and rinsed thoroughly with ethanol for 3 times. Then, the glass was cleaned in a piranha solution (3:1 H_2SO_4: H_2O_2), and rinsed thoroughly with distilled water and absolute ethanol. The cleaned slide glass was treated in 2% (v/v) aminopropyltriethoxysilane (APTES) in absolute ethanol for 15 min.

3. Results and discussion

3.1. Detection principle

As shown in Scheme 1, the detection method relies on the affinity binding between the target K^+ and aptamers-induced DNA hybridization and hybridization-triggered the formation of AuNP