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Nickel-mediated allosteric manipulation of G-quadruplex DNAzyme for highly selective detection of histidine

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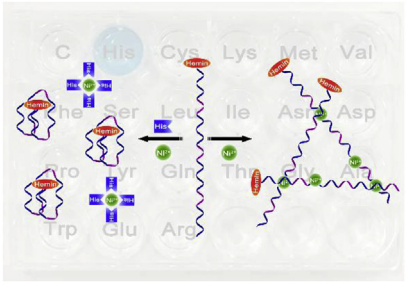
HIGHLIGHTS

- Nickel-mediated allostery of G-quadruplex is reported for the first time.
- Activity of G-quadruplex DNAzyme is manipulated by nickel-mediated allostery and nickel-histidine affinity pair.
- Histidine in biological fluids can be facilely and directly distinguished in the absence of additional reagents.

GRAPHICAL ABSTRACT



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ABSTRACT

Since abnormal metabolism of histidine (His) is defined as an indicator of several diseases, detection of His in biological fluids becomes increasingly urgent to us. However, due to similar structures and properties of different amino acids, selective quantification of His is difficulty, and typically needs the participation of special reagents. In this work, we report for the first time that nickel ions (Ni^{2+}) can induce the allostery of G-quadruplex, and is thus able to manipulate the activity of G-quadruplex DNAzyme. Experimental results indicate the interaction between Ni^{2+} and guanine is critical to the allostery. In comparison with Ni^{2+}-guanine interaction, Ni^{2+}-His interaction exhibits higher affinity. Therefore, a colorimetric His biosensor is fabricated, and His can be facilely discriminated by naked eyes. Relying on the high activity of DNAzyme, His in a range of 50 nM–400 μM is determined with this method, and low detection limit (36 nM) is obtained. More importantly, His can be directly distinguished in the absence of other toxic reagents. In addition, the amount of His in serum is also measured, suggesting the applicability of this biosensor in real sample detection. Overall, this work provides an alternative way to design G-quadruplex DNAzyme-based analytical approaches.

1. Introduction

Since specific DNA structures are the basis of molecular recognition and signal transduction, metal ions-mediated DNA allostery plays an important role in designing analytical protocols [1,2]. According to metal ions-induced mismatches, such as T-Hg^{2+}-T and C-

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Ag^+-C [3,4], single-stranded DNA may form metal ions-bridged duplex structures, which are key principles of various Hg^{2+} and Ag^+ biosensors [5–7]. In addition, with the help of metal ions, diverse DNA structures can be constructed, broadening the detection realm from small molecules to whole cells [8–12]. Besides as building blocks, DNA can also be used as catalytic oligonucleotides that are so-called DNAzyme [13–15]. Structures of DNAzymes are fundamental to their activities, thus metal ions can manipulate activities of DNAzymes by allosteric regulation. Obviously, to design more advanced biosensors, surveying metal ions-mediated allosteric manipulation of DNAzyme is of great value.

Histidine (His) is one of essential amino acids (AAs), and abnormal metabolism of His has been defined as an indicator of several diseases. The decrease of His will cause Friedreich ataxia, Parkinson's disease, and epilepsy [16], while the increase of His may lead to symptoms of intoxication [17]. Accordingly, detection of His in biological fluids has become increasingly urgent, and a number of bioanalytical methods have been developed. Currently, His biosensors are designed mainly using fluorescent probe [18], His aptamer [19], Cu^{2+}-modulated silver nanoclusters [20], and Ni^{2+}-based nanomaterials [21,22]. Although the aforementioned approaches have their own merits, these assays suffer from complicated operation and high cost. Recently, Liu and coworkers proposed two attractive strategies for the detection of His based on Cu^{2+}-regulated guanine (G)-quadruplex complexes [23,24]. However, Cu^{2+} can bind to His and cysteine (Cys), simultaneously. Therefore, in these two and some other studies [25], to realize selective detection of His, *N*-Ethylmaleimide, a toxic and unstable reagent, has to be employed, which inevitably limits applications of these biosensors. Because AAs have very similar structures, and normally coexist in biological samples, selective detection of an individual AA with simple methods is still a great challenge.

Taking the versatility of metal ions-DNA interactions into account, we believe Ni^{2+} may mediate allosteric manipulation of G-quadruplex DNAzyme, which is promising to create a facile His biosensor with improved selectivity. First, G-quadruplex DNAzyme is constructed using G-rich DNA. Ni^{2+} is able to interact with G (particularly the N7 of the G residue), and introduce a purine-like Ni^{2+} base pair in DNA [26]. Second, G-quadruplex DNAzyme is low cost, high stability, and ease of use [27,28]. Activity of G-quadruplex DNAzyme can be conveniently characterized with colorimetric methods [29]. Third, in comparison with other AAs, His can selectively bind to Ni^{2+}. The selectivity of Ni^{2+}-His affinity pair has been repeatedly confirmed in various biological applications, especially in isolation and purification of peptides and proteins with His tail [30,31]. As expected, our experimental results identify for the first time that Ni^{2+} can destruct the G-quadruplex structure, and thus depress the peroxidase-mimicking activity of G-quadruplex DNAzyme. More importantly, Ni^{2+}-mediated allosteric manipulation can be impeded by His, resulting in recovery of activity. On a basis of these principles, a novel His biosensor with outstanding selectivity is designed.

2. Materials and methods

2.1. Chemicals and materials

All kinds of amino acids were purchased from Shanghai Sangon Biotechnology Co. Ltd. (Shanghai, China). Nickel acetate tetrahydrate ($Ni(Ac)_2 \cdot 4H_2O$), thioflavin T (ThT), and 3,3′,5,5′-Tetramethylbenzidine (TMB)-H_2O_2 solution were obtained from Sigma-Aldrich Co., Ltd. (Shanghai, China). Tris(hydroxymethyl)aminomethane (Tris) was obtained from Alfa Aesar Co. Ltd. (Shanghai, China). Single-stranded DNA probe (ssDNA probe) was purchased from Promega Biotech Co., Ltd. (Beijing, China). Hemin modified G-rich DNA (hemin-DNA: 5′-hemin-GGGAAAGGGAAAGGGAAAGGG-3′) and poly(24G) (5′-GGGGGGGGGGGGGGGGGGGGGGGG-3′) were obtained and purified with HPLC by TaKaRa Co., Ltd. (Dalian, China). The oligonucleotide was dissolved in the 10 mM Tris-HCl buffer solution (pH 8.0). All other chemicals used in this work were of analytical grade and directly used without additional purification. All solutions were prepared with ultrapure water (18.2 MΩ cm) from a Milli-Q purification system (Bedford, MA).

2.2. Instrumentation

The UV-vis tests were performed on a UV-vis absorption spectrometer (Cary 50, Varian, USA). The fluorescence measurements were carried out on an Fluoromax-4 spectrometer (Horiba, France). Circular Dichroism (CD) measurements were conducted on a Chirascan (Applied Photophysics, Britain).

2.3. UV-vis detection of His

10 μL of 100 μM Ni^{2+} and 10 μL of His at different concentrations were first mixed and reacted for 30 min. Then, 10 μL of 10 μM hemin-DNA was added into the mixture. Above mixed solutions were incubated at 90 °C for 5 min, then cooled to room temperature slowly. After that, 170 μL of TMB-H_2O_2 solution was added, and the mixture was kept for 15 min. Afterwards, 200 μL of 2 M H_2SO_4 was added into the above solution to stop reaction. Then, the mixed solution was diluted with 1000 μL of 10 mM Tris-HCl buffer (pH 8.0), and was ready for Uv-vis measurement.

2.4. CD assay

Sample preparation for CD assay was the same with that for Uv-vis detection, while higher concentrations of DNA and Ni^{2+} were needed. The final concentrations of hemin-DNA, Ni^{2+} and His were 10 μM, 300 μM and 1.2 mM, respectively.

2.5. Fluorescent characterization

ThT and ssDNA probe were used in this work to survey Ni^{2+}-mediated allostery. For ThT assay, 10 μL of 50 μM ThT was added into related solutions, and the mixed solutions were kept for 30 min. After that, the mixed solutions were diluted with 300 μL of 10 mM Tris-HCl buffer (pH 8.0) for fluorescent measurement. For ssDNA probe assay, 10 μL of 100 μM Ni^{2+}, 10 μL of 10 μM poly(24G), and 10 μL of 10 μM ssDNA probe were mixed and incubated at 90 °C for 5 min. After that, the mixed solution was cooled to room temperature for fluorescent measurement.

3. Results and discussion

3.1. Sensing mechanism of a colorimetric His biosensor

Sensing mechanism of the proposed His biosensor has been illustrated in Scheme 1. The sensing system consists two components, *i.e.*, hemin-modified G-rich oligonucleotides (hemin-DNA) and Ni^{2+}. In our previous work, we demonstrated that hemin-DNA can construct G-quadruplex DNAzyme in one step without the participation of metal ions [32]. In this study, hemin-DNA is further used to investigate Ni^{2+}-mediated allosteric manipulation. Ni^{2+} plays different roles in different cases. In the absence of His, G-quadruplex structure is destroyed by Ni^{2+}-G interaction, thus inhibiting peroxidase-mimicking activity of G-quadruplex DNAzyme. However, in the presence of His, His presents stronger binding affinity to Ni^{2+}, which protects the intact structure of G-quadruplex DNAzyme. Due to the high peroxidase-mimicking