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ORIGINAL PAPER

Resonance light scattering aptasensor for urinary 8-hydroxy-2′-deoxyguanosine based on magnetic nanoparticles: a preliminary study of oxidative stress association with air pollution

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Abstract

An aptamer based method is described for the determination of 8-hydroxy-2′-deoxyguanosine (8-OHdG) using resonance light scattering (RLS). Magnetic nanoparticles (MNPs) were employed as RLS probes. The probe DNA was placed on the surface of MNPs, which produces a rather low RLS signal. If, however, probe DNA hybridizes with the aptamer against 8-OHdG, a sandwich structure will be formed. This results in a significant enhancement of RLS intensity. The aptamer was used as the recognition element to capture 8-OHdG. 8-OHdG has a stronger affinity for the aptamer than probe DNA, and the conformation of the aptamer therefore switches from a double-stranded to a G-quadruplex structure. As a result, MNPs labeled with probe DNA are released, and RLS intensity decreases. The method allows 8-OHdG to be detected with a linear response in the 32 pM − 12.0 nM concentration range and an 11 pM limit of detection (at $3.29S_B/m$, according to the recent recommendation of IUPAC). The MNPs can be reused 5 times by applying an external magnetic field for collection. The method was successfully applied to analyze human urine samples for its content of 8-OHdG. It was also found that the levels of 8-OHdG noticeably increased with the increase of the Air Quality Index. Conceivably, the method is a viable tool to investigate the relationship between 8-OHdG levels and the effect of air pollution.

Keywords 8-OHdG · Biomarker · Oxidation of DNA · Aptamer · Conformational change · G-quadruplex · Magnetic biosensor · Reusability · Urine samples · Air quality index

Introduction

8-Hydroxy-2′-deoxyguanosine (8-OHdG) is an indicator for damaged nucleotide. The formation of 8-OHdG results from the oxidation of guanosine at the C8 site in DNA sequences by free hydroxyl radicals [1]. 8-OHdG is considered being a biomarker of oxidative stress, which occurs when a normal pro-oxidant to antioxidant ratio is imbalanced. Even though they are not directly lethal to affected cells, 8-OHdG lesions are highly mutagenic and significantly contribute to the development and progression of cancer [2]. Moreover, it was reported that the increase of 8-OHdG was associated with neurological disorders such as Alzheimer's, Parkinson's disease, and atherosclerosis [3]. Therefore, it is significantly important to develop methods for sensitive and selective detection of 8-OHdG.

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Various methods were introduced to measure 8-OHdG. They were high-performance liquid chromatography/tandem mass spectrometry system (HPLC/MS/MS) [4], enzyme-linked immunoabsorbent assay (ELISA) [5], electrophoresis [6], and electroanalytical chemistry methods [7]. Spectroscopic methods were also explored for the detection of 8-OHdG, including ultraviolet spectroscopy [8], fluorescence spectroscopy [9], as well as resonance light scattering (RLS) [10]. By comparison, among the above assays, the RLS technique seems to stand apart with its promising sensitivity. RLS spectra can be obtained by the synchronous scan of excitation and emission monochromators on a conventional fluorescence spectrophotometer. The RLS method was first established by Pasternack et al., which was used to study the aggregation of biological macromolecules with small molecules [11]. Since then the RLS technique has been widely applied for the study of molecular recognition and the interaction of biological macromolecules. RLS spectra and intensity are significantly affected by the molecular size, conformation, shape, and interfacial properties [12]. As RLS probes, the nanomaterials attracted great attention such as gold, silver, and gold-silver alloy nanoparticles [13–15], gold nanorods [16], gold and silver nanoclusters [17, 18] and magnetic silica nanoparticles [19]. In addition, gold nanoparticles were also used as RLS probes for the determination of 8-OHdG [10]. We also did some research works using magnetic nanoparticles (MNPs) as RLS probes [20, 21]. For the above RLS systems, the detection mechanism used was "turn-on" mode, i.e., RLS signal was enhanced with the addition of analyte. A "turn-off" RLS biosensor of 8-OHdG was fabricated here based on MNPs and aptamer.

It was reported previously that certain constituents of air pollution can induce or increase oxidative stress in biological systems. However, the scientific knowledge on the exact mechanism is limited [22]. The amount of 8-OHdG in human urine sample is linked to both total mass concentration and constituents of PM2.5, which is responsible for causing oxidative stress [23]. There is also evidence that links human exposure to polycyclic aromatic hydrocarbons (PAHs) [4], and the risk of colorectal cancer with oxidative damage by analyzing urinary 8-OHdG [24]. An association also exists between the amount of 8-OHdG and the genotoxicity in mice exposed to CdSe quantum dots [25], and the mitochondrial damage presence in the aging process of rats [26]. Therefore, the determination of the damaged guanine has great significance to the biomedical chemistry and clinical diagnosis. However, there is few report to pay attention to the 8-OHdG content in human urine samples correlation with the Air Quality Index (AQI). Our aim is to investigate if there is a correlation between urinary 8-OHdG concentration and healthy people exposure to atmosphere in different seasons at a little town of China. A novel method was constructed and validated for the determination of 8-OHdG in human urine samples. The urinary samples were collected from 16 healthy volunteers in summer and winter for 1 year, respectively. The new assay not only provides the specific affinity between 8-OHdG and its aptamer but also supplies a reusable aptasensor to evaluate the preliminary potential health effects of atmosphere pollution. The experimental results have potential to add valuable spatial data to evaluate local air quality model performance.

Experimental section

Apparatus

A LS 55 spectrofluorometer (Perkin Elmer, USA) was used to carry out all RLS measurements with a 1.0 cm length sample cell. A Lambda 750 spectrophotometer (Perkin Elmer, USA) was employed to record absorption spectra. The pHs-3C digital pH meter (Shanghai Leici Device Works, China) was used for the pH test with a combined glass-calomel electrode. Circular dichroism (CD) measurements were obtained on a J-810 CD spectrometer (Jasco, Japan). Urine samples were pretreated with a Hitachi Micro Ultracentrifuge CS150FNX (Japan). The content of 8-OHdG in urine samples was confirmed with a Thermo Scientific Microplate Reader (USA) in a 96-well Plate.

Chemicals and materials

50 nm sized iron oxide MNPs coated with streptavidin were purchased from micromod (GmbH Germany, http://www.micmod.com/). For MNPs used, on average 2 molecules of streptavidin per particle were coated on the surface of 50 nm nanoparticles, according to the product information. The DNA probes, 8-OHdG aptamer, and other sequences for length test were synthesized and purified by Shanghai Sangon Biotechnology Co., Ltd. (http://www.sangon.com/) (with sequences listed in Table S1 in Supplementary Material). 8-OHdG, 2′-deoxyguanosin, ganciclovir, thymidine, and guanine were purchased from Sigma (https://www.sigmaaldrich.com/china-mainland.html/). Tris (hydroxy-methyl)-aminomethane (Tris) and 4-(2-hydroxyethyl)piperazine-1-ethane-sulfonic acid (HEPES) were ordered from Fluka (Buchs, Switzerland, http://www.fluka.org/fluka.php). NaOAc, NaH_2PO_4, Na_2HPO_4, HOAc, HCl (employed for the buffer composition test) and creatinine, glucose, urea, albumin from bovine serum (BSA), ascorbic acid, disodium oxalate, sucrose, $CuSO_4$, $CaCl_2$, $MgCl_2$, KCl, $FeCl_3$, and uric acid (used for specificity study) were obtained from Beijing Chemical Works (Beijing, China, http://www.beijingchemworks.com/). All chemicals were used without further purification. Deionized water (≥18.2 MΩ·cm) was prepared using a Millipore water system with an ion exchange column by feeding distilled water. An ELISA kit purchased from Japan Institute for the Control of Aging (Shizuoka, Japan, http://www.jaica.com/e/index.html) was employed to confirm the content of 8-OHdG in human urine.

Procedures for 8-OHdG sensing

5.0 μg mL^{-1} MNPs modified with streptavidin were treated directly with 10 mM HEPES solution and diluted to 1.0 mL. There are about 2 molecules of streptavidin on the surface of one nanoparticle and 8 probe DNA sequences labeled with biotin were also incorporated onto every particle surface. It is a 0.25 streptavidin monomer-biotin binding mode for the reaction of streptavidin and biotin. Thus, there are 8 probes on each MNP. A 100 nM probe 1 (7.5 μL) and 100 nM probe 2 (7.5 μL) were added to a 1.0 mL MNP solution, respectively. The mixture solution was then incubated for about 15 min at 30 °C to form the composite of MNPs and probe DNA (denoted as MNPs@probe 1 and MNPs@probe 2, respectively). Subsequently, after the dispersions of MNPs@probe 1 and MNPs@probe 2 were mixed together, 8-OHdG aptamer was added to the mixture. The final mixture was incubated for 15 min at 30 °C to form the sandwich structure of MNPs@probe 1-aptamer-MNPs@probe 2. A series of 8-OHdG standard solutions (0.03 nM–10.0 nM) were then added to the dispersion of MNPs@probe 1-aptamer-MNPs@probe 2. The resulting mixture was incubated for 15 min at 30 °C and then used for the RLS measurement.

The selectivity for 8-OHdG analysis was studied using the RLS aptasensor. The possible interferences included creatinine, glucose, urea, bovine serum albumin (BSA), ascorbic acid, disodium oxalate, sucrose, Cu^{2+}, Ca^{2+}, Mg^{2+}, K^{+}, Fe^{3+}, uric acid, 2′-deoxyguanosin, 2′-deoxythymidine, 2′-deoxycytidine, and 2′-deoxyadenosine. It was carried out by the parallel addition of interferences with 50-times higher concentration than that of 8-OHdG under the same experimental conditions.

Collection and pretreatment of human urine samples

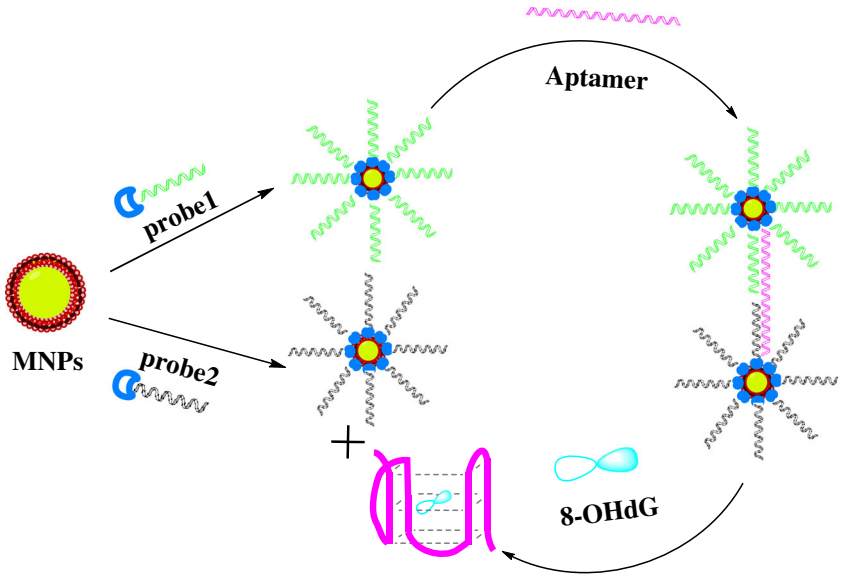
Urine samples were collected from 16 healthy young volunteers, not on any medications. The group was composed of 8 female and 8 male master degree candidates in Liaocheng University. 20 samples were collected per person every month by collection of first urine samples everyday. The influence of menstruation for ladies was accounted for by excluding those particular samples. According to the air quality monitoring result of a whole year from January to December in 2016 in Liaocheng City, China, the air pollution of December was the most serious, while it was the weakest in August. We selected 3 months for both weak and serious air pollution, respectively. Therefore, sampling procedure continued 6 months including July, August, September, and December in 2016, and January and February in 2017.

All samples collected were stored at −4 °C, and centrifuged at 5000 rpm for 10 min before use. The supernatant fluid was filtered through a 0.22-μm membrane and the filtrate was dialysed using a dialysis bag with a molecular weight cut-off (MWCO) of 100 Da. Subsequently, the solution in the dialysis bag was analyzed directly with the developed method.

Results and discussion

Principle of the aptasensor for 8-OHdG

The present sensor, based on the RLS technique, was explored for detection of 8-OHdG by combining 8-OHdG and an aptamer that binds with MNPs, as shown in Scheme 1. As a biomolecular pair existing in nature, the binding between streptavidin and biotin was regarded as the strongest



Scheme 1 Schematic illustration of the biosensor principle for 8-OHdG assay

noncovalent biological interaction [27]. The interaction of streptavidin and biotin forms the basis for the formation of an irreversible and specific linkage between biological macromolecules. Herein, the specific affinity of biotin and streptavidin was used to link DNA probes and MNPs. Probe 1 and probe 2, labeled with biotin, can be modified on streptavidin-coated MNPs, forming MNPs@probe 1 and MNPs@probe 2, respectively. DNA probe with some complementary sequences can partially hybridize with 8-OHdG aptamer. Due to partial hybridization, MNPs@probe 1-aptamer-MNPs@probe 2 formed and MNPs was in aggregated state. Aggregation of MNPs resulted in the increase of RLS intensity. When 8-OHdG was added to the dispersion of MNPs@probe 1-aptamer-MNPs@probe 2, 8-OHdG reacted with the aptamer with priority. 8-OHdG can destroy the double straining structure of probe DNA and aptamer. The aggregated MNPs formation can disaggregate gradually with increasing concentration of 8-OHdG. The larger sized aggregates of MNPs@probe 1-aptamer-MNPs@probe 2 reverted back to MNPs@probe 1 and MNPs@probe 2 with small sizes. Simutaneously, 8-OHdG inserted in the G-quadruplex structure of the aptamer. The RLS signal thus decreased, and the decrement of RLS intensity was linear with the logarithm of 8-OHdG concentration. Therefore, the determination of 8-OHdG can be easily realized by recording the decrement of RLS signal. In addition, the aptasensor can be repeatedly used through several cycling times with the assistance of an external magnetic field. Furthermore, the aptasensor was successfully used to detect 8-OHdG in human urine samples.

Optimization of conditions

The following parameters were optimized: (a) MNPs concentration; (b) Buffer composition and pH; (c) Reaction time and temperature for stability; (d) Probe DNA's length. Respective data and Figures were illustrated in the Electronic Supporting Material. The following experimental conditions were found to give best results: (a) 5.0 μg mL^{-1} MNPs; (b) HEPES buffer with pH 7.4; (c) Reaction for 20 min under 30 °C; (d) Sequences of probe 1–3 and probe 2–3 with 18 bases. And they were selected as optimum conditions.

Sensitivity and reusability

Different concentrations of 8-OHdG were detected under optimum conditions as described above. The result of RLS_0-RLS was a linearly response to the logarithm of 8-OHdG concentration in the range of 32 pM-12.0 nM (Fig. 1a) (with concentration unit of pM). The limit of detection (LOD) can be obtained as 11 pM using $3.29S_B/m$. The equation derived from the criterion of the IUPAC recommendation. S_B was the standard deviation of the blank ($n = 11$) and m was the slope of the linear calibration curve, respectively. The LOD of the present aptasensor for 8-OHdG was lower than those of previous reports, with the detailed results listed in Table 1.

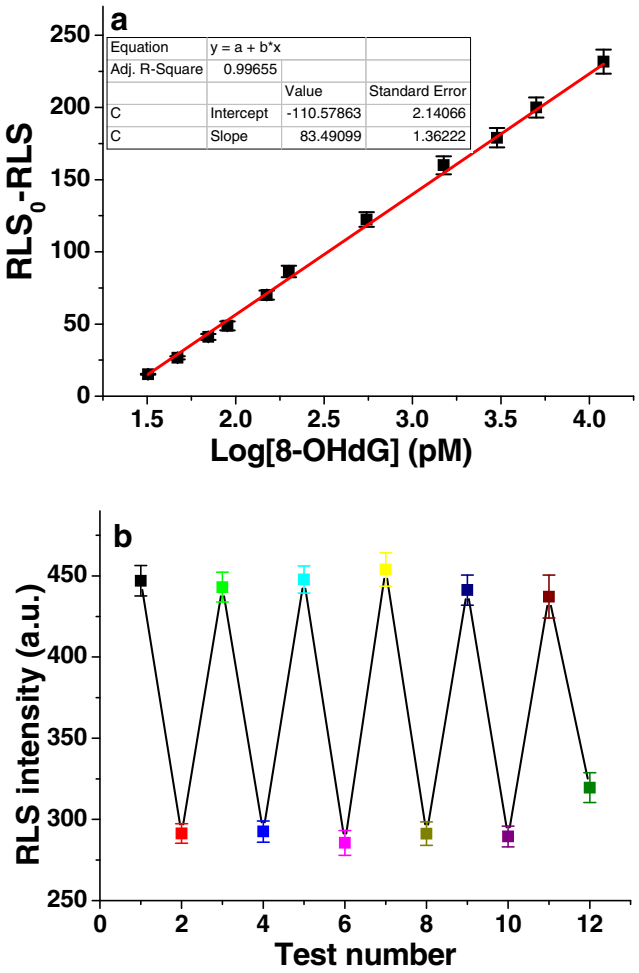


Fig. 1 Linear response of RLS decrease on 8-OHdG concentration in the range of 32 pM–12.0 nM (**a**), and the RLS intensity of MNPs@probe DNA-aptamer decreased by 8-OHdG (1.0 nM) (**b**). The RLS intensity was recorded at 403.0 nm. The error bars were obtained from three separate measurements with RSD less than 4.0%

The reusability of the aptasensor for the detection of 8-OHdG can be easily investigated because the aptamer can selectively react with 8-OHdG rather than probes. MNPs modified with probe DNA dispersed in solution. MNPs can then be collected with the assistance of an external magnetic field and used repeatedly. After MNPs' redispersion, aptamers and 8-OHdG were added orderly into the system subsequently. RLS signal was recorded in the presence and absence of 8-OHdG, respectively (Fig. 1b). It can be

Table 1 Comparison of this strategy with other methods for the determination of 8-OHdG

Method	Material	Analytical range	LOD (nM)	Ref.
HPLC/MS/MS	–	0.313–10.0 μg/L	–	[4]
Colorimetric	AuNPs	5.6–282 nM	1.7	[8]
Circular dichroism	AuNPs	0.05–2 nM	0.033	[28]
Electrochemical	Carbon nanotube	2.9–3061 nM	1.0	[29]
Electrochemical	Grapheme oxide	5.0–5000 nM	1.25	[30]
Fluorescence	–	3.96–211 nM	1.19	[31]
HPLC-ECD	PAMAM dendrimer	0.1–0.7 nM	1.2	[32]
Resonance light scattering	MNPs	0.032–12 nM	0.011	This work

observed that the RLS intensity for 8-OHdG increased slightly when the aptasensor was reused for 6 times. In other words, the value of RLS_0-RLS was almost unchangeable for 5 cycling times.

Specificity

Specificity for 8-OHdG detection was also investigated. It can be observed from Fig. 2 that a dramatic change of RLS intensity was obtained in the presence of 8-OHdG. Various 8-OHdG analogs and metal ions caused insignificant change of RLS signal, even at 100 times higher concentration than that of 8-OHdG. The species were tested including creatinine, glucose, urea, BSA, ascorbic acid, disodium oxalate, sucrose, uric acid, 2′-deoxyguanosin (dG), ganciclovir, thymidine, guanine, Cu^{2+}, Ca^{2+}, Mg^{2+}, K^+, and Fe^{3+}. The interference of K^+ was slightly higher than other species due to its promotion of the formation of the G-quadruplex structure via coordination with the carbonyl oxygen in the planes of the G-quarters [33]. Considering the possible disturbance of K^+ in urine samples, the sample solution was pretreated using a dialysis bag with a molecular weight cut-off (MWCO) of 100 Da as shown in "Collection and pretreatment of human urine samples" Section. Based on these results, it can be demonstrated that the RLS strategy for 8-OHdG detection exhibited great specificity.

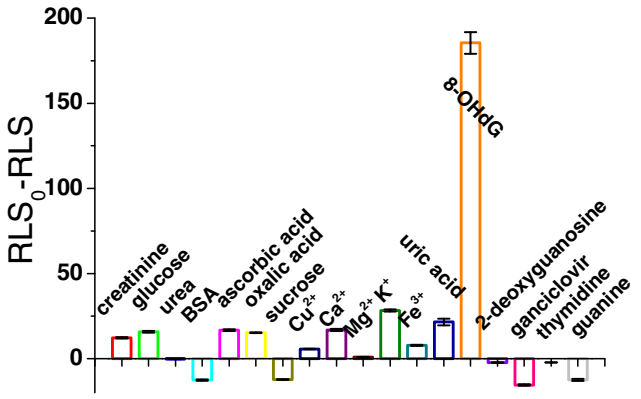


Fig. 2 RLS decrease in the presence of different possible interfering materials for urine samples. Conditions: 100 μg mL^{-1} MNPs, 5.0 nM probe 1, 5.0 nM probe 2, 3.0 nM 8-OHdG, and 5.0 μM other possible interfere

Determination of 8-OHdG in human urine samples

Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. 8-OHdG has been used as a marker that represents cumulative oxidative DNA damage in animals and humans exposed to mutagenic agents such as those found in urban air pollution [34]. Urinary 8-OHdG levels were investigated in healthy individuals for the primary discussion of the effect of air pollution on people, in summer and winter time at Liaocheng City, a little town in North China.

After pretreatment, as described in the Experimental section, 8-OHdG in urine samples was tested using the present aptasensor and an ELISA kit with results shown in Table 2. It can be found that the urinary 8-OHdG levels obtained from the present sensor was consistent with those of the ELISA kit, indicating that the method had comparable accuracy. Furthermore, the F-test and Student's test (t-test) were obtained by comparison of the results from the two methods. The data were in a good confidence level with $\alpha = 0.05$. 8-OHdG levels were detected and ranged from 4.3 to 13.6 and from 3.3 to 10.6 μg g^{-1} creatinine for female and male urines, respectively. The levels of urinary 8-OHdG for females were higher than those of males. The average concentrations of 8-OHdG were about 6.4 and 3.5 μg g^{-1} creatinine in female and male urines on July, August (Aug.), and September (Sep.), respectively. However, a significant increase of 8-OHdG level was detected in female and male urine samples on December

Table 2 Results of 8-OHdG determination in urine samples

Sample		8-OHdG (μg g^{-1} creatinine)[a]	ELSA kit (μg g^{-1} creatinine)[a]	F-test ($\alpha = 0.05$)	t-test ($\alpha = 0.05$)	AQI (Range)[b]
Females ($n = 8$)	July	8.6 ± 1.1	8.5 ± 3.7	0.001	0.476	98 (44–185)
	Aug.	7.9 ± 0.8	8.2 ± 4.4	0.0005	0.011	89 (53–131)
	Sep.	8.9 ± 2.7	9.1 ± 5.3	0.031	0.029	115 (58–186)
	Dec.	15.1 ± 3.9	15.2 ± 4.9	0.258	0.245	182 (68–469)
	Jan.	13.6 ± 5.0	13.6 ± 2.8	0.049	0.163	175 (53–341)
	Feb.	13.1 ± 2.9	12.6 ± 2.7	9.26×10^{-7}	0.315	139 (68–266)
Males ($n = 8$)	July	8.0 ± 0.6	8.7 ± 1.3	0.357	0.031	98 (44–185)
	Aug.	6.8 ± 0.6	6.7 ± 1.8	1.36×10^{-7}	0.093	89 (53–131)
	Sep.	7.9 ± 1.4	8.5 ± 2.1	2.86×10^{-5}	0.024	115 (58–186)
	Dec.	13.5 ± 3.4	12.5 ± 4.3	0.760	0.251	182 (68–469)
	Jan.	12.4 ± 5.2	12.4 ± 4.7	0.269	0.433	175 (53–341)
	Feb.	11.3 ± 4.3	11.7 ± 3.1	0.0006	0.019	139 (68–266)

[a] Values represented by mean ± standard deviation (SD) for 8-OHdG levels

[b] AQI data were obtained from the web at https://www.aqistudy.cn/

(Dec.), January (Jan.), and February (Feb.), respectively. The respective average levels of 8-OHdG reached 12.6 and 10.2 μg g^{-1} creatinine for female and male. It was interesting that the content of 8-OHdG in urine samples was dependent on the Air Quality Index (AQI) results. AQI data was obtained from the web of China air quality online monitoring and analysis platform (https://www.aqistudy.cn/). It can be deduced that there may be a possible correlation between the concentration of 8-OHdG and the air pollution index. The results suggested that air pollution may induce or increase the oxidative stress for healthy people. It can provide some valuable spatial data for evaluation of local air quality performance.

Conclusion

A sensitive, specific, as well as reusable RLS method was constructed for the assay of 8-OHdG. It was carried out by coupling the high specific aptamer to capture 8-OHdG and easy collection of MNPs. Biotin labeled DNA probes can be modified on the surface of streptavidin coated MNPs. Aptamer can induce the aggregation of MNPs due to the partial hybridization of aptamer and DNA probes. In this case, the RLS signal was enhanced significantly. In the presence of 8-OHdG, 8-OHdG can interact with aptamer and induce the dispersion of MNPs. And then RLS intensity decreased with the increase of 8-OHdG concentration with the LOD at 11 pM. The aptasensor showed good sensitivity by comparison with previous works. More importantly, the aptasensor has been successfully applied in the analysis of complex human urine samples with good accuracy. It was suggested from the results of urine samples that the content of 8-OHdG significantly depended on the AQI. These results indicated that the method may have good applicability and huge potential to evaluate local air quality model performance.

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Compliance with ethical standards The author(s) declare that they have no competing interests.

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