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Dual-Color Plasmonic Nanosensor for Radiation Dosimetry

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Abstract

Radiation dosimeters are critical for accurately assessing the levels of radiation exposure of tumor sites and surrounding tissues and for optimizing therapeutic interventions as well as for monitoring environmental exposure. To fill the need for a simple, user-friendly, and inexpensive dosimeter, we designed an innovative colorimetric nanosensor-based assay for detecting ionizing radiation. We show that hydroxyl radicals generated by ionizing radiation can be used to etch gold nanorods (AuNRs) and silver nanoprisms (AgNPRs), yielding reproducible color changes for radiation dose detection in the range of 50–2000 rad, broad enough to cover doses used in hyperfractionated,

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsami.0c03001>.

Typical photographs and absorption spectra of AuNRs and AgNPRs after being stored for 6 months at room temperature, TEM image of AgNPRs following storage for 6 months at room temperature, absorption spectra of AuNRs and AgNPRs irradiated with X-ray after different time intervals (PDF)

The authors declare no competing financial interest.

conventional, and hypofractionated radiotherapy. This range of doses detected by this assay correlates with radiation-induced DNA damage response in mammalian cells. Furthermore, this AuNR- and AgNPR-based sensing platform has been established in a paper format that can be readily adopted for a wide range of applications and translation.

Graphical Abstract

Keywords

radiation dosimetry; colorimetric detection; silver nanoprisms; gold nanorods; dual-color nanosensor

1. INTRODUCTION

Radiation therapy is a common and effective therapeutic modality for cancer treatment as more than half of all cancer patients receive radiotherapy as a part of their treatment. Radiation therapy uses high-energy radiation (X-rays, γ -rays, electron beams, protons, and charged particles) to eliminate cancer cells, control their growth, and metastasis.¹ However, if not properly controlled, radiation can also damage normal cells and induce rate-limiting toxicity in nearby healthy tissues.² Radiation-induced skin pathologies, osteonecrosis, and other complications have been reported. In addition, cases of inaccurate dosing and accidental overdose owing to errors in machine calibration have also been known to occur.³ Therefore, to evaluate and minimize radiation-induced side effects, it is critical to develop radiation dosimeters to accurately measure radiation exposure both within the tumor and at surrounding tissues. In addition, radiation dosimetry is used to monitor environmental exposure and low-dose irradiation in the workplace or around industrial settings.

We sought to develop a simple, quick, and effective methodology for radiation dosimetry based on a nanoplasmonic colorimetric assay. Similar sensing technologies have proven to have significant benefits over conventional sensors such as high biocompatibility, good stability, high sensitivity, and low cost.^{4,5} In contrast, traditional radiation dosimeters, such as the metal–oxide–semiconductor field-effect transistor (MOS-FET) dosimeter, thermoluminescent dosimeter (TLD), and quartz fiber dosimeter (QFD),^{6,7} usually require sophisticated and expensive fabrication technology, separate readout instruments, and professional operators. These drawbacks may limit their application in resource-constrained

areas or countries. Additionally, since no equipment is needed to read the output signal except for the naked eye, it exhibits great potential for commercial portable daily life and medical applications.

Plasmonic nanoparticles, especially gold and silver nanoparticles, have been extensively applied to colorimetric bioanalytical assays for detecting various analytes. They exhibit strong localized surface plasmon resonance (LSPR) as well as characteristic size- and distance-dependent optical absorption properties.^{8,9} Rege and co-workers recently developed a gel-based colorimetric nanosensor dosimeter for proton radiation.¹⁰ In their assay, proton irradiation triggers the reduction of gold ions to gold nanoparticles within the gel matrix with a detection range of 0–3 Gy. Radiation-induced color changes of this platform range from colorless to red, which may be difficult to distinguish at low doses. Recently, gold nanoparticles of various shapes have been synthesized.^{11,12} Among anisotropic gold nanoparticles, gold nanorods (AuNRs) in particular have received a great deal of attention owing to their simple synthesis and modification process, uniquely tunable optical properties, and excellent thermal sensitivity.^{13,14} Multiple applications including medical imaging, cancer therapy, and bioanalysis have been proposed.^{15,16} AuNRs exhibit two optical absorption peaks arising from strong LSPR characteristics in the transverse and longitudinal directions. Specifically, the longitudinal LSPR can be tailored to absorb the light-spanning wavelength range from visible to near-infrared of up to 1600 nm by modulating the AuNR length to diameter ratio.¹⁷ The longitudinal LSPR peaks of AuNRs are extremely sensitive to minute changes in the aspect ratio of AuNRs,¹⁸ and the absorption peak shifts corresponding to the color changes can be precisely tuned by altering the aspect ratio by etching of the AuNRs.¹⁹ Silver-based nanoparticles can also be utilized as a colorimetric sensor owing to their morphology-dependent optical properties.^{20,21} In particular, triangular silver nanoprisms (AgNPRs) containing three sharp vertices exhibit unique resonance optical characteristics.^{22,23} Etching of the AgNPRs induces a blue shift of the LSPR peak concomitant with the shape changes of the nanoprisms into round nanodiscs.^{24,25} Previous studies indicated that AuNRs and AgNPRs could be efficiently etched by reactive oxygen species.²⁶ Because of these unique features, we decided to design AuNR- and AgNPR-based wavelength-variation sensing platforms for effective radiation detection based on the radiation-induced etching of the nanoparticles. To the best of our knowledge, no work about AuNR- and AgNPR-based colorimetric radiation detection has been reported so far, making this system the first example of the usage of AuNRs and AgNPRs as an efficient radiation dosimeter.

2. EXPERIMENTAL SECTION

2.1. Operative and Preferred Ranges of Process Parameters.

The JL Shepherd Mark I irradiator was utilized to irradiate samples at a dose rate of 1.19 Gy/min. Then, the prepared silver nanoprisms were radiated at doses of 0 (control), 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 Gy. The prepared gold nanorod samples were irradiated at doses of 0 (control), 1, 3, 5, 8, 10, 15, 20, 25, and 30 Gy. After irradiation, the samples were kept in dark for 2 h before measured with a UV–vis spectrophotometer.

2.2. Preparation of the Gold Nanorod- and Silver Nanoprism-Based Paper Sensor.

Adsorption of gold nanorods and silver nanoprisms on the paper substrate was achieved by immersing the filter paper in gold nanorod or silver nanoprism solution for 2 h and then air-dried.

2.3. Cell Cultures.

Murine embryonic fibroblasts (MEFs) were cultured in Dulbecco's modified Eagle medium (DMEM) supplemented with heat-inactivated fetal bovine serum (FBS) and 200 unit/mL penicillin/streptomycin plus 1× nonessential amino acids (GIBCO). The cells were kept at 37 °C in a humidified atmosphere containing 5% CO₂.

2.4. Western Blotting.

Cell lysates were prepared in RIPA buffer (50 mM Tris pH 8.0, 1% NP40 0.1% SDS, 150 mM NaCl, 0.5% Na deoxycholate, and the fresh proteinase inhibitor cocktail). Protein extracts were analyzed by Western blotting according to standard procedures using primary antibodies specific for KAP1 (TIF1 β , C42G12 Cell Signaling, #4124), phosphor-KAP1 (A300-767A, Bethyl Laboratories), and α -tubulin (CP06, Calbiochem). HRP-conjugated antimouse and -rabbit secondary antibodies were utilized and the signal was detected using an ECL Western blotting detection system.

3. RESULTS AND DISCUSSION

The working principle of AuNR and AgNPR etching-based colorimetric assay for radiation dosimetry is illustrated in Figure 1. Ionizing radiation induces water splitting to generate oxidizing hydroxyl radicals (OH•), which efficiently shorten the length of AuNRs (Figure 1a) as well as etch triangular AgNPRs into smaller round Ag nanodisks (Figure 1b), thereby triggering substantial blue shifts of LSPR peaks and corresponding color changes of AuNRs (burgundy → blue → green → pink → pale yellow) and AgNPRs (blue → purple → red → colorless).²⁴ The changes in the morphology are dose-dependent, leading to a gradation of color variation that allows detection of radiation doses by direct colorimetric visualization.

AuNRs were coated with cetyltrimethylammonium bromide (CTAB), which facilitates the generation of nanorods and protects AuNRs from aggregating in solution. CTAB has higher coverage density along the long-side facets than the tip facets of AuNRs, resulting in less passivation and higher accessibility to irradiation at the tips of AuNRs.²⁷ Therefore, etching of AuNRs initiates preferentially at the more exposed tip facets, resulting in nanorod shortening (Figure 1a). Accordingly, the longitudinal LSPR peak, which is highly dependent on the aspect ratio change of AuNRs, progressively blue-shifted to shorter wavelengths, consequently leading to the color change from burgundy to bluish green.²⁸ Further radiation yields spherical gold nanoparticles, which in solution range from pink to pale yellow. The progressive color changes and concomitant plasmonic shifts are the consequence of the progressive etching of AuNRs by following ionizing radiation. Conveniently, these color changes are apparent even to the naked eye.²⁹ Similarly, radiation-mediated etching of AgNPRs leads to the formation of smaller round Ag nanodisks (Figure 1b), and the

concomitant blue shift of the LSPR band results in significant color variations (blue → purple → red → colorless). These characteristics make the AuNRs and AgNPRs ideal for designing colorimetric-based sensors for radiation dosimetry.

AuNRs and AgNPRs were synthesized according to the published protocols with slight modification^{24,30} (see details in the Supporting Information section). We first assessed the properties of the nanoparticles. We monitored the UV–vis absorption spectra (Figure 2a,d), the ζ -potentials (Figure 2b,e), and the size and shape by transmission electron microscopy (TEM) (Figure 2c,f). The absorbance spectrum in Figure 2a shows the characteristic transverse and longitudinal bands of AuNRs at 520 and 760 nm, respectively. ζ -Potential measurements indicate that the AuNRs are highly positively charged (42.3 mV) consistent with the formation of the CTAB bilayer around AuNRs (Figure 2b).³⁰ The measurement of the hydrodynamic size of the AuNRs by dynamic light scattering (DLS) reveals the size of 55 ± 3.20 nm (data not shown). The morphology and size of AuNRs were further assessed by TEM. Figure 2c shows a representative TEM image of AuNRs, which are dispersed and show uniform size distribution with an aspect ratio of approximately 3.7. Similarly, Figure 2d shows the UV–vis absorption spectrum of AgNPRs with two characteristic bands at 665 nm ascribed to in-plane dipole resonance and at 335 nm corresponding to out-of-plane quadrupolar resonance.³¹ We further characterized AgNPR morphology by combining DLS and TEM analyses. Size and ζ -potential measurements (Figure 2e) indicate that the average hydrodynamic size and surface charge are 42 nm and -15 mV, respectively. The representative TEM picture in Figure 2f shows that AgNPRs exhibited a triangular prism structure with an edge length between 25 and 45 nm. Notably, AuNR and AgNPR nanoparticles were stable for at least 6 months at room temperature (Figures S1 and S2).

Next, we assessed the behavior of AuNRs and AgNPRs by following ionizing radiation exposure by monitoring the absorption spectra. We sought to assess how radiation-induced etching correlates with shifts in spectra. We observed a progressive shift in the absorbance with increasing radiation doses (Figure 3a), with gradual bleaching and shifting from 760 nm toward blue light due to the shortening of AuNRs as the etching process progresses. The wavelength shifts were time-dependent, reached a constant value after 2 h and did not further increase for at least 160 h (Figures 4 and S3). Therefore, 2 h incubation time was selected. The etching process is highly radiation dose dependent and the wavelength shift increases linearly between 1 and 20 Gy (Figure 3b). Higher radiation doses induce stronger bleaching and larger blue shifts of the LSPR peak, a prerequisite for developing an efficient radiation detector. In addition, radiation-induced LSPR peak shifts are highly reproducible within the 1–20 Gy range, where radiation doses could be quantitatively evaluated. Although we could detect absorbance changes for AuNRs in the 1–30 Gy range, the absorbance did not significantly shift below 1 Gy, showing the lower limit of detection of the AuNR-based nanosensor. Next, we assessed the impact of ionizing radiation on AgNPRs. Figure 3c shows the absorbance spectra of AgNPRs at increasing radiation doses. Similar to what we observed for AuNRs, the maximum absorbance of AgNPRs gradually shifted to shorter wavelengths with a concomitant decrease in absorbance intensity at radiation doses ranging from 0.5 to 5 Gy, establishing that AgNPR etching is also proportional to radiation doses. Notably, the increase in LSPR peak shift was linear within the 0.5–3 Gy radiation range, where the radiation doses could be accurately measured, with a lower detection limit of 0.5

Gy. Thus, the AgNPR further extends the detection limits of AuNRs to lower ranges important for biological applications. The higher detection sensitivity of AgNPRs compared to AuNRs can be attributed to the inherent susceptibility of triangular AgNPRs to reactive oxygen species (hydroxyl radical and H_2O_2) generated by ionizing radiation.

We originally hypothesized (see above) that progressive etching of the nanorods and/or nanoparticles and their subsequent size changes should take place upon irradiation. Next, we used DLS and TEM measurements to follow the changes in the shape and size of AuNRs and AgNPRs following irradiation. Figure 5a shows TEM images of AuNRs subjected to increasing radiation doses. Etching of AuNRs was proportional to radiation dosage. AuNRs were etched along the longitudinal direction, resulting in the shortening of AuNRs. Ultimately, AuNRs were transformed from nanorods into smaller spherical nanoparticles and even to complete dissolution at high radiation doses. This observation was consistent with the previous reports, confirming that the lower surface coverage of surfactant CTAB at the tips of AuNRs was responsible for preferential etching along the length of the nanorod.^{32,33} Similarly, we could observe morphological transitions of AgNPRs during radiation by TEM (Figure 5d). The morphology of the AgNPRs gradually changed from triangle nanosheets to round nanodisks accompanied by size reduction following irradiation, ultimately resulting in very small silver nanoparticles at high radiation doses. This could explain the significant absorption spectral shifts and color changes of AgNPRs during the etching process. Using DLS and ζ -potential measurements (Figure 5c,f), we also found a reduction in the hydrodynamic size and ζ -potential of the AuNRs and AgNPRs with increasing radiation doses. High radiation doses produced a larger number of free radicals as compared to lower radiation doses, which could lead to more severe etching and the formation of smaller metal nanoparticles. High radiation-mediated etching of AuNRs and AgNPRs finally led to the formation of metal ions, which was confirmed by X-ray photon spectroscopy (XPS) analysis (Figure 6).

Prompted by the sensitivity of the AuNR- and AgNPR-based biosensing platform in solution, we next attempted to develop a simple paper-based biosensor platform for onsite naked-eye detection of radiation doses using AuNRs and AgNPRs as the colorimetric reporters. Paper-based platforms are attractive and user-friendly methodologies in analytical and clinical chemistry applied to food quality testing, public health and environmental monitoring, “point-of-care” medical diagnosis, and forensic sciences.^{34–36} As analytical support, the paper provides great advantages including low cost, portability, compatibility, and ease of usage, storage, transport, and modification.^{37,38} Notably, the utilization of colorimetric AuNR- and AgNPR-based paper tests for the detection of the radiation dosage has not been assessed.

To adapt the assay to paper format, AuNRs and AgNPRs were immobilized by immersing the filter paper in AuNR and AgNPR solution for 2 h and then air-dried.³⁹ For each of the metal nanoparticles, colorimetric paper tests were performed over the same ranges of radiation doses, as shown in Figure 7. We observed that the color of AuNRs gradually changed from burgundy to bluish green, then pink, and finally to pale yellow with increasing radiation doses (Figure 7a). Similarly, immobilized AgNPRs exhibited color-change properties in response to ionizing radiation. Figure 7b indicated that the changes in color

could be detected even with 0.5 Gy increments of the radiation dose. Importantly, the paper color did not change over time in the absence of radiation. Together, these results indicated that the paper test was suitable to determine radiation doses in the 0.5–20 Gy range. This range covered therapeutic doses employed in hyperfractionated (0.5–1.8 Gy), conventional (1.8–2.2 Gy), and hypofractionated (3–10 Gy) radiotherapy.^{3,40} Importantly, paper-based assays using colorimetric nanoparticles circumvented the requirements for expensive equipment and provided low detection limits, offering a user-friendly alternative for convenient onsite assay and widespread implementation.

We next evaluated how the radiation doses detected by AuNR and AgNPR dosimetry correlated with the biological impact of radiation or oxidative damage detected on cells. In cells, ionizing radiation (IR) triggers the production of excess reactive oxygen species (ROS), including hydroxyl radicals, which subsequently result in DNA damage. IR-induced DNA double-stranded breaks (DSBs) activate the ataxia-telangiectasia mutated (ATM) protein kinase, which in turn phosphorylates numerous substrates.⁴¹ Among the ATM substrates, KAP1 (also called tripartite motif-containing 28, TRIM28) is phosphorylated at serine 824 by ATM,⁴² facilitating DNA repair together with other DNA damage proteins.⁴³ First, we assessed the levels of phosphorylated KAP1 at serine 824 (pKAP1) after varying doses of IR exposure as an indicator of DNA damage response (Figure 8a). As anticipated, we observed increasing pKAP1 signals by Western blotting with increasing IR doses, suggesting a concomitant increase of ATM activation. In independent experiments, cells were treated with increasing concentrations of organic peroxide *tert*-butyl hydroperoxide (TBH), which generates ROS in the absence of IR. This resulted in a similar increase in the pKAP1 signal (Figure 8b). This validates our approach to use AuNR- and AgNPR-based colorimetric nanosensors for radiation dosimetry within radiation ranges that cause measurable DNA damage in cells. By combining AuNR- and AgNPR-based colorimetric dosimeters, our method is capable of quantifying a broad range of environmental damage, including but not limited to, radiation- and ROS-inducing agents. This, in turn, may open up new research avenues for the characterization of DNA damage and ROS.

4. CONCLUSIONS

In summary, we have established a simple yet powerful nanosensor for detecting ionizing radiation through etching of AuNRs and AgNPRs induced by hydroxyl radicals generated by ionizing radiation, yielding reproducible color changes. This colorimetric sensor can detect radiation doses ranging from 0.5 to 20 Gy. This approach allows for visible detection of radiation doses with high sensitivity and excellent reproducibility. In addition, the unique properties of AuNRs and AgNPRs, such as facile synthesis and modification, low cost, uniquely tunable optical properties, and excellent thermal sensitivity and aqueous solubility, add benefits to the sensing platform. Moreover, this AuNR- and AgNPR-based sensing platform has been established as a paper test. The translational potential of this dosimeter includes assisting oncologists with treatment planning and improving the therapy effectiveness, thus resulting in better patient outcomes. Taken together, this AuNR- and AgNPR-based colorimetric sensing platform presents a new dosimetry of therapeutic radiation dose with potential applications in radiation therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Schematic illustration of radiation-based etching of gold nanorods and silver nanoprisms. (a) Radiation-mediated etching of gold nanorods leads to the formation of short gold nanorods and finally to the gold nanoparticles and gold ions. (b) Radiation-mediated etching of silver nanoprisms leads to the formation of smaller round Ag nanodisks and finally to the silver ions.

Figure 2.

Characterization of AuNRs and AgNPRs. Characterization of (a–c) gold nanorods and (d–f) silver nanoprisms, including absorbance spectra (a, d), ζ -potentials and hydrodynamic sizes (b, e), and transmission electron microscopy (TEM) images (c, f) of the nanoparticles. In (b) and (e), the red columns represent the ζ -potential and the green columns represent the hydrodynamic size.

Figure 3.

Absorption spectra. Absorption spectra and linear calibration curves of (a, b) gold nanorods and (c, d) silver nanoprisms irradiated with a range of X-ray doses (Gy). Absorption spectra of gold nanorods irradiated with increasing X-ray doses (0, 1, 3, 5, 8, 10, 15, 20, 25, and 30 Gy) (a). The linear plot of longitudinal peak shift as a function of radiation dose from 1 to 20 Gy (b). Absorption spectra responses of the silver nanoprisms irradiated with different X-ray doses (0, 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 Gy) (c). Linear plot of wavelength shift as a function of the radiation dose from 0.5 to 3 Gy (d).

Figure 4.

(a) Absorption spectra of gold nanorods irradiated with X-ray (30 Gy) at different times. (b) Time-dependent longitudinal peak shift of gold nanorods as a function of X-ray radiation (30 Gy). (c) Absorption spectra of silver nanoprisms irradiated with X-ray (5 Gy) at different times. (d) Time-dependent wavelength shift of silver nanoprisms as a function of X-ray radiation (5 Gy).

Figure 5. Shapes and properties of nanoparticles upon irradiation. TEM images (a, d), ζ -potentials (b, e), and hydrodynamic sizes (c, f) of gold nanorods (a–c) and silver nanoprisms (d–f) after different radiation doses (gold nanorods: 0 Gy $\rightarrow$ 5 Gy $\rightarrow$ 20 Gy $\rightarrow$ 30 Gy; silver nanoprisms: 0 Gy $\rightarrow$ 2.5 Gy $\rightarrow$ 5 Gy).

Figure 6.

(a, b) XPS spectra of gold nanorods (a) before and (b) after irradiated with X-ray (30 Gy).

(c, d) XPS spectra of silver nanoprisms (c) before and (d) after X-ray irradiation (5 Gy).

Figure 7.

Paper-based colorimetric assay. (a) Gold nanorods and (b) silver nanoprisms were irradiated at the indicated doses and spotted on the filter paper (gold nanorods: 0, 1, 3, 5, 8, 10, 15, 20, 25, and 30 Gy, silver nanoprisms: 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 Gy).

Figure 8. ATM activation by IR and ROS. Mouse embryonic fibroblasts (MEFs) were treated with (a) IR (0–10 Gy) or (b) TBH (0–1000 μ M). Cellular protein extracts were prepared for 2 h by following radiation exposure or 2 h after TBH treatment, then immunoblotted with the indicated antibodies: phospho-KAP1 (pKAP1), KAP1, and tubulin. The increase in the intensity of pKAP1 is indicated on top of the Western blots.