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Overcoming Barriers in Topical Administration of Gold Nanoparticles for Optical Coherence Tomography Using Multi-Modal Delivery

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ABSTRACT

Optical coherence tomography (OCT) is a non-invasive and promising imaging modality with high resolution that is an order of magnitude higher than current diagnostic techniques. However, its use in detecting early-stage cancer is limited due to insufficient contrast level in biological tissue, which can be enhanced by harnessing contrast agents [e.g., gold nanoparticles (Au NPs)]. Enhanced penetration by creating micropassages and distribution by ultrasonic force (multi-modal topical delivery) was proven to overcome two major barriers (stratum corneum and epithelial barriers) in topically administering Au NPs using an in vivo oral dysplasia hamster model (overall 150% enhanced OCT contrast). Expanded progress on a highly efficient and versatile Au NP-releasing polymer microneedle platform showed a promising next generation multi-modal delivery of Au NPs.

Keywords: Optical coherence tomography, contrast agent, gold nanoparticles, enhanced delivery, ultrasound, microneedle, early-stage cancer

1. INTRODUCTION

Recently, optical imaging tools have been developed to diagnose diseases, particularly cancer, in cost effective and minimally/non-invasive ways. Among many optical imaging tools, OCT, which detects a reflected light from the sample using refractive index mismatching, is a promising diagnostic tool to detect early-stage cancer with its high resolution that, in theory, is an order of magnitude higher than other conventionally practiced diagnostic techniques such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) ^{1,2}. In addition, cross sectional OCT images can be reconstructed in two- and three-dimensions for various biological applications. However, its low contrast in biological tissue limits the use of OCT in detecting early-stage cancer ³. Doppler OCT ^{4,5}, polarization-sensitive OCT ^{6,7}, chemico-physical enhancers ^{8,9}, and contrast agents ^{10,11} have been employed to overcome/ameliorate this fundamental limitation of OCT. Gold nanoparticles (Au NPs) are promising contrast agents. They are easy to synthesize in a desired size and shape, and possess optical properties suitable for OCT such as high light scattering and surface plasmon resonance (SPR) effects, which could contribute to differentiating early-stage cancer lesions from normal tissues. Regardless of shapes and sizes of Au NPs (e.g., nanospheres, nanorods and nanoshells), efficient Au NPs delivery play determining roles in obtaining sufficient optical signals from phantom or tissue samples. Topical delivery of Au NPs offers many advantages over systemic delivery, including significantly lower systemic toxicity and dosage. However, poor penetration through stratum cornea and distribution of Au NPs in tissue remain major barriers. It is hypothesized that scattering dominant Au NPs (i.e., over 60 nm in diameter) are able to penetrate through micropassages created by microneedles and dispersed by ultrasound afterwards (multi-modal delivery). The combination of microneedle and ultrasound techniques may significantly enhance OCT contrast and allow differentiating dysplasia area and normal area. In vivo hamster oral dysplasia models with antibody conjugated Au NPs proved that the multi-modal delivery is indeed an effective delivery strategy for overcoming biological barriers in topical administration of Au NPs for OCT¹².

2. METHODS

2.1 Au NP synthesis

Au NPs (70 nm in diameter) were synthesized by Frens' method with a slight modification¹³. Size of Au NPs was determined by dynamic light scattering (DLS) particle analysis and transmission electron microscope (TEM). The final concentration of Au NPs was calculated to be 2.19×10^{10} particles/mL by UV-visible spectroscopy. Anti-epidermal growth factor receptor (EGFR) antibodies were conjugated on the gold nanoparticles, followed by PEGylation (MW = 4 kDa). EGFR is over-expressed in hamster oral cancer model. The anti-EGFR conjugated Au NP solution was centrifuged at 8000 rpm for 10 min and resuspended in phosphate buffer saline (Fisher scientific, Fair Lawn, NJ). The final concentration of anti-EGFR conjugated Au NP was 1.78×10^{10} particles/mL.

2.2 Spectral Domain (SD)-OCT system

Spectral-domain OCT (SD-OCT) was used to obtain the images (Figure 1). Low-coherence light had a 1310 nm of center wavelength and 90 nm of FWHM. A 130 nm wide spectrum was sampled by a 1x1024 InGaAs detector array at 7.7 kHz frame rate. Imaging depth and depth resolution were 3.4 mm and 8 μ m in air, respectively. A 2-axis scanner with two galvanometers was located at the same sample arm. SD-OCT images were obtained with the same focal point.

Figure 1. Schematic of fiber-based spectral-domain OCT: CM, Collimator; DAQ, Data Acquisition System; DG, Diffraction Grating; FL, Focusing Lens; LCL, Low-Coherence Light; LSC, Line Scan Camera.

2.3 Oral cancer animal model

Golden Syrian hamsters (*Mesocricetus auratus*) were treated topically with 0.5% (v/v) 9, 10-dimethyl-1,2-benzanthracene (DMBA, Sigma, St. Louis, MO) in mineral oil three times per week for five months to induce early-stage of cancer. The anesthetized hamster's cheek pouch was attached to a microscope stage using a custom-built ring-shaped clamp (Figure 2).

Figure 2. Hamster cheek pouch image. The cheek pouch was attached to a microscope stage using a custom-built ring-shaped clamp (1 cm in diameter).

2.4 Multi-modal delivery method

SD-OCT images were obtained before and after Au NPs were administered with and without applying microneedles and ultrasound. Three-hundred μm microneedle roller was applied on the tissue at three different angles (i.e., 0, 45, and 90 degree). Two hundred μL of the anti-EGFR antibody conjugated PEGylated Au NPs was applied on the hamster's cheek pouch for 10 min. An ultrasonic force of 1 MHz at $0.3 \text{ W}/\text{cm}^2$ power density was applied with ultrasound gels using a Dynatron 125 ultrasonicator (Dynatronics Corporation, Salt Lake City, UT) on the cheek pouch for 1 min. The administered tissues were imaged with SD-OCT at various time points up to two hours.

2.5 Histology

After OCT imaging, DMBA-treated and untreated hamster cheek pouch tissues were excised and fixed in 0.1 M cacodylate buffer and postfixed for Richardson's stain. Five hundred nm semi thin sections of plastic tissue block were prepared and observed by an upright microscope (BH-2, Olympus, Tokyo, Japan).

3. RESULTS

SD-OCT images showed that Au NPs were able to efficiently penetrate and spread throughout in the hamster cheek pouch tissue only after the multimodal delivery method (microneedles and ultrasound application) was used, which resulted in significantly enhanced optical contrast in tissue (Figure 3). The mean scattering intensities in DMBA-untreated and DMBA-treated sides of a hamster were increased 149 and 177%, respectively. Interestingly, OCT combined with multi-modal delivery of anti-EGFR conjugated Au NPs was able to identify very early-stage dysplasia lesions in the DMBA-untreated side of the hamster (yellow-dotted areas in Figure 3).

Figure 3. In vivo SD-OCT images of (A) DMBA-untreated and (B) DMBA-treated hamster cheek pouches. MNs: applied microneedle only (middle images); MNs-Au NPs-US: Au NPs were administered after MNs were applied, followed by applying ultrasound. Yellow-dotted areas indicate early-stage dysplasia in DMBA-untreated side of the hamster. Scale bar: 100 μm .

While DMBA-untreated hamster was considered as the control in the study, SD-OCT imaging with multimodal delivery of anti-EGFR conjugated Au NPs showed dysplasia in cheek pouch, which further was confirmed by histology (Figure 4). Usually a hamster develops dysplasia with oral carcinogen for 4 to 6 weeks, but the hamster was treated for 5 months, which developed dysplasia on the DMBA-untreated cheek pouch side. Interestingly, Au NPs were able to deliver deeper in the dysplasia region than in the normal region, which explains the increased contrast in the upper epithelial layers of dysplasia tissue.

Figure 4. Richardson's stain image of DMBA-untreated hamster cheek pouch.

Further progress has also been made to address improved use of Au NPs using dissolvable polymer microneedles. Polymer microneedles are biocompatible, can penetrate tissue layers, and simultaneously release encapsulated Au NPs under a baseline membrane (Figure 5). Polymer microneedles can penetrate the tissue with desired depth and deliver the exact amount of gold nanoparticles in the specific area of interest. Delivery efficiency can be increased by orders of magnitude using this efficient, convenient, and versatile platform for topical delivery of Au NPs for OCT.

Figure 5. SD-OCT images showing Au NP-encapsulating polymer microneedles applied to hamster oral tissue

4. CONCLUSION AND DISCUSSION

The 70 nm PEGylated, EGFR-conjugated Au NPs were efficiently delivered by the improved penetration (microneedles) and the distribution (ultrasound). Multi-modal delivery (microneedles and ultrasound) method of EGFR-conjugated Au NPs overcame epithelial barriers of the oral dysplasia in a hamster model, significantly increasing approximately 150% optical contrast in SD-OCT images. Therefore, early-stage dysplasia was clearly diagnosed by using multimodal delivery of Au NPs. Furthermore, biocompatible Au NP-releasing dissolvable polymer microneedles in association with ultrasound administration can be a promising platform for efficient and convenient administration of OCT contrast agent via topical routes.

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