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Ultrasmall gold nanosatellite-bearing transformable hybrid nanoparticles for deep tumor penetration

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ABSTRACT

Since delivering drugs to an entire tumoral region leads to high therapeutic efficacy and good prognosis, achieving deep tumoral penetration of drugs is a major issue in cancer treatment. In this regard, conventional nanomedicines (>50 nm) have shown limitations in cancer therapy, primarily attributed to the heterogeneous distribution of drugs because of the physiological barrier of the tumor interstitial space. To address this issue, we prepared transformable hybrid nanoparticles (TNPs) consisting of a pH-responsive nanocarrier (PEG-PBAE) and doxorubicin (DOX)-conjugated ultrasmall (<3 nm) gold nanoparticles (nanosatellites). It has been shown that PEG-PBAE can serve as a reservoir for nanosatellites and release them in mildly acidic conditions (pH 6.5), mimicking the tumor microenvironment. When DOX-loaded TNPs (DOX-TNPs) were intravenously injected into tumor-bearing mice, they successfully accumulated and dissociated at the extracellular level of the tumor, leading to the disclosure of nanosatellites and free DOX. While the free DOX accumulated in tumor tissue near blood vessels, the deeply diffused nanosatellites were taken up by the tumor cell, followed by the release of DOX via cleavage of pH-responsive ester linkages in the nanosatellites at the intracellular level. Consequently, the DOX-TNPs effectively suppressed tumor growth through improved tumor penetration of DOX, suggesting their promising potential as a cancer nanomedicine.

Statement of Significance

Deep tumor penetration of anticancer drug is an important issue for high therapeutic efficacy. If the drugs cannot reach cancer cells in a sufficient concentration, their effectiveness will be limited. In this regard, conventional nanomedicine showed only modest therapeutic efficacy since they cannot deliver their payloads to the deep site of tumor tissue. This heterogeneous distribution of the drug is primarily attributed to the physiological barriers of the tumor microenvironment, including a dense extracellular matrix. To surmount this challenge, we developed tumor acidity-triggered transformable nanoparticles. By encapsulating doxorubicin-conjugated ultrasmall gold nanosatellites into the nanoparticles, the drug was not significantly bound to genetic materials, resulting in its minimal sequestration near the vasculature and deep tumor penetration. Our strategy could resolve not only the poor penetration issue of the drug but also its restricted tumor accumulation, suggesting the potential as an effective nanotherapeutics.

1. Introduction

Nanotechnology has been extensively leveraged to develop efficient delivery systems of anticancer drugs for minimizing their systemic side effects [1,2]. The major rationale is the enhanced permeation and retention of nanoparticles in solid tumors through distinct leaky vasculature and dysfunctional lymphatic drainage [3,4]. Numerous nanomedicines, including Doxil® (100 nm) and Abraxane® (130 nm), have exhibited substantial benefits in cancer therapy [5–7]. However, compared with free drug molecules, no significant improvement in the therapeutic efficacy of these nanomedicines has been observed in clinical trials using passive

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targeting regimes [8–10]. This is primarily due to the predominant accumulation of nanoparticles in perivascular tissues, leading to a heterogeneous distribution of the drug [11,12]. A reduced transcapillary pressure gradient, elevated tumor interstitial fluid pressure, and a dense heterogeneous structure of the extracellular matrix (ECM) in the tumor interstitium are known to hinder the diffusion of nanoparticles, leaving them mainly in the perivascular region [10,13–15]. Delivering drugs to the entire tumoral region is key to achieving high therapeutic efficacy and a good prognosis [16,17]. If drugs cannot access all cancer cells, their effectiveness will be compromised regardless of drug potency [18,19].

Correspondingly, many efforts have been made in the field to overcome the physiological barriers of the tumor interstitial space by engineering the physicochemical properties of drug delivery systems [20–23]. In general, reducing the size of nanocarriers contributes to their tumor penetration efficiency and allows better drug distribution [24–26]. Gold nanoparticles have been especially well-studied in this regard because of their biocompatibility and size tunability [27,28]. Particles smaller than 10 nm have been shown to deeply diffuse into the tumor spheroid [24]. Nevertheless, ultrasmall gold nanoparticles have not been widely used as effective drug carriers because they are rapidly cleared by renal filtration, leading to poor tumor accumulation and retention [29]. On the other hand, large nanoparticles (~100 nm) are beneficial at the initial stage of intravascular anticancer drug delivery, with long circulation times and preferential extravasation into the tumor interstitium [30]. Thus, there is a strong need to develop a delivery system by combining advantages of large and small nanoparticles to satisfy the requirement for tumor homing and for deep tumor penetration.

In view of the above challenges, we propose a tumor site-specific, sheddable delivery system that can launch ultrasmall gold nanoparticle-drug conjugates in the tumor interstitium to further transport therapeutic agents deep into the solid tumor (Fig. 1). Accordingly, we developed tumor acidity-triggered transformable nanoparticles (TNPs) containing doxorubicin (DOX)-conjugated ultrasmall gold nanoparticles (nanosatellites). We chose an acidic pH as a stimulus to trigger release of the payload because the ECM of most solid tumors is mildly acidic (pH 6.5–6.8) due to the Warburg effect [31–33]. As TNPs exhibit the micellization-demicellization transition at the extracellular level within an acidic tumor, encapsulated nanosatellites can be protected from serum degradation and nonspecific interactions in the bloodstream (pH 7.4), allowing for prolonged circulation. Consequently, pH-responsive, DOX-loaded TNPs (DOX-TNPs) preferentially accumulate and dissociate at the extracellular level in the tumor, followed by a disclosure of nanosatellites and free DOX. The released free DOX is expected to reside in the perivascular region following intercalation with genetic materials of the cell debris [16], while the released nanosatellites can diffuse into deep sites. Sequentially, nanosatellites will be taken up by the tumor cell and pH-sensitive ester linkage of nanosatellites is cleaved, resulting in the release of DOX at the intracellular level. We hypothesize that the addition of deep tumor-penetrating nanosatellites will improve the overall therapeutic efficacy of conventional drug-loaded nanocarriers.

2. Materials and methods

2.1. Materials

Didodecyldimethylammonium bromide (DDAB), decanoic acid, tetrabutylammonium borohydride (TBAB), gold (III) chloride hydrate ($HAuCl_4$), α-lipoic acid (LA), toluene, doxorubicin hydrochloride (DOX·HCl), Fmoc *N*-hydroxysuccinimide ester (Fmoc-OSu), anhydrous dimethylformamide (DMF), N,N-

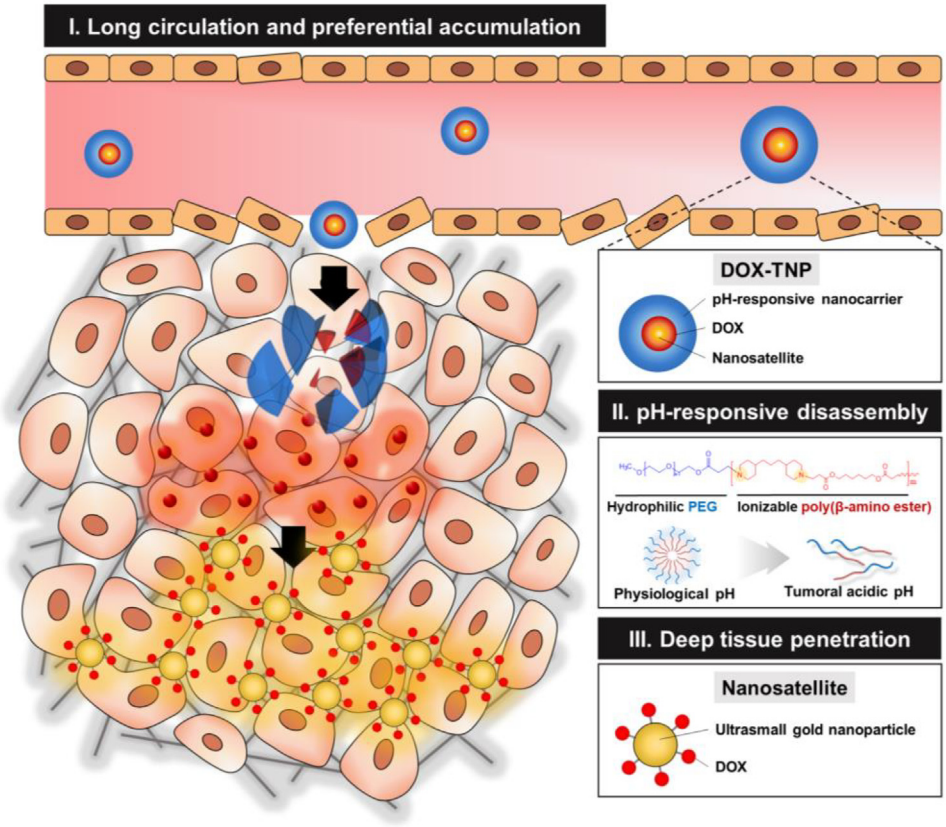

Fig. 1. Schematic illustration of DOX-TNPs for enhanced tumor accumulation and deep tumor penetration.

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