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ARTICLE

Injectable Single-Component Peptide Depot: Autonomously Rechargeable Tumor Photosensitization for Repeated Photodynamic Therapy

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Cite This: *ACS Nano* 2020, 14, 15793–15805

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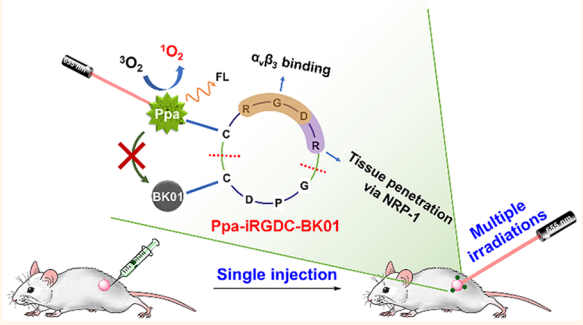
ABSTRACT: The general practice of photodynamic therapy (PDT) comprises repeated multiple sessions, where photosensitizers are repeatedly administered prior to each operation of light irradiation. To address potential problems arising from the total overdose of photosensitizer by such repeated injections, we here introduce an internalizing RGD peptide (iRGD) derivative (Ppa-iRGDC-BK01) that self-aggregates into an injectable single-component supramolecular depot. Ppa-iRGDC-BK01 is designed as an *in situ* self-implantable photosensitizer so that it forms a depot by itself upon injection, and its molecular functions (cancer cell internalization and photosensitization) are activated by sustained release, tumor targeting, and tumor-selective proteolytic/reductive cleavage of the iRGD segment. The experimental and theoretical studies revealed that when exposed to body temperature, Ppa-iRGDC-BK01 undergoes thermally accelerated self-assembly to form a supramolecular depot through the hydrophobic interaction of the Ppa pendants and the reorganization of the interpeptide hydrogen bonding. It turned out that the self-aggregation of Ppa-iRGDC-BK01 into a depot exerts a multiple-quenching effect on the photosensitivity to effectively prevent nonspecific phototoxicity and protect it from photobleaching outside the tumor, while enabling autonomous tumor rephotosensitization by long sustained release, tumor accumulation, and intratumoral activation over time. We demonstrate that depot formation through a single peritumoral injection and subsequent quintuple laser irradiations at intervals resulted in complete eradication of the tumor. During the repeated PDT, depot-implanted normal tissues around the tumor exhibited no phototoxic damage under laser exposure. Our approach of single-component photosensitizing supramolecular depot, combined with a strategy of tumor-targeted therapeutic activation, would be a safer and more precise operation of PDT through a nonconventional protocol composed of one-time photosensitizer injection and multiple laser irradiations.



KEYWORDS: *photodynamic therapy, internalizing RGD (iRGD), activatable photosensitizer, molecular depot, sustained release*

Photodynamic therapy (PDT) is a minimally invasive therapeutic modality relevant for a variety of cancers and precancerous diseases.[1−5] PDT exerts a localized therapeutic effect by combining safe components (photosensitizers, light, and oxygen) in a confined disease area where photosensitizers (PSs) are accumulated and excited by light to convert tissue oxygen to cytotoxic singlet oxygen ($^1O_2$).[6] In spite of the clinical benefits of PDT such as high precision and less invasiveness, there remain challenges to overcome, among which nonspecific phototoxicity is recognized as a critical side effect because PSs remaining in the body leave patients light-sensitive to cause indiscriminate oxidative damage in the skin and eye even under ambient light. As a decent solution to this problem, activatable PSs have been proposed, whose phototoxicity is selectively activated in response to tumor microenvironments while remaining inactive in normal tissues.[7−9]

Another overlooked issue in PDT is a potential side effect caused by total overdose of repeatedly injected PSs.[10] Since

Received: August 16, 2020
Accepted: November 5, 2020
Published: November 11, 2020