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Photodynamic efficacy of photosensitizers under an attenuated light dose via lipid nano-carrier-mediated nuclear targeting

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ABSTRACT

Photodynamic therapy (PDT) has emerged as a treatment for certain malignant-like skin, head and neck, gastrointestinal, and gynecological cancers. The broader acceptance of PDT treatment for large or deep-seated tumors is still hindered, at least in part, by the low photodynamic efficiency of photosensitizers (PS) in the deep-seated tumor environment where the light energy fluency rate is severely attenuated after propagation via skin and/or tissue barriers. In this report, efficient nuclear-targeted intracellular delivery of PS is achieved using an easily fabricated yet entirely biocompatible and inexpensive polysaccharide-functionalized nanoscale lipid carrier, which triggers the intracellular release of photosensitizers inside cancer cells and targets cell nuclear to achieve a significantly enhanced photocytotoxicity. Cancer cells are killed efficiently even under an extremely low light fluency of 1 mW/cm^2 attenuated via an interval meat layer with a thickness of 3 mm. Therefore, this nuclei-targeting system may contribute to the development of a new generation of PS carriers that fight against deep-seated tumors and that exhibit excellent photodynamic efficiency under faint light irradiation.

1. Introduction

Photodynamic therapy (PDT) depends on the reaction of excited photosensitizers (PS) with molecular oxygen in situ to produce cytotoxic reactive oxygen species, such as singlet oxygen, to kill target cells. In principle, the photodynamic efficiency of PS is directly related to the total fluency of light absorbed [1]. Unlike traditional chemotherapy, the use of PS for PDT can be nontoxic at both cellular and organ levels even at relatively high concentrations. Therefore, PDT has emerged as a relatively safe treatment for certain malignancies, including skin, head and neck, gastrointestinal, and gynecological cancers [2].

However, a broader acceptance by the medical community of the application of PS to treat large or deep-seated tumors is still hindered, at least in part, by the low photodynamic efficiency of PS in the deep-seated tumor environment where the light intensity is severely attenuated after propagation via skin and/or tissue barriers [3]. However, when the administration of PDT light exceeds a certain threshold, excessive heating and photochemical reactions that induce the necrosis of surrounding normal tissue can occur [3,4]. The only appropriate way to overcome the difficulties associated with PDT for the treatment of deep-seated tumors is to enhance the photodynamic efficiency of PS under attenuated light doses. These circumstances have sparked a worldwide search for new functionalized sensitizers, which has led to the discovery of new compounds. Because the use of most organic dyes as PDT candidates results in low triplet quantum yields, a recent study incorporated heavy atoms, such as bromine, iodine, selenium, and lanthanides, into the structure to improve the spin–orbit coupling leading to facilitated intersystem crossing [5,6]. While this approach appears fail safe, the incorporation of heavy atoms leads to increased “dark toxicity” [7,8]. On the other hand, singlet oxygen generated by PS causes single-strand breaks and alkali-labile lesions in the DNA and inactivates enzymes involved in DNA repair [9]. Consequently, the nucleus represents the most vulnerable target for PDT [10–13]. However, singlet oxygen exhibits an instantaneous lifetime (<200 ns) and a short diffusion range (approximately 20 nm) and from the site of generation, the intracellular damage by singlet oxygen is limited to the subcellular location of PS. Thus, another approach to enhance the photocytotoxicity of PS is the targeted intracellular delivery of PS to the hypersensitive cell nucleus. Indeed, in addition to PDT, numerous drugs and anti-cancer drugs in particular, are typically designed to localize to the nucleus and cause DNA damage and/or topoisomerase inhibition, which

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