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Synthesis of a near infrared-actuated phthalocyanine-lipid vesicle system for augmented photodynamic therapy

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ABSTRACT

The efficacy of photodynamic therapy (PDT) is often limited by the poor bio-distributive properties of conventional photosensitizers and the local hypoxic microenvironment that characterises most solid tumours. Herein, a novel in situ oxygenic lipid formulation for photodynamic therapy (PDT) is reported. Such a hybrid was synthesized by adsorbing bimetallic nanozymes, MnO_2@PtNPs (NPs = nanoparticles) onto graphene quantum dots (GQDs) – zinc (II) phthalocyanine conjugates, followed by liposomal encapsulation, affording it enhanced water solubility. The MnO_2@PtNPs, which are is shown to possess excellent catalase-like properties surpassing that of MnO_2 or PtNPs alone, serves to catalyze H_2O_2 to O_2, while the zinc (II) phthalocyanine (**1**) serves to transform the formed oxygen to generate cytotoxic singlet oxygen immediately. We show that by combining each function of the respective building blocks, the as-synthesized **1**-GQDs-MnO_2@PtNPs-liposomes not only maintains the properties of oxygen supplementation through H_2O_2 catalysis but also displays cooperative properties for enhanced singlet oxygen production. Consequently, a remarkably improved PDT efficacy was observed for **1**-GQDs-MnO_2@PtNPs-liposomes in both normoxia and hypoxia. These results demonstrate the potential applicability of such nanozyme constituted **1**-GQDs-MnO_2@PtNPs-liposomes for achieving tumour treatment in hypoxic conditions by PDT.

1. Introduction

Growing research interest in photodynamic therapy (PDT), a non-invasive therapeutic modality for cancer, has continued as an alternative to more conventional modalities (such as chemotherapy and radiation). PDT's local light-controllable activation, as well as its tolerance to repeated doses [1–3], have been largely responsible for such sustained interest. In principle, the photosensitizer (PS), in its excited triplet state, transfers energy to molecular oxygen to produce reactive singlet oxygen ($^1O_2$), which is responsible for cancer cell death [4]. Most PSs that have been applied for PDT have been porphyrin derivatives, many of which are hydrophobic. As a result, they easily aggregate, leading to low tumour cell accumulation, and ultimately, poor clinical outcomes. Effective PSs delivery systems can help ensure a high degree of cellular uptake, where rapid PS release can alleviate the problem of the short half-life as well as limited diffusion distance of singlet oxygen [5,6].

Most tumour cells exist within a local hypoxic microenvironment, characterised by both a reduced oxygen supply and acidulated microenvironments [7,8]. Hypoxia is an essential consideration in any cancer-related therapy, particularly photodynamic therapy (PDT) since oxygen is a limiting factor. As a result, hypoxic cells are largely considered PDT resistant [9]. Thus, overcoming hypoxia by replenishing the tumour oxygen supply is recognized as vital to PDT success [10–12]. To this end, numerous reports have explored strategies to modulate tumour hypoxia. To date, two major pathways have been highlighted to overcome tumour hypoxia: oxygen-independent PDT (Type I PDT) [13,14], and tumour oxygenation [15]. Although promising, oxygen -independent PDT does not alter the tumour microenvironment and as such, issues such as drug-resistant gene expression remain largely unresolved [15]. In contrast, tumour oxygenation has aroused considerable research interest owing to its ability to alter the tumour microenvironment, as well as attenuating resistance [16,17]. Traditional approaches such as extending tumour irradiation with low fluence rates, only work

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