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Orthogonal near-infrared upconversion co-regulated site-specific O_2 delivery and photodynamic therapy for hypoxia tumor by using red blood cell microcarriers

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ABSTRACT

Pre-existing hypoxia in tumors can result in an inadequate oxygen supply during photodynamic therapy (PDT), which in turn hampers photodynamic efficacy. To overcome this problem, we developed an orthogonal near-infrared upconversion controlled red blood cell (RBC) microcarriers to selectively deliver O_2 in hypoxia area. Moreover, this RBC microcarriers are able to overcome a series of complex biological barriers which include transporting across the inflamed endothelium, evading mononuclear phagocyte system, reducing reticuloendothelial system uptake. Based on these abilities, RBC microcarriers have efficient tumors accumulation and are capable of delivery a large amount of O_2 for PDT under near-infrared (NIR) irradiation to realize effective solid tumor eradication.

1. Introduction

Hypoxia influences many aspects of the biology of tumors and their responses to therapy [1–4]. For example, hypoxia is a negative prognostic and predictive factor owing to its multiple contributions to chemo-resistance [5,6], radio-resistance [7,8], angiogenesis [9,10], vasculogenesis [11], invasiveness [12], and metastasis [13], altered metabolism and genomic instability [14]. Especially, several investigators have demonstrated unequivocally that the extent of tumor hypoxia has an obviously negative impact on the ability of photodynamic therapy (PDT) which kills cancer cells by converting tumor oxygen into reactive singlet oxygen ($^1O_2$) [15–19]. Moreover, PDT worsens hypoxia through oxygen consumption and vascular shutdown effects [20–22]. Over the years, various strategies to overcome hypoxia have been explored by using anti-hypoxia nanocarriers, including O_2 loaded perfluorocarbon nanoparticles [23,24], hyaluronidase improved tumor oxygenation *via* increase of tumor vessel densities and effective vascular areas, [25] or intracellular H_2O_2 activatable nanoparticles for oxygenation [26–28]. However, to selectively delivery O_2 in hypoxia tumor is still difficult to realize. Hypoxia activated site-specific O_2 delivery is critical desired to overcome the tumor hypoxia in an efficient way and minimize the side effect of PDT for the normal tissues, because the photosensitizers for PDT can only be activated with the increase of O_2 for effectively producing $^1O_2$ [15]. This permits high therapeutic efficacy against cancer in localized hypoxia area to minimize the side effects. On the other hand, intravenously injected artificial materials are tagged with proteins (a process called opsonization) and subsequently removed by the mononuclear phagocyte system [29,30]. To function properly, systemic agents must therefore avoid clearance by the immune system, negotiate their way past the biological barriers, and localize at the target tissues in sufficient quantities to be effective [31]. So far, there have been no tentative along this direction that endow drug-loaded particles with the immune escaping ability as well as controllable and efficient O_2 delivering to hypoxia tumors for cancer therapy.

As the primary source of oxygen to our body tissues, red blood cell (RBC) carries 270 million hemoglobin molecules (each

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hemoglobin binds up to four O_2 molecules) [32]. RBC have a long history of being investigated for drug delivery [33–35] and microparticles camouflaged with natural RBC membranes had been reported for successful overcoming biological barriers with long blood-circulation time [36–38]. Furthermore, remotely triggered drug delivery systems (DDSs) by near-infrared (NIR) light have recently been realized to reduce tissue autofluorescence and scattering, which can efficiently and harmlessly improve the tissue penetration depth at controlled doses and exposure time [39–43]. Based on above inspiration, herein we report a novel strategy for overcoming hypoxia and biological barriers, which consists of preparing orthogonal excitation-emission upconversion nanoparticles (UCNPs) functionalized with a novel ultrasensitive site-specific hypoxia probe (HP) and the PDT photosensitizer (Rose Bengal, RB) and subsequently installing on the red blood cell (RBC) surfaces to obtain the RBC microcarriers (Fig. 1a). Under a hypoxic condition, the inactive HP can be transformed into active state specifically to trigger the O_2 release from oxygenated hemoglobin under 980-nm NIR excitation (Fig. 1b). Then the PDT efficiency can be enhanced greatly under 808-nm NIR excitation because of the increasing of O_2 amount. Remotely triggered O_2 release and PDT by NIR light can efficiently and harmlessly improve tissue penetration depth. Significantly, RBC microcarriers exhibit abilities to overcome biological barriers with delaying uptake by the mononuclear phagocyte system, preferentially binding endothelium, and reducing reticuloendothelial system (RES) uptake. To the best of our knowledge, this is the first report of constructing intelligent RBC based microcarriers for biological barriers overcoming and site-specific hypoxia cancer therapy under the NIR control, which may be extended to the efficient treatment of various solid tumors.

2. Materials and methods

2.1. UCNPs synthesis

Lanthanide doped core-multishell structured NaGdF4: Yb,

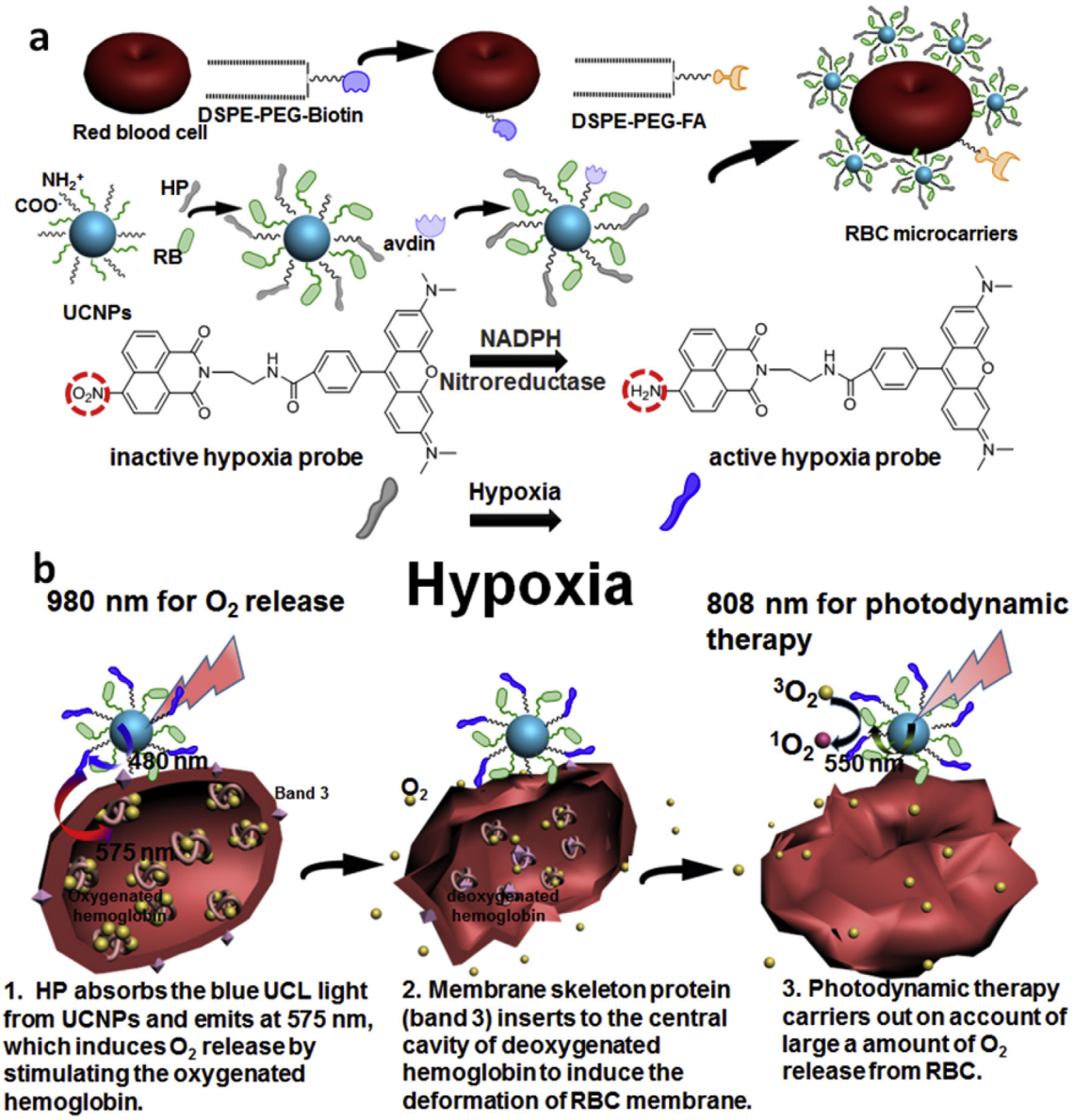

Fig. 1. Schematic illustration. a) Stepwise engineering of NIR-controlled orthogonal excitation-emission UCNPs anchored RBC microcarrier and (b) O_2 release followed by RBC membrane deformation under 980-nm excitation to enhance PDT under 808-nm NIR excitation.