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Editorial

Oxygenating the way for enhanced chemophototherapy

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Abstract

Hypoxia is behind tumor resistance in both chemotherapy and photodynamic therapy. This editorial highlights a study by Cai et al. [12] that a hemoglobin and human serum albumin hybrid protein nanoparticle can simultaneously deliver O_2, chemotherapeutics, and photosensitizers to tumors for enhanced chemophototherapy.

Key words: hypoxia, photodynamic therapy, chemotherapy, nanoparticles

The combination of chemotherapy and photodynamic therapy (PDT), or chemophototherapy (CPT), is a newly emerging concept [1, 2]. On the one hand, chemotherapy can sensitize cancer cells to PDT and/or kill cancer cells that survived from incomplete PDT. On the other hand, PDT can be utilized to enhance chemotherapeutic drug (often in the form of a nanoparticle) deposition or penetration in tumors. However, the efficacy of CPT is limited by tumor hypoxia, a result of rapid oxygen consumption by cancer cells and insufficient vascular supply [1, 3, 4]. Hypoxia is associated with increased resistance to chemotherapy, inducing hypoxia-inducible factor (HIF-1α) that in turn activates multi-drug resistance protein 1 (MDR1) and mediates the efflux of a wide range of chemotherapeutic drugs [5, 6]. Hypoxia also affects PDT, in which toxicity is produced when a photo-activated photosensitizer transfers electrons to oxygen molecules [1].

Despite extensive research, delivering oxygen to tumors to reverse the course of hypoxia remains a challenge. Conventional methods such as hyperbaric oxygen chambers have been tested in the clinic but have shown limited benefits for tumor oxygenation [4, 7]; rather, increased oxygen blood levels may cause oxygen toxicity to the lungs and the central nervous system [8]. Recently, nanoparticle-based oxygen carriers [9] or generators [10, 11] have been developed and tested. Unlike conventional oxygen delivery, these nanoparticles can selectively accumulate in tumors through either active or passive targeting approaches, and then release oxygen *in situ*. To maximize therapeutic efficacy, it is reasoned that photosensitizers and chemotherapeutics should be loaded onto the same nanoplatform as the oxygen carrier. This brings additional requirements in design and fabrication of the nanoparticles.

A recent study by Prof. Lintao Cai and his colleagues reports a novel, hybrid protein-oxygen carrier (HPOC) approach to address this aforementioned need [12]. The hybrid consists of two natural proteins, hemoglobin (Hb) and human serum albumin (HSA), which are linked together through a disulfide-bond reconfiguration strategy. Hb is the major oxygen carrier in mammals [9, 13], but has a short blood circulation half-life if administrated alone [14]. Linked with HSA and assembled into a nanoparticle improves the pharmacokinetics of Hb and its accumulation in tumors. Meanwhile, HSA nanoparticles have proven to be an excellent carrier for small molecule drugs, including many types of chemotherapeutics and photosensitizers [15, 16]. In this study, Cai et al. loaded oxygen (by binding with Hb), doxorubicin (DOX), and chlorin e6 (Ce6, a photosensitizer) onto the hybrid protein to form a 30 nm nanoparticle referred to as ODC-HPOC. They

showed that oxygen molecules could be slowly released from the nanoparticles. Incubation with ODC-HPOC reversed cell P-glycoprotein (P-gp) upregulation under hypoxic stress. This led to reduced drug efflux, which was confirmed in a cell uptake study performed in a low oxygen chamber with ODC-HPOC, finding increased intracellular DOX and Ce6 contents relative to the control. They also observed enhanced cell killing under photoirradiation where ODC-HPOC were incubated with MCF-7 cells in a low oxygen chamber. It is expected that the same or greater treatment benefits would be seen *in vivo* since continuous PDT often exacerbates hypoxia.

The group also evaluated the nanoplatform *in vivo* in a MCF-7 xenograft model. They found improved tumor accumulation of ODC-HPOCs relative to free DOX or Ce6, which is probably attributed to the enhanced permeability and retention (EPR) effect. Moreover, HSA may have bound with 60-kDa glycoprotein (gp60) receptors, leading to improved nanoparticle transcytosis at tumor sites [17, 18]. Once inside the tumors, oxygen is slowly released from ODC-HPOCs and populates the tumor tissues. Photoacoustic imaging found a 25% increase in HbO_2 signals in tumors in ODC-HPOC injected mice, and the impact lasted for hours. The improved drug delivery, drug retention, and oxygenation led to significantly enhanced treatment outcomes. A single dose treatment caused 89.5% tumor suppression, without inducing systemic toxicity.

Hypoxia has long been a target in cancer therapy but selective oxygen delivery to tumors is non-trivial [3]. Compared with inorganic nanoparticle-based oxygen suppliers [10, 11], a hemoglobin containing protein particle certainly has its advantages regarding toxicity and biodegradability. Coupling with HSA to improve the pharmacokinetics of Hb is both novel and clinically relevant. The resulting nanoparticles are function intensive but the components seem to be well integrated with minimal inter-species interference. The compact size is beneficial from delivery and tissue penetration perspectives. It is believed that the nanoplatform can be extended to other chemotherapeutics or even a group of them, which may further enhance treatment efficacy or precision.

Despite these promises, several questions need to be addressed before moving the technology forward. For instance, the nanoplatform essentially delivers three agents (oxygen, chemotherapeutic, and photosensitizer) that play different roles in the combination therapy. It is not clear what the best ratio among these agents is with regard to treatment outcomes. Moreover, it is observed that Abraxane, a paclitaxel-bound HSA nanoparticle, is rapidly disassociated in the blood circulation [17]. Whether this happens to ODC-HPOCs and how this affects drug delivery and therapy remain to be investigated. Additionally, it will be interesting to explore the nanoparticles in the context of other treatment modalities such as radiochemotherapy or even immunotherapy. Overall, this highly innovative approach represents an excellent example of nanoparticle-enabled multifunctional therapeutics and should be of interest to many readers of *Theranostics*.

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Competing Interests

The authors have declared that no competing interest exists.

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