Accepted Article

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: ChemBioChem 10.1002/cbic.201900387

Link to VoR: http://dx.doi.org/10.1002/cbic.201900387
In situ Oxygen Evolving Photoactive Nano-Cocktail: Future of the Hypoxic Tumor Photodynamic Therapy

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Hypoxic tumor core is one of the main hallmarks of solid tumors.[1-3] This tumor microenvironment generally results from the imbalance between uptake and consumption of oxygen, mainly due to the development of abnormal tumor blood vessels, poor blood flow and very fast proliferation of cancer cells.[2,3] Tumor hypoxia is linked to the tumor progression and an important marker of tumor malignancy leading to resistance to common therapeutic approaches such as chemotherapy, radiation therapy and photodynamic therapy (PDT).[4,5] In recent years, few therapeutic modalities based on (i) reducing oxygen consumption rates of tumors, (ii) O2-evolving synergistic chemoradiotherapy, (iii) artificial blood to transport oxygen to the hypoxic core and (iv) combinations of oxygen-enriched gases with vasodilators have emerged to overcome the therapeutic resistance originating from hypoxia.[6-9] But the clinical application of these treatment modalities is very much restricted due to low drug delivery to hypoxic core and limited oxygen loading capacity.[10] Moreover, photodynamic therapy relies on local oxygen concentration at the target tumor site and hypoxic tumors with 0.5-2% oxygen levels are one of the main challenges for PDT to overcome.[11] In fact, many researchers are in search of suitable molecules/materials which can simultaneously act as the in situ source of triplet oxygen (O2) at the hypoxic core as well as a photosensitizer to convert the in situ generated O2 to reactive oxygen species (ROS) such as singlet oxygen (O2). All this provided the backdrop for X. Dong and co-workers’ research in O2-evolving synergistic chemo-phototherapy.[12,13] To overcome hypoxia related therapeutic resistance, they have co-loaded a near-infrared light absorbing aza-BODIPY photosensitizer and anti-cancer drug viz., doxorubicin (DOX) over the hydrangea-structured MnO2 nanoparticles to generate an in situ oxygen-self-generating nanocomposite (Scheme 1). The use MnO2 NPs is for its well known O2 production ability to increase the O2 concentration within the hypoxic environment in tumors.[13] They improved the bioavailability by encapsulating the nanocomposite within an amphiphilic polymer PVP and achieved tumor microenvironment responsive degradable nanoparticle (MDSP NP).

The MDSP NPs with strong red light absorption degraded in the presence of H2O2 and under acidic environment to generate O2 efficiently which in turn converted to O2. This result is highly significant considering the fact that the upregulated metabolism and limited blood supply in solid tumors result in not only the acidic tumor microenvironment, but also significant enhancement of the intra-tumor H2O2 concentration.

Scheme 1: Chemo-phototherapeutic strategy developed by X. Dong et al., to overcome hypoxic tumor resistance.

In vitro experiments show high intracellular uptake of these MDSP NPs in tumor cells and effective release of doxorubicin thereafter along with ROS generation. After intravenous injection to the tumor-bearing mice, the NPs were selectively accumulated at the tumor site and upon xenon lamp irradiation induced hyperthermia which improved the vascular perfusion, cell membrane permeability and cellular uptake of therapeutic nanoparticles, thus alleviate hypoxia related resistance. Both the in vitro and in vivo studies demonstrate the effective oxygen generation at the tumor site by this NPs. Overall, for the first time, X. Dong and co-workers have developed a MDSP NPs to address the so far unrevealed very important questions (i) How to effectively generate oxygen at the hypoxic core of solid tumor to overcome PDT resistance and (ii) how to develop multifunctional theranostic cocktail for synergistic chemotherapy, photodynamic therapy and photothermal therapy with outstanding anti-tumor efficiency.

D. Hu et al., in 2019 reported tumor-targeting perfluorocarbon-loaded, oxygen self-enriched nanoparticle developed from hyaluronic acid conjugated chlorin e6 (a well known photosensitizer) and encapsulating perfluorohexane within the nanoparticles to overcome tumor hypoxia related resistance in PDT.[14] The redox-activatable nanoparticles are reported to load oxygen from the lungs and thereafter release the loaded oxygen within the hypoxic core of tumors to supply the required O2 for PDT. Moreover, due to the presence of chlorin e6, an excellent imaging agent, the nanoparticles are of significance for developing imaging-guided PDT.
Again in this year (2019), X.-Z. Zhang et al., also reported an in situ O$_2$ generating two-photon light controlled and [Ru(bpy)$_3$]$^{2+}$-sensitized nanocomposite for PDT to overcome the hypoxia related PDT resistance (Scheme 2).[15] The water splitting ability of the Ru(II) complex loaded iron-doped carbon nitride (Fe-C$_3$N$_4$) nanoparticle was employed to generate O$_2$. [Ru(bpy)$_3$]$^{2+}$-complex loaded Fe-C$_3$N$_4$ was coated by the copolymer HOP with hyperbranched conjugated polymer core and many linear poly(ethylene glycol) arms. In the resultant material, HOP worked as both the two-photon light-harvesting agent as well as the donor of Förster resonance energy transfer to generate O$_2$ upon two photon light irradiation. The resultant material shows significantly higher accumulation of the nanocomposite within tumors due to the improved permeability and conversion of that generated oxygen to reactive oxygen species. In order to translate the application of O$_2$ evolving photoactive nano-Cocktail from in-vivo studies to the clinic for PDT, the following challenges/questions need to answer (i) suitable design of the optical fibre for irradiation of deeply buried tumor (ii) synthesis of nanoparticles with uniform and well defined size: to have a clear idea about the final composition of the nanomedicines (ii) Ultimate fate of the nanomaterial in the human body along with their excretions and most importantly (iv) standardization of process of drug administration.

Acknowledgements

SB thanks Royal Society and SERB for Newton International fellowship (NF151429).

Keywords: Hypoxic tumor • Oxygen Generation • Photodynamic therapy • Nanocomposite • Photo-irradiation

References:


Scheme 2: In situ oxygen generation strategy within the hypoxic core of solid tumor by Ru(bpy)$_3^{2+}$ induced H$_2$O splitting developed by X.-Z. Zhang et al., to overcome hypoxic resistance of PDT.
Hypoxia related resistance is one of the main challenges for photodynamic therapy to overcome. This highlight discusses a few current works on possible ways to overcome this problem by in situ oxygen generation in the hypoxic core of tumors.