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Oxygen Delivery Microcapsules provide a Novel Strategy for the Treatment of Cancer

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Abstract

Intratumoral hypoxia is a primary characteristic of tumors and leads to increased activity of hypoxia-inducible factors (HIFs), which contributes to tumor growth, aggressiveness, metastasis, immune evasion, cancer stem cell maintenance, drug resistance, and so on. In the past years, many studies focus on different strategies to target HIFs. Recently, Wu et al. created an effective oxygen delivery vehicle of polydopamine-microcapsules, which effectively improves the hypoxia microenvironment. The review was carried out from three aspects: the mechanism of hypoxia promoting tumor progression, the characteristic and preparation of oxygen microcapsules, and the prospect of oxygen microcapsules in tumor therapy. In summary, oxygen microcapsules provide a new strategy for targeting hypoxia tumor microenvironment and may shed light on the treatment of cancer.

Keywords: Cancer therapy; Hypoxia; Oxygen Microcapsules; Hypoxia-inducible factors (HIFs); Tumor microenvironment

Introduction

In the background of cancer, hypoxia is deemed to an obvious hallmark of the tumor microenvironment (TME) [1] and a common characteristic of malignant solid tumors [2]. HIFs plays an important role in tumor progression and affect malignant tumor hallmarks including cell proliferation, differentiation, apoptosis, genetic instability, tumor metabolism, vascularization/angiogenesis, immunosuppression, metastasis, invasion and so on. As a result, HIFs mediated drug resistance and are associated with poor prognosis. Therefore, in the past years, many studies focus on different strategies to target HIFs include hypoxia-activated prodrugs and suppression of HIF dimerization, transcriptional activity, DNA binding capacity, mRNA or protein expression, and so on [3]. Recently, Wu et al. created an effective oxygen delivery vehicle of polydopamine-nanoparticle-stabilized oxygen microcapsules. Oxygen microcapsules could effectively improve the hypoxia microenvironment to maintain the microenvironment at an oxygen-rich state, which provides a new treatment strategy for tumor [4].

Discussion

The Mechanism of hypoxia promoting tumor progression

Hypoxia, the status of ungenerous oxygen, is a primary characteristic of solid tumors [5]. Hypoxia promotes tumor growth, aggressiveness, metastasis, and immune evasion in a variety of ways including drug resistance, altering the tumor microenvironment, and so on [6-9]. The exact mechanisms of drug resistance in malignant tumors are complicated, but the TME plays an important role in drug resistance. In this process, the hypoxia-inducible factor 1α (HIF-1α) is a key hallmark and plays an important role in the cellular response to hypoxia [10]. A variety of interactions of HIFs with apoptosis, p53, DNA damage, autophagy, and mitochondrial activity plays an important role in drug resistance of HIF-mediated therapy. Furthermore, the condition of hypoxia creates a tumor acidic microenvironment, which leads to multidrug resistance (MDR) for a decreased drug

concentration caused by "ion trapping", genetic mutations (such as p53 mutations), lowered apoptotic potential, and increased activity levels of a multidrug transporter p-glycoprotein (P-gp) [11].

Hypoxia is also a major suppressor of the immune system and induces infiltration of myeloid-derived suppressive cells (MDSCs) and regulatory T cells (Tregs), which reduces activation and infiltration of cytotoxic T lymphocytes (CTLs) [12]. The hypoxic tumor environment enhances recruitment of tumor-associated macrophages (TAMs) toward the tumoral milieu [13]. Anti-tumor activity of natural killer (NK) cells is also weakened by hypoxia [14].

Based on the reasons discussed above, disruption of hypoxia is a promising and tempting strategy for cancer therapies.

The characteristic and preparation of oxygen microcapsules

Recently, with the help of interfacial polymerization, Wu et al create an effective oxygen delivery vehicle of polydopamine-nanoparticle-stabilized oxygen microcapsules [4]. Oxygen could easily diffuse out from the microcapsules and improve the hypoxia state of TME was improved. Due to the solid shells availably enclose oxygen in the core and effectively keep oxygen microbubbles from coalescing, the oxygen microcapsules keep stable without observable changes for at least one week [4].

To prepare nanoparticle-stabilized oxygen microcapsules, at first, under vigorous and rapid shearing, dopamine, a neurotransmitter that assists cells to transmit pulses, is oxidized to form polydopamine nanoparticles at the oxygen/water interface. With the help of amino-rich polylysine and chitosan, uniform polydopamine nanoparticles were achieved and the overoxidation of polydopamine nanoparticles was prevented. By optimizing the interfacial adsorption kinetics of polydopamine nanoparticles chitosan increases the life of oxygen microbubbles. Due to the decline of the interfacial tension, polydopamine nanoparticles temporarily assemble at the surface of oxygen microbubbles. Then, to achieve stable polydopamine-nanoparticle-stabilized oxygen microcapsules, glutaral dehyde was added to permanently crosslink polydopamine nanoparticles. After removing excess solvents and residual polydopamine nanoparticles, nanoparticle-stabilized oxygen microcapsules are well dispersed in oxygen-enriched water [4].

The prospect of oxygen microcapsules in tumor therapy

Tumour hypoxia refers to solid tumor regions characterized by low oxygen levels. Hypoxia results in diverse changes in gene expression and subsequent proteomic changes that have many significant effects on diverse cellular and physiological functions, ultimately limiting patient prognosis [15]. Hypoxia is one of the key elements that lead to drug resistance and immunosuppression. Therefore, improving the hypoxic microenvironment of solid tumors is important for boosting the therapeutic effect of the tumor [16]. Many cancer research laboratories are actively involved in the identification of novel therapies to target hypoxia. Several approaches for targeting hypoxic tumor cells have been proposed, including specific targeting of HIFs, or targeting pathways important in hypoxic cells such as mTOR and UPR pathways. Therefore, targeting hypoxia is a potentially effective therapy to restrain the development of a solid tumor and improve patient survival rate [11]. Wu et al. create an effective oxygen delivery vehicle of polydopamine-nanoparticle-stabilized oxygen microcapsules, which maintains the microenvironment at an oxygen-rich state. Oxygen microcapsules could effectually improve the hypoxia microenvironment in vitro and in vivo experiments. They indicated that the combination of gemcitabine drugs and oxygen microcapsules was a helpful strategy for the therapy of pancreatic carcinoma, indicating that improving tumor hypoxia holds a great potential for oncotherapy [4].

Conclusion

Numerous studies have indicated that tumor hypoxic microenvironment is associated with poor prognosis in patients. Tumor hypoxic microenvironment cause drug resistance, immunosuppression, and other factors that promote tumor development. Therefore, changing the hypoxia status of the tumor microenvironment is a promising strategy for tumor treatment. Oxygen microcapsules, as a useful tool to improve the anoxic condition of the tumor microenvironment, will provide a new treatment strategy for tumor treatment.

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