Nanoscale Advances

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Nanoscale Adv.*, 2022, **4**, 894

Targeted therapy for the treatment of gliomas with multifunctional orange emissive carbon dots†

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As a nano-material, carbon dots have been extensively studied and applied in many ways. Herein, iron-doped orange emissive carbon dots (ICDs) were easily synthesized using the hydrothermal method and coupled with Trf and glucose oxidase (GOD) simply by virtue of the abundant functional groups on their surface. The resulting carbon dots were named IGTCDs. The obtained IGTCDs possessed targeting, therapeutic and imaging functions, achieving the enzymolysis of glucose, the decomposition of H_2O_2 and the release of reactive oxygen species (ROS) sequentially in gliomas as a multifunctional nano-catalyst, and achieving an efficient glioma targeted killing effect. On the basis of the ideal biocompatibility of the IGTCDs with a cell survival rate of over 85%, even at a high concentration (500 μg ml^{-1}), the IGTCDs, which were coupled substances present within the organism, glucose oxidase and transferrins, showed an obvious inhibitory effect on the growth of tumor cells, and the survival rate of the C6 cells was only 28.10% at 300 μg ml^{-1}. The highly efficient anti-tumor effect was further demonstrated in the treatment of mice suffering from glioma, and the tumor inhibition rate was increased to 56.21–98.32%. This safe and effective multifunctional tumor inhibitor could be conveniently synthesized in large quantities, verifying the feasibility of the anti-tumor therapy based on the tumor microenvironment (TME), creating a novel method for the application of carbon dots in tumor treatment and providing a novel, reasonable and effective method for the treatment of cancer and gliomas.

Received 30th September 2021
Accepted 30th November 2021

DOI: 10.1039/d1na00722j

rsc.li/nanoscale-advances

Introduction

Glioblastomas, a type of primary brain tumor, are characterized by having a low cure rate, poor prognosis, short survival time and so on. They are generally treated using radiotherapy and chemotherapy, which rarely completely eliminate the invasive growth of the tumor and cause obvious toxic side effects. These methods also lack effective and reasonable treatment means, therefore, the development of novel and efficient treatment methods is desirable.[1–3] Compared with normal tissues, the tumor microenvironment (TME) has unusual characteristics, such as internal hypoxia, interstitial hypertension and a hyper-inflammatory response, and is weakly acidic (pH = 6.0–6.5) owing to the Warburg effect resulting from the accumulation of lactic acid and a high glucose uptake.[4–6] This arises from the bypassed metabolism of glucose through glycolysis at the tumor site owing to the high enzyme activity of glucose-6-phosphate dehydrogenase and the rapid transportation of glucose *via* GLUT1.[7–10] Vigorous glucose-dependent glycolysis provides the tumor cells with the energy to maintain a normal metabolism and proliferation, which could trigger the apoptosis of tumor cells when inhibited, meaning the normal energy supply is affected. Utilizing the properties of glucose metabolism and the subacidity in the TME, as well as the discrepancy between normal tissues, could enable the specific release of the drug or the transformation of the inherent substances at the nidus,[11,12] which simultaneously improves the treatment precision, enhancing the curative effect and reducing the side effects. Tumor specific imaging and treatment based on the characteristics of the microenvironment show significant potential, and several related studies on pH-responsive drug release and targeted vector construction in the microenvironment have been published.[13,14]

Carbon dots, an emerging fluorescent nano-material, are widely used in photoelectric, physical and chemical detection and biological imaging owing to their economical and available raw materials,[15–17] simple synthesis, excellent optical properties and biocompatibility, and are commonly used in blue and green fluorescence,[18,19] which restricts their applications in biological imaging as a long wavelength emission is required.[20–22] Traditional quantum dots are limited in biological applications owing to their inherent toxicity and rapid elimination.[23–25] In contrast, carbon-based dots (particle size: 1–10 nm), with a better biocompatibility, have abundant functional groups on

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