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Hypoxia-Responsive Lipid–Polymer Nanoparticle-Combined Imaging-Guided Surgery and Multitherapy Strategies for Glioma

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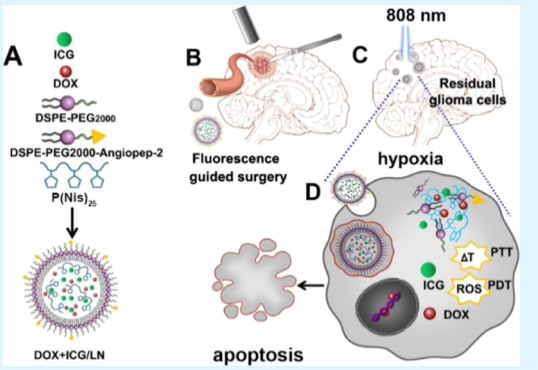
ABSTRACT: Glioma is the most prevalent type of malignant brain tumor and is usually very aggressive. Because of the high invasiveness and aggressive proliferative growth of glioma, it is difficult to resect completely or cure with surgery. Residual glioma cells are a primary cause of postoperative recurrence. Herein, we describe a hypoxia-responsive lipid polymer nanoparticle (LN) for fluorescence-guided surgery, chemotherapy, photodynamic therapy (PDT), and photothermal therapy (PTT) combination multitherapy strategies targeting glioma. The hypoxia-responsive LN [LN (DOX + ICG)] contains a hypoxia-responsive component poly(nitroimidazole)$_{25}$ [P-(Nis)$_{25}$], the glioma-targeting peptide angiopep-2 (A2), indocyanine green (ICG), and doxorubicin (DOX). LN (DOX + ICG) comprises four distinct functional components: (1) A2: A2 modified nanoparticles effectively target gliomas, enhancing drug concentration in gliomas; (2) P-(Nis)$_{25}$: (i) the hydrophobic component of LN (DOX + ICG) with hypoxia responsive ability to encapsulate DOX and ICG; (ii) allows rapid release of DOX from LN (DOX + ICG) after 808 nm laser irradiation; (3) ICG: (i) ICG allows imaging-guided surgery, combining PDT and PTT therapies; (ii) upon irradiation with an 808 nm laser, ICG creates a hypoxic environment; (4) DOX inhibits glioma growth. This work demonstrates that LN (DOX + ICG) might provide a novel clinical approach to preventing post-surgical recurrence of glioma.



KEYWORDS: *fluorescence-guided surgery, indocyanine green, hypoxia-responsive, multitherapies, glioma recurrence*

1. INTRODUCTION

Glioma is the primary and most common type of intracranial tumor.[1] Current therapies are unsatisfactory because gliomas infiltrate surrounding tissues as they grow.[2−4] Owing to their highly invasive nature and aggressive proliferation, it is difficult to completely excise gliomas to surgically cure glioma patients.[5] Postoperative residual glioma cells in the brain are a main cause of postoperative recurrence in patients.[6,7] Therefore, more effective treatments need to be developed.

Fluorescence-guided surgery (FGS) methods, which selectively identify cancer cells by enhancing visual differences between normal and tumor tissues, are becoming more prevalent.[8−11] Real-time localization and visualization of glioma is now being provided with FGS during surgery to increase the completeness of glioma resection. Indocyanine green (ICG) is a widely used near-infrared (NIR) dye, which is approved by the U. S. Food and Drug Administration (FDA) as a clinical photosensitizer.[12] It has fluorescence properties that can be used for imaging and can produce reactive oxygen species (ROS) for photodynamic therapy (PDT) and be induced by 808 nm laser irradiation to produce local hyperthermia for photothermal therapy (PTT). Moreover, ICG is inexpensive and widely available.[13−18] Consequently, ICG may be an ideal diagnostic material for biomedical imaging.[19] During treatment by PDT, tumor tissue oxygen can be significantly depleted, leading to hypoxia. Hypoxia can cause poor responses in PDT and conventional procedures including radiotherapy and chemotherapy.[20,21]

PDT is known to increase hypoxia,[22] and nitroimidazoles have been reported to be hypoxia-responsive because hydrophobic nitroimidazole can convert into hydrophilic 2-aminoimidazoles through single-electron reduction under hypoxic conditions.[23,24] Therefore, nitroimidazole has been widely used to design drug delivery carriers.[25,26] Nitroimidazole-conjugated nanoparticles are hypoxia-responsive and can be depolymerized under hypoxic conditions.[27−29] Based on these features of nitroimidazole, we hypothesized that nitroimidazole-conjugated nanoparticles could rapidly release drugs after PDT.

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