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ORIGINAL RESEARCH

Fe_3O_4@Au composite magnetic nanoparticles modified with cetuximab for targeted magneto-photothermal therapy of glioma cells

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Background: Thermoresponsive nanoparticles have become an attractive candidate for designing combined multimodal therapy strategies because of the onset of hyperthermia and their advantages in synergistic cancer treatment. In this paper, novel cetuximab (C225)-encapsulated core-shell Fe_3O_4@Au magnetic nanoparticles (Fe_3O_4@Au-C225 composite-targeted MNPs) were created and applied as a therapeutic nanocarrier to conduct targeted magneto-photothermal therapy against glioma cells.

Methods: The core-shell Fe_3O_4@Au magnetic nanoparticles (MNPs) were prepared, and then C225 was further absorbed to synthesize Fe_3O_4@Au-C225 composite-targeted MNPs. Their morphology, mean particle size, zeta potential, optical property, magnetic property and thermal dynamic profiles were characterized. After that, the glioma-destructive effect of magnetic fluid hyperthermia (MFH) combined with near-infrared (NIR) hyperthermia mediated by Fe_3O_4@Au-C225 composite-targeted MNPs was evaluated through in vitro and in vivo experiments.

Results: The inhibitory and apoptotic rates of Fe_3O_4@Au-C225 composite-targeted MNPs-mediated combined hyperthermia (MFH+NIR) group were significantly higher than other groups in vitro and the marked upregulation of caspase-3, caspase-8, and caspase-9 expression indicated excellent antitumor effect by inducing intrinsic apoptosis. Furthermore, Fe_3O_4@Au-C225 composite-targeted MNPs-mediated combined hyperthermia (MFH+NIR) group exhibited significant tumor growth suppression compared with other groups in vivo.

Conclusion: Our studies illustrated that Fe_3O_4@Au-C225 composite-targeted MNPs have great potential as a promising nanoplatform for human glioma therapy and could be of great value in medical use in the future.

Keywords: Fe_3O_4@Au-C225 composite-targeted magnetic nanoparticles, U251 cells, human glioma therapy, magnetic fluid hyperthermia, near-infrared hyperthermia

Introduction

Gliomas are primary brain tumors arising from the supporting cells of the brain or spinal cord. Accounting for >30% of all primary brain and central nervous system (CNS) malignant tumors, gliomas are the most common tumors of the CNS. They involve almost 80% of primary malignant type of brain tumors and are responsible for a higher rate of mortality than other forms.[1] Overall incidence rate for primary malignant brain and CNS tumors is estimated to be 7.27/100,000 per year for all age groups.[2] The International Agency for Research on Cancer data estimate 256,213 worldwide cases of brain and CNS tumors, which is 1.8% of all estimated cancers, and 189,394 deaths, which is 2.3% of all cancer-related deaths.[3] An estimated 16,700 deaths were attributed to high-grade gliomas in the brain and CNS in the USA in 2017.[4] These aggressive brain tumors

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grow invasively and cause discernible neurologic symptoms within months with an extremely poor prognosis. Even treated with aggressive open surgery combined with adjuvant chemo/radiotherapy, the median survival time is still <15 months,[5–8] and current treatment paradigms appear to have reached their maximum benefit. Therefore, for decades, considerable efforts have been devoted to developing more effective antitumor agents and better strategies for targeting human glioma.[9,10]

Recently, nanostructures with combined diagnostic and therapeutic functions represent a potential application for tumor therapy.[11–14] Many inorganic nanoparticles with various compositions, physical features, and functionalities have been widely synthesized and used as drug vehicles, for instance, polymer Prussian blue, zeolitic imidazolate framework, alginate, and calcium phosphate.[15–18] Likewise, metal nanoparticles and their oxides with special shapes (sphere, tadpole, and pearl chain) have been successfully generated. Magnetic nanoparticles (MNPs), such as iron oxide, have been widely studied because of their combination of properties such as superparamagnetism, biocompatibility, and ease of synthesis. The most common form of iron oxide used is magnetite (Fe_3O_4) with a tendency to oxidize, which alters its magnetic properties.[19] That is why iron oxide nanoparticles are generally coated with a biocompatible layer such as polymers, silica, or gold (Au).[20–27]

In particular, core-shell-structured Fe_3O_4@Au composite MNPs have been the focus of study owing to their intriguing bifunctional properties.[28,29] As a form of multifunctional magnetoplasmonic nanomaterials, the nanoparticles combining Au and magnetic materials inherit from the two components excellent surface chemistry, special optical properties, and superparamagnetic properties, all of which would greatly enhance the potential and broaden the practical applications of such nanomaterials.[30]

Advances in the area of nanotechnology have contributed to the development of magnetic fluid hyperthermia (MFH). In vivo MFH is expected to be one of the best solutions for destroying tumor cells that are deeply seated and localized inside the human body for unlimited tissue penetration and the possibility of multiple hyperthermia cycles. Additionally, high selectivity and heating homogeneity can be expected in the use of MFH. Nevertheless, the practical limitation with MFH is that heating efficiency declines markedly when nanoparticles are taken up by cancer cells, because their endocytosis and aggregation inhibit their Brownian motion. Similarly, the diffusion (thereby local dilution) or enhanced distribution of nanoparticles also decreases nanoparticle heating.[31] The drawbacks of MFH could be overcome by combination with near-infrared (NIR) hyperthermia. With local plasmonic heating caused by NIR laser excitation, its efficiency is not impacted by intracellular confinement.[31] As a form of multifunctional magnetoplasmonic nanomaterials, Fe_3O_4@Au composite MNPs are the designs of choice to implement a magneto-photothermal strategy to optimize nanoparticles' heating efficiency.

We previously reported self-prepared Fe_3O_4@Au composite MNPs, which are intrinsically magnetic, and exhibit high biocompatibility and safety according to the evaluation of toxicity in vivo and in vitro.[32] Moreover, these MNPs have a potential to be used as safe optical and thermal agents, allowing the combination of cancer detection and cancer-specific hyperthermic treatment.[32] The present study is aimed at the functionalization of Fe_3O_4@Au composite MNPs with cetuximab (C225), a monoclonal antibody (McAb) targeting the epidermal growth factor receptor (EGFR) overexpressed in cancer cells. Additionally, the antiglioma effects of MFH combined with NIR hyperthermia mediated by Fe_3O_4@Au-C225 composite-targeted MNPs were also investigated with in vitro and in vivo experiments.

Experimental

Materials

4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid and trypsin were purchased from AMRESCO. Bovine serum albumin (BSA) was purchased from Sijiqing Hangzhou Bioengineering Company. Dulbecco's Modified Eagle's Medium (DMEM) was purchased from GIBCO BD. MTT, diethylpyrocarbonate, and ethidium bromide were purchased from Sigma. Dimethyl sulfoxide was purchased from Shanghai Ling Feng Chemical Co., Ltd. RNAiso Reagent, AMV reverse transcriptase, deoxyribonucleoside triphosphate (dNTP), Oligo(dT)18, Taq DNA polymerase, 100 bp DNA Marker, RNasin, and RNase free DNase I were purchased from Takara. From Shanghai Shenneng Gaming Biotechnology Co. Ltd. (Whitehouse Station, NJ, USA), 20×TBE, agarose, caspase-3 primer, caspase-8 primer, caspase-9 primer, and β-actin primer were purchased. C225 solution for infusion was purchased from Merck & Co, Germany. All other chemicals were commercially available and of analytical grade.

Cells and animals

U251 cells (human glioma cells) were purchased from Shanghai Cell Research Institute of Chinese Academy of Sciences. Balb/c nu/nu nude mice (5–7 weeks old, male and female, SPF grade) were purchased from Slaccas (Shanghai, China). License number: SCXK (Shanghai) 2002-0010. All of them were raised in Experimental Animal Center of Southeast University, Nanjing, China. All experiments involving