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多功能纳米粒子的构建及其抗脑胶质瘤
研究

The construction of multifunctional nanoparticles and anti-
glioblastoma research

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摘要

脑胶质瘤是最常见的中枢神经系统恶性肿瘤，由于其呈恶性浸润性生长，因此传统的治疗方式难以达到良好的治疗效果。光热治疗、光动力治疗、基因治疗等新型肿瘤治疗方式正逐步被应用到抗脑胶质瘤的研究中。但是单一的治疗方式始终难以实现彻底的治疗，因此，联合治疗成为脑胶质瘤治疗的新策略。

本课题构建了两种联合治疗的纳米粒递送系统，以期能够达到更好的脑胶质瘤治疗效果。首先以金纳米棒为核心，包覆二氧化硅，外侧连接近红外染料 IR795，构建了 AuNRs@SiO₂-IR795 被动靶向纳米粒子，实现光热和光动力的联合治疗。进一步采用阳离子脂质体包载金纳米棒、阿霉素和 YAP-siRNA，以 ANG2 为靶标进行修饰，旨在构建一种通过低密度脂蛋白受体相关蛋白介导的靶向载药系统，同时实现对脑内皮细胞和胶质瘤的双重靶向。课题主要包括以下四个部分：

第一，AuNRs@SiO₂-IR795 的合成和表征。首先制备不同长径比的金纳米棒，包覆不同厚度的二氧化硅壳层，表面的氨基修饰，连接 IR795 染料。通过控制变量法，研究金纳米棒长径比、金纳米棒与 IR795 的摩尔比以及二氧化硅壳层厚度对 IR795 荧光性能的影响，得到最佳配方的 AuNRs-3.3@SiO₂(12.2 nm)-IR795 纳米粒子，使得染料的荧光增强了 51.7 倍。

第二，AuNRs@SiO₂-IR795 纳米粒子抗肿瘤活性研究。使用荧光成像、暗场显微镜和 ICP-MS 考察纳米粒子的细胞摄取情况。采用 ABDA 法和热成像仪检测 AuNRs@SiO₂-IR795 纳米粒子产生单线态氧的能力和产热效能。然后，采用 MTT 法检测了纳米粒子在激光照射条件下对细胞存活率的影响。结果显示，AuNRs@SiO₂-IR795 纳米粒子生物相容性好，光热和光动力联合的抗肿瘤治疗效应强。

第三，ANG2-Au-DOX-LP/siRNA 靶向脂质纳米载体的构建。采用 FT-IR、¹H-NMR 对合成的 DSPE-PEG₂₀₀₀-ANG2 靶向配体进行表征。通过单因素考察，确定纳米粒制备处方，得 ANG2-Au-DOX-LP 纳米载药系统，测定了其粒径、电位、包封率、载药量、体外释放特征等。并以其为载体包载 YAP-siRNA，得到靶向载药系统 ANG2-Au-DOX-LP/siRNA，琼脂糖凝胶电泳显示 siRNA 能够很好的荷载于纳米粒上。

第四，ANG2-Au-DOX-LP/siRNA 靶向脂质纳米载体的体内外抗脑胶质瘤活

性研究。激光共聚焦显微镜和流式细胞仪考察了纳米载体的细胞摄取情况。Westen blot 和 QPCR 法检测携带 YAP-siRNA 的纳米载体的基因沉默效果。MTT 法检测了各载药系统对细胞增殖的影响。最后构建裸鼠脑胶质瘤原位模型，考察体内抗脑胶质瘤活性。结果显示：ANG2-Au-DOX-LP/siRNA 靶向脂质纳米载体能同时将阿霉素和 siRNA 递送到细胞内，显著降低 U87MG 细胞中 YAP 的 mRNA 和蛋白水平。共载系统比单独载药系统的抗肿瘤活性更为显著。尾静脉注射后，ANG2-Au-DOX-LP/siRNA 能够有效穿透血脑屏障，浓集于脑肿瘤部位。初步体内药效结果显示 ANG2-Au-DOX-LP/siRNA 可以显著增强抗脑胶质瘤的作用。

关键词：脑胶质瘤；联合治疗；Angiopep-2

Abstract

Glioma is the most common malignant tumors of the central nervous system. Due to its malignant invasive growth, it was different to achieve the better therapeutic effect. Nowadays, photothermal therapy, photodynamic therapy, gene therapy, *et.al*, was gradually being applied to antiglioma. But none of the single treatment could completely satisfy the clinical treatment. Therefore, the multimodal therapy becomes the new strategy for glioma therapy.

In this topic, two delivery systems were constructed in order to achieve better effect of glioma treatment. First, silica-coated gold nanorods were loaded with IR795 to form AuNRs@SiO₂-IR795 nanoparticle as the passive targeting delivery systems combining photothermal and photodynamic therapy. Then, cationic liposomes carried gold nanorods, doxorubicin, YAP-siRNA and ANG2 to build a targeting drug delivery system mediated by low density lipoprotein receptor related protein receptor (LRP). It could achieve dual target to endothelial cells and glioma. The main content of the project includes four parts as follows:

First, the synthesis and characterization of AuNRs@SiO₂-IR795. The gold nanorods with different aspect ratio were prepared and the AuNRs@SiO₂ was carried out with amino modified for the linking of IR795 dye. The effect of several factors on the fluorescence properties of IR795 was researched, such as the aspect ratio of gold nanorods, the molar ratio of gold nanorods/IR795 and the silica shell thickness. We found the best formula as AuNRs-3.3@SiO₂ (12.2 nm)-IR795, which has 51.7 folds fluorescence enhanced.

Second, the antitumor efficiency of AuNRs@SiO₂-IR795 nanoparticles *in vitro*. Fluorescent images, dark field microscope and ICP-MS were used to examine the uptake of nanoparticle in tumor cells. The ability of AuNRs@SiO₂-IR795 to generate singlet oxygen and photothermal efficiency were detected by ABDA method and thermal imager. Then, MTT method was used to determine the cell survival rate incubating with a variety of nanoparticles under laser irradiation. According to the results, AuNRs@SiO₂-IR795 had good biological compatibility and strong antitumor

effect with PDT/PTT.

Third, the synthesis of ANG2-Au-DOX-LP/siRNA targeting drug delivery system. Use the FT-IR and $^1\text{H-NMR}$ for characterization of DSPE-PEG₂₀₀₀-ANG2. ANG2-Au-DOX-LP nanoparticle is determined by the single factor investigation to finding the best prescription, and we determined the size, zeta potential, encapsulation efficiency, drug loadings and release study *in vitro*. After incubation with siRNA, we get the ANG2-Au-DOX-LP/siRNA targeting drug delivery system and agarose gel electrophoresis showed that siRNA was well load on the nanoparticles.

Fourth, Antiglioma efficiency of ANG2-Au-DOX-LP/siRNA *in vitro*. Using laser confocal microscope and flow cytometry to examine the cell uptake. The Westen blot and QPCR was applied to test the gene silencing effect of YAP. MTT method were used to detect the effect of various drug delivery systems for cell proliferation. We established orthotopic glioma model. Results showed that ANG2-Au-DOX-LP/siRNA can simultaneously delivery DOX and siRNA into cells and the YAP mRNA and protein levels in U87MG cells was significantly dropped. The combination therapy was better than single therapy. Moreover, ANG2-Au-DOX-LP/siRNA could effectively penetrate the blood-brain barrier and concentration in brain at 6 h. Preliminary antiglioma efficiency *in vivo* showed that ANG2-Au-DOX-LP/siRNA can significantly enhance the antiglioma efficiency.

Keywords: glioblastoma; multimodal therapy; angiopep-2

缩略词表

| 缩略语 | 英文全称 | 中文全称 |
|------------------------------------|---|------------------------------------|
| ABDA | 9,10-Anthracenedipropanoic acid | 9,10-蒽基-双(亚甲基)二丙二酸 |
| ANG2 | Angiopep-2 | 穿膜肽 |
| APTMS | (3-Aminopropyl)triethoxysilane | 3-氨基丙基三乙氧基硅烷 |
| AuNRs | Gold nanorods | 金纳米棒 |
| BCA | Bicinchoninic acid | 二喹啉甲酸 |
| CTAB | Hexadecyl trimethyl ammonium bromide | 十六烷基三甲基溴化铵 |
| Chol | Cholesterol | 胆固醇 |
| DAPI | 4',6-diamidino-2-phenylindole | 4,6-二脒基-2-苯基吲哚 |
| DEPC | Diethyl pyrocarbonate | 焦碳酸二乙酯 |
| DOTAP | (2,3-Dioleoyloxypropyl)-trimethylammonium | (2,3-二油酰基-丙基)-三甲胺 |
| DOPE | Dioleoyl Phosphoethanolamine | 二油酰磷脂酰乙醇胺 |
| DOX | Doxorubicin | 阿霉素 |
| DSPE-PEG₂₀₀₀-Mal | 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide(polyethylene glycol)-2000] | 磷脂酰乙醇胺-聚乙二醇 ₂₀₀₀ -马来酰亚胺 |
| DTT | DL-Dithiothreitol | 二硫苏糖醇 |
| EDC | 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide methiodide | 1-(3-二甲基氨基丙基)-3-乙基碳二亚胺盐酸盐 |
| FAM | Carboxyfluorescein | 羧基香豆素 |
| FBS | Fetal Bovine Serum | 胎牛血清 |
| FT-IR | Fourier transform infrared spectroscopy | 傅里叶红外光谱 |
| HSPC | Hydrogenated Soybean Phospholipids | 高纯氢化大豆磷脂 |

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