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Development of bioactive materials for glioblastoma therapy

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ABSTRACT

Glioblastoma is the most common and deadly human brain cancers. Unique barriers hinder the drug delivering pathway due to the individual position of glioblastoma, including blood-brain barrier and blood-brain tumor barrier. Numerous bioactive materials have been exploited and applied as the transvascular delivery carriers of therapeutic drugs. They promote site-specific accumulation and long term release of the encapsulated drugs at the tumor sites and reduce side effects with systemic delivery. And the delivery systems exhibit a certain extent of anti-glioblastoma effect and extend the median survival time. However, few of them step into the clinical trials. In this review, we will investigate the recent studies of bioactive materials for glioblastoma chemotherapy, including the inorganic materials, lipids and polymers. These bioactive materials construct diverse delivery vehicles to trigger tumor sites in brain intravenously. Herein, we exploit their functionality in drug delivery and discuss the deficiency for the featured tumors, to provide guidance for establishing optimized therapeutic drug formulation for anti-glioblastoma therapy and pave the way for clinical application.

Contents

Abbreviations: ALA, α-lipoic acid; BAG3, Bcl-2 associated athanogene 3; BBB, blood-brain barrier; BTB, blood-brain tumor barrier; CNS, central nervous system; CPT, camptothecin; cRGD, cyclic Arg-Gly-Asp; DACHPt, dichloro-(1,2-diaminocyclohexane)platinum (II); DCs, dendritic cells; DHA, dehydroascorbic acid; DOX, doxorubicin; DPPC, 1,2-dihexadecanoyl-rac-glycero-3-phosphocholine; FA, folate; GCV, ganciclovir; GLUT1, glucose transporter isoform 1; IL, interleukin; MMPs, matrix metalloproteinases; PTX, paclitaxel; ROS, reactive oxygen species; SN38, 7-ethyl-10-hydroxy-camptothecin; TAT, transactivator of transcription; TEG, tetra(ethylene glycol); TfR, transferrin receptor; TMZ, temozolomide; TNF, tumor necrosis factor.

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1. Introduction

Glioblastoma is the most common and malignant primary brain tumors. The median survival time of the patients is only 14.6 months after diagnosis, and the 5-year survival rate is less than 10% [1,2]. Glioblastoma cells rarely metastasize to other body organs, but they exhibit high aggressiveness and infiltration in brain tissues [3]. With these features, surgical resection cannot completely eliminate the tumor, and unavoidably leads to recurrence [4].

Numerous therapeutic agents, including chemical drugs, proteins and gene drugs, have emerged to show great potential to treat glioblastoma [5–7]. Like temozolomide (TMZ), a derivative of the alkylating agent dacarbazine, has been approved by oral administration for treating the newly diagnosed and recurrent malignant glioma [8–10]. However, the oral route offers insufficient drug concentration, and high daily doses leads to tumor resistance to the alkylating agents [11]. Due to the characteristics of the anti-tumor drugs, they always have poor solubility, short circulation and quick clearance. Most importantly, unlike other tumors, the intracranial tumors set up unique barriers to hinder effective therapy due to their individual position [12]. One is the blood-brain barrier (BBB), which is composed of brain endothelial cells, pericytes and astrocytic endfeet. It undertakes the responsibility to strictly regulate the transportation of large and small molecules between the blood and the brain parenchyma [13]. This structure is very essential to protect the healthy brain and prevent toxic transportation from blood [14]. However, it also impairs drug delivery into the lesion in the brain for effective therapy. The other one is the blood-brain tumor barrier (BTB), which refers to the transport obstacles between the blood vessels and brain tumor cells [15,16]. The blood vessels around the glioblastoma had the similar features with vessels in other tumor microenvironment, like permeability for drug entry. And the brain tumor cells also express transport protein for drug efflux. Due to these barriers in brain tumors, it is generally difficult for the free drugs to get appropriate targeting and suitable delivery penetrating into the glioma parenchyma. These all result in poor therapeutic responses against the tumor and severe side-effects to normal tissues. Herein, a more efficient strategy is urgently needed for glioblastoma therapy.

Recently, a variety of biomaterials has been exploited and applied as agents and delivery vehicles [17], including inorganic materials, lipids and polymers. They are widely used to overcome the problems including drug solubility and stability, and long circulation. They could be easily modified and manufactured to construct a more suitable and efficient delivery system for glioblastoma. With the development of nanotechnology, the drug delivery system could trigger these drugs to the tumor sites with minimal adverse effects. There had some reviews reported about the glioblastoma therapy. For example, Buddy D. Ratner's group detailed the intracranial tumor therapy by a localized application of polymeric microspheres with encapsulated drugs [18]. GLIADEL® wafer was the only FDA approved product for locally intracranial tumor therapy at the site of tumor resection, and its application for treatment of glioblastoma had been reported by Scott D. Wait et al. [19]. The therapeutic strategies and drug delivery process with nanoparticles against brain cancers had also covered in previous reports [20,21]. However, these reviews didn't exploit the structures and functionality of the applied bioactive materials for glioblastoma therapy *via* intravenous injection (*i.v.*). Here, in this review, we will focus on the bioactive materials applied in the treatment of glioblastoma, exploit their functionality in drug delivery and deficiency and discuss the influence of material structures on the transvascular transportation for drug delivery to brain tumors, to provide guidance for development of rational delivery vectors for effective anti-glioblastoma therapy.

2. Inorganic material-based nanoparticles

Many inorganic biomaterials were exploited as delivery platforms to deliver therapeutic drugs [22–24]. They could regulate the size of nanoparticles to overcome the limitation of unique structures of brain tumors. For example, Maciej S. Lesniak et al. exploited a blood-brain barrier permeable platform with ultra-small gold nanoparticles (5 nm) to deliver anticancer drug doxorubicin (DOX) to brain tumor tissues (Fig. 1) [25]. The pH-sensitive Au nanoparticles modified with a transactivator of transcription (TAT)

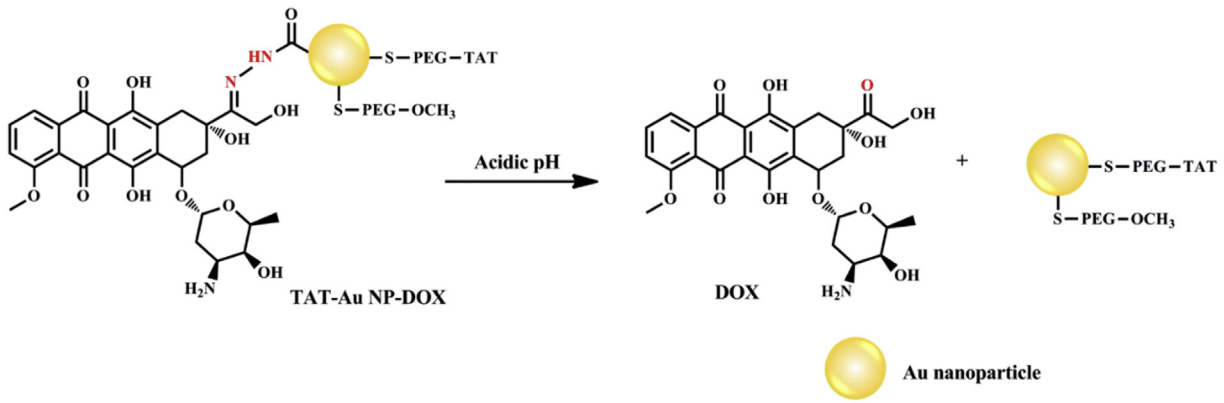

Fig. 1. The chemical structure of TAT-Au NP-DOX, and the release process under acidic conditions. Reprinted and modified with the permission from Ref. [25].