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Transferrin-targeted, resveratrol-loaded liposomes for the treatment of glioblastoma

Aditi Jhaveri, Pranali Deshpande, Bhushan Pattni, Vladimir Torchilin*

Center for Pharmaceutical Biotechnology and Nanomedicine, Department of Pharmaceutical Sciences, Northeastern University, Boston, MA 02115, USA

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ABSTRACT

Glioblastomas (GBMs) are highly aggressive brain tumors with a very grim prognosis even after multi-modal therapeutic regimens. Conventional chemotherapeutic agents frequently lead to drug resistance and result in severe toxicities to non-cancerous tissues. Resveratrol (RES), a natural polyphenol with pleiotropic health benefits, has proven chemopreventive effects in all the stages of cancer including initiation, promotion and progression. However, the poor physico-chemical properties of RES severely limit its use as a free drug. In this study, RES was loaded into PEGylated liposomes (RES-L) to counter its drawbacks as a free drug. Since transferrin receptors (TfRs) are up-regulated in GBM, the liposome surface was modified with transferrin moieties (Tf-RES-L) to make them cancer cell-specific. The liposomal nanomedicines developed in this project were aimed at enhancing the physico-chemical properties of RES and exploiting the passive and active targeting capabilities of liposomes to effectively treat GBM.

The RES-L were stable, had a good drug-loading capacity, prolonged drug-release *in vitro* and were easily scalable. Flow cytometry and confocal microscopy were used to study the association with, and internalization of, Tf-L into U-87 MG cells. The Tf-RES-Ls were significantly more cytotoxic and induced higher levels of apoptosis accompanied by activation of caspases 3/7 in GBM cells when compared to free RES or RES-L. The ability of RES to arrest cells in the S-phase of the cell cycle, and selectively induce production of reactive oxygen species in cancer cells were probably responsible for its cytotoxic effects. The therapeutic efficacy of RES formulations was evaluated in a subcutaneous xenograft mouse model of GBM. A tumor growth inhibition study and a modified survival study showed that Tf-RES-Ls were more effective than other treatments in their ability to inhibit tumor growth and improve survival in mice. Overall, the liposomal nanomedicines of RES developed in this project exhibited favorable *in vitro* and *in vivo* efficacies, which warrant their further investigation for the treatment of GBMs.

1. Introduction

Glioblastoma (GBM) is the most lethal of primary malignant brain tumors in adults, and accounts for the majority of all malignant gliomas [1,2]. In spite of aggressive treatments including surgical resection, radiation and chemotherapy, the median survival for patients post diagnosis is dismal and has remained unchanged at < 15 months [2]. Various factors including the molecular and cellular heterogeneity in GBMs, their varying mutation status and the identification of sub-populations of cells known as cancer stem-like cells (CSCs) or tumor-initiating cells (TICs), which drive resistance to conventional chemotherapeutics and radiation resulting in tumor recurrence, further complicate GBM therapy [3–6]. Another substantial hurdle for successful chemotherapy in GBM is the low permeability of the blood-brain barrier (BBB), the tight junction of endothelial cells in the brain, that restricts the systemic delivery of drugs to the brain [7]. This necessitates administration of higher doses of chemotherapeutics to achieve effective concentrations in the brain, which may lead to systemic toxicity, thus severely compromising the quality of life of patients. Moreover, conventional chemotherapeutics often lead to toxicity in normal cells due to their off-target effects. This situation warrants investigation into drugs that are relatively well tolerated and can effectively eliminate GBM.

Resveratrol (3,5,4′-trihydroxystilbene) (RES) is a naturally occurring polyphenol and phytoalexin, found in large quantities in red wine, berries, peanuts and soybeans (Fig. 1A). It exhibits pleiotropic health benefits due to its anti-inflammatory, anti-oxidant, anti-carcinogenic, cardio-protective and neuro-protective effects [8–10]. The interest in

* Corresponding author at: Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, 360 Huntington Ave, 140 The Fenway, Room 216, Boston, MA 02115, USA.
E-mail address: v.torchilin@neu.edu (V. Torchilin).

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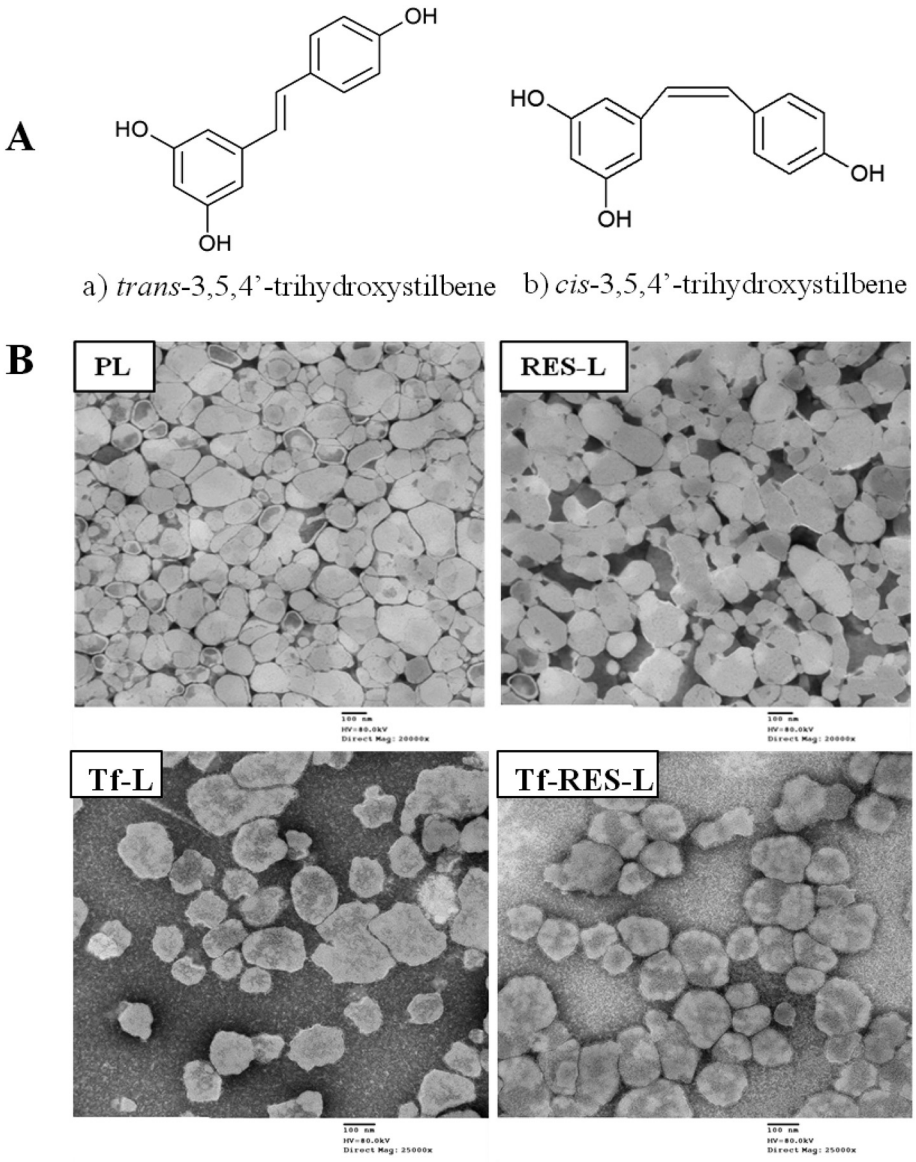

Fig. 1. Chemical structure of resveratrol and TEM images (A) Stereoisomers of resveratrol (a & b). The *trans* isomer is the biologically active form of the drug (B) Transmission electron microscopy (TEM) images of PL and RES-L at 20000× direct magnification and of Tf-L and Tf-RES-L at 25,000× direct magnification (Scale bar 100 nm).

anti-cancer properties of RES was heightened after its chemopreventive effects were demonstrated at all the stages of cancer including initiation, promotion and progression [11]. RES has been shown to be effective in the treatment of gliomas through a myriad of mechanisms, where it affects both the bulk tumor cells and the glioma stem cells (GSC) or TICs [12–15]. Resveratrol induces apoptosis and suppresses angiogenesis in gliomas by reducing VEGF expression, down-regulates matrix metalloproteinase-9 (MMP-9) expression, enhances radiosensitivity in primary brain TICs, induces autophagy-triggered apoptosis, arrests cell-cycle progression in the S-G2/M phase and induces necrosis in GSCs at higher doses [12,13,15,16]. Recent studies have also shown that RES improves the apoptosis inducing ability of therapeutics like TRAIL through various mechanisms, and can be used as a sensitizer to other cancer therapeutics [17,18]. RES potently inhibits both glioma and GSC growth and infiltration by partial deactivation of AKT and p53 induction, resulting in transcription of downstream p53 target genes [19]. In spite of an impressive array of molecular targets and a strong efficacy in gliomas, the therapeutic use of RES is limited due to its poor physico-chemical and pharmacokinetic (PK) properties. It exhibits a high oral absorption (~70%), but a rapid and extensive metabolism resulting in only trace amounts of unchanged drug in the systemic circulation [20]. The poor bioavailability of RES severely compromises its biological and pharmacological benefits. Other limitations of administering RES as a free drug include its poor water solubility, short biological half-life (~9–14 min for the primary molecule), chemical instability (oxidation and photosensitivity) and a rapid metabolism and elimination [10,20–22].

A number of drug carriers have been employed to overcome the physico-chemical and pharmacokinetic drawbacks of RES and improve its therapeutic efficacy against various cancers. These include liposomes, micelles, polymeric nanoparticles, solid-lipid nanoparticles and cyclodextrin complexes [8]. Nanocarriers can accumulate passively in tumors by virtue of their size and by taking advantage of the enhanced permeability and retention (EPR) effect [23,24]. Passive targeting however, suffers from drawbacks that may lead to a non-homogenous distribution of nanocarriers in tumors and may not alone suffice to achieve a therapeutic outcome [25–29]. Active targeting employs nanocarriers decorated with ligands specific for molecules on the tumor cell surface. After extravasation through the tumor vasculature, these nanocarriers can bind to their specific cell targets [30]. Glioblastomas

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