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Monitoring HSV-TK/ganciclovir cancer suicide gene therapy using CdTe/CdS core/shell quantum dots

Dan Shao [a,1], Qinghui Zeng [b,1], Zheng Fan [a,1], Jing Li [a], Ming Zhang [a], Youlin Zhang [b], Ou Li [a], Li Chen [a,*], Xianggui Kong [b,**], Hong Zhang [c]

[a] Department of Pharmacology, School of Basic Medical Sciences, Jilin University, Changchun 130021, China
[b] State Key Laboratory of Luminescence and Applications, Changchun Institute of Optics, Fine Mechanics and Physics, Chinese Academy of Sciences, 3888 Eastern South Lake Road, Changchun 130033, China
[c] Van't Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands

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ABSTRACT

To be able to label a gene and monitor its migration are key important approaches for the clinical application of cancer suicide gene therapy. Photonic nanomaterials are introduced in this work. One of the most promised suicide genes - herpes simplex virus thymidine kinase (HSV-TK) gene - is successfully linked with CdTe/CdS core/shell quantum dots (QDs) via EDC/NHS coupling method. From confocal microscopy it was demonstrated that plasmid TK intracellular trafficking can be effectively and distinctly traced via monitoring the luminescence of the QDs up to 96 h after transfection of QDs-TK conjugates into Hela cells. MTT results show that the QDs-TK conjugates have a high efficient cytotoxicity after adding GCV into Hela cells, whereas the QDs exert no detectable deleterious effects on the cellular processes. The apoptosis induced by QDs-TK conjugates with GCV is distinctly traced partly due to the strong luminescence of the QDs. Our results indicate that photonic nanomaterials, e.g. QDs, provide a tool for monitoring TK gene delivery and anti-cancer activity.

1. Introduction

Cancer is becoming the leading cause of death worldwide. This fact accentuates the need for a new generation of more effective therapies for cancer. Current treatment of cancer with chemotherapy or radiotherapy is insufficient in selectivity, thus induces toxicity to normal cells [1]. Cancer gene therapy offers a better alternative in this respect since it has higher efficiency and lower side effect characteristics. Cancer gene therapy includes a number of possible approaches, one of which utilizes "suicide" gene systems. Herpes simplex virus thymidine kinase gene (HSV-TK) is one of the most promising "suicide" genes. Cells expressing the HSV-TK gene metabolize ganciclovir (GCV) to ganciclovir monophosphate, which is further converted into ganciclovir triphosphate by cellular kinases. As the resulting compound is an analog of deoxyguanosine triphosphate, inhibition of DNA polymerase and/or incorporation into DNA will occur, leading to chain termination and tumor cell death [2–4]. Till now HSV-TK/GCV has been the only gene directed enzyme prodrug therapy combination to reach phase III human trials. It was reported that a subsequent phase II trial that utilized a replication defective adenovirus for delivery of HSV-TK into patients with glioma produced a clinically and statistically significant increase in median survival from 38 to 62 weeks over standard chemotherapy (surgery and radiotherapy) [5,6].

However, TK gene can also transfer to normal human cells. Cytotoxic compounds do not discriminate between neoplastic cells and rapidly dividing healthy cells, such as bone-marrow (hematopoietic) precursors and gastrointestinal mucosal epithelial cells, thus leading to a range of toxic side effects such as neutropenia, thrombocytopenia, anemia, and mucositis [7,8]. It might to a certain extent restrict the application of this promising method. Up to now, there is no systematic research of tracing and identifying the intracellular localization of a TK gene. Therefore a stable and good tracing means is very necessary to label TK gene and monitor its migration so that the TK gene is proved to access into tumor tissue before adding GCV to kill tumor cells exclusively without destruction of normal cells.

As a new kind of biological label, quantum dots (QDs) are nanometer-sized semiconducting crystals with unique fluorescent

* Corresponding author. Tel.: +86 431 85619799; fax: +86 431 85619483.
** Corresponding author. Tel.: +86 431 86176313.
E-mail addresses: zhouweichen@yahoo.com (L. Chen), xgkong14@ciomp.ac.cn (X. Kong).
[1] These authors contributed equally to this work.

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