Magnetoelectric Chitosan nanoparticles loaded with DAPT, effectively inhibit NOTCH1 signaling pathway in Breast Cancer Stem Cells

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Overview

This project reports major improvements in the therapy of human Breast Cancer Stem Cells (BCSCs) with DAPT (a γ-secretase inhibitor). Taking advantage of the unique properties of MECNs, these results suggest that GMO-MECNs effectively bind DAPT, provide controlled intracellular drug delivery and specifically target human BCSCs. We formulated magnetoelectric Chitosan nanoparticles (MECNs) (Fe_3O_4 @Chitosan nanostructures). that can distinguish (BCSCs) from the normal cells through the membrane's electric properties since BCSCs have a significantly smaller threshold field to induce electroporation.

Introduction

Targeted cancer therapy remains a major challenge in the eradication of tumors. Drug delivery systems using nanoparticles offer a novel approach to specifically delivering drugs to cancer cells while sparing normal cells.

BCSCs are a small cell population with unique characteristics such as self-renewal, high proliferation rate, and the ability to generate heterogenic lineages of cancer cells. the Notch signaling pathway is one of the most commonly activated signaling pathways in cancer it is involved in cell proliferation, Differentiation and survival, alterations include activating mutations and amplification of the Notch pathway, play key roles in the progression of the cancer.

The NOTCH signaling could be inhibited by γ-secretase inhibitors. DAPT is a γ-secretase inhibitor that catalyzes the proteolytic cleavages of NOTCH receptor, resulted in the release of NOTCH intracellular domain (NICD), the NICD then moves to the nucleus, where it interacts with CSL (RBP-JK/CBF1) and mastermind to activate transduction of downstream target genes such as Hes1, HRT, Deltes-1, Meltrin- β and NOTCH receptors themselves.

MECNs are a novel class of nanoparticles its unique properties allow it to specifically target human BCSCs only. Therefore, the primary aim is to bind the drug efficiently to MECNs.

Drug-loaded MECNs could be delivered into BCSCs via application of a d.c field and the drug could be released off MECNs on demand via application of an a.c field without thermal damage, the physics is due to electric-field interactions (i) between MECNs and a drug and (ii) between drug-loaded MECNs and cells.

Methods and Materials

I. Fe_3O_4 NPs were added to Sigma -Aldrich chitosan solution, NaOH was added drop by drop to the solution and sonicated with heat, the result dispersed nanoparticles were dried overnight to obtain the powder.
II. To obtain the coat, GMO was added to MECNs in PBS buffer, PH 7.4, incubate with shaker then collect the pellet.
III. Loading GMO-MECNs with DAPT.
IV. TEM & IR were used for checking the prepared NPs.

Results

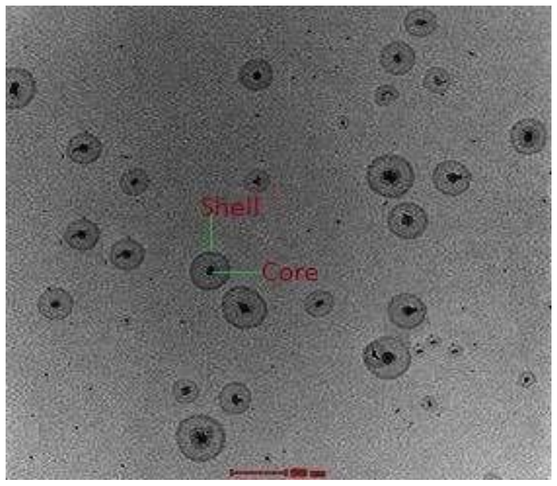

Figure 1. Transmission Electron Microscopy (TEM) image.
showing the core shell nanostructure of MECNs (Fe_3O_4 Core and Chitosan Shell).

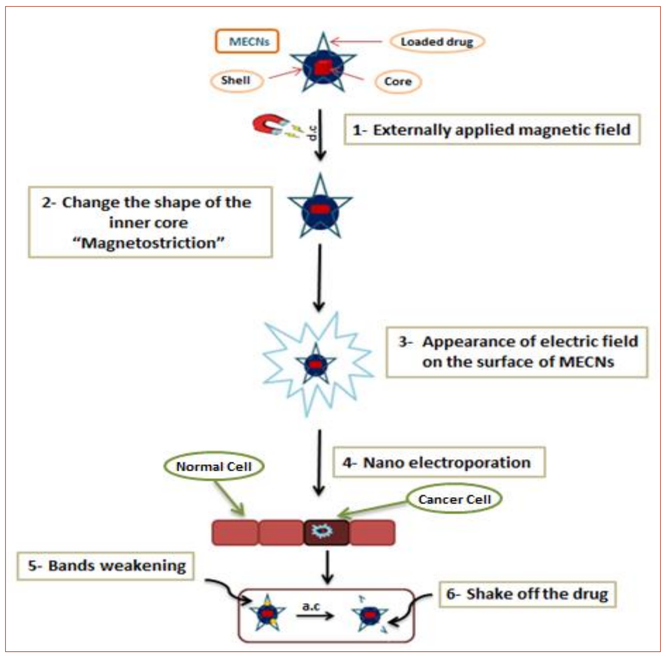

Figure 2. The MECNs drug delivery. The Drug loaded MECNs could be delivered into cancer via application of d.c field, the drug could be released off MECNs on demand via application of an a.c field.

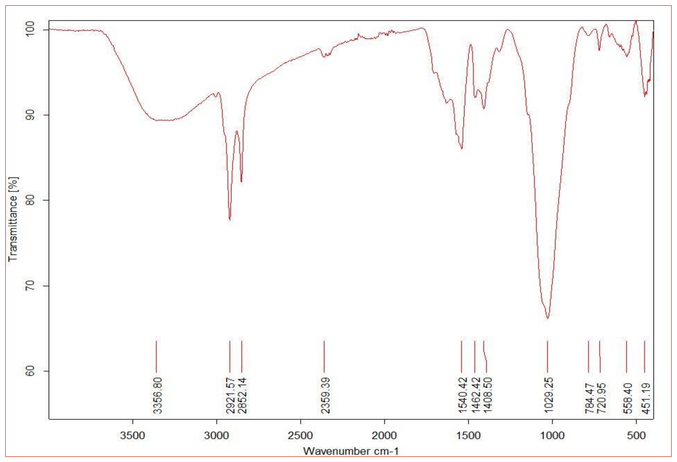

Figure3. FTIR. oleic acid Coated MECNs

Conclusions

Recently Developed magnetoelectric Chitosan nanoparticles (MECNs) are a novel class of nanoparticles to enable targeted drug delivery to cancer cells only. the unique properties of MECNs allow enhancement of drug uptake due to the magnetic core (Fe_3O_4) and increasing specificity of drug loaded MECNs due to electric shell of chitosan.

The data of western blot and immunohistochemistry supposed to show that magnetically sorted DAPT loaded MECNs have a fast and accurate drug delivery to the BCSCs compared to the untreated BCSCs which in turn showed a significant expression of Notch1 inhibition.

chitosan is a nontoxic polymer as well as safe drug delivery material it can be cleared by kidney in vivo, the biodegradability of chitosan is mainly by chemical process and enzyme catalysis, the higher the degree of deacetylation, the greater the degradation rate. while the bio distribution of the iron oxide particles is eventually phagocytosed or endocytosed by the reticuloendothelial System of the liver, spleen, lymph and bone marrow. Once compartmentalized within the lysosomes of RES cells the iron oxide particles are broken down with the majority of the SPIO iron stored as ferritin and/or hemosiderin which are antiferromagnetic forms of iron.

Future research prospective

- In Vitro / In Vivo studies of Magnetoelectric Chitosan nanoparticles loaded with DAPT, effectively inhibit NOTCH1 signaling pathway in Breast Cancer Stem Cells.
- Magnetic Directed enzyme prodrug therapy(DEPT) involves Coupling the bioactive prodrug-activating enzyme to(MECNs) that are then selectively delivered to the tumor by applying an external magnetic field.
- Diagnosis & prognosis of BCSCs by MECNs.
- MECNs induces MET to EMT reverting transition in BCSCs.

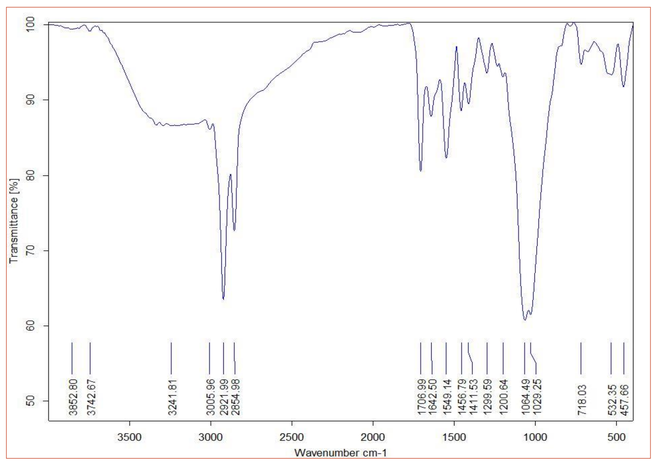

Figure4. FTIR. Nexavar drug loaded MECNs

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