Commentary
Volume 6:4, 2022

Reports in Thyroid Research

ISSN: 2684-4273 **Open Access**

Targeting the Thyroid Gland with Thyroid-Stimulating Hormone

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Description

Various tissue-specific antibodies have been attached to nanoparticles to obtain targeted delivery. In particular, nanodelivery systems with selectivity for breast, prostate and cancer tissue have been developed. Here, we have developed a nanodelivery system that targets the thyroid gland. Nanoliposomes have been conjugated to the thyroid-stimulating hormone (TSH), which binds to the TSH receptor (TSHr) on the surface of thyrocytes. The results indicate that the intracellular uptake of TSH-nanoliposomes is increased in cells expressing the TSHr. The accumulation of targeted nanoliposomes in the thyroid gland following intravenous injection was 3.5-fold higher in comparison to untargeted nanoliposomes.Furthermore,TSH-nanoliposomes encapsulated with gemcitabine showed improved anticancer efficacy *in vitro* and in a tumor model of follicular thyroid carcinoma.This drug delivery system could be used for the treatment of a broad spectrum of thyroid diseases to reduce side effects and improve therapeutic efficacy.

The field of targeted therapy was born from the introduction of the “magic bullet” concept, which entails the selective delivery of a drug to a tissue of interest.The concept involves reducing side effect, broadening the therapeutic window and increasing drug efficacy, through the selective delivery of an agent to a specific site in the body. Such selectivity is especially desired for diseases characterized by a low therapeutic index, such as cancer. Among various approaches adopted for drug delivery, liposomes provide a strategy for improving the biopharmaceutical properties of drugs.In particular, pegylated liposomes can avoid immunological recognition and rapid clearance by macrophages. Accordingly, several liposomal formulations have gained clinical approval and many more are currently undergoing clinical trials. In an attempt to achieve selectivity, antibodies that are specific for surface molecules on target cells have been conjugated to liposomes. For instance, an antibody fragment against the human epidermal growth factor receptor 2 (HER2), frequently expressed in breast cancer, has been attached to liposomes. Similarly, liposomes have been coated with the monoclonal antibody (mAb) 2C5, which binds to nucleosomes on the surface of cancer cells. In addition, folate-moieties have been incorporated in supramolecular vesicular aggregates to obtain preferential uptake by cancer cells that express the folate receptor.

Although several tissue-specific antibodies have been conjugated to nanoparticles, there are several organs, such as the thyroid gland, that have not been the focus of targeted drug delivery. We propose a strategy for obtaining preferential accumulation of nanoparticles in the thyroid. Thyroid-stimulating hormone (TSH) has been attached to the surface of pegylated nanoliposomes with the aim of targeting the TSH receptor (TSHr). The TSHr is a glycoprotein G-protein-coupled receptor expressed in the plasma membrane of thyrocytes. This receptor binds to TSH with high affinity and specificity and mediates the ligands biological effects on the thyroid gland. TSHr expression is maintained in most thyroid pathologies, including benign and malignant tumors.More importantly, the receptor is also present in the majority of less differentiated and more aggressive tumors, making it an optimal target for the delivery of chemotherapeutics.

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Date of Submission: 02 July 2022, Manuscript No. rtr-22-80030; **Editor assigned:** 04 July 2022, PreQC No. P-80030; **Reviewed:** 16 July 2022, QC No. Q-80030; **Revised:** 21 July 2022, Manuscript No. R-80030; **Published:** 28 July 2022, DOI: 10.37421/2684-4273.2022.07.23

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Nanoliposomes were made from DPPC/cholesterol/DSPEmPEG2000/DSPE-mPEG2000-PDP (6:3:0.6:0.4 M ratio). The lipid mixture (20 mg) was dissolved in a round-bottom flask, using a chloroform/methanol mixture (3:1 v/v). Fluorescein-labeled and radiolabelled nanoliposomes where obtained by adding fluorescein-DHPE (0.1% molar) or CHE to the lipid mixture. The organic solvents were removed with a rotary evaporator (Büchi R-210 Switzerland), followed by overnight incubation in a Büchi T51 glass-drying oven connected to a vacuum pump. Multilamellar nanoliposomes were prepared by hydrating the lipid film with 1ml of saline solution (NaCl 0.9% w/v) and performing three alternate cycles (3 min each) of heating at 58°C (water bath) and vortex mixing at 700 rpm. To reduce the disulfide bond the nanoliposomes were incubated with a 50 mM DTT solution (1:2 v/v respectively) for 30 min. Excess DTT was then removed after centrifugation at 20,000 × *g* for 60 min at 4°C with a Beckman Coulter Allegra 64R centrifuge. Successively, the pellet was resuspended in 250 mM ammonium sulfate solution and subjected to ten cycles of freezing (liquid nitrogen) and thawing (water bath at 40°C), thus achieving a pH gradient with an acid environment in the aqueous compartment [1-5].

Acknowledgement

None.

Conflict of interest

No potential conflict of interest was reported by the authors.

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How to cite this article: Sheng, Lei. "Targeting the Thyroid Gland with Thyroid-Stimulating Hormone." Rep Thyroid Res 06 (2022): 23.