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MAIN FIELDS OF RESEARCH; ABSTRACT

G-protein coupled receptor (GPCR) family is involved in many crucial physiological processes via regulation of signal transduction pathways and GPCRs deregulation leads to various pathologies including cancer[1]. Cholecystokinin-B receptor (CCKBR), a member of GPCR family, is overexpressed in different types of cancers, and targeting CCKBR by radiolabeled minigastrin shows potential diagnostic and therapeutic effect in medullary thyroid cancer (MTC).

Currently, ^{177}Lu-DOTA-PPF11N, which is internalized through CCKBR, is being studied in the 1st clinical trial for MTC treatment. However, insufficient delivery of radiation dose to tumor sites, whereby the injected dose is limited by cytotoxic effects on healthy organs (especially in kidneys and stomach), as well as possible activation of radioresistence mechanisms, can lead to tumor reoccurrence and therapy failure in treated patients. Thus, it is important to develop novel therapeutic strategies for efficient TRTs in cancer patients. In the proposed study, first we will screen kinase inhibitor and FDA approved drug libraries to identify compounds which increase internalization of the radiopharmaceuticals. In the second step, we will investigate the potential therapeutic applications as well as molecular mechanisms that improve internalization. As a result, our new combinatory treatments will not only improve cancer response to TRT but also can reduce side effects on healthy organs by applying lower dose of radio-medicine after cancer pre-treatment.

The Beta/Gamma emitter ^{177}Lu is currently under clinical investigation, its decay energy is 0.5MeV with average tissue range of 0.28 mm, which shows great potential in the treatment of large, heterogeneous tumors, where the cross-fire effect is important[2]. However, the toxicity to surrounding healthy tissues limits its application. Targeted alpha therapy (TAT), with high linear energy transfer (LET 50–100 keV/μm) and short range (40–80 μm), might be an advantageous strategy to eradicate residual tumors. Since the therapeutic effect of TAT is basically caused by radionuclides delivered into cancer cells, it is rational and necessary to characterize the cellular responses and potential resistance mechanisms. Identification of survival mechanisms induced by alpha emitters can provide with basis to develop novel sensitizing approaches.

In this study, proteomics and phosphoproteomics analysis on proteins isolated from MTC cells after ^{225}Ac–labeled minigastrin (PPF11N) treatment will also be performed, which will help us better understand the cell responses to alpha-emitters and to identify potential radioresistance mechanisms (activated pathways) suitable for therapeutic interference.

SPECIAL TECHNIQUES AND EQUIPMENT

Special techniques: Kinase Inhibitor Library and Drug Library screening, Radiolabelling and purification of radiolabelled compound, Proteomics and Phosphoproteomics analysis

Equipment: Liquid Scintillation Counter, HPLC, MS

References:

[1] Rithwik Ramachandran *et al.* Targeting proteinase-activated receptors: therapeutic potential and challenges. NATURE REVIEWS | DRUG DISCOVERY. Jan 2012.
[2] Marek Pruszynski *et al.* Evaluation of an Anti-HER2 Nanobody Labeled with ^{225}Ac for Targeted α-Particle Therapy of Cancer. 2018. Mol. Pharmaceutics.