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Entitled

THE ROLE OF PARATHYROID HORMONE 1 RECEPTOR (PTH1R) SIGNALING IN GASTRIC EPITHELIAL HOMEOSTASIS

by

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Abstract

In the stomach, the epithelial stem cells are responsible for glandular homeostasis. These stem cells continuously undergo cellular proliferation and differentiation to balance death of senescent cells. Studies conducted on gastric cancers showed significant increase in parathyroid hormone like hormone (PTHLH). Moreover, both PTHLH along with parathyroid hormone (PTH) act as endogenous ligands for parathyroid hormone 1 receptor (PTH1R) which belongs to family B of G- protein coupled receptors (GPCRs). This receptor functions by mediating many different signaling pathways and the most studied pathway is the stimulation of cyclic adenosine mono-phosphate (cAMP) as second messenger. There are very little studies on understanding the normal function of gastric PTH1R. Specifically, how PTH1R and its ligands are associated with gastric cancer. The goal of this project is to investigate the expression of PTH1R in gastric epithelium, and to understand its possible function and signaling in maintaining gastric homeostasis. Firstly, gene expression analysis suggested that PTH1R is expressed *in vivo* in normal human stomach, and in mouse forestomach, corpus and antrum. *In vitro* studies on HeLa, and human embryonic kidney 293 cells (HEK293), also showed positive expression of PTH1R. However, mouse gastric epithelium progenitor cells (mGEP) and human gastric cancer cell line (AGS) showed no expression of PTH1R. To study the mechanism of PTH1R function, transfection of PTH1R plasmid was successfully conducted in mGEP and AGS cells. Next, we investigated the signaling pathways activated upon PTH1R stimulation. cAMP assay in transfected AGS cells treated with PTH1R agonist suggests activation of $G\alpha_s$ signaling pathway. On the other hand, transfected mGEP cells successfully activated ERK1/2 pathway. Morphological studies suggested difference in the cell morphology of transfected mGEP cells in which large cell to cell spaces was reported. Furthermore, cell viability results showed statistically a non-significant agonist and antagonist trend. Finally, several target genes were studied by Real-Time PCR. Low density lipoprotein receptor (*LDLR*) showed significant upregulation when comparing transfected and activated mGEP cells to control. However, calcium sensing receptor (*CaSR*), fibroblast growth factor 23 (*FGF23*), interleukin-6 (*IL-6*), and Na+/H+ exchanger regulatory factor 1 (*NHERF1*) did not show a significant change. This work highlights the importance of PTH1R in the stomach which might open new perspectives in studying PTH1R signaling in gastric cancer patients. This might set new therapeutic modalities for gastric cancer, especially since PTH1R agonists are used in treatment of bone cancer and osteoporosis.

Keywords: PTH1R, PTHLH, PTH, Gastric epithelium, Stem cell.