CALIFORNIA STATE SCIENCE FAIR
2013 PROJECT SUMMARY

Name(s)

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Project Number

33124

Project Title

Halting Colorectal Cancer Progression through Chemokine G Protein-Coupled Receptor Signaling

Abstract

Objectives/Goals

The Wnt/beta-catenin signal transduction pathway is a critical regulator of colorectal cancer development. However, the progression of cancer is remarkably complex and frequently relies on interplay between multiple signaling cascades. The main purpose of this research was to ascertain whether interactions exist between Wnt/beta-catenin signaling and chemokine G protein-coupled receptor (GPCR) signaling and how such crosstalk might affect colorectal cancer progression. A second objective was to determine the consequences of observed mutant chemokine receptor 7 (CCR7) in colorectal cancer cells.

Methods/Materials

Cells from the colon carcinoma cell line SW480 were incubated with CCR7's agonists CCL19 and CCL21 for predetermined time periods. The subsequent impact on levels of CCR7, active beta-catenin, and total (membranous and intracellular) beta-catenin were analyzed through Western blotting. Additionally, immunofluorescence microscopy was used to analyze the expression and localization of actively transcriptional beta-catenin and Ki67, a marker for cellular proliferation.

Results

Immunofluorescence microscopy demonstrated that greater time of pre-treatment with the agonist CCL19 causes drastic inhibition of Ki67. Western blot and immunofluorescence analyses both confirmed that active beta-catenin is down-regulated upon increased CCL19 incubation. Levels of total beta-catenin, however, were not significantly impacted after agonist treatment. Finally, Western blot experiments showed that the receptor CCR7 is inhibited after shorter periods of CCL19 incubation but up-regulated after longer periods of treatment. The same response was observed in cells which were pre-treated with cycloheximide, an inhibitor of protein synthesis.

Conclusions/Discussion

This study demonstrates that activated CCR7 suppresses colorectal cancer cell proliferation and dramatically inhibits levels of the oncogenic protein beta-catenin. Additionally, this research illuminates mechanisms of CCR7's activation and signal transduction by revealing that receptor recycling mediates the plasma membrane recovery of this GPCR. Overall, these findings delineate a novel tumor-suppressing function of chemokine GPCR signaling in colorectal cancer cells. By interfering with the Wnt/beta-catenin pathway in such a manner, CCR7 can serve as a plausible target for medicinal drugs and therapeutic measures against colorectal cancer.

Summary Statement

My project identifies a novel tumor-suppressing function of CCR7, a chemokine G protein-coupled receptor which may therefore be targeted in colorectal cancer therapy.

Help Received

Dr. Mariana Beltcheva provided guidance and feedback throughout the course of this project. Luba Ezerskiy assisted in the instruction of laboratory techniques. This project was conducted in the laboratory of Dr. Lila Solnica-Krezel at the Washington University School of Medicine in St. Louis.