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Targeting the cGMP Pathway to Treat Colorectal Cancer

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Translational Medicine

Laboratory

Molecular Biology
Cell Culture
Organ Culture
Animal Models
Clinical Trials

Clinic
Translational Research Project: from the cGMP Pathway to Colorectal Cancer

Targeting Strategies:

1. Cyclic GMP-Dependent Pathway as a Tumor Suppressor System to Prevent Colorectal Tumorigenesis

2. Cyclic GMP-Dependent Pathway as an Antimetastatic Strategy to Disrupt Colorectal Cancer Metastatic Progression
Cyclic GMP Signaling

General Model for cGMP Signaling


Guanylyl Cyclases

Lucas, et al. (2000)
Pharmacol. Rev. 52: 375-413
Guanylyl Cyclase C (GCC)

GCC is selectively expressed at brush-border membranes of intestinal epithelial cells and regulates fluid homeostasis.

Crypt and Villus Enterocytes

Brush Border Microvilli

Antiproliferative cGMP Signaling Targets
Cyclic Nucleotide-Gated Channel

Antiproliferative cGMP Signaling Undergoes Negative Feedback Regulation

The Antiproliferative cGMP Signaling Pathway in Intestinal Epithelial Cells

Cyclic GMP Signaling by GCC Controls The Crypt-Villus Homeostasis

Colon Cancer: the 2nd Most Deadly Cancer in Developed Nations

More developed regions
Number of cases (all ages)
The Pathological Sequence of Colorectal Cancer

- Early Genetic Mutations
- Aberrant Crypt Foci
- Adenomatous Polyps
- Dysplastic Adenomas
- Carcinomas

Cancer Risk

Reversibility

Incidence
Colon Cancer: Diagnosis and Therapy

Stage I
Invasion up to the *muscularis propria*

- Surgery

5-years survival
~ 95%

Stage II
Invasion of the serosa and adjacent organs

- Surgery
- Chemotherapy

~ 80%

Stage III
Invasion of regional lymph nodes

- Surgery
- Chemotherapy

~ 65%

Stage IV
Distant Metastasis

- Surgery
- Chemotherapy

~ 7%
ETEC Infections Confer Resistance to Colon Cancer

Risk for ETEC infection
low medium high

Colorectal Cancer Incidence (ASR-W)

New Zealand Australia West Europe United States Canada Northern Europe South Europe East Europe Caribbean Islands East Asia South America Southeast Asia Middle East Central America Africa Indian Subcontinent

$r^2=0.99$
GCC is a Therapeutic Target in Colon Cancer

N T F Y C C E L C C N P A C A G C Y

ST

NDDCEL CVNV ACT GCL
PGTCEI CAYAAC TGC

uroguanylin
guanylin

GCC is a Novel Intestinal Tumor Suppressor
GCC Signaling through cGMP Potentiates Cytostatic Calcium Effects

GCC Regulates the Function of Calcium-Sensing Receptor (CaR) in the Intestine

Pitari, G.M. et al. (2008)
Carcinogenesis 29:1601-7
GCC-Targeted Therapy in Combination with Dietary Calcium

A Tumor Suppressor cGMP Signaling Pathway in Colon Cancer

Pitari, G.M. et al. (2008) 
Carcinogenesis 29:1601-7
Colon Cancer Mortality Reflects Metastatic Disease Progression


Cyclic GMP Induces Functional Remodeling of Cancer Cell MMP-9

Protein Gelatinolytic Activity,

MMP-9 Dependent

Relative Levels of MMP-9 mRNA

Primary Neoplasms

MMP-9

Growth

Vascularization

Invasion

Detachment

Migration

Extravasation

Proliferation/angiogenesis

Metastasis

MMP-9 Promotes Metastasis in Colon Cancer

Colon Cancer Cell MMP-9 Induces Metastatic Seeding

GCC and cGMP Signaling through MMP-9 Regulates Colon Cancer Cell Shape and Spreading

GCC and cGMP Signaling through MMP-9 Suppresses Metastatic Seeding by Colon Cancer Cells

The Antimetastatic cGMP Signaling Pathway in Colon Cancer Cells

(-) cGMP Pathway

GCC → cGMP → MMP-9 secretion → Matrix Degradation → Cell Spreading → Metastatic Seeding

Tumor Containment / Vascular Clearance

(+ ) cGMP Pathway

Metastasis

Summary

• The cGMP pathway in intestinal epithelial cells regulates the crypt-villus axis and opposes colorectal tumorigenesis

• GCC, a guanylyl cyclase receptor selectively expressed by normal and malignant intestinal epithelial cells, coordinates a paracrine tumor suppressor system in the intestine

• The cGMP pathway potentiates the cytostatic effects of extracellular calcium by regulating the activity of CaR

• The cGMP pathway reduces the metastatic potential of colorectal cancer cells, in vitro and in vivo, in part by regulating the function of MMP-9

• Cancer cell MMP-9 regulates metastatic functions, including actin polymerization and cell spreading, and in vivo seeding of target organs
Translational Significance

• GCC ligands represents novel agents for the prevention of primary and metastatic colon cancer
• GCC ligands represents novel agents for the treatment of primary and metastatic colon cancer
• Combinatorial strategies with GCC ligands and dietary calcium may provide a novel paradigm for the treatment of colon cancer
• Cancer cell MMP-9 is a highly selective and effective molecular target for preventing metastatic progression of colorectal cancer