Targeting the cGMP Pathway to Treat Colorectal Cancer

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Targeting the cGMP Pathway to Treat Colorectal Cancer

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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

Agonist → CNG

CNG → cGMP

CNG → PKA

CNG → PKG

CNG → PDE

CNG → GTP

GTP → GC

GC → cGMP

GC → PKG

GC → PDE

PDE → cGMP

PDE → PKG

PDE → PKA

PDE → GTP

PDE → CNG

Ca^{2+} → CNG

Ca^{2+} → PKG

Ca^{2+} → cNOS

Ca^{2+} → Plasma membrane

Ca^{2+} → L-type Ca^{2+} Channels

NO → cNOS


Guanylyl Cyclases

Guanylyl Cyclase C (GCC) is selectively expressed at brush-border membranes of intestinal epithelial cells and regulates fluid homeostasis.
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

Differentiation

Proliferation

Migration

Inactive fibroblast

Active fibroblast

Guanylin
Uroguanylin

Pitari, G.M. et al. (2007)
Clin. Pharmacol. Ther. 82:441-7
Colon Cancer: the 2nd Most Deadly Cancer in Developed Nations
The Pathological Sequence of Colorectal Cancer

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

Cancer Risk

Incidence

Reversibility
## Colon Cancer: Diagnosis and Therapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Therapy</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Invasion up to the muscularis propria</td>
<td>Surgery</td>
<td>~95%</td>
</tr>
<tr>
<td>II</td>
<td>Invasion of the serosa and adjacent organs</td>
<td>Surgery, Chemotherapy</td>
<td>~80%</td>
</tr>
<tr>
<td>III</td>
<td>Invasion of regional lymph nodes</td>
<td>Surgery, Chemotherapy</td>
<td>~65%</td>
</tr>
<tr>
<td>IV</td>
<td>Distant Metastasis</td>
<td>Surgery, Chemotherapy</td>
<td>~7%</td>
</tr>
</tbody>
</table>
ETEC Infections Confer Resistance to Colon Cancer

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

GLN-stimulated thymidine incorporation (%)

NDDCEL CVNVA CT GCL
uroguanylin

PGTCEI CAYAA CTGCL
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

GCC-Targeted Therapy in Combination with Dietary Calcium

Inhibition of Proliferation, %

Control

Proliferation, %

ST + Ca²⁺

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

Tumor Stage


Cyclic GMP Induces Functional Remodeling of Cancer Cell MMP-9


Primary Neoplasm
- Growth
- Vascularization
- Invasion
- Detachment
- Migration
- Extravasation
- Proliferation/angiogenesis

Metastasis

**Graphs and Figures**

A. Relative Levels of MMP-9 mRNA

B. MMP-9 Dependent Gelatinolytic Activity

C. MMP-9-Dependent Gelatinolytic Activity

D. Relative Levels of MMP Protein
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

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 represent novel agents for the prevention of primary and metastatic colon cancer.
- GCC ligands represent 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.