Targeting the cGMP Pathway to Treat Colorectal Cancer

Giovanni Mario Pitari
Thomas Jefferson University, gmpitari@gmail.com

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Targeting the cGMP Pathway to Treat Colorectal Cancer

GianMario Pitari, M.D., Ph.D.

Department of Pharmacology and Experimental Therapeutics

Thomas Jefferson University

Philadelphia, PA 19107
Translational Medicine

Molecular Biology
Cell Culture
Organ Culture
Animal Models
Clinical Trials

Laboratory  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

Agonist → CNG → cGMP → PKA,PKG → GC → GTP → PDE

Pituitary Cells

Ca^{2+} → CNG → Ca^{2+} → PKG → Ca^{2+} → Pituitary Cells


Guanylyl Cyclases

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

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

More developed regions
Number of cases (all ages)

Lung
Colon and rectum
Breast
Prostate
Stomach
Bladder
Non-Hodgkin lymphoma
Kidney etc.
Corpus uteri
Pancreas
Melanoma of skin
Leukaemia
Liver
Ovary etc.
Oral cavity
Cervix uteri
Brain, nervous system
Oesophagus
Larynx
Thyroid
Multiple myeloma
Other pharynx
Testis
Hodgkin lymphoma
Nasopharynx

Cases vs Deaths

GLOBOCAN 2002, IARC
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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Treatment</th>
<th>5-years Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Invasion up to the <em>muscularis propria</em></td>
<td>Surgery</td>
<td>~ 95%</td>
</tr>
<tr>
<td>II</td>
<td>Invasion of the serosa and adjacent organs</td>
<td>Surgery</td>
<td>~ 80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemiotherapy</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Invasion of regional lymph nodes</td>
<td>Surgery</td>
<td>~ 65%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemiotherapy</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Distant Metastasis</td>
<td>Surgery</td>
<td>~ 7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemiotherapy</td>
<td></td>
</tr>
</tbody>
</table>
ETEC Infections Confer Resistance to Colon Cancer

Pitari, G.M. et al. (2003)
GCC is a Therapeutic Target in Colon Cancer

N D D C E L C V N V A C T G C L
uroguanylin

P G T C E I C A Y A A C T G C
guanylin

GCC is a Novel Intestinal Tumor Suppressor

Li, P. et al. (2007) Gastroenterology 133:599-607
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

Colon Cancer Mortality Reflects Metastatic Disease Progression


Cyclic GMP Induces Functional Remodeling of Cancer Cell MMP-9

A

Relative Levels of MMP-9 mRNA

B

T84

Caco-2

proMMP-9 (92-kDa)

MMP-9, %

C

proMMP-9

Active MMP-9

MMP-9-Dependent Gelatinolytic Activity, %

D

proMMP-9

GAPDH

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

(-) cGMP Pathway

Metastasis

GCC → cGMP → MMP-9 secretion

Matrix Degradation → Cell Spreading → Metastatic Seeding

(+) cGMP Pathway

Tumor Containment / Vascular Clearance

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