

## HIGHLIGHT ADVISORS

### ANTON BERNS

NETHERLANDS CANCER INSTITUTE, AMSTERDAM, THE NETHERLANDS

### PETER BOYLE

EUROPEAN INSTITUTE OF ONCOLOGY, MILAN, ITALY

### PETER CARMELIET

CATHOLIC UNIVERSITY LEUVEN, LEUVEN, BELGIUM

### RON DEPINHO

HARVARD MEDICAL SCHOOL, BOSTON, MA, USA

### STEPHEN W. FESIK

ABBOTT LABORATORIES, ABBOTT PARK, IL, USA

### ELI GILBOA

DUKE UNIVERSITY MEDICAL CENTER, DURHAM, NC, USA

### TOMAS LINDAHL

IMPERIAL CANCER RESEARCH FUND, HERTFORDSHIRE, UK

### LANCE LIOTTA

NATIONAL CANCER INSTITUTE, BETHESDA, MD, USA

### JANET D. ROWLEY

UNIVERSITY OF CHICAGO MEDICAL CENTER, CHICAGO, IL, USA

### DAVID SIDRANSKY

JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, BALTIMORE, MD, USA

### JÜRIG TSCHOPP

UNIVERSITY OF LAUSANNE, EPALINGES, SWITZERLAND

### BERT VOGELSTEIN

JOHNS HOPKINS ONCOLOGY CENTER, BALTIMORE, MD, USA

### ROBERT A. WEINBERG

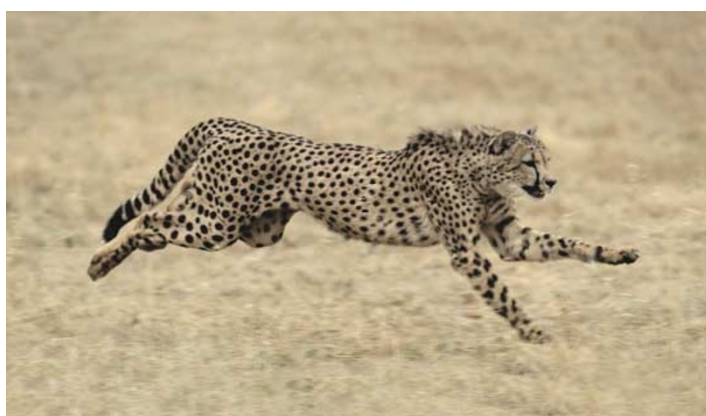
WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH, CAMBRIDGE, MA, USA

### SAVIO WOO

MOUNT SINAI SCHOOL OF MEDICINE, NEW YORK, NY, USA

## TUMOUR SUPPRESSORS

# Keep cancer on the run



Colorectal cancer is the third most common neoplasm worldwide, but epidemiologists have long been puzzled by the fact that the incidence of this disease is lower in underdeveloped countries. There is also an unexplained inverse correlation between colorectal cancer and enterotoxigenic *Escherichia coli* infections. In fact, the age-adjusted incidence of colorectal cancer is lowest in underdeveloped countries in which enterotoxigenic *E. coli* occurs at the highest rates. In *Proceedings of the National Academy of Sciences*, Pitari *et al.* describe a mechanism by which these bacteria might prevent colon cancer.

Enterotoxigenic *E. coli* produce heat-stable peptides (STs) that cause the diarrhoea that is associated with this bacterial infection. STs are likely to cause this complication because they are structurally similar to the endogenous peptides guanylin and uroguanylin, which mediate control of intestinal fluid and electrolyte

homeostasis. This structure allows STs to bind to guanylyl cyclase C, which is specifically expressed by intestinal epithelial cells. The interaction activates the conversion of GTP to cyclic GMP (cGMP), activating a downstream signalling pathway that results in secretory diarrhoea.

Expression of guanylyl cyclase C, and also guanylin and uroguanylin, is frequently lost during cancer progression, so this might be a tumour-suppressive pathway. To support this idea, inactivation of the mouse guanylin gene results in increased colonic proliferation. So how could this pathway prevent cancer?

Pitari *et al.* investigated the cGMP signalling pathway in human colon cancer cells. They found that addition of STs to cancer cells led to increased intracellular cGMP concentrations, and also inhibited DNA synthesis and proliferation — but not in guanylyl-cyclase-C-null tumour cells. So cGMP signalling

must be involved in the growth-suppressive effects of STs. Further examination of ST-treated cancer cells revealed that the antiproliferative actions were not mediated by the conventional downstream cGMP signalling pathway (which involves protein kinase G and phosphodiesterase-3). But how does cGMP production prevent proliferation of colon cancer cells?

cGMP has also been shown to activate cyclic nucleotide gated (CNG) channels. Pitari *et al.* found that STs activate these channels in colon cancer cells, leading to direct influx of  $Ca^{2+}$ . Depletion of extracellular  $Ca^{2+}$  abolished the ability of STs to inhibit cancer-cell proliferation, whereas increasing  $Ca^{2+}$  levels restored the antiproliferative effect of STs.

This is the first study to show regulation of cell proliferation by CNG channels. Further research is required to determine the mechanism by which the ST-induced  $Ca^{2+}$  influx regulates DNA synthesis. The authors indicate, however, that oral administration of agents that are involved in the intestinal salt and water transport process might prevent or treat colorectal cancer.

Kristine Novak

## References and links

**ORIGINAL RESEARCH PAPER** Pitari, G. M. *et al.* Bacterial endotoxins are associated with resistance to colon cancer. *Proc. Natl Acad. Sci. USA* 10 Feb 2003 (doi: 10.1073/pnas.0434905100)

**FURTHER READING** Carrithers, S. L. Diarrhea of colorectal cancer: can bacterial toxins serve as a treatment for colon cancer? *Proc. Natl Acad. Sci. USA* 10 Feb 2003 [epub ahead of print]