

# HIGHLIGHTS

## HIGHLIGHTS ADVISORS

### JOAN S. BRUGGE

HARVARD MEDICAL SCHOOL,  
BOSTON, MA, USA

### PASCALE COSSART

INSTITUT PASTEUR, PARIS,  
FRANCE

### GIDEON DREYFUSS

UNIVERSITY OF PENNSYLVANIA,  
PHILADELPHIA, PA, USA

### PAMELA GANNON

CELL AND MOLECULAR  
BIOLOGY ONLINE

### JEAN GRUENBERG

UNIVERSITY OF GENEVA,  
SWITZERLAND

### ULRICH HARTL

MAX-PLANCK-INSTITUTE,  
MARTINSRIED, GERMANY

### NOBUTAKA HIROKAWA

UNIVERSITY OF TOKYO, JAPAN

### STEPHEN P. JACKSON

WELLCOME/CRC INSTITUTE,  
CAMBRIDGE, UK

### ROBERT JENSEN

JOHNS HOPKINS UNIVERSITY,  
BALTIMORE, MD, USA

### VICKI LUNDBLAD

BAYLOR COLLEGE OF  
MEDICINE, HOUSTON, TX, USA

### TONY PAWSON

SAMUEL LUNENFELD RESEARCH  
INSTITUTE, TORONTO, CANADA

### NORBERT PERRIMON

HARVARD MEDICAL SCHOOL,  
BOSTON, MA, USA

### THOMAS D. POLLARD

THE SALK INSTITUTE,  
LA JOLLA, CA, USA

### JOHN C. REED

THE BURNHAM INSTITUTE,  
LA JOLLA, CA, USA

### KAREN VOUSDEN

NATIONAL CANCER INSTITUTE,  
FREDERICK, MD, USA

### JOHN WALKER

MRC DUNN HUMAN NUTRITION  
UNIT, CAMBRIDGE, UK

## CANCER

### Death by PUMA

The p53 protein has a two-pronged approach to keeping tumours at bay: by modulating the transcription of genes involved in the cell cycle or apoptosis, it can either inhibit cell growth or stimulate cell death. Several genes have been implicated in the path to apoptosis, and two papers in *Molecular Cell* now report the identification of a new target — the p53 upregulated modulator of apoptosis, or *PUMA* for short.

The two groups used different strategies to identify PUMA. Yu *et al.* were exploring the roles of other known apoptotic targets — Bax, Noxa and p53AIP1 — in human colorectal cancer cells. They found that expression of these three genes was neither early nor strong enough to account for the observed apoptosis, so they looked for other candidates by the serial analysis of gene expression (SAGE) technique. Nakano and Vousden, on the other hand, used microarrays to compare gene-expression patterns in the presence and absence of p53.

Although there are differences in the transcription products identified by the two groups, the reported functional and biochemical properties of PUMA are nearly identical. The *PUMA* promoter contains two consensus p53-binding sites, BS1 and BS2, although BS2 seems to be the main p53-responsive element. PUMA also contains a Bcl-2 homology 3 (BH3) domain, a conserved motif found in many pro-apoptotic members of the Bcl-2 family.

Such 'BH3-only' proteins are known to form heterodimers, leading



to the release of cytochrome *c* from the mitochondria. This activates an apoptotic cascade involving caspase-9/Apaf-1 and caspase-3. So could human PUMA be involved in this pathway? Both groups found that human PUMA indeed localizes to the mitochondria, and used immunoprecipitation to show that PUMA binds to Bcl-2. Yu *et al.* also showed that PUMA interacts with Bcl-x<sub>L</sub>, which is ubiquitously expressed in many colon cancer cells. The PUMA BH3 domain is essential for its interactions with both Bcl-2 and Bcl-x<sub>L</sub>.

Finally, the two groups showed that expression of PUMA leads to extremely rapid cell death *in vitro*. Nakano and Vousden showed that this death was accompanied by the release of cytochrome *c* and the cleavage of procaspase-9 and procaspase-3

to their activated forms. They also used antisense oligonucleotides against PUMA to confirm its contribution to apoptosis in a p53-inducible cell line.

What next, then, for PUMA? As Yu *et al.* point out, we need to know PUMA's normal function and whether it is really necessary for apoptosis. Because PUMA leads to such a rapid and profound apoptosis, they also raise the tantalising possibility that it might one day be considered as a substitute for p53 in cancer gene therapy.

Alison Mitchell

## References and links

**ORIGINAL RESEARCH PAPERS** Yu, J. *et al.* PUMA induces the rapid apoptosis of colorectal cancer cells. *Mol. Cell* **7**, 673–682 (2001) | Nakano, K. & Vousden, K. H. *PUMA*, a novel proapoptotic gene, is induced by p53. *Mol. Cell* **7**, 683–694 (2001)

**FURTHER READING** Vousden, K. H. p53: death star. *Cell* **103**, 691–694 (2000)