

EACR Cancer Researcher Award Lecture

The EACR Cancer Researcher Award Lecture is presented annually at the EACR Conference or the EACR Special Session at The European Multidisciplinary Congress

The EACR
Cancer Researcher
Award Lecture 2010
was given in Oslo at
EACR-21

by

Kevin M Ryan

The feature that follows
is based on his
lecture



cells for the degradation of proteins and it is the only mechanism cells have for degrading organelles. Autophagy is considered to be active in all cells at a basal rate where it serves to remove damaged cytoplasmic constituents. Cargoes for degradation are encapsulated in double-membraned organelles called autophagosomes which traffic through the cell until they fuse with lysosomes to form new organelles called autolysosomes. The contents of the autophagosome are degraded in the autolysosome by hydrolases provided by the lysosome. Constituent parts of degraded cargoes are then recycled back into the cytoplasm and are either subject to further catabolism or synthesise into new macromolecules.

In response to a variety of stimuli, the levels and cargoes of autophagy can change to bring about bespoke effects within the cell. The selectivity of autophagy activation is no more relevant than in the control of programmed cell death. It is clear that in response to catabolic defects or nutrient deprivation, autophagy can be activated to degrade cellular constituents to provide a limited intracellular supply of ATP to maintain cell survival. In terms of the development of cancer, it could be conceived that prior to neovascularization, regions of tumours that lack oxygen and nutrients could be sustained by autophagy linking the process to oncogenesis.

In other contexts, a role for autophagy in the promotion of programmed cell death has been proposed. Although it is no longer widely considered that autophagy is on its own a form of programmed

Cell death and cancer

The cells in our body undergo damage to DNA and proteins on a daily basis. If damage is allowed to persist then these cells can be predisposed to tumour development. Mechanisms exist within the cells to repair damage but if this is not done effectively then cell death pathways are invoked to eradicate the damaged cell. Ultimately this is the last resort for the cell but is beneficial for the survival of the organism. Since damaged cells are frequently eliminated from the body, cell death pathways are considered one of the central mechanisms of tumour suppression and evading these pathways is considered to be one of the key characteristics of most forms of cancer.

Cell death pathways are tightly connected to the major tumour suppressor pathways within the cell. In particular, the p53 tumour suppressor is known to induce cell death in response to multiple

cues including DNA damage, ribonucleotide stress and oncogene activation. Classically, p53 has been considered to induce cell death via apoptotic pathways. Members of the TNF receptor superfamily that are intrinsically connected to the 'extrinsic' cell death pathway are activated by p53 and pro-apoptotic member of the Bcl-2 family are also activated by p53 to induce the 'intrinsic' cell death pathway. p53 and members of these two apoptotic pathways are known to be frequently inactivated in human cancer.

Autophagy and cell death

In addition to apoptosis, other processes within the cell are considered to determine cell viability. One such process that has received considerable attention in recent years, and which is now the main focus of our laboratory, is autophagy. When translated from Greek, autophagy literally means 'Self-eating' (Auto – self, phagy – eating) and is a major mechanism in

cell death, there is ample evidence indicating that autophagy can be a contributing factor in pro-death scenarios in combination with other signals. A dichotomy therefore exists as to the role of autophagy in cancer, since in this context autophagy could be considered a contributing factor in tumour suppression.

p53 and autophagy in cancer

In a search for cell death regulators downstream of p53, our laboratory discovered a previously uncharacterised factor activated by p53 which resides primarily within the lysosome. Our further studies revealed that this factor was critical for the ability of p53 to regulate autophagy and so we named this factor DRAM for Damage-Regulated Autophagy Modulator (Crighton et al. *Cell* **126**(1): 121-134). In line with a role for autophagy in tumour suppression, we also found that while DRAM was unable to induce cell death when expressed alone, it was important for the ability of p53 to induce a complete cell death response. Genome searches for DRAM-related proteins revealed that DRAM, and its ability to modulate autophagy, are conserved in simpler organisms such as *Drosophila*. In addition, we found that DRAM belongs to a new family of proteins with 5 family members in human cells (O'Prey et al. *Cell Cycle* **8**(14): 2260-2265)

Targeting autophagy in cancer

Since autophagy has dual roles in promoting cell death and survival, this caused us to question whether autophagy could theoretically be selectively targeted for tumour therapy. In addition to its role in cancer, it must also be pointed out that autophagy is critical for many processes that protect us against other forms of human disease including neurodegeneration, inflammatory disorders and infection. The question therefore is not just whether we can selectively target oncogenic and not tumour suppressive autophagy in cancer, but whether we can also do it in a way without impact on these other beneficial forms of autophagy in

our normal cells. To address this point, we embarked on a screen in *Drosophila* cells aimed at identifying signalling pathways that specifically regulate autophagy in response to hypoxia – a tumour associated state. Translation of the results from the *Drosophila* screen into human cells revealed that hypoxia-induced autophagy in tumour cells is critically dependent on an autocrine feedback loop involving receptor tyrosine kinases of the platelet-derived growth factor family (Wilkinson et al. *Genes Dev.* **23**(11): 1283-1288). Other forms of autophagy tested were, however, not

dependent on the activity of these kinases indicating that the regulation of autophagy by these factors was selective. Although translation of these findings into a treatment for human cancer is unlikely, this study provided the first proof-of-principle paradigm that the selective targeting autophagy for the treatment of cancer may be distinct and exciting prospect in the years to come.

Kevin M. Ryan, The Beatson Institute for Cancer Research, Glasgow, UK



Pierre Sonveaux

The EACR Cancer Researcher Award Highly Commended

EACR-21

Oslo

The tumour microenvironment, comprising host cells and extracellular components is an attractive anticancer target. As a young independent researcher, my aim is to identify new therapeutic strategies targeting this peculiar environment using basic and translational research.

Our first focus was the tumour vasculature, a heterogeneous network comprising immature and mature vessels. In the past decades, the main approach was to destroy aberrant vessels to starve tumours (anti-angiogenic and anti-vascular therapies). However, considering that tumour perfusion (modulating drug delivery) and tumour oxygenation (impacting radiosensitivity) can be modulated using vasoactive treatments, we have developed an

alternative strategy that we have termed 'provascular'. It consists in selectively and transiently dilating tumour blood vessels at the time of chemotherapy or radiotherapy (reviewed in Sonveaux P. *Radiother Oncol* 2008;86:300-313). Among other treatments, X-rays turned out to induce vasodilation through stimulating nitric oxide production, thus offering a rationale for fractionated radiotherapy. These researches were carried out at the University of Louvain (UCL) under the supervision of Prof. O. Feron.

Our second focus was lactate, the end-product of glycolysis. In solid tumours, we have identified a metabolic symbiosis based on the exchange of lactate between glycolytic/hypoxic tumour cells (that consume

glucose and produce lactate) and oxidative/oxygenated tumour cells (that consume lactate thus sparing glucose). We have further shown that targeting the monocarboxylate transporter MCT1, that we have identified as the main path for lactate uptake, selectively destroys hypoxic tumour cells through glucose starvation (Sonveaux P. et al. *J Clin Invest* 2008;118:3930-3942).

These researches were conducted at UCL (Prof. O. Feron) and at Duke University (Prof. MW. Dewhirst) and are ongoing at UCL with support from the European Research Council (ERC Starting Grant #243188 TUMETABO), the F.R.S.-FNRS, the French Community of Belgium and the Belgian Foundation Against Cancer.

Pierre Sonveaux

EACR Cancer Researcher Award Lecture

This prestigious award lecture is presented annually at the EACR Congress and the European Multidisciplinary Congress

The Award includes 2,000 Euro plus expenses: travel, accommodation and congress fees

The award is open to cancer researchers from European countries with no more than 15 years post doctoral experience

2011 Presentation at
The European Multidisciplinary Congress
23-27 September 2011
Stockholm, Sweden

Carcinogenesis Awards

Oxford University Press is pleased to invite nominations for the seventh biennial *Carcinogenesis* Awards. The awards are presented at the biennial meetings of the European Association for Cancer Research. The next presentation will be at the EACR's Biennial Congress: EACR-22, Barcelona, 7-10 July 2012.

SENIOR AWARD

For major contributions to research in the field of carcinogenesis. The winner will be invited to lecture on his or her work at the EACR meeting and be presented with this award and a prize of \$2500.

Previous winners of the Anthony Dipple Carcinogenesis Award: David Lane, UK (2004), Raymond N. Dubois, USA (2006), Robert A Weinberg, USA (2008), and David Livingston, USA (2010).

YOUNG INVESTIGATOR AWARD

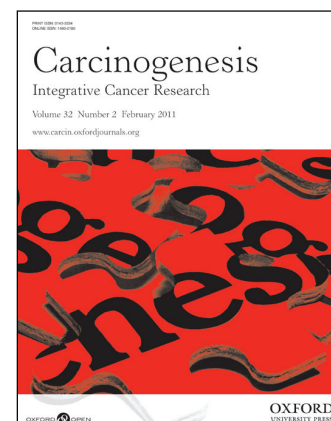
A prize of \$2500 is offered for a recent, significant contribution to carcinogenesis research by an investigator under the age of 40 on 1 July 2011. The winner will be invited to the EACR meeting to give a lecture and be presented with this award.

Previous winners of the Carcinogenesis Young Investigator Award: Maria Blasco, Spain (2004), Manel Esteller, Spain (2006), Victor Velculescu, USA (2008) and Thomas Helleday, UK (2010).

Nominations are now invited for these awards. Please send the name(s) and address(es) of nominee(s) to the e-mail address below by 1 July 2011, together with reasons for the recommendation, details of relevant publications and a curriculum vitae. Self nominations cannot be accepted. The decision making panel comprises the editors of *Carcinogenesis* and members of the Editorial Board. A final decision will be made by the end of 2011.

Address for nominations by 1 July 2011 to:
carcinogenesis.editorialoffice@oup.com

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