

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 ECCO-ESMO Congress

The EACR Cancer Researcher Award Lecture was given in Berlin at ECCO15-34 ESMO by

Fabrizio d'Adda di Fagagna

The feature that follows is based on his lecture



Cancer is a disease of the genes. In a normal cell, the balance between proliferation and quiescence is finely tuned and cell division is induced only if proliferation is required to maintain tissue homeostasis. Differently, tumour cells carry genes' alterations that force them to proliferate in an uncontrolled fashion, ultimately compromising the viability of the whole organism. Oncogenes are the mutated forms of cellular genes that are responsible for driving rampant cellular proliferation. Tumours often carry many activated oncogenes. Recently, we discovered that the expression of activated Ras, a prototypical human oncogene, in normal cells leads to a biphasic response. It induces a transient hyperproliferative phase that is followed by a permanent cell cycle arrest, termed cellular senescence. Senescence is a powerful tumour-suppressive mechanism because of its ability to restrain the spread of oncogene-expressing cells. We also gained some fundamental insights into the mechanisms that control this biphasic response:

cellular hyperproliferation driven by the expression of oncogenic Ras leads to the accumulation of DNA damage and to the activation of a robust DNA damage checkpoint response (DDR) culminating with a cell cycle arrest. DDR inactivation allows oncogene-expressing cells to bypass senescence and to proliferate despite the presence of DNA damage and to become transformed. Oncogene-induced DNA damage generation is the result of profound alterations of the DNA replication process: oncogene activation leads to increased firing of DNA replication origins and to re-replication of genomic DNA. Our findings have been extended by others to several other oncogenes and provide a general paradigm of the impact of activated oncogenes on genome stability.

Historically, the finite capacity of human normal cells to proliferate in culture was first reported by Leonard Hayflick more than forty years ago. Replicative cellular senescence is the term used to define the cell condition induced by proliferative

exhaustion. Senescent cells remain metabolically active and alive for prolonged periods in culture, yet unable to progress through the cell cycle and duplicate. Unexpectedly, a strikingly similar but more precocious proliferative arrest was observed under different circumstances more recently. It was noticed that, while the constitutively activated, and therefore oncogenic, form of RAS, a cytoplasmic transducer of extracellular growth stimuli, efficiently transforms rodent cells when expressed in combination with other oncogenes, its sole expression results paradoxically in a prolonged and irreversible arrest in a range of mammalian cell types with many features of cellular senescence. The discovery of oncogene-induced cellular senescence (OIS) suggested that cell-intrinsic mechanisms respond to oncogene activation. The discovery of Ras-induced cellular senescence was successively confirmed and extended to other oncogenes.

The relevance of OIS in an in vivo setting has been addressed by a

number of independent reports demonstrating that expression of distinct oncogenes or the loss of some tumour suppressors leads to cellular senescence in vivo in murine models and in human skin. Indeed, the discovery that common human naevi are constituted of senescent melanocytes makes the phenomenon of cellular senescence a very common physiological occurrence. Therefore, cellular senescence occurs following oncogenic activation in vivo and it is a tumour suppressive mechanism acting as a gate between a dormant benign lesion and a malignant highly proliferative tumour.

Oncogene activation induces the formation of senescence associated DNA damage foci (SDF), evidence of the activation of a robust DDR, the mechanism responsible for cell cycle arrest following generation of DNA damage. DDR is a signalling cascade initiated by the detection of DNA breaks or exposed single stranded DNA by sensors, which trigger the activation of two large related protein kinases: ATM and ATR. These modify a large number of substrates including signal amplifying kinases. These signals converge on p53 and lead to p21 induction, halting cell cycle progression.

Our results indicate that oncogene activation can be an intrinsically genotoxic event, to which cells respond by mounting a robust DDR and enforce senescence. Consistent with the observation that in vitro oncogene activation leads to DDR activation, the engagement of DDR factors has been observed by us and others in vivo in a number of different tumours. These results indicate that spontaneous in vivo tumorigenesis is associated with DDR activation in the early, dysplastic phase, concomitant to the establishment of cellular senescence. This generates a selective pressure for the inactivation of senescence enforcing pathways, escape from the senescence proliferative inhibition and progression toward full malignancy.



Fabrizio d'Adda di Fagagna receives his award from EACR President Anne-Lise Børresen-Dale

Anchit Khanna
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Protein Phosphatase 2A (PP2A), a widely conserved protein serine/threonine Phosphatase (PSP), has recently been experimentally established as one of the important tumour suppressors in humans. It has been experimentally shown to be a prerequisite for human cell transformation (Westermarck and Hahn, 2008; Janssens et al., 2005). Moreover, dephosphorylation by PP2A of the target molecules which are critical for its tumour suppressor activity, have been recently identified.

Cancerous Inhibitor of Protein Phosphatase 2A (CIP2A), a PP2A inhibiting oncoprotein recently identified by our research group, promotes malignant cell growth and cellular transformation. Additionally, CIP2A was shown to be over

expressed in human head and neck squamous cell carcinomas (HNSCC) and in colon cancer as compared to control tissue (Junttila et al., 2007). However, the mechanisms of regulation and its role in human malignancies are not clear. We have attempted to address these questions by investigating expression and role of CIP2A in gastric carcinogenesis. Over expression of c-Myc has been shown previously to play a contributing role in gastric carcinogenesis. But a majority of the studies are limited to the role of c-Myc amplifications, which in turn holds true for less than 20 % of gastric cancers with c-Myc protein over expression. Therefore, other mechanisms by which c-Myc may play a role are still unknown.

We demonstrate, for the first time, the prognostic role of CIP2A in gastric cancer patients along with its role in promoting cell proliferation and c-Myc stability in gastric cancer cells. Interestingly, we identify c-Myc as one of the first stimulator of CIP2A expression in these cells, thereby establishing a positive feedback mechanism between the two human oncoproteins. Additionally, there is co-expression of both the human oncoproteins in human gastric cancer specimens.

Rolf I Skotheim

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Genome biology of cancer, the research I have been involved with, is mostly concerning investigation of cancer genomes and transcriptomes by integrated computational and laboratory based approaches. The research is carried out at the Department of Cancer Prevention at the Norwegian Radium Hospital, Oslo University Hospital, where I have been working under supervision of Professor Ragnhild A. Lothe, and I am now establishing my own research group in the field of cancer genomics.

Our aim is to identify and characterise critical genes involved in the cancer development. Such genes may serve as diagnostic or prognostic biomarkers and also as targets for future molecularly tailored therapy. Our studies are mainly focused on testicular and colorectal cancer.

Primarily, we seek to discover cancer-specific transcript variants, such as those originating from alternative splicing, alternative promoter usage, and fusion genes. We use methods such as exon level microarrays and high-throughput sequencing. We have also recently published a novel oligonucleotide microarray strategy whereby one can screen for all known oncogenic fusion transcripts in a single experiment (Skotheim *et al.*, Mol. Cancer, 2009). Here, we provided proof-of-principle data identifying fusion genes from a set of leukaemia and prostate cancers. We have continued with the aim of establishing this as a robust tool that can be used to test for an extended set of known and candidate fusion genes in both research and clinical diagnostic settings.



Rolf I Skotheim, Fabrizio d'Adda di Fagagna and Anchit Khanna with EACR President Anne-Lise Børresen-Dale at the award reception

EACR Cancer Researcher Award Lecture 2010

will be given at

EACR-21 in Oslo by

Kevin Ryan

Highly Commended

Pierre Sonveaux



Kevin Ryan



Pierre Sonveaux

EACR Cancer Researcher Award Lecture

This prestigious award lecture is presented annually
at the EACR Conference and ECCO/ESMO 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
ECCO 16 - 36 ESMO Multidisciplinary Congress
23-27 September 2011
Stockholm, Sweden

Deadline for receipt of applications: to be announced via www.eacr.org