EACR Young Cancer Researcher Award

At ECCO-14 in Barcelona, awards were made both to the winner of the Young Cancer Researcher Award Lecture and to members whose submissions were highly commended by the panel.

The EACR Young Cancer Researcher Award Lecture was given in Barcelona by Thomas Hellday

Exploiting cancer-specific DNA lesions to target cancer is based on his ECCO-14 lecture

Exploiting cancer-specific DNA lesions to target cancer

Many anti-cancer drugs are chemically reactive and cause DNA modifications, which result in toxic lesions when the cell attempts to replicate the damaged DNA. There are also many anti-cancer drugs that directly target DNA replication, such as anti-metabolites or inhibitors of enzymes that participate in the replication machinery. Thus, targeting DNA replication is a highly successful current strategy to kill cancer cells.

Recent studies from others and our laboratory suggest that many cancer cells have an elevated level of endogenous replication lesions as compared to non-transformed normal cells. Replication stress in early cancer cells originates from the expression of oncogenes that cause unscheduled initiation of DNA replication. This replication stress leads to activation of DNA damage response pathways involving the Ataxia-telangiectasia mutated (ATM)-Chk2 and the ATM- and Rad3-related (ATR)-Chk1 signalling cascades, which activate a p53 dependent tumour barrier in early cancer cells. Inactivation of the DNA damage response pathway (e.g., p53 mutation) results in evasion of the tumour barrier and continued growth. Under those conditions the cancer cells cannot sense or respond to the DNA replication lesions, which may contribute to genetic instability that further drives the cancer. Our laboratory and many others focus on understanding the replication lesions present in early tumours and the pathways that repair them, with the aim to make these cancer-specific lesions more toxic to specifically kill the cancer cells. Anti-cancer treatments based on this concept are likely a lot less toxic to non-cancerous cells as these do not suffer from oncogene-induced replication stress.

Amplification of endogenous tumour-specific DNA lesions to specifically kill tumour cells can be achieved by inhibition of DNA repair. An example of this is our recently reported use of inhibitors of poly(ADP-ribose) polymerase (PARP) to specifically kill BRCA1 or BRCA2 defective tumours. The efficiency of PARP inhibitors to kill this tumour type is related to the role of PARP in DNA single-strand break repair and the role of BRCA1 and BRCA2 in homologous recombination. In normal cells, efficient repair of DNA single-strand breaks is required to prevent the collapse of replication forks. Homologous recombination is an efficient error-free repair pathway of broken replication forks. Thus, both the DNA single-strand break and recombination repair pathways collaborate to prevent lethal replication lesions.
Heterozygous carriers of a mutation in the BRCA1 or BRCA2 genes have a considerably increased risk of developing breast or ovarian cancers arising from cells that have lost the wild type copy. Cell lines homozygous for either the BRCA1 or BRCA2 mutation are 100-1000 fold more sensitive to PARP inhibitors than the heterozygous or the wild-type cell lines and PARP inhibitors can induce regression only in BRCA1 and BRCA2 defective tumours. Thus, PARP inhibitors are likely to selectively kill tumours, as only they are homozygously mutated in BRCA1 or BRCA2. Phase I clinical trials using PARP inhibitors are completed and phase II clinical trials are commenced with the PARP inhibitors AZD2281 (AstraZeneca, Lund, Sweden) and AG014699 (Pfizer GRD, La Jolla, CA).

Heterozygous carriers of BRCA1 or BRCA2 mutant alleles are currently offered mastectomy and oophorectomy to prevent cancer. Heterozygotes still possess homologous recombination as an error-free backup pathway to repair broken replication forks caused by inhibition of PARP, and it is expected that PARP inhibitors will cause minimal side effects. Indeed, PARP-1 deficient mice are overall very healthy and PARP inhibitors are well tolerated in humans. This raises an interesting potential use of PARP inhibitors as a prophylactic treatment for carriers of BRCA1 or BRCA2 mutations to kill cancer cells before they grow out into tumours. This could be a very good alternative to prevent cancer in those patients that for various reasons decline mastectomy and oophorectomy.

In conclusion, cancer cells likely have high levels of endogenous replication stress, caused by oncogenes or mutations in DNA repair or damage signalling genes. A future challenge will be to find ways to exploit these replication lesions and convert them into toxic lesions that specifically kill tumour cells.

Thomas Hellday
Radiation Oncology & Biology, University of Oxford, UK. Genetics, Microbiology and Toxicology, Stockholm University, Sweden.

EACR Young Cancer Researcher Award 2007
Winner: Thomas Hellday
Highly Commended: Claudia Chiodoni, Monica Fedele, Chris Marine

The EACR Young Cancer Researcher Award Lecture, EACR’s ‘prestigious blue ribbon award’, is presented annually at EACR and ECCO meetings.

It is awarded in recognition of an outstanding contribution in the field of fundamental research in cancer

The 2008 Award Lecture will be given at EACR-20 in Lyon 13.45 -14.35 Sunday 6th July

The award winner will shortly be announced in the EACR e-news bulletin and on the website

Further information about applying for this award can be found at www.eacr.org or please contact the EACR Secretariat
CD40 Triggering: A double-edged sword in Tumour Immunotherapy

Regardless of the recent progress made in terms of preventive care, breast cancer remains the most frequent malignancy in women worldwide. Transgenic mouse models resembling human mammary carcinogenesis are useful tools to investigate the pathogenesis of the disease as well to evaluate possible therapeutic intervention. We have taken advantage of one of such models, called BALB/NeuT, in which the rat activated HER-2/neu (p185) oncogene is expressed under the control of the MMTV promoter and causes the development of spontaneous mammary carcinomas. These mice have been fully characterized during the steps of malignant transformation, from initial lobular hyperplasia to invasive and metastatic lobular carcinoma, a progression that has been similarly described for human breast cancer.

Most solid tumours consist of tumour cells as well as many non-malignant cells, such as immune cells and blood vessel cells that are physiologically involved in inflammatory processes and actively contribute to tumour development and progression. We used the BALB/NeuT model to investigate the role of immune and inflammatory mediators in mammary carcinogenesis. Firstly we have focused on a key factor for the induction of an efficient immune response, the CD40 molecule, which is mainly expressed on B cells, activated dendritic cells and macrophages, but also on non-immune cells such as endothelial cells, fibroblasts, and epithelial cells.

We transferred the HER2/neu oncogene into CD40-null background to obtain the CD40-KO/NeuT strain. Unexpectedly in light of the critical role of CD40 in the immune response, the new transgenic strain showed delayed tumour onset and reduced tumour multiplicity. To investigate the mechanisms behind this attenuated tumour phenotype we performed bone marrow (BM) transplantation experiments that excluded a role of BM-derived cells in the reduced tumorigenicity associated with CD40 deficiency. Rather, these experiments indicated that CD40 expressed by host endothelial cells takes part in the angiogenic process fostering tumour growth.

Moreover we identified activated platelets, which may interact with and activate endothelial cells, as the likely source of CD40L in this model. Indeed treating BALB/NeuT and CD40-KO/NeuT mice chronically with the anti-platelet drug clopidogrel, known to inhibit platelet CD40L expression, we observed a reduction in tumour growth in BALB/NeuT mice to a level similar to CD40-deficient mice, whereas CD40-KO/NeuT mice treated or not showed the same attenuated tumour outgrowth.

These findings sustain the hypothesis of using anticoagulants in combined cancer therapy to prevent platelet interaction with tumour vasculature, but at the same time, revealing an underestimated role of CD40 in fostering tumour neo-angiogenesis, raises a concern on the use of antibodies to CD40 to enhance antitumour immune responses. Stimulation of CD40 may indeed be a double-edged sword, and therefore a careful evaluation of the pros (antitumour effect by means of APC activation) and cons (angiogenesis promotion through EC activation) of CD40 triggering is needed in the design of new immunotherapeutic approaches.

Claudia Chiodoni

The role of the High Mobility Group A (HMGA) proteins in the process of carcinogenesis

My principal field of investigation in cancer research involves the study of the role of the High Mobility Group A (HMGA) proteins in the process of carcinogenesis.

The HMGA are non-histone chromatin proteins highly expressed during embryogenesis but not significantly expressed in adult tissues. They alter chromatin structure and thereby regulate the transcription of several genes by either enhancing or suppressing transcription factors. HMGA proteins are implicated, through different mechanisms, in both benign and malignant neoplasias, behaving as cellular oncogenes. In particular, we demonstrated, through the study of transgenic mice, that they play a critical role in pituitary tumorigenesis, by enhancing the activity of the E2F1 protein. Such a mechanism entails the interaction of HMGA with pRB and the consequent displacement of HDAC1 from the pRB/E2F1 complex.

Now I am focusing my efforts in the identification of genes regulated by HMGA proteins and isolation and characterization of proteins interacting with them. Among the HMGA-interacting proteins, we concentrated on PATZ, another chromatin protein involved in the epigenetic control of gene transcription. Our and others’ very recent functional and genetic data suggest that PATZ might be directly involved in human tumours. In particular, the PATZ gene has been found rearranged and deleted in a Small Round Cell Sarcoma and the chromosomal region where it is located suffers loss of heterozygosity in several solid tumours, suggesting that it may be a tumour suppressor gene. Consistently with these data, knockout mice for the Patz gene, recently generated in our laboratory, spontaneously develop...
Our research unit is interested in the genetic events that contribute to the development of cancer. Much of our research effort stems from our studies on the tumour suppressor and transcriptional regulator p53. This protein functions as a central component of most cellular stress responses and, as such, acts at multiple levels to protect against cancer. A central role for the p53 protein in tumour suppression has been clearly demonstrated by genetic and clinical studies. p53-deficient mice are highly tumour prone and all human cancers have a dysfunctional p53 pathway, either through direct mutation of the p53 gene or through aberrant expression of upstream regulators and/or downstream effectors. In our laboratory, we study those factors that act upstream or downstream of p53 and can influence p53-induced biological responses. Our approach emphasizes genetics, and we often develop and exploit mouse and primary cell culture models to study the function of these factors in vivo.

One of our aims is to search for new putative modulators of the p53 pathway and for genes whose inactivation is toxic only in cells deficient for p53. To this end, RNAi-based genetic screens are performed in mammalian cells. Mouse models are developed to validate the relevance of selected targets. Intercrosses of these mutant mouse lines with various classical and conditional knockout and knock-in alleles of p53 often allow us to establish clear genetic interactions. For instance, we have shown in the past that germline inactivation of Mdmx, a key negative regulator of p53, leads to an embryonic lethality, which is completely rescued on a p53-deficient background. Once such genetic links can be established, experiments are designed to further dissect the molecular mechanisms through which the molecules of interest affect p53 biological activities. The long-term goal of our research is take advantage of our genetic studies in mice to determine how to make chemotherapy agents more effective.

Monica Fedele

Tumour suppressor and transcriptional regulator p53.

As part of their New Year activities the Biosciences division of ThermoFisher Scientific, chose to make a donation to EACR to support the work of the Association in its 40th Anniversary year.

The company’s account manager for the Heidelberg region, Jürgen Huber, is pictured (left) presenting a cheque to Joerg Schlehofer, EACR Treasurer.