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Meeting Report

First EACR Conference on Cell Death in Cancer, Amsterdam, Netherlands, 26–28 January 2012

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As part of the novel initiative of the European Association of Cancer Research (EACR) to support small focused cancer research meetings, the 1st EACR Conference on Cell Death in Cancer was held in January 2012 at De Rode Hoed, Amsterdam, The Netherlands. The excellent scientific program attracted 177 researchers from 34 countries all over the world, including 56 students. The program was completed by two poster sessions covering a total of 95 posters. The conference provided an exciting forum for young researchers and leading scientists engaged in basic, translational and clinical cancer research to discuss key areas of current interest and the latest discoveries in the field. The feedback from speakers and delegates was extremely positive so that we consider this event as a starting point for a series of EACR conferences on Cell Death in Cancer that will be held on a regular basis.

Immunogenic Cell Death

In the first keynote lecture, Guido Kroemer (Villejuif, France) highlighted the role of the type of therapy-induced cell death and the importance of the co-option of the immune system for the outcome of anticancer treatment. Using immunocompetent and immunodeficient mice, he demonstrated that therapy-induced immunogenic cell death of tumor cells improves long-term tumor control by mounting an immune response against residual tumor cells. These findings were corroborated by studies in patients with genetic defects of the innate immune system. An improved understanding of the type of cell death induced by a specific anticancer treatment modality and its impact on the immune system is of utmost importance for the design of efficient treatment concepts for cancer patients.

Patrizia Agostinis (Leuven, Belgium) reported on a novel pathway of ROS-mediated ER stress in response to photodynamic therapy (PDT) that leads to PERK-dependent calreticulin exposure and secreted ATP as crucial damage-associated molecular patterns (DAMPs) to trigger immunogenic cancer cell death. Furthermore, she discussed the interplay between ER stress and ROS signaling in PDT, disclosing a new function for PERK beyond the unfolded protein response (UPR). PERK was identified as an important link of the ER–mitochondrial network that localizes to mitochondria-associated membranes (MAMs), which are required to propagate lethal ROS and Ca^{2+} signals to the mitochondria.

Autophagy, Metabolism and Cancer

In the second keynote lecture, Eileen White (New Jersey, USA) provided new insights into the role of autophagy during cancer development and progression. She presented the findings that Ras expression upregulates basal autophagy and that Ras-driven cancers are dependent on autophagy for survival and for tumorigenesis. This supports the concept that some cancers display autophagy addiction as autophagy compensates for the metabolic reprogramming by, for example, RAS. She proposed that autophagy-supplied substrates, such as amino acids from protein degradation, are required to support the metabolism of mitochondria, without which tumor metabolism and growth is impaired. Preliminary evidence that autophagy functions similarly in genetically engineered mouse models for cancer driven by B-raf^{V600E} or Kras^{G12D} activation in the lung was presented. As a consequence, addiction of cancers with Ras mutations to autophagy opens novel routes to treat these aggressive cancers by simultaneous targeting of autophagy and mitochondrial metabolism.

Examination of the role of autophagy in Kras-mediated tumorigenesis *in vivo* was also presented by Kevin Ryan (Glasgow, UK). He utilized a mouse model of pancreatic cancer to understand the role played by autophagy at different stages of tumor development. The role of autophagy in cancer can conceivably be either pro- or anti-tumorigenic, and his findings highlighted the importance of knowing where, when and in which tumor types autophagy is promoting or impeding

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cancer if we are to fully understand where promoting or inhibiting autophagy would be therapeutically beneficial. In this regard, he also presented data related to the accumulation of DNA damage in autophagy-deficient cells and how this may be one way in which the loss of autophagy could contribute to tumor development.

To gain insights into the mechanisms how cells without a functional tricarboxylic acid (TCA) cycle due to deficiency in fumarate hydratase (FH) can survive, Eyal Gottlieb (Glasgow, UK) and colleagues performed an extensive metabolomics survey and applied a newly developed computer model of the metabolism of these cells to predict and experimentally validate metabolic pathways. FH is an enzyme of the TCA cycle that catalyzes the generation of malate from fumarate, which is mutated in the germline of patients with hereditary leiomyomatosis and renal cell cancer. They identified a compensatory metabolic pathway involving the biosynthesis and degradation of heme to be activated in FH-deficient cells that enables the use of accumulated TCA cycle metabolites and mitochondrial NADH production. Importantly, inhibition of this pathway, for example, by blocking heme oxygenase was synthetically lethal with FH, thus identifying a novel molecular target for cancers with FH mutations.

Apoptotic and Non-apoptotic Functions of Death Receptor Ligands

There has been accumulating evidence over the last years that death receptors and their ligands may exert non-apoptotic functions in addition to triggering cell death. In this context, Seamus Martin (Dublin, Ireland) reported that stimulation of CD95 resulted in the production and release of proinflammatory cytokines and chemokines, including interleukin (IL)-8, TNFα and MCP, in cells of the immune system, which in turn promoted survival and increased colony formation. Inhibition of apoptosis by the addition of caspase inhibitors further enhanced the release of cytokines and chemokines.

Frank Kruyt (Groningen, The Netherlands) reported on the non-apoptotic functions of TRAIL. In TRAIL-resistant lung carcinoma cells, TRAIL was found to increase migration and invasion. Experiments using TRAIL receptor-selective mutants identified TRAIL-R2 as a predominant mediator of these non-apoptotic functions of TRAIL. Kinome profiling revealed a number of TRAIL-induced kinase pathways in resistant lung cancer cells compared with sensitive cells. Their role in TRAIL-induced invasion and in resistance was examined. Inhibition of identified kinase pathways is expected to enhance the therapeutic effect of TRAIL.

Irmela Jeremias (Munich, Germany) showed that treatment with TRAIL of primary leukemic blasts derived from children with acute lymphoblastic leukemia significantly impaired the engraftment of leukemia cells upon serial transplantation in a NOD/SCID mouse model, indicating that TRAIL exerts anti-leukemic activity against leukemia-initiating stem cells. Also, systemic administration of TRAIL increased the survival of leukemia-bearing mice, suggesting that TRAIL is a promising therapeutic agent for the treatment of childhood ALL.

Alternative Cell Death Pathways

Peter Vandenabeele (Gent, Belgium) identified a RIPK1–RIPK3-mediated necroptotic pathway as a critical mediator that drives the lethal systemic inflammatory response syndrome (SIRS). Deletion of RIPK3 conferred complete protection against lethal SIRS, whereas deletion of caspase-3, -7 or -1 had no impact on lethal SIRS. These findings have important implications for the exploitation of potential new therapeutic targets for the treatment of SIRS and sepsis.

Clemens Schmitt (Berlin, Germany) discussed the impact of therapy-induced senescence (TIS) on the long-term outcome of chemotherapy in lymphoma-prone Eμ-*myc* transgenic mice lacking the histone methyltransferase Suv39h1, a senescence-related histone methyltransferase that is essential for the methylation of histone H3 lysine 9 (H3K9).

Targeting Cell Death Pathways in Cancer

Anthony Letai (Boston, USA) showed that the clinical response to chemotherapeutic drugs correlates with mitochondrial priming that means the pretreatment proximity of tumor cell mitochondria to the apoptotic threshold. BH3 profiling, an assay that assesses mitochondrial response to proapoptotic BH3 peptides, was used to determine the priming in tumor cells from patients with multiple myeloma, acute myelogenous and lymphoblastic leukemia and ovarian cancer. Importantly, patients with highly primed mitochondria had a better clinical response to chemotherapy, whereas chemoresistant cases and normal tissues exhibited low mitochondrial priming. This indicates that mitochondrial priming might serve as a biomarker to predict chemosensitivity and that modulation of the mitochondrial threshold to apoptosis might represent a key decision point for the efficacy of chemotherapeutics.

Domagoj Vucic (San Francisco, USA) used a structural and biochemical approach to investigate how the binding of small-molecule antagonists of inhibitor of apoptosis (IAP) proteins to the BIR domain of IAP proteins influences the activity of their RING domain. He showed that the unliganded, multidomain cIAP1 sequesters the RING domain within a compact, monomeric structure that blocks the dimerization of the RING domain. Binding of IAP antagonists triggers conformational rearrangements that promote RING dimerization and formation of the active E3 ligase. These results provide the structural basis how small-molecule IAP antagonists can stimulate autoubiquitination and proteasomal degradation of IAP proteins.

Simone Fulda (Frankfurt am Main, Germany) reported that IAP antagonists can enhance cell death in leukemia cells via two distinct pathways in a context-dependent manner: first, they sensitize apoptosis-proficient cells to caspase-dependent apoptosis. RIP1 was identified as a critical regulator of the synergism of IAP antagonists and chemotherapeutics that mediates the formation of a RIP1/FADD/caspase-8 complex via an autocrine/paracrine loop of TNFα. Second, IAP antagonists prime apoptosis-resistant cells lacking FADD or caspase-8 to TNFα-induced, RIP1-dependent and caspase-independent necroptosis.

Steven De Jong (Groningen, The Netherlands) provided new insights into the molecular mechanisms of cisplatin resistance in testicular carcinoma. Cisplatin-resistant cells exhibited low levels of Oct4 and miR-106b family members, which negatively regulate p21 expression, and corresponding high amounts of cytoplasmic p21, leading to p21-mediated inhibition of CDK2 and concomitant suppression of cisplatin-induced apoptosis. Reversal of cisplatin resistance was achieved by inhibition of Akt, which in turn resulted in nuclear translocation of p21 and in the release of p21-imposed blockage of apoptosis. Alternatively, overexpression of pre-miR-17-5p caused p21 downregulation and increased cisplatin-induced apoptosis.

Verena Jendrossek (Essen, Germany) discussed mechanisms of radiotherapy resistance caused by acute and chronic hypoxia. Moreover, she proposed the use of the radical-forming endoperoxide dihydroartemisinin as a novel strategy to overcome therapy resistance of apoptosis-proficient and apoptosis-deficient solid tumor cells under acute hypoxia and to increase the efficacy of ionizing radiation. Finally, she presented novel potential therapeutic targets for the treatment of chronically hypoxic tumor cells.

Jan Paul Medema (Amsterdam, The Netherlands) discussed the role of cancer stem cells (CSCs) in tumor growth and therapy resistance. In an innovative approach to define colon CSC, he demonstrated that high Wnt activity functionally designates the colon CSC population. In primary cancers, the tumor cells with high Wnt pathway activity were preferentially located close to stromal myofibroblasts, suggesting that Wnt activity could be regulated by the tumor stroma. In agreement, myofibroblast-secreted factors, specifically hepatocyte growth factor, enhanced the CSC phenotype both *in vitro* and *in vivo*. Furthermore, stemness was associated with a metastatic phenotype and resistance to chemotherapy that could, however, be overcome by HDAC inhibitors.

Biomarkers and micro-RNAs

Caroline Dive (Manchester, UK) reported on the clinical significance and molecular characteristics of circulating tumor cells (CTCs) and circulating tumor microemboli (CTM) in patients with small-cell lung carcinoma (SCLC). Notably, baseline CTC numbers as well as change in CTC numbers after one cycle of chemotherapy were identified as new independent prognostic factors for SCLC. Molecular comparison of CTCs to cells in CTM pointed to protection from anoikis and relative resistance to cytotoxic drugs for cells within CTM.

Roya Khosravi-Far (Boston, USA) provided new insights into the interplay of FOXO tumor suppressors and micro-RNAs (miRNAs) regulating or being regulated by FOXOs. Accordingly, the Let-7 cluster of miRNAs and miR-99 were identified as transcriptional targets of FOXO3, while miR-182 was found to act as a negative regulator of FOXO3 transcription factors. These results provide insight into signaling networks involving miRNAs that mediate the tumor suppressive function of FOXO proteins.

Conflict of Interest

The authors declare no conflict of interest.

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