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Meeting Report

14th Euroconference on Apoptosis: 'death or survival? Fate in Sardinia'

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14th Euroconference on Apoptosis (*Death or Survival*): Sardinia, Italy, 29 September – 4 October, 2006.

The 14th Euroconference on Apoptosis was held in *Le Meridien Chia Laguna*, located about 50 km west of Cagliari, the capital city of Sardinia, near some of the most beautiful beaches in Sardinia. The annual European Cell Death Organization (ECDO) meeting, supported by EC within the framework of the Marie Curie Conferences and Training Courses, with strong participation of PhD students together with young/senior postdoctoral fellows, represents an excellent and well-established forum in Europe to discuss the latest results in the field of apoptosis and provides an ideal opportunity for establishing collaboration particularly for young researchers. Moreover, during the meeting, young people are encouraged to present their own work in terms of poster presentations and/or short talk, representing educational encouragement for their 'scientific growth'. In addition, participation of eminent researchers from all continents is a guarantee of the quality of science.

The first day was dedicated entirely to a training course aimed at summarizing the DNA damage checkpoints and cell death (Jiri Bartek), caspase biology and function (Sharad Kumar), the role of mitochondria (Jean-Claude Martinou) and endoplasmic reticulum (ER) stress (Randal J Kaufman) in cell death, together with the introduction of new technology applied to study dying cells: proteomics (Kris Gevaert). The training course was concluded by an overview on the new and attractive field of apoptosis represented by the role of autophagy: killer or preserver? (Eric Baehrecke).

The 14th ECDO Euroconference was opened by the keynote lecture given by Paolo Comoglio who presented a high profile overview on his seminal work on the regulation of cancer by the Met receptor family. In his brilliant talk, Professor Comoglio highlighted the complex biology regulated by this receptor, encompassing all the signaling pathways that may lead to cell spreading vs apoptosis and in some instances to proliferation.

p53 Family, DNA Damage and BH3-only Proteins in Cancer Malignancies

G Melino examined the role of the p53 family member p63 in the development of both skin and thymic epithelia formation. In particular, he explored the role of the two proteins encoded by the TP63 gene: TAp63 (with the N-terminal transactivation domain) and ΔNp63 (lacking the transactivation domain). While ΔNp63α complementation (a double ΔN/TA complementation) allows a degree of basal layer formation in both skin and thymus, TA complementation does not. However, TAp63α may direct epithelial differentiation subsequently and synergistically to ΔNp63α. The role of the key DNA damage-response molecule Nbs1 in Nijmegen breakage syndrome (NBS) was shown by Zhao-Qi Wang. Mice carrying mutated Nbs1 show a combination of the neurological anomalies of NBS, including microcephaly, growth retardation, cerebellar defects and ataxia, strongly supporting the hypothesis that the DNA damage-response pathway, including DNA repair, plays an important role in the phenotypes associated with these syndromes.

Maria Balakirela pointed out the role of Ral in oncogenesis using *Drosophila melanogaster* as an *in vivo* model. As cancer cells have to sustain proliferative signals and counteract pro-apoptotic signals, Ral may contribute to cell escape from proapoptotic signals through inhibiting c-Jun N-terminal kinase activation and inducing the p38 MAP kinase pathway. Carla O'Connor focused on the molecular function of XIAP in the mitochondrial apoptotic pathway involving MOMP (mitochondrial outer-membrane permeabilization), demonstrating that physiological concentrations of XIAP do not restrict effector caspase activity but delay effector caspase activation.

The relationship between p53 and intracellular reactive oxygen species (ROS) accumulation was reported by Peter M Chumacov, who showed that physiological levels of p53 are sufficient for maintaining relatively low intracellular levels of ROS, while p53 loss results in accumulation of intracellular ROS resulting in DNA oxidation, increased mutation rate and

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genome instability. Thus, antioxidant function of p53 plays a substantial role in its tumor suppressor function. Like p53, many other players of the apoptotic pathway are involved in both cell death and cell growth/senescence as Raf-1. In fact, Manuela Baccarini demonstrated that Raf-1 has a kinase-independent function in migration and, in particular, in Fas-mediated apoptosis, based on its ability to inhibit by physical interaction other serine/threonine kinase resulting in Fas signaling repression. In contrast, Raf-1 regulates terminal differentiation in erythroblasts by inhibiting Fas expression. These data identify Raf-1 and Fas as key molecules whose expression finely tunes both apoptosis and erythropoiesis.

Interestingly, a different form of cell death characterized by mtDNA mutations was observed by Anna Maria Porcelli in which no DNA degradation or caspase activation were detected, even if several cellular proteins underwent proteolytic destruction, and the process was abolished by Bcl-2 overexpression. Another 'unconventional' type of cell death may be represented by keratinocyte terminal differentiation where classical apoptotic caspases are not activated and where, instead, caspase 14 activity may play a key role, as reported by Wim Declercq.

Andreas Strasser discussed the role of BH3-only proteins in apoptosis induced by different stimuli, and in several apoptotic pathways. Moreover, as BH3-only proteins play key roles in anti-cancer therapy-induced cell death, their activation may represent a target for new anti-cancer drug development. Alan Gross reinforced the role of a BH3-only protein, BID, as an essential mediator of the TNFα/Fas death–receptor pathway *in vivo* by triggering a mitochondrial apoptotic program and emphasized that Mtch2 may represent an excellent candidate for the regulation of apoptosis triggered by tBID at the mitochondria. Another new Bax interactor was presented by Lorainne E Kerr who identified nucleophosmin as a protein that specifically binds to the activated C-terminal tail of Bax. Furthermore, Patricia Rigou described a new Apaf-1 interactor, AAP, able to potentiate Apaf-1-dependent, but not Apaf-1-independent cell death.

ROS, Neurodegeneration and Survival Pathways in Cancer

Piez Giuseppe Pelicci highlighted the complex biological network controlled by Shc, focusing on the involvement of this intriguing molecule on the aging process.

Guido Kroemer presented the latest data regarding the immunogenicity of cancer cell death. He showed that anthracyclins, capable of eliciting an anticancer immune response, are able to induce specifically translocation of calreticulin to the cell surface, suggesting a possible new strategy for immunogenic chemotherapy.

Christian Frezza and Tomas Rudka gave an account on the distinct functions of OPA1 and the OPA1-related protein PARL in mitochondrial fusion and in cristae remodeling during apoptosis, where as Pierre Vanderhaeghen proposed that epherin, a gene family implicated mainly in several developmental and apoptotic processes, can control different functions depending on the cellular context. In contrast, RS Slack discussed the physiological function of apoptosis-inducing factor (AIF), showing that mitochondria-anchored AIF is physiologically involved in controlling mitochondrial structure and cristae remodeling.

By electron microscopy in *Drosophila melanogaster*, Viktor Takàcs tried to correlate autophagy malfunction to neuronal loss observed in neuronal degeneration typical of human disorders like Alzheimer's, Huntington's and Parkinson's diseases. Using another approach, Michael Blank investigated the mitotic catastrophe, a poorly defined form of cell death, depicting a functional link between the induction of DNA damage and such mitotic abnormalities.

Because evasion from apoptosis represents a hallmark of cancer, the identification of anti-apoptotic pathways may represent a new anti-cancer strategy. In this respect, John Blanis presented an RNA interference approach to systematically screen the kinase and phosphatase components of the human genome. Intriguingly, he identified several new survival kinases together with a subset of phosphatases with tumor-suppressor-like activity. The development of inhibitors for these enzymes may represent a new anti-tumor strategy. Moreover, Silvia Cursi demonstrated that aberrantly activated Src mediates caspase-8 phosphorylation at Tyr380 resulting in impairment of Fas-induced cell death in human colon cancer. In the same context, Delphine Mèrino showed that DcR1 and DcR2 are able to bind DR4 and DR5 respectively, inhibiting TRAIL-mediated apoptosis.

Cell Death and Inflammation Pathways

Frank Madeo showed that yeast represents a very useful model to study cell death regulation, presenting new data on AIF roles in cell death and in mitochondrial physiology.

Guillermo Velasco presented new insights on the potential application of cannabinoids in antitumoral therapy. The observed antitumoral actions of cannabinoids rely, at least in part, on the ability of these compounds to induce apoptosis of tumor cells. The data presented demonstrated that cannabinoids are able to induce the expression of the stress-related protein p8 in several tumor cell lines. Moreover, p8 mediates its apoptotic effect by inducing ER stress. The role of PACS-2 during ER stress-mediated apoptosis was investigated by Thomas Simmen, who described the interaction between PACS-2 and several ER-related proteins such as calnexin and members of the TMX protein family. PACS-2 also regulates ER-localization of BAP31, whose p20 caspase cleavage product promotes mitochondrial fragmentation. These data highlight a possible link between ER protein folding and apoptosis induction during ER stress. Although the mammalian and plant apoptotic pathways have been relatively well characterized, at present, less information is available about cell death in the fungus kingdom. Some new data on this field were presented by Diana Brust, who identified by *in-silico* analysis several putative apoptosis factors such as metacaspases, AIF and AMID (AIF-homologous mitochondrion-associated inducer of death) homologs.

In a further demonstration of a link between autophagy and apoptosis, Sharon Reef showed that the well-characterized apoptotic-related gene p19ARF has a novel isoform of p19 named smARF, which induces autophagy and is linked to the ATG5-Beclin-1-mediated autophagic pathway. A new

autophagy-related gene known as Ambra-1 was presented by Mauro Piacentini. Ambra-1 can interact with Beclin-1 and seems to be implicated in nervous system development/remodeling during embryogenesis.

Since loss of cell–cell contacts is an important step of apoptosis, it is believed that to ensure a fast and efficient detachment of a dying cell, components of cell–cell contacts have to be cleaved. This hypothesis has been supported by data discussed by Saska Ivanova on the caspase-mediated cleavage of membrane-associated guanylate kinases (MAGUKs) during apoptosis execution. On the contrary, Helena Paidassi presented data demonstrating that the C1 complex of complement (C1q) is able to bind phosphatidylserine (PS) on the apoptotic cell surface and may represent the major PS ligand. The C1q–PS interaction takes place at early stages of apoptosis and may represent the well known but less characterized 'eat me' signal.

The last speaker Naohiro Inohara overviewed the role of nucleotide oligomerizaton domain (Nod) proteins in pathogen responses and cell death. The great potential of the Nod family members and their importance in biology and medicine has also been the topic of the ECDO honorary lecture given in 2006 by Jurg Tschopp. In his fantastic plenary lecture, Jurg Tschopp has emphasized how basic science linked to clinical practice now, highlighting the possibilities of controlling inflammation using knowledge derived by basic biological studies on the NALP3 gene product and its regulation of the inflammosome.

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