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Meeting Report

13th Euroconference on apoptosis

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13th Euroconference on Apoptosis: Danubius Thermal and Conference Hotel Helia, Budapest, October 1–4, 2005.

Survival on the Danube. This slogan was chosen for the 13th Euroconference on Apoptosis in Budapest. The choice was motivated by several reasons. *First*, the city of Budapest situated at the cross-roads of ambitious nations has survived many wars and fierce battles during the centuries. Still, the spirit of people living here, the rich history, the art and cultural attractions has made the city one of the most charming and attractive capitals of Europe to visit. *Second*, ECDO and the Euroconference on Apoptosis have survived 13 years of existence; not only that, it prospers better than ever. The European apoptosis research community are all grateful to Michel Lanotte and Tom Cotter who started the Euroconferences organizing the first two in Paris and Kinsale and obtaining funds from the EU – with the help of the European Society of Hematology – also for the next four ones in Cuenca, Capri, Bingen and Stockholm. After these very successful conferences, ECDO had to proceed on its own resources, and with the efforts of our colleagues in Israel (Ein Geddi), Switzerland (Davos) Austria (Vienna) and France (Paris), we reached the 10th Euroconference. This was followed by the legal restructuring of ECDO and another successful EU application, bringing us to the Ghent and the Chania meetings and finally to Budapest. The rich series of apoptosis meetings clearly shows that apoptosis research has been very strong in Europe for the last 13 years, and we all are sure that it will be increasingly influential during the coming years. Third, perhaps it has never been so clear how much the pro- and antiapoptotic mechanisms are intertwined in cells. The same molecules might be involved in both the induction of the cell death and cell proliferation or survival, depending on the cell type or local milieu. As it was shown by a number of lectures and posters at the conference, the survival mechanisms in cells have recruited many of the biochemical systems, which have been originally selected for other purposes in diverse metabolic and signaling pathways, and in endocrine, neuronal or transcriptional regulation. Survival and death are two opposite fates of cells, often played out by the same molecular machinery of which more and more details have been revealed during the years covered by Apoptosis Euroconferences.

The Training Course

The 13th Euroconference on apoptosis, continuing the tradition initiated a year before, was preceded by a Training Course on 'Concepts and Methods of Programmed Cell Death'. Similarly to last year, there was great interest in the training course; we hosted 150 participants, mostly Ph.D. students, but also young postdoctoral fellows, emphasizing the need of giving guiding talks to young scientists on various aspects of this rapidly developing scientific field. The training course aimed at coverage of model systems and methodological aspects of apoptosis. First, the animal experimental models were introduced with the focus of showing how these models helped us to understand the molecular programs of apoptosis. Then, the methods that can be used for apoptosis and cell death studies were summarized. *Natalie Franc* gave an excellent overview of the *Ceanorhabolitis elegans* and the *Drosophila* systems emphasizing how very important these animal systems were in proving the existence of cell death genes. *Francesco Cecconi* painted a nice picture about our present understanding of the genetic pathways that regulate cell death in the mouse as we understand them by integrating the transgenic and knockout as well as knock-in data. In the methodological part, *Walter Malorni* spoke about the importance and details of the morphological techniques, *Marie-Lise Gougeon* summarized how flow cytometry can be applied for analyzing apoptosis in mixed cell cultures, whereas *Boris Zhivotovsky* gave an excellent overview about the *in vitro* and *in vivo* biochemical techniques with the help of which we can detect cell death. Finally, *Ian Dransfield* reviewed methods for the detection of phagocytosis of apoptotic cells. For the first time, these lectures have been put on the ECDO website (www.dmbr.ugent.be/ecdo/) and can therefore be accessed by the young researchers as they need.

Oxidative Stress, Genomic Instability

Stuart Lipton has demonstrated that overstimulation of glutamate receptors, that has been implicated in a final common pathway contributing to neuronal injury and death in

a wide variety of acute and chronic neurologic disorders, is coupled to free radical formation including NO. As a result some proteins are *S*-nitrosylated, and this reaction can mimic the effect of genetic mutations. *Boudewijn* Burgering pointed out that forkhead box O (FOXO) transcription factors are negatively regulated by the food availability/insulin signal-transduction pathway. Activation of FOXO in *C. elegans*, however, is associated with a longer lifespan. It seems that aging, oxidative stress and nutritional availability are associated phenomena and converge at the level of FOXO transcription factors. In addition to FOXO transcription factors, c-raf also protects against oxidative stress by maintaining mitochondrial Ca^{2+} homeostasis as reported by *Christine Doblander-Gruber*. *Lucy Elphick* added further evidence to the theory that oxidative neuronal cell damage results in cell cycle arrest and calpain-mediated cells death.

As illustrated by the experiments of *Maria Castedo,* genomic instability and apoptosis are intimately linked phenomena with important implications for the pathophysiology of cancer. She showed that chromosomal and microsatellite instability cause inactivation of proapoptotic pathways in colon carcinoma cells. *Simone Fulda* reported that the loss of caspase-8 occurs in the majority of neuroblastomas, and is not restricted to advanced disease stages as suggested previously. Her data have also challenged the previous concept of MYCN-driven inactivation of caspase-8 in advanced neuroblastoma. It was demonstrated by *Peter Daniel* that multiple, consecutively involved p53 pathway components such as p53/Bax or p53/APAF-1 or multiple BH3-only proteins such as Nbk/Bim must be disrupted to yield a poor prognosis cancer phenotype. He also suggested that cellular senescence does not appear to be a desirable therapeutic goal in cancer, especially in apoptosis-deficient tumors where escape mechanisms facilitate clonogenic survival and clinical relapse. A novel mechanism by which Bcr-Abl can promote cell survival and prevent apoptosis was reported by *Roya Khosravi-Far*: oncogene-induced downregulation of the proteasomal pathway involving downregulation of FOXO3a and consequent degradation of components in the extrinsic as well as intrinsic apoptotic machinery, thus allowing transformed hematopoietic cells to evade apoptosis. *Vicente Planelles* provided evidence that the cell cycle arrest and apoptosis induction mediated by the HIV-1-encoded vpr gene are initiated at a common signaling node, which involves the ATR, BCR-1 and GADD45α.

Variations on Death and Survival Themes

Among the transcription factors that protect against death, NFκB plays a central role. It can promote the upregulation of the ferritin heavy-chain molecule and thus suppresses the formation of ROS. However, it can also induce the transcription of GADD45β that inhibits the c-Jun-N-terminal kinase pathway as reported by *Guido Franzoso*. Interestingly, although apoptosis is thought to be inhibited by NFκB, caspases-1, -2 and -8 are themselves able to activate NFκB as discussed by *Peter Vandenabeele*. According to *Arturo Sala*, in neuroblastoma cells ApoJ/clusterin seems to be involved in the regulation of NFκB activity. NFκB is also activated, as reported by *Dirk Brenner*, in T cells by the haematopoietic protein kinase 1 following T-cell receptor (TCR) stimulation resulting in protection of T cells against the TCR-induced death. Interestingly, two lipid-derived molecules, which themselves are apoptosis inducers for the immature thymocytes, also inhibit TCR-induced death of thymocytes. The effect of glucocorticoids is mediated via GILZ, whereas that of retinoids is mediated via the nur77 transcription factor as reported by *Carlo Riccardi* and *Zsuzsa Szondy*, respectively.

Cleavage of RasGAP by caspases can also influence the fate of the cells as reported by *Christian Widmann*. Upon mild caspase activation, RasGAP is cleaved providing an N-terminal fragment that protect cells against apoptosis by activating AKT. If caspase activity increases, however, this fragment is further cleaved annihilating its protective capacity. A protective mechanism that rescue B cells from apoptosis during antigen-dependent selection is mediated by the inner mitochondrial protein PRELI as described by *Morgan McKeller*.

Regulation of caspase activity by caspase inhibitors is still an important regulatory mechanism by survival stimuli. Survivin, in addition, also plays an essential role in the regulation of microtubule dynamics by enhancing microtubule stability during metaphase transition—as discussed by *Dario Altieri*. The mechanism of IAP action differs from molecule to molecule—reported *Pascal Meier*. Although XIAP acts as an enzyme inhibitor binding to the catalytic active pocket, DIAP and cIAP work by modulating caspase molecules in an indirect manner.

The antiapoptotic bcl-2 family members are also well-known potent inhibitors of apoptosis. In hepatocytes, for example, the alpha 1B adrenergic signaling pathway, which involves tissue transglutaminase as a G protein, is activated during hepatic regeneration. This pathway upregulates bcl-xL, as reported by *Zsolt Sarang*. In prostate cancer cells, on the other hand, some antiapoptotic signaling pathways converge on Bad as shown by *George Kulik*. Interestingly, in pancreatic β-cells Bad also integrates glucose and antiapoptotic signaling as demonstrated by *Nika Danial*. Although phosphorylated Bad promotes mitochondrial glucokinase activity and is involved in glucose-regulated insulin secretion, dephosphorylated Bad mediates apoptosis. According to *Craig Thompson*, the requirement of efficient energy-producing metabolic pathways for cell survival is directly enforced by prosurvival members of the bcl-2 family proteins. He showed that Bcl-xL activates IP_3R channel gating in the endoplasmic reticulum, making it 100 times more sensitive for the release of Ca^{2+}, which subsequently stimulates ATP production in the mitochondria. Cells can remain alive for a long time after the loss of extrinsic survival signals by mobilizing internal energy sources through autophagy but finally die by necrosis. This hierarchy of cell death forms was also recognized by *Eileen White*. Under ischemic conditions, death of tumor cells that had lost their capacity to undergo apoptosis might be still maintained by initiating autophagy. However, activation of AKT inhibits autophagy and leads to necrosis.

Autophagy, Anoikis, Ways of Clearance

Autophagy was further discussed in several other talks. *Eeva-Liisa Eskelinen* introduced lysosome-associated membrane protein 2 (LAMP-2) as a protein required for the maturation of autophagic vacuoles, Rab7 delivery and cholesterol traffic. *María Isabel Columbo* presented evidence that members of the Rab family of GTPases, Rab7 and Rab24, are involved in the autophagic pathway. Interestingly, autophagy-related proteins, such as Atg5 when cleaved, might act as molecular switch by promoting apoptosis as demonstrated by *Hans-Uwe Simon* Anoikis. Another form of cell death, however, was found to be Bax dependent, as reported by *Andrew Gilmore*. Autophagy can also be initiated also following/during anoikis, as reported by *Goran Petrovski*, and both cell types of dead cells can be taken up by professional macrophages or by their surviving neighbours. Phagocytosis was also investigated in the work of *David Ucker*, who found that engulfment of apoptotic cells produced a profound anti-inflammatory effect by immediately inhibiting proinflammatory cytokine formation. The ability to recognize and respond to apoptotic targets appears to be ubiquitous among cells of all lineages and is conserved widely between species.

For the induction of apoptosis, several new pathways have been implicated. *Bernard Gillisen* suggested that Nbk localized in the ER induces apoptosis in a Bax-dependent, Bak-independent manner, and the communication between ER and mitochondria may be mediated via caspase-8. DNA damage, on the other hand, as shown by *Helin Vakifahmetoglu*, is mediated via the PIDDosome complex. According to *Valerian Cagan*, cytochrome *c* can participate in catalytic redox interactions with cardiolipin, which is required for the release of proinflammatory factors from the mitochondria. As reported by *Richard Flavell*, the presence of effector caspases is also required for the execution of apoptosis. Although caspase-7-null mice have only mild apoptotic deficiencies, the caspase-3/7 double-knockout mice are embryonically lethal.

Keynote Address and the ECDO Award

In his keynote address, *Vishva Dixit* introduced the inflammasome as a dynamic caspase-1-activating apparatus. The influence of the adaptors ASC, Ipaf and RIP2 on caspase-1 activity and IL-1β activation was evaluated in knockout mice. ASC was found to be essential for the activation of caspase-1 to Toll-like receptor stimulation and ASC-null mice were resistant to LPS-induced endotoxic shock and death. In addition, ASC-null mice were protected against the *Salmonella typhimurium* infection. The presence of ASC, however, proved to be protective against tularaemia infection.

The 2005 ECDO award was given to *Peter Krammer* for his fundamental discoveries and achievements in apoptosis research and for his outstanding contributions to establishing ECDO as well as serving as one of its previous presidents. In his honorary lecture, it was suggested that Annexin I might be the molecule that mediates the anti-inflammatory effect of apoptotic cells. He also found that the induction of FasL in T cells following TCR stimulation is mediated by H_2O_2 produced by Complex I and the increase in the cytosolic Ca^{2+}. Tat, a HIV protein can replace the oxidative signaling pathway promoting FasL-induced apoptosis in HIV-infected individuals providing a possible new therapeutic approach for AIDS patients.

Is 13 a Lucky Number for Apoptosis Research?

In many countries, 13 is considered to be an unlucky number. However, we did not take it as a discouraging sign and decided to invite the apoptosis research community to enjoy a hopefully memorable 13th get together in Budapest. Many came, and the important highlights of the Conference were manifold. In general, there were lots of discussions in response to the talks. The organization of the breaks and the meals in a stimulating and informal environment added to the many contacts scientists were able to establish during the course of the conference. The farewell dinner accompanied by good music, a traditional Hungarian dance performance and final discussions of the most important topics took place on a boat cruising beside the historical and beautiful buildings of Budapest and gave us the impression that apoptosis research will survive for many decades ahead.

Acknowledgements

As organizers, we are very glad that more than 250 posters were brought by colleagues to the conference providing a wide spectrum of new findings and making the scientific level and atmosphere unique. The support of the EU Marie Curie program and the University of Debrecen is highly appreciated. The conference would not have been so successful without the expert assistance of Diamond Congress Budapest and the ECDO Secretariat.