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Meeting Report

Mechanisms of Cell Death 2000

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Mechanisms of Cell Death, Escorial, Spain, 6–10 May 2000

On May 6–10, 2000 The International Cell Death Society held its third biannual meeting, its first in Europe, on Mechanisms of Cell Death, organized by Zahra Zakeri, Richard A. Lockshin and Carlos Martínez-A, in Escorial, Spain. The over 300 participants heard presentations covering diverse viewpoints on control and mechanisms of cell death. The speakers included both junior (55%) and senior (45%) scientists with 42% women. The attendees were 47% post-doctoral and graduate students. The broad perspective covered six sections: Development and Aging; Extracellular Signaling; Cell Death in Disease; Cellular Signaling; Cell Survival; and Proteolysis, ending with a workshop on phagocytosis.

The theme of the meeting was perhaps best expressed by a quotation used to open the meeting,

> 'Truth does not become more true by virtue of the fact that the entire world agrees with it, nor less so even if the whole world disagrees with it' (Maimonides).

Many of the speakers either challenged ideas that recently dominated the field, or elaborated and nuanced ideas that previously were considered to be straightforward.

Initiation of cell death remains as complex a question as ever. Numerous promoter sites for the *Drosophila* gene, *reaper*, indicate very complex regulation (Abrams). In AIDS, there is a complex balance between host-driven pro-apoptotic and virus-driven anti-apoptotic forces (Cossarizza) and a dysregulation of cytokines (Gougeon). Several researchers identified specific gene products potentially responsible for activation of apoptosis, some of which were previously unsuspected. The role of mitochondria in apoptosis is more complex than previously appreciated and was addressed at several levels. At the molecular level, Kroemer demonstrated that Bcl2 could inhibit a liposome-embedded Permeability Transition Pore Complex. Martinou considered that Bax can release cytochrome *c* but also can act by a secondary mechanism. Several other issues were raised when the role of mitochondria was addressed at a cellular level. Bcl2 and bax differed in their capacities to localize to different compartments, indicating that their functions in intact cells could differ from strictly biochemical measurements (Borner). Tolkovsky argued that the death commitment point, distinct from other steps of apoptosis, was established by the physical, autophagic, loss of mitochondria: Depolarization of only a subset of mitochondria could initiate the apoptotic program (D'Herde).

The most rapidly changing subject proved to be the means of activation and functions of the caspases, and the relationship of caspase-dependent to caspase-independent death. Several researchers suggested functions other than apoptosis for caspases. Hardwick found that proteolysis converted anti-apoptotic proteins into pro-apoptotic proteins, thus guaranteeing the launching of apoptosis. Roy contended that the dormancy of caspases is controlled by a DDD (Asp-Asp-Asp) 'safety catch' sequence in caspases. Caspase 8 was shown to correlate inversely with tumor radiosensitivity (Zhivotovsky). FLIP inhibits casp8 (Thomé) and HSP72 blocks casp3 activation (Anderson). Jäätellä reported the intriguing finding that depletion of HSP70 (by antisense mRNA) activated a tumor-specific death program, which was independent of caspases and bypassed bcl-2. Several researchers raised the issue of other biological functions of caspases. Apaf1 and caspase 9 are important in tumor development (Soengas). Woo, looking at casp3 knockouts, demonstrated a role for casp3 in proliferation, perhaps by downregulating p21. Silke, using a novel screen in yeast, found that XIAPs inhibit UV-induced apoptosis, a surprising finding because they were supposed to act at a downstream point.

Although most researchers consider caspases to be the only proteases involved in apoptosis, destruction of extracellular matrix by matrix metaloproteinases and stromelysin is an extremely important part of autophagic death in tadpole metamorphosis (Shi; also noted by Linden) and granzyme B can produce reactive oxygen substances and $\Delta\Psi_m$ without the participation of caspases (Greenberg). Torriglia, studying differentiation of lens, found that cleavage of leukocyte elastase inhibitor (LEI) achieved a double purpose: it relieved inhibition of a serine protease; and it turned LEI into L-DNase II, which is involved in degradation of the DNA. Roberg found that, in oxidative stress-induced apoptosis, lysosomal destabilization preceded mitochondrial changes, and pepstatin, an inhibitor of cathepsin D, blocked progress of apoptosis. Cells aged *in vitro* are marked by induction of lysosomal enzymes rather than enzymes associated with apoptosis (Hubbard and Zakeri). Bursch, arguing that autophagic death differed from chemical apoptosis, emphasized that autophagic death requires ATP, is specific for elimination of different types of organelles, and requires extensive involvement of the cytoskeleton.

The meeting was one of the first to emphasize phagocytosis, both in the primary meeting and in the following workshop. Plants, lacking phagocytosis, use

internal lysis by many hydrolases to eliminate cells, which nevertheless show some signs of apoptosis such as positive TUNEL assay (Jones). In PC12 cells, DOCK180 triggers phagocytosis (Birge). The *Caenorhabditis* phagocytosis gene *ced6* is highly conserved, with homologues found in the human genome (Hengartner). The cytoskeleton is important in phagocytosis (Abmayer), who finds that the myoblast fusion gene, *myoblast city*, also functions in apoptosis and transformation; and actin rearrangements are important for phagocytosis (Chavrier). Similarly, Leverrier, activating macrophages in culture, finds involvement of cytoskeleton and Rho GTPases. Energy, particularly the ATP-dependent transporter cassette ABC1 was emphasized by Chimini. Reutelingsperger developed a technique to detect exteriorized phosphatidylserine (PS) *in vivo*, rendering it possible to assess size of an infarct in living patients. Nevertheless, several researchers considered that the role of PS was still incompletely understood.

There were 177 posters, from which five were selected for prizes. The winners were Buzzard KA *et al*, 'Regulation of stress-induced apoptosis by HSP72'; Claveria C *et al*, 'Drosophila GRIM induces apoptosis in mammalian cells'; Lane JD *et al*, 'Caspase-dependent cleavage of cytoplasmic dynein intermediate chain during apoptosis arrests microtubule-based membrane movement'; Manji GA *et al*, 'BIR1 and BIR2 motifs of baculovirus OpIAP have distinct activities'; and Torcia M *et al*, 'Nerve growth factor inhibits apoptosis via inactivation of p38 MAPK, prevention of Bcl-2 phosphorylation and cytochrome *c* release'. The proceedings of the meeting will be published as an annal of the New York Academy of Sciences. The meeting was supported by the National Institutes of Health and The European Commission, with further support from Queens College of CUNY, St. John's University, BD-Biosci, Biocolor, Biomol, Intergen, Merck, the New York Academy of Sciences, Nexin, Pharmacia, R&D Systems, Sociedad Iberoamericana de Informacion Cientifica, and Nature. The next ICD meeting is tentatively scheduled for May 2002 in Europe. All are welcome.