Cell Death and Differentiation (2002) 9, 1158–1159

www.nature.com/cdd

Meeting Report

Calabria: sun, sand, and cell death

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Cell Death and Differentiation (2002) **9,** 1158–1159. doi:10.1038/sj.cdd.4401100

The VI Workshop on Apoptosis in Biology and Medicine, Parghelia, Calabria, Italy, 25–29th May, 2002

With the last vestiges of winter still hanging on in northern Europe, a group of international researchers enjoyed the sun and sand of southern Italy at the VI Workshop on Apoptosis in Biology and Medicine. This conference, held in the lovely Calabrian costal town of Parghelia on the 25–29th May, 2002, brought together around 30 scientists and 30 PhD students to share results and ideas on topics ranging from basic mechanisms of neuronal cell death to immune-modulation in the nervous system, and from experimental models of neurodegenerative diseases to novel pharmacological targets and therapeutical interventions. Organized as a PhD training course on 'Pharmacology and Biochemistry of Cell Death', the meeting provided lively discussions during the morning sessions and intense interactions with young scientists presenting posters during the early afternoon. The winning combination of a beautiful setting, a relaxed atmosphere, fresh ideas from the PhD students and plenty of time to discuss results combined to provide an excellent idea-sharing environment, and, overall, a very successful meeting. What's more, Dr. Freda Miller (Montreal) was shocked to learn that an entire Canadian television crew, tired of the endless Canadian winter, had stowed away in her luggage! Actually, a Canadian television channel was in the process of producing a documentary on Dr. Miller's work, and the crew had cleverly convinced its superiors to pay for their Italian vacation so that they could document Dr. Miller's Italian vacation. In all seriousness, with biologists getting more bad press than good lately (think human cloning, the stem cell debate, etc.), the initiative to document the life of a hard working scientist, particularly a woman scientist, was much appreciated. Regardless, all proceedings were exhaustively documented for posterity, and all the participants who were NOT Freda Miller were left vying to make enough of an impression to survive the final edit and earn a cameo on Canadian TV. A brief summary of presentations follows:

The highlight of the first full day of proceedings was the provocatively-named presentation series on 'The immune and nervous system; a dangerous liaison', which was in turn highlighted by the work presented by Dr. Adriano Aguzzi (Zurich) on prion disease.[1] In studies of murine prion disease it is suggested that synapses and axons degenerate, i.e. undergo apoptosis, evoking an anti-inflammatory profile in the resident microglia indicative of phagocytosis of cellular material. This process is believed to balance perpetuation of inflammation and cell demise. Histological damage associated with prion disease is absent in mice that are deficient in the normal prion protein. It is now concluded that certain components of the immune and complement system play important roles in pathogenesis and, interestingly, that transgenic expression of an anti-PrP antibody heavy chain suffices to confer antiprion protection in mice. It is hoped that these findings will open the way to the development of vaccines.

On Day 2, with the cameras whirring away, Freda Miller took the podium to deliver the findings that have made her a TV superstar, and Gerry Melino (Rome) followed her with a related talk already buzzed as a contender for the 'Best Supporting Actor' Emmy.[2–4] Both researchers presented findings on neuronal development and apoptosis, and the way in which the p53-family proteins govern both processes. These findings indicate that during the developmental period of the sympathetic neuron, the life-*versus*-death balance is determined by the ratio of p53 and truncated p73. A model is proposed wherein the p53 family members provide a major apoptotic checkpoint in neurons, with life *versus* death being determined by the balance of full-length, proapoptotic *versus* N-termial truncated antiapoptotic family members. P53 and p73 transcriptionally regulate N-terminal truncated p73, which in turn functionally inactivates p53 and p73 to attenuate the proapoptotic function of these proteins. This pathway creates a regulatory dominant negative feedback loop to regulate cell demise. Most scientists would balk at the prospect of following such a performance, but Xin Lu (London) is not most scientists. She presented her findings on the ASPP (apoptosis stimulating p53 proteins) protein family, a group of regulatory proteins that, as you might expect, regulate p53 to stimulate apoptosis.[5] These proteins act by stimulating the transactivation function of p53 specifically on the promoters of apoptosis-related

genes such as Bax and PIG-3, but not on promoters of Mdm2 or cyclins.

Such heady science before lunch is enough to damage anyone's brain, and indeed the second session of the day focused on 'Mechanisms of Neuronal Apoptosis in Brain Injury'. Pierluigi Nicotera (Leicester) and Stuart Lipton (San Diego) delivered fine presentations on the cellular switch between apoptosis and necrosis.[6,7] It is known that the cellular ATP level is critical for deciding the mode of death and that the cleavage of SNARE proteins can initiate a caspase-independent program of neurite self-destruction that is sensitive to neurotrophic stimulation, and a caspase-mediated execution program. Furthermore, recent findings indicate that PARP inhibitors attenuate ischemia or excitotoxic-induced necrosis but not apoptosis, and G Gasic (Boston) turned the proceedings clinical with a talk on neuronal apoptosis as it relates to neuropsychiatric diseases. A new concept in producing NMDA-receptor antagonists postulates the use of low-affinity agents instead of high affinity blockers as proposed in the past, which would block the NMDA-receptor associated ion channel only when it is excessively activated. Emerging from initial studies on NMDA-receptor S-nitrosylation, one may envision using this post-translational protein modification to selectively down-regulate receptor activity. NitroMemantines, drugs that target the NO group to the NMDA-receptor are leading compounds.

The final day of the conference kicked off with a presentation series titled 'Modulators of Cell Signalling in Apoptosis and Injury', focused on redox regulation of cell death. V Ullrich presented interesting findings on superoxide (O_2^-), a rather unreactive radical which serves as a cellular signaling molecule.[8] NO can act as a superoxide antagonist under physiological conditions; O_2^- combines with NO to form peroxynitrite, a species found to nitrate tyrosine, as well as to attenuate activity of prostacyclin synthase with consequences for vascular tone. Peroxynitrite in turn reacts with NO to generate an efficient nitrosating species. The current model proposes that nitration can be compensated at the expense of nitrosation when the flux of NO overrides that of O_2^-. Thus, relative rates of O_2^- *versus* NO formation act as key players in redox-regulation and thus in affecting cell demise.

The final presentation series, which featured talks by the likes of Carlo Riccardi (Perugia) and JB Schultze (Tubingen), focused on neuroimmune regulation, and especially on implications for human pathologies such as Parkinson's and HIV-associated dementia.[9] Reports are accumulating to suggest that molecular and biochemical pathways of apoptosis are involved in dopaminergic cell death in Parkinson's disease and in patients suffering from HIV-associated dementia (HAD). It is becoming clear that for full functional recovery of e.g. dopaminergic neurons the combination of an anti-apoptotic together with a neuro-restorative therapy is advised. Thus, attacking proapoptotic pathways only may attenuate cell demise but generate a dysfunctional neuron. HAD, Alzheimer and Parkinson disease point to an important role for IL-1β, most likely generated by microglia. Rat models have been developed for the characterization of the neuroprotective profile of drugs which interfere with mediators of neuroinflammation and crucial steps involved in the activation of the death program. Mediators identified by this strategy are prostanoids derived from cyclooxygenase-2. These and other models such as monocular deprivation point to the action and cross-talk between excitotoxic-, radical- (O_2^-, NO), cytokine- and prostanoid-mediators in affecting the balance between life and death.

Alas, the conference had to come to an end, and so in the end the attendees packed up and prepared to journey home, a little older, a little wiser, and a lot browner. The meeting really shone in its ability to initiate stimulating interaction between PhD students and the more senior scientists recalling the sparkling culture of *Magna Graecia*. Although we significantly increased our knowledge on the formation and action of individual molecular messengers, we still lack sufficiently detailed insights into the cross talk of mediators of cell death and development to predict consequences for therapy. However, the VI worksphop on apoptosis in biology and medicine which focused on the role of proinflammatory and chemotactic cytokines in neuronal and pathological brain helped to update current information, to exchange ideas, and certainly will stimulate further experiments that will advance the field in the future.

Acknowledgements

Thanks go to Calabria Region, The National Council for Research, University of Calabria and University of Catanzaro 'Magna Graecia'.

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