Cell Death and Differentiation (2007) 14, 885–886

www.nature.com/cdd

Meeting Report

Death in the Alps

A Hague*,[1] and LM Martins[2]

Cell Death and Differentiation (2007) **14,** 885–886. doi:10.1038/sj.cdd.4402100; published online 2 February 2007

First International Workshop on Animal Models in Cell Death Signaling and Cancer, 25–29th January 2006. Obergurgl, Austria.

This outstanding informal conference was organised by Andreas Villunger and Gerry Melino. The meeting was held in Obergurgl, a small village in the Austrian Tyrol. Accommodation was provided in the University of Innsbruck conference centre, conveniently located by the main ski lifts. The small number of participants contributed to stimulate discussion. Most speakers presented unpublished work and this is a feature that we feel should be encouraged in the future.

Much discussion revolved around the BH3-only proteins, in particular debating the two models for their function. In one model, BH3-only proteins bind Bcl-2-like proteins to displace Bax/Bak. In the other, 'direct activator' BH3-only proteins like Bid and Bim bind and directly activate the pro-apoptotic function of Bax/Bak after their displacement from Bcl-2-like proteins by other BH3 proteins acting as 'de-repressors' of apoptosis. *Andreas Villunger* (Innsbruck, Austria) reported derivation of viable bim$^{-/-}$, bmf$^{-/-}$ double-knockout mice and discovery of different isoforms of mouse Bmf, generated through alternative translational start sites. *Atan Gross* (Rehovot, Israel) described TNFα-induced interaction of tBID with mitochondrial carrier homologue 2 (Mtch2), a 33 kDa protein residing in the outer mitochondrial membrane. New data using shRNA knockdown of Mtch2 and its overexpression in HeLa cells suggest that Mtch2 is a negative regulator of tBID-mediated cytochrome *c* release.

Puma is upregulated by p53-independent and –dependent mechanisms. *Christoph Borner* (Freiburg, Germany) described a role for Puma in apoptosis induced by IL-3 deprivation. Puma$^{-/-}$ cells were less susceptible to apoptosis than cells deficient in both Bim and Bad. This is an example of p53-independent regulation of apoptosis by Puma. *Jochen Prehn* (Dublin, Ireland) reported a p53-independent role for Puma in cell death mediated by endoplasmic reticulum stress, but a p53-dependent role in cell death induced by proteasome stress.

For treatment of human cancer there is considerable interest in reactivating or mimicking BH3-only protein function in conjunction with an apoptotic stimulus. *David Huang* (Melbourne, Australia) illustrated selectivity of BH3 protein binding to anti-apoptotic Bcl-2 family members. For example, Bak is held in check by Bcl-xL and Mcl-1, but not Bcl-2, Bcl-w, or A1, and is displaced by BH3-only proteins such as Noxa to transmit a death signal. Most unbound BH3-only proteins are unstructured, perhaps facilitating binding to multiple partners. However, interactions between Bcl-2 family members are very specific. Using the BH3 (Bad-like) mimetic ABT-737, David illustrated how understanding these interactions will allow us to manipulate this system to optimise cancer therapy. *Martin Schuler* (Mainz, Germany) reported that induction of Bak overcomes drug resistance of lung cancer cell lines and that ABT737 sensitizes particular lung cancer cell lines to chemotherapy-induced apoptosis. The BH3-only protein Bim has been shown by *Reinhard Kofler* (Innsbruck, Austria) to be upregulated in response to glucocorticoid treatment in childhood acute lymphoblastic lymphoma (ALL). *In vitro* and *in vivo* glucocorticoid sensitivity are major prognostic factors in childhood ALL and understanding the molecular basis of glucocorticoid-induced apoptosis and development of resistance will lead to improvements in treatment of lymphoid malignancies.

JP Medema (Amsterdam, The Netherlands) reported on function of the murine serpin SPI-6 and its human homologue, PI-9, that inhibits apoptosis induced by cytotoxic T lymphocytes through covalent binding to Granzyme B, without inhibiting CD95/Fas-mediated apoptosis. Expression of serpins by cancer cells may allow them to escape from apoptosis induced by cytotoxic T lymphocytes. However, *Thomi Brunner* (Bern, Switzerland) illustrated how FasL clustering in lipid rafts leads to enhanced FasL mediated T-cell killing.

Shairaz Baksh (Alberta, Canada) reported that RASSF1A binds the BH3-like protein MAP-1 resulting in recruitment of Bax to MAP-1 complexes. This leads to a conformation switch in Bax, mitochondrial membrane insertion, cytochrome c release and apoptosis. This can be initiated by TNF-α or TRAIL and provides a novel link between death receptor signalling and the mitochondrial pathway.

Luca Scorrano (Padova, Italy) explained how, following an apoptotic stimulus, mitochondrial cristae fuse and cristae

[1]Department of Oral and Dental Science, University of Bristol, Lower Maudlin Street, Bristol BS1 2LY, UK and [2]MRC Toxicology Unit, Hodgkin Building, University of Leicester, PO Box 138, Lancaster Road, Leicester LE1 9HN, UK
*Corresponding author: A Hague, Department of Oral and Dental Science, University of Bristol, Lower Maudlin Street, Bristol BS1 2LY, UK. Tel: +44 117 9284114; Fax: +44 117 9284428; E-mail: a.hague@bristol.ac.uk; published online 02.2.06

junctions widen to allow complete cytochrome *c* release. The dynamin-related protein, Optic Atrophy 1, OPA1, is an inner mitochondrial membrane protein reported to be involved in mitochondrial fusion. OPA1 protects mouse embryonic fibroblasts from apoptosis induced by staurosporine, etoposide, tBid and hydrogen peroxide by decreasing release of cytochrome *c* and loss of mitochondrial membrane potential. OPA1 is mainly an integral membrane protein, but a small fraction is processed and released into the intermembrane space by a rhomboid protease, Presenilin-associated rhomboid-like, PARL. Although dispensable for mitochondrial fusion, PARL is absolutely required for cleavage, oligomerisation and anti-apoptotic function of OPA1.

Miguel Martins (Leicester, UK) reported that, even though serine protease Omi/HtrA2 has been reported to be pro-apoptotic, its deletion in mice leads to enhanced cell death, indicating that its main role is related to regulation of mitochondrial homeostasis rather than contributing to cell death.

Huseyin Mehmet (London, UK) is interested in apoptosis associated with cerebral hypoxic-ischaemic injury in newborn infants. Rat models show that late oligodendrocyte precursors are particularly vulnerable to death in this context. JNK3, rather than JNK1 or JNK2 is involved in apoptosis signalling in response to hypoxia and glucose deprivation in precursor cells, but mature oligodendrocytes are more resistant. Mild hypothermia reduces apoptosis in this model and we were interested to hear how reducing the body temperature of babies suffering hypoxia at birth by means of a 'cooling cap' looks to be a promising way to combat potential brain damage.

Gerry Melino (Rome, Italy) explained how *p63*$^{-/-}$ mice die at birth with severe developmental abnormalities, including very limited epidermalisation. *p63* produces two proteins originating from different promoters, TAp63 and ΔNp63. Both proteins are ubiquitinated and downregulated by Itch E3 ligase which controls the steady-state level of p63. To determine p63 function in skin, TAp63 and/or ΔNp63 were reintroduced under the cytokeratin 5 promoter in *p63*$^{-/-}$ mice. ΔNp63 showed limited epidermal basal layer formation and expression of basal cytokeratins, but reintroduction of both isoforms resulted in increased numbers of keratinocytes exhibiting later skin differentiation markers. Hence, both TAp63 and ΔNp63 are synergistically required for epidermal development.

In mouse models, MDM2 and Mdm4/Mdmx act synergistically to limit p53 activity in neural progenitor cells and in post-mitotic neurons. *Jean Christoph Marine* (Ghent, Belgium) suggested, perhaps controversially, that Mdm4 inhibits transcriptional activity of p53 independently of Mdm2. Conditional inactivation of *mdm2* in smooth muscle cells resulted in necrotic-like death of these quiescent cells; however no histological defects were observed following inactivation of *mdm4*. p53 induces caspase-3-independent cell death in this context.

Michael Hengartner (Zürich, Switzerland) described the hunt for engulfment mutants of *Caenorhabditis elegans* by feeding nematodes RNAi. He identified arx3 and arx5, components of the Arp2/3 complex required for formation of branched actin filaments, and dyn-1, a dynamin GTPase that modifies the curvature of lipid membranes. *Anton Gartner* (Dundee, UK) used *C. elegans* to examine apoptosis in the germ line – the only proliferating tissue in *C. elegans* –to find negative regulators of the p53 pathway. Cep1 (*C. elegans* homologue of p53), regulates transcription of Egl-1 (Puma homologue) and Ced 13 (Noxa homologue). GLD-1 is a negative regulator of Cep-1 by binding to the 3′ untranslated region.

The conference covered broad topic areas within the cell death field and gave opportunities for poster presentations and discussion of current work. The enthusiasm of the organisers and participants, not to mention the excellent venue, made the meeting a resounding success.