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**Meeting Report**

# Molecular pharmacology and cell death research in St-Petersburg

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**Workshop on Therapeutic Targets in Cell Death,** St-Petersburg, Russia, 6–7 June 2012

As a part of the initiative of the Russian Federation Government to support the research under the guidance of world-leading scientists in the Russian Institutions of Higher Education, an international Workshop on Therapeutic Targets in Cell Death was held at the Institute of Technology, St Petersburg. The discussant's panel included presentations from the leading international scientists. The Workshop provided a unique platform for the Russian researchers and leading western scientists to discuss key areas of basic, translational and clinical research and the latest discoveries in the field, and establish productive collaborations. The occasion allowed the inauguration of the novel laboratory for Molecular Pharmacology in the St Petersburg Institute of Technology, as part of the Russian Federation's Mega Grants for science.

## From immunogenicity to autophagy and neuronal cell death

In the opening keynote lecture, Guido Kroemer (Villejuif) highlighted the role of autophagy as a cytoprotective mechanism against therapy-induced cell death. Resveratrol and spermidine potently induced autophagy, underscoring the importance of autophagy as a mechanism for cell surviving and longevity. They induced autophagy in a synergistic manner, as they stimulate convergent pathways of activation of deacetylation and repression of acetylation, respectively. Thus, their combined effect culminated in concordant modifications of the whole acetylproteome. Collectively, these data underscore the importance of an autophagy-regulatory network of antagonistic deacetylases and acetylases that can be pharmacologically manipulated.

Mauro Piacentini (Rome) reported on the role of Ambra1 in regulation of autophagy. Ambra 1 interacts with a number of proteins, including the lysosomal protein Spinster, which, in turn, binds the anti-apoptotic protein Bcl2 and is involved in the execution of a caspase-independent cell death associated to autophagic vacuole formation. He showed that Ambra1 negatively regulated Spinster activity by modulating its levels of ubiquitination via binding different subunits of Cullin-RING E3 ubiquitin-ligase complexes. Taken together, the data presented suggest that Ambra1 is an essential positive regulator of autophagy, as potential novel therapeutic targets.

Similarly, Hans-Uwe Simon (Bern) presented the data on the dual role for ATG5 upon anticancer drug treatment. Otherwise cytoplasmic, ATG5 translocates to the nucleus following radio- and/or chemotherapy. ATG5 antagonizes survivin function thus leading to mitotic catastrophe. These results show that ATG5 acts in two distinct pathways in cytosol and nucleus, an insight which, appropriately realized, promises better and safer elimination of cancer cells.

Peter Vandenabeele (Gent) discussed how necroptosis has an important role *in vivo*, via RIPK3. Genetic deletion of RIPK3 rescued caspase-8-deficient mice from embryonic lethality, suggesting that RIPK3-dependent necroptosis was suppressed by apoptotic regulatory mechanisms. RIPK3-null mice are tolerant to the injection of high dose of TNF that normally causes systemic inflammatory response syndrome (SIRS), resulting in septic shock because of necrotic cell death. Pre-treatment with the RIPK1 kinase inhibitor, necrostatin-1, had a similar protective effect on mortality and resulted in reduced levels of markers of organ damage and circulating inflammatory cytokines. RIPK1/RIPK3-mediated necroptosis has an indispensable role in TNF-induced SIRS as the determinant between life and death, thus making them appealing therapeutic targets for treatment of SIRS and sepsis. The identification of this distinct pathway of cell death, and the involvement of specific kinases, as novel potential therapeutic targets, will open the possibility to screen and design novel pharmacological regulators of cell death.

Daniele Bano (Bonn) discussed non-lysosomal cysteine proteases, caplains, in autophagy. Neuronal-specific *Capn4* knockout mice showed an altered autophagic flux of engulfed materials to the lysosomes. The lack of calpain activity in the

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central nervous system modulated the PI3K/Akt pathway and the downstream targets therefore compromising the survival of calpains-deficient primary dissociated neurons. Autophagy regulation by calpains might be of interest for potential clinical intervention in brain disorders, especially in those pathologies resulting from aggregate-prone proteins.

Boris Zhivotovsky (Stockholm, Moscow) provided insights into the mechanisms of resistance of small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC), highly resistant to therapy. Eighty percent of all SCLC cell lines and tumours do not express caspase-8 because of hypermethylation or mutations in CASP8. Mechanisms responsible for intrinsic or acquired resistance to treatment involve defects/deregulation of the apoptotic programme. In this respect, PKC inhibitors can reactivate the full apoptotic 'response' in NSCLC via ROS generation and increased intracellular $Ca^{2+}$ concentration. Why caspase-8 is selectively repressed in NSCLC, as well as in other cancers such as melanoma and neuroblastoma? This is an important open question that could potentially open up novel insight in the progression of these lethal diseases.

Finally, Marie-Lise Gougeon (Paris) discussed the mechanisms of viral escape from immunity. HIV-1 exploits dendritic cells (DCs) as reservoirs, thereby facilitating viral dissemination and persistence in target cells. She showed the data suggesting that the ability of DCs to replicate HIV and to establish HIV reservoirs was dependent on their interaction with autologous natural killer (NK) cells. She also discussed the role of the HMGB1 protein, produced by NK cells in response to viral infection, which rendered DCs resistant to TRAIL-dependent NK-mediated killing. Resistance to TRAIL killing was associated with an upregulation of two key inhibitors of apoptosis, cIAP-2 and c-FLIP. Accordingly, blocking HMGB1 activity restored the susceptibility of HIV-infected DCs to NK cell killing.

## Translation and micro-RNA in cell death

Gerry Melino (Rome, Leicester) discussed the role of p73, a p53-family member, in aging and metabolism. According to his results, TAp73-null mice showed a significant premature spontaneous aging. In addition, TAp73-null mice showed unbalanced redox defences because of the attenuation of expression of specific metabolic promoters, suggesting that TAp73 regulates metabolic pathways.

Eleonora Candi (Rome) demonstrated that miR-24 is involved in regulation of actin cable dynamics, intercellular adhesion and cell migration during keratinocyte terminal differentiation. During this process, cells undergo extensive remodelling of their actin cytoskeleton, which is important to control cell mobility and to coordinate and stabilize adhesive structures necessary for functional epithelia. Using keratinocytes and mouse epidermis as models she showed that miR-24 is sufficient to trigger keratinocyte differentiation both *in vitro* and *in vivo* and directly represses cytoskeletal modulators (PAK4, Tks5, ArhGAP19). In line with this, silencing of these targets recapitulates the effects of micro-RNA-24 overexpression.

Nickolai Barlev (Leicester, St-Petersburg) provided evidence for the role of p53 in regulation of expression of two micro-RNAs, miR-15/16 and miR-26a, in response to DNA damage. Although miR-16 is likely regulated by 53 on the post-transcriptional level, miR-26a was the direct target of p53. Ectopic expression of miR-26a induced apoptosis of tumour cells in a p53-dependent manner. Moreover, he presented the data for one of the target of miR-26a, the *WEE1* gene, whose product is critical for cell cycle progression through G2/M phase. Attenuation of WEE1 expression causes apoptosis of tumour cells, thus making this protein an important therapeutic target.

Functions of Daxx, an apoptotic protein associated with the nuclear structures called PML-containing nuclear bodies (NB), was the topic of discussion by Alexander Ishov (Gainesville). Daxx intra-nuclear distribution revealed that upon heat shock it re-localized from NBs to centromeres and pericentromeres (CEN/periCEN). The functional consequences of Daxx deposition at CEN/periCEN: (i) regulation of loading of the transcription-associated histone H3 variant, H3.3 onto CEN/periCEN, and (ii) protection of the epigenetic status of CEN/periCEN. The latter is achieved by repressing H3K4 methylation, an hallmark of transcription initiation. Hence, Daxx serves as a guardian of epigenetic identity of CEN/periCEN heterochromatin.

## Conflict of interest

The authors declare no conflict of interest.

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