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Meeting Report

OMICS, a multidisciplinary friendship

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Cancer is a disease that requires a multidisciplinary approach to fight it. The study of specific mutations is no longer sufficient to explain the onset of complex pathologies including cancer, diabetes or neurodegenerative diseases. This observation urges to integrate various omics technologies in order to unravel novel regulatory networks allowing to better understanding the development of these diseases. The merge of high-throughput screening techniques (genomics, transcriptomics, proteomics and metabolomics) with other disciplines including mathematics, bioinformatics and systems biology will allow the discovery of fundamental insights that would remain obscure otherwise. This interdisciplinary approach thus permits to better understand and interpret complex biological phenomena by taking into consideration multiple parameters. Results can then be confirmed by various techniques strengthening the importance of the interdisciplinary OMICS.

In this context, the 'Cell Signal-omics 2011' conference took place last January (26–28) in Luxembourg. This congress, focusing on 'Integrated cellular pathology and Systems Biology of human disease', gathered together more than 350 international scientists implicated in the different branches of OMICS at the European Congress Center in Luxembourg.

The opening keynote session was given by Professor Mario Capecchi, molecular geneticist and 2007 Nobel Prize winner in Physiology or Medicine, for discovering a method introducing homologous recombination in mice by employing embryonic stem cells. Professor Capecchi presented the importance of gene targeting in mouse models of various human diseases, including cancer and neuropsychiatric disorders. He underlined the fact that synovial sarcoma mouse models expressing the chimeric SYT–SSX2 fusion protein were useful to identify the skeletal muscle lineage as a source of synovial sarcoma. In the case of neuropsychiatric disorders he pointed out the hematopoietic origin of pathological grooming in Hoxb8 mutant mice by explaining that Hoxb8-cell lineage exclusively labels bone marrow-derived microglia and that disruption of Hoxb8 in the hematopoietic system recapitulates the obsessive-grooming behavior disorder.

The importance of gene targeting was reinforced by several discussions dedicated to the role of gene expression networks in health and disease. As presented by Dr. François Fuks (Free University of Brussels, Belgium), cellular transformation and malignant evolution are connected to gene expression and silencing mediated by epigenetics perturbations, such as histone modifications and DNA methylation mediated by DNA methyltransferases, thus leading to aberrant chromatin dynamic. According to Fuks, DNA methylation profiling appeared as a potent tool to characterize cancer tissues and to optimize personalized medicine. In addition, a large panel of promising molecules exhibiting histone de-acetylase inhibitory activity is under investigation for the development of new anticancer therapies as reported by Dr. Michael Bots (Peter MacCallum Cancer Centre, Victoria, Australia). Dr. Luciano Di Croce's team from the CRG/ICREA in Barcelona, Spain identified a protein complex of ZRF1/histone mutant macroH2A that is involved in the establishment and maintenance of the abnormal silencing of tumor suppressor genes during transformation.

Furthermore, Professor Guido Kroemer (IGR, Paris, France) highlighted the importance of autophagy-regulatory networks represented by acetylases and de-acetylases, and discussed an interconnection between autophagy and life span. Both types of autophagy-inducing pharmacological agents, SIRT1-dependent (resveratrol) as well as SIRT1-independent (spermidine), extend longevity in an autophagy-dependent manner. Hence, autophagy promotes mostly cytoprotective rather than cytotoxic effects. The pharmacological targeting of control points of the autophagy system by combining established cancer treatments with autophagy inhibitors such as Atg5/7 silencing or hydroxychloroquine was presented by Professor Eileen White of Rutgers University (NJ, USA). The emerging understanding of the role of autophagy in common resistance to chemotherapy leads to the development of therapeutic strategies that target cell death pathways. Nevertheless, the balance between activation of cell death in cancer cells and protection of healthy tissue remains a concern. In that sense, the impact of cell death of oocytes in healthy and chemotherapeutic agent-treated women was

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discussed and correlated to p53 family members (eg. p63, p73). The oocytes competence was shown to be age-related. A proteomic approach presented by Cinzia Di Pietro (University of Catania, Italy) pointed out that 40 genes are differentially expressed between old (women > 38 years old) and young (women < 32 years old) oocytes with an upregulation of pro-apoptotic genes including *TAp73* and caspases and downregulation of anti-apoptotic (*Bcl-2*, *Mcl-1*, *NF-κB*) genes in old oocytes. As explained by Dr. Stefania Gonfloni (University of Rome Tor Vergata and LBMCC, Luxembourg), germ cells are sensitive to genotoxins and oocytes of women treated with chemotherapeutic agents are massively degraded. This type of cell death is the cause of infertility and could be explained by TAp63 accumulation in early post-natal oocytes and by p63-dependent activation of pro-apoptotic promoters. Gonfloni hypothetized that cisplatin-induced side effects could be neutralized by a pre-treatment with the Bcr–abl inhibitor Imatinib that is able to protect oocytes from cisplatin treatment in modulation of *p63* transcription through its c-Abl kinase inhibitor activity. Professor Gerry Melino also from Tro Vergata (Rome, Italy) also underlined the important implication of p53 family members as guardians of maternal reproduction and their impact at the evolutionary level. He presented the novel involvement of p73 in neuronal development and the role of TAp73 as a driver of miR-34a; its expression contributes to the commitment of embryonic stem cells in neurons and modulates the expression of specific synaptic genes.

This is in line with Professor Capecchi and other groups who underlined the importance of stem cell line models. Ninety percent of cancer mortality is due to therapy resistance and metastasis. The fatal evolution of the disease suggests the presence of cancer stem cells that survive because of their embryonic or pluripotent characteristics. During the meeting Dr. Anne Grosse-Wilde (ISB, Seattle, WA, USA) highlighted the importance of the identification and the in-depth characterization of such cells.

Nowadays, systems biology becomes essential in various disciplines of life sciences and reaches researchers progressively. As emphasized by Professor Antonio del Sol (ISBM, Luxembourg), molecular therapeutic strategies could benefit from a better understanding of disease-related network perturbations that could be highlighted by the analysis of cellular network components. Dr. Nicolai Lavrik (DKFZ, Heidelberg, Germany) focused on the importance of systems biology to understand the regulation and balance between life and death in CD95 system. This integrated concept allowed the identification of novel mechanisms of regulation of CD95 signaling as well as the ratio pro/anti-apoptotic death effector domain-containing proteins requested to determine the decision between life and death by describing the complex dynamics of CD95-mediated apoptosis and NF-κB signaling. In addition, Professor Jacques Piette's group at the ULg in Liège, Belgium pointed out the importance of CD95-glycosylation mediated by the anti-apoptotic role of SHIP-1 in order to reduce T-cell death by apoptosis. His attention was directed to search for novel SHIP-1 interaction partners. Interestingly, this team identified interactions between SHIP-1 and two IAP family members (cIAP-1 and XIAP).

Interplay between immunity, cell death and chronic viral infection was underlined by Professor Marie-Lise Gougeon (Pasteur Institute, Paris, France) on the basis of an HIV-infected dendritic cell model. The main role seems to be played by cross talks between dendritic cells and autologous natural killer (NK) cells. NK cells are usually responsible for the elimination of infected dendritic cells and this process is believed to be an essential step for early control of viral replication and dissemination. Interestingly, Gougeon's team discovered that upon HIV infection, dendritic cells become resistant to NK-dependent lysis. Moreover, they showed that NK interaction with dendritic cells triggered apoptosis resistance owing to dramatic upregulation of two major inhibitors of apoptosis cIAP-2 and c-FLIP and thus contributing to the constitution of long-term viral reservoirs. Identification of the essential role of HMGB1 in this signaling chain provided a novel therapeutic target to eliminate viral reservoirs. Dr. Andrew Koff (Memorial Sloan–Kettering Cancer Center, NY, USA) has presented a new insight into the usage of the cdk inhibitor p27 as a biomarker in human cancer prognosis. He elaborated a bioinformatic approach to test the relationship between SV40 small *t*-antigen and oncogenes. Through *in silico* pathway analysis, they showed a negative correlation between expression of SV40 small *t*-antigen and p27 accumulation. Finally, the developed network identified p27 levels as a witness of the activation of oncogenic signaling pathways and as a valuable trait of cancer prognosis. The immune system is a complex machinery strictly dependent on homeostatic control. The GTPase immunity associated protein 5 (Gimap5) has been previously identified as a mediator of immune homeostasis. Professor Kasper Hoebe (Cincinnati Children's Hospital Research Foundation, Cincinnati, OH, USA) pointed out the role of this protein as a key regulator of hematopoietic integrity and as a critical mediator of lymphocyte homeostasis. Hoebe's team focused on a recessive ENU-induced germline mutation destabilizing Gimap5 and leading to lymphopenia, hepatic extramedullary hematopoiesis, weight loss and intestinal inflammation in homozygote mutant mice.

Besides previously mentioned population diseases, several talks focused on obesity and neurodegenerative diseases. Differential risk of metabolic syndrome between central and peripheral obesity was investigated by the team of Professor Yong Sang Song (Seoul National University, South Korea). According to Song, more than 500 genes related to energy metabolism showed differential expression patterns in human subcutaneous *versus* human visceral adipose-derived stem cells. Observed differences could be responsible for the important involvement of central obesity in metabolic syndrome. At the present time, much attention is also dedicated to neurodegenerative diseases. In case of Alzheimer's disease, Dr. Xin-Fu Zhou (Flinders University, Adelaide, South Australia) presented data supporting that the neurotropin receptor, p75NTR, has a critical role in regulating amyloid-beta levels by both increasing amyloid-beta production and attenuating its aggregation in the cerebral cortex and hippocampus. Moreover, Professor Vittorio Calabrese (University of Catania, Italy) pointed out the importance of vitagenes, metabolic stress, hormesis and of the modulation of endogenous cellular pathways. The interplay between metabolism, mitochondrial energetics and activation of critical

vitagene cascades should be included in order to confer protection against chronic degenerative damage associated to aging and neurodegenerative disorders. He also showed that the induction of hormetic pathways by dietary antioxidants compounds confer them an interesting neuroprotective potential. Other strategies to fight neuronal disorders were presented by Dr. Mark Mattson (National Institute on Aging, Baltimore, MD, USA). He underlined the impact of dietary energy intake as well as sedentary lifestyle and drugs, (e.g. plumbagin) as activators of adaptive stress response pathways, on cognitive aging.

Altogether, this excellently organized meeting provided a detailed insight into one of the most exciting scientific fields moving rapidly. Congratulations to the organizers!

Conflict of Interest

The authors declare no conflict of interest.

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Next meetings

Phytochemicals and compounds from natural origins are nowadays under investigation for their therapeutic and medicinal potential role on human health and diseases. The last findings of worldwide research on this topic will be presented during our next meetings:

Redox regulation – Natural compounds as regulators of inflammation signaling

(RedCat satellite meeting to Natural Compounds 2012)

25–27 January 2012

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