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Editorial

Integrated cellular pathology—Systems biology of human diseases

Systems biology is an evolving field of multidisciplinary science that enables the characterization of the interactions between the various components of complex biological systems (e.g., cell cycle, proliferation, differentiation, death regulator, etc.) to provide the means to study cellular process in a holistic and integrated manner. This approach involves a variety of 'omics' disciplines including genomics, epigenomics, proteomics, metabolomics and signalomics that can be integrated using computational simulations to elaborate on mathematically predictive models of the molecular interaction networks occurring within the various systems.

The 9th international meeting in the field of signal transduction and gene expression, "Cell Signalomics 2011 – Integrated cellular pathology – Systems biology of human disease", took place January 26–29th at the New European Conference Center in Luxembourg. This meeting gathered 350 participants and outstanding speakers who shared their most recent findings. Fundamental mechanisms related to cell death, epigenetics, immunology, transcriptional control, proteomics and signaling networks involved in human disease states as well as translational applications were discussed during the meeting.

The interface between experimental biology and computational biology was highlighted as a means to enhance knowledge related to systems biology and the mechanisms of disease pathology. Systems biology approaches have already proved useful in diabetes, multiple types of cancer and AIDS. Nonetheless, experimental biology remains a key pillar in biomedical release and this was elegantly demonstrated in the keynote session. Indeed, the first presentation by Professor Mario Capecchi reinforced the critical role of animal models to study and understand the molecular and cellular mechanisms involved in human disease states. In providing examples of genetically modified mice, Professor Capecchi highlighted the link between gene mutations, neuropsychiatric disorders and behavioral phenotypes. As illustrated by the correlation between the *Hoxb*-8 gene mutation in mice and excessive and unrestrained grooming.

Several presentations focused on the process of cell death, specifically apoptosis and autophagy, and also highlighted aspects of cell differentiation. A common approach to initiate cancer cell death is the activation of apoptotic pathways, a process frequently altered in cancer cells. Advancements in knowledge in this field provide the means to identify new approaches to anticancer drug development such as targeting of the *Frizzled* pathway and CD95 signaling. Drug-induced apoptosis can, however, lead to severe side effects in cancer patients. One example, illustrated by Dr. Stefania Gonfloni, is the infertility resulting from apoptosis in oocytes, an effect observed after cisplatin-induced DNA damage. This was linked to an increase in *Abl* proto-oncogene expression by p63, which codes for the tyrosine kinase, *Bcr-Abl*. Imatinib, an inhibitor of *Bcr-Abl* is used for the treatment of chronic myeloid leukemia (CML). Imatinib can counteract cisplatin-induced oocyte apoptosis, which preserves fertility, suggesting its use as fertoprotective adjuvants for female patients treated with chemotherapeutics.

The control of apoptosis is also critical in AIDS. The presentation by Dr. Marie-Lise Gougeon concerned the ability of the HIV-1 retrovirus to subvert dendritic cell (DC) signaling pathways to promote viral replication and dissemination. The idea behind this study was that the DCs infected by HIV are resistant to TRAIL-induced apoptosis mediated by natural killer cells (NKs), an antiviral strategy developed by the immune system to rapidly eliminate infected DCs that act as HIV reservoirs. The high-mobility group box 1 (HMGB1) protein, located on NK–DC synapses, was identified as an essential effector of DC resistance to NK-dependent apoptosis. Indeed, HMGB1 is responsible for the up-regulation of the apoptosis inhibitors c-Flip and c-IAP2. Therefore, Dr. Marie-Lise Gougeon, as a strategy to eliminate viral persistence in DCs suggested targeting HMGB1. Other proteins related to the immune system are also important in apoptosis control. For example, SHIP-1 inhibits CD95-induced apoptosis in a T-cell leukemia cell type. Using a yeast two hybrid screening and hORFeome v5.1, a central resource of cloned human open reading frames (ORFs), Miss Claude Condé from Dr. Jacques Piette's Laboratory demonstrated that SHIP-1 interacts with the anti-apoptotic proteins, cIAP-1 and XIAP.

Inflammation plays a critical role in apoptosis and therefore in cancer. Cyclooxygenase-2 (COX-2), an enzyme induced by pro-inflammatory stimuli (e.g., TNFα, IL-1β), is responsible for the metabolism of arachidonic acid and leads to the production of prostaglandins. Pr. Young-Joon Surh showed that prostaglandin 15d-PGJ_2 has anti-inflammatory and cytoprotective activity by inhibiting NF-κB and redox-sensitive transcription factors as well as their regulators, AP-1, Nrf2-Keap1, STAT3 and p53. 15d-PGJ_2 can rescue cancer cells from peroxynitrite- and hydrogen peroxide-induced apoptosis by upregulating Nrf2. Moreover, Pr. Surh reported that 15d-PGJ_2 is also implicated in carcinogenesis by stimulating angiogenesis through the induction of vascular endothelium growth factor. Nowadays, according to the role of COX-2 in carcinogenesis, many COX-2 specific inhibitors as well as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been developed to prevent tumor progression.

Autophagy is another form of cell death. It is a catabolic process characterized by the engulfment of intracellular components inside double membrane vesicles, autophagosomes. Induction of autophagy has been suggested as a novel strategy to treat diseases. However, recent data suggest that autophagy could be considered more as a survival pathway developed by cells to overcome environmental stressors like starvation or oxidation. Pr. Guido Kroemer reported that spermidine- and resveratrol-mediated

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prevention of acetylation of many autophagy related proteins can activate these and prolong life span in *C. elegans*. According to Dr. Eileen White, autophagy has also been implicated in cancer chemoresistance. Aggressive cancers bearing activating mutations in the proto-oncogene *Ras* have high basal levels of autophagy with the latter seemingly being required to maintain mitochondrial metabolism and tumorigenesis.

The correlation between the potential protective effects of autophagy and drug resistance in cancer cells was highlighted in studies by Pr. Anna Ivana Scovassi. The presentation demonstrated that 2-methoxyestradiol-induced apoptosis in HeLa, HCT116 and SW613-B3 cancer cell lines occurred concomitantly with the expression of autophagy-related markers. Similarly, the alkaloid berberine and its analogs also led to the expression of both apoptosis and autophagy markers in the same cells. These results should contribute to the understanding of the cross talk between autophagy and apoptosis in cancer cells.

The session related to epigenetic has been introduced by Dr. François Fuks who underlined the relevance of epigenetic in cancer. As it is known that cancers are associated with a global DNA methylation leading to silencing of tumor suppressor genes, understanding the pathways implicated in such mechanisms should bring novel strategies for cancer treatment. In this context, Dr. Fuks showed that the kinase CK2 can phosphorylate DNA methyltransferase 3a (DNMT3a), leading to an inhibition of its enzymatic activity and thus an inhibition of global DNA methylation. Phosphorylation also inhibits the nuclear translocation of DNMT3a. The second part of the presentation focused on the innovative infinium technology that allows the study of gene methylation. This method based on genome-wide DNA methylation array technology should permit to identify new cellular subgroups in cancer tissues. On the other hand, epigenetic events can affect cell differentiation. Pr. Gerry Melino showed that induction of miR-34a by a carboxy-terminal spliced variant of the tumor suppressor p73 (TAp73) during synaptogenesis leads to a decrease in the number of synapses via effects on synaptotagmin or syntaxin-1A.

Furthermore, the level of histone deacetylase (HDAC) is strongly increased in several cancers. Mr. Michael Bots from Pr. Ricky Johnstone's team, reported the beneficial effects of the HDAC inhibitors, vorinostat and panobinostat, in comparison to chemotherapy in a murin model. As an example, leukemic cells defective in p53, were resistant to chemotherapy but sensitive to HDAC inhibitors. Moreover, HDAC inhibitors treatment displayed less side effects compared to chemotherapy. Together, these findings underlined the importance of modulating epigenetic in treating cancer, as another alternative to chemotherapy. Valproic acid (VPA), the well-known anti-epileptic drug, is also an HDAC inhibitor and has potential anticancer properties. It can inhibit erythroid differentiation as described by Dr. Sébastien Chateauvieux. VPA down-regulated the expression of key transcription factors and erythroid specific genes (e.g., GATA-1, EPO-R, γ-globin) while increasing expression of PU-1, an inhibitor of erythroid differentiation. Conversely, PU-1 activation facilitated myeloid and lymphoid differentiation of hematopoietic stem-progenitor cells suggesting a potential side effect in VPA treatment of cancer patients.

A major challenge in cancer therapy is to develop newer approaches that specifically target cancer cells having minimal effects on normal cells. Dr. Evan T. Keller discussed the use of small RNA or DNA oligonucleotides and aptamers, as therapeutics for the treatment of cancer. Using SELEX (systemic evolution of ligands by exponential enrichment) an anti-invasive aptamer has been developed that can inhibit highly invasive prostate cancer and osteosarcoma cell lines *in vitro* as well as *in vivo*.

Studies focused on understanding neurodegenerative disease especially Alzheimer's disease (AD) represented an important part of the meeting. Amyloid-β plaques are thought to be associated with neuronal death in the cerebral cortex and the hippocampus, an effect that may involve the neurotrophin receptor (p75NTR). Pr. Xin-Fu Zhou showed that deletion of p75NTR in transgenic mice leads to a reduction of amyloid-β production together with an increase in the aggregation of these peptides suggesting that reducing p75NTR may exacerbate AD. As presented by Miss Sophie Losciuto from Pr. Paul Heuschling's laboratory, inflammation may also play a critical role in AD by enhancing neuronal death. Agonists of LXR, a nuclear receptor that can repress pro-inflammatory responses in microglia, down-regulate astrocyte activation via actions on microglia. Thus, indirect activation of astrocytes by LXR agonists can preserve neuronal viability.

The use of natural products for the treatment of AD was also discussed at the meeting. As shown by Miss Chan Lee, the flavone Luteolin, from *Perilla* leaves, can inhibit amyloid-β-mediated oxidative stress induced cell death. Pr. Vittorio Calabrese showed that dietary antioxidants, e.g., polyphenols and L-carnitine, are neuroprotective via the activation of hormetic effectors including vitagenes, a group of genes involved in preserving cellular homeostasis during stressful conditions.

The importance of computational biology in cancer research was underlined through The Cancer Genome Atlas (TCGA) project. Dr. Ilya Shmulevich presented data on integrated analyses of TCGA-derived high throughput experimental data sets that are designed to identify mechanisms for the regulation of gene expression, to differentiate the transcriptional profiles of different cancer cell types and to identify molecules that target members of the identified networks as potential starting points for therapeutics. Comparison of cancer-associated features of several cancer types is also feasible using the TCGA.

Understanding systems biology is fundamental in elucidating mechanisms of pathophysiology and in identifying novel therapeutic approaches to treat human disease states. The meeting in Luxembourg provided an excellent overview of the status of cutting-edge research in diseases like cancer, neurodegeneration and AIDS. As such diseases are multifactorial in their etiology, combination therapy seems an inevitable to address complex pathologies. Clarification of the mechanisms implicated in the side effects of existing therapies will be important in selecting the best targets and best compounds to treat patients.

Next meetings

Redox regulation – Natural compounds as regulators of inflammation signaling

(A RedCat – satellite meeting to Natural Compounds 2012) – January 24–26, 2012

Natural compounds 2012 – Regulators of cell signaling pathways and novel therapeutic tools – January 26–28, 2012

Under the patronage of Corena, a network aiming to create an internationally competitive cluster within the Greater Region (Saarland, Lorraine, Luxembourg, Wallonia, Rheinland-Pfalz). Corena is co-funded by European Regional development fund within the INTERREG IVA Greater Region program. The European Union invests in your future.

Meeting information: http://www.transduction-meeting.lu

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