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Editorial

Metabolism 2014 – Alterations of metabolic pathways as therapeutic targets

Uncontrolled cell proliferation is an essential characteristic of neoplastic diseases. It is well known that rapid cell growth and division both need reprogramming of their energy metabolism. This concept is well explained by the "Warburg effect" or "aerobic glycolysis" [1]. Activated oncogenes, mutant tumor suppressor genes or mutated genes encoding metabolic enzymes regulate glycolysis but emerging cell signaling pathways of many aspects of cellular metabolism remain elusive. Metabolic reprogramming that occurs at early stages of carcinogenesis leads to altered metabolic profiles, an interesting future target for cancer chemoprevention and therapy.

The meeting entitled "Metabolism 2014: alterations of metabolic pathways as therapeutic targets" was a valuable opportunity to disseminate research in this new scientific field. This meeting took place from January 29th to 31st in Esch-sur-Alzette, Luxembourg. "Recherches Scientifiques Luxembourg asbl" organized and supported this meeting that brought excellent scientists together and encouraged an active discussion by all participants from basic concepts of cancer metabolism to clinical trials. We report here some of the most interesting and innovating aspects of this conference.

Professor Guido Kroemer (University of Paris Descartes, Cordeliers Research Center, France) keynoted the meeting. In his lecture, he discussed inactivation of Atg5, an essential autophagy gene that leads to acceleration of the early phases of tumorigenesis. Combination of Atg5 inactivation and KRAS activation induces expression of ENTPD1/CD39, an ecto-ATPase. It converts extracellular ATP causing an immunostimulatory response into adenosine eventually leading to an immunosuppressive response. Kroemer underlined the importance of targeting ENTPD1/adenosinergic receptors for reversing accelerated oncogenesis.

Professor Johan Auwerx (Ecole Polytechnique Fédérale de Lausanne, Switzerland) further addressed the relationship between metabolic systems and longevity. Auwerx highlighted the importance of mitochondrial ribosomal proteins (MRPs) as metabolic and longevity regulators. MRP knockdown triggered mitonuclear protein imbalance, which extends lifespan in *Caenorhabditis elegans* as well as in mammalian cells. Altogether, MRPs represent an evolutionary conserved protein family expressed in different species.

Professor Eileen White described the role of autophagy in KRAS and BRAF-driven lung cancer as a second speaker of keynote session. Deficiency of Atg7, essential for autophagy formation, reduced fatty acid oxidation (FAO) and increased sensitivity to FAO inhibition is indicating that autophagy is required for mitochondrial function and lipid catabolism in RAS-driven tumors without Trp53. Thus, autophagy plays a crucial role for carcinoma fate, and performs distinct roles in metabolism that are oncogene and tumor suppressor gene-specific.

Many scientists discussed diverse characteristics of tumor cell metabolism. Professor Jacques Pouysségur (University of Nice, France) and Doctor Bassam Janji (Public Research Center for Health, Luxembourg) focused on hypoxia in cancer cell metabolism. Pouysségur presented key pHi regulating systems such as Na^+-H^+ Exchangers (NHE) or Na^+-dependent Bicarbonate Transporters (NBTs) as a target for eradicating fast growing tumors. Janji highlighted the effect of hypoxia-induced autophagy on natural killer-mediated tumor cell lysis. In their study, hypoxia decreased breast cancer cell susceptibility to Natural Killer (NK)-mediated anti-tumor immune response by activating autophagy. He demonstrated that activated autophagy degrades NK-derived granzyme B in lysosomes of hypoxic cells leading to cancer cells that are less sensitive to NK-mediated killing.

Professor Navdeep S. Chandel (Northwestern University, USA) introduced mitochondria-generated reactive oxygen species (ROS) and suggested new paradigm for cancer therapy. Based on the fact that ROS are required for cancer initiation and progression, most scientists are focusing on an anti-oxidant strategy to treat cancer. However, high levels of ROS induce cell death, as cancer cells cannot survive in such a high levels of ROS. Chandel focused on this fact and his strategy consists in inducing ROS levels, inducing cancer cell death. He provided evidence that elevated ROS levels can be induced by inhibiting anti-oxidant enzymes such as SOD1 (superoxide dismutase 1), GPX (glutathione peroxidase). Accordingly, he underlined the importance of a pro-oxidant strategy as a new way of cancer therapy.

Professor Xiaolu Yang (University of Pennsylvania, USA) focused on p53 family proteins and discussed the role of those proteins in tumor cell metabolism. His group revealed an important function of p53 in inhibiting NADPH-producing enzymes including glucose-6-phosphate dehydrogenase (G6PD) and malic enzyme. By inhibiting these enzymes, p53 modulates NADPH production, the metabolism of both glucose and glutamine, and biosynthesis of essential precursors.

More specifically, many scientists were interested in various more specific aspects of energy metabolism in cancer cells. Professor Nissim Hay (University of Illinois at Chicago, USA) targets glucose metabolism for cancer therapy. As many speakers mentioned before, accelerated glycolysis is a unique characteristic in cancer cells even under aerobic conditions. Hay's group researched hexokinase (HK), which is involved in catalyzing the first step of glucose metabolism, and HK2 is abundantly expressed in cancer cells. Here, Hay highlighted an effective and novel cancer therapy *via* HK2 inhibition.

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0006-2952/

Besides the discovery of effective and novel targets for tumor cell metabolism, pharmacological targeting was also an actively discussed topic in this meeting. Doctor Claudia Cerella (LBMCC, Hôpital Kirchberg, Luxembourg) started the session about novel pharmacological approaches by addressing the effect of natural compound regulators of cancer cell metabolism. Cerella introduced mammalian target of rapamycin (mTOR) signaling and provided new insights into the control of downstream effectors and upstream regulators of mTOR signaling as well as into interplay with other existing nutrient-sensing intracellular pathways. Furthermore, Cerella described the effect of natural compounds with the potential to preventing mitochondrial dysfunctions and modulating cancer cell metabolism: Curcumin and resveratrol are known to decrease mitochondrial membrane potential (MMP), to modulate Bcl-2 family protein expression, to increase ROS and to abrogate hypoxia inducing factor (HIF)-1α. She convinced the audience that natural compounds efficiently regulate both mitochondrial and metabolic pathways.

Professor Young-Joon Surh (Seoul National University, South Korea) highlighted the importance of docosahexaenoic acid (DHA), a representative of ω-3 polyunsaturated fatty acids abundantly present in fish and some plant seed oil with antioxidative, anti-inflammatory and chemopreventive properties. He demonstrated inhibition of UVB-induced expression of cyclooxygenase (COX)-2 and nitric oxide (NOX)-4 in mouse skin by blocking the activation of NF-κB through inhibition of ERK- and p38 MAP kinase-mediated phosphorylation of MSK1.

Professor Frank Madeo (University of Graz, Austria) focused on the aging process in the context of autophagy using Drosophila. Administration of a natural polyamine, spermidine, triggered epigenetic deacetylation of histone H3 through inhibition of histone acetyltransferase. This altered chromatin acetylation status led to a significant upregulation of autophagy-related transcripts; therefore Madeo considers autophagy as a key regulator of aging in response of endogenous metabolites polyamines.

Prof. Atanas G. Atanasov (University of Vienna, Austria) identified honokiol as a promising lead for peroxisome proliferator-activated receptor (PPAR) γ agonists to fight metabolic diseases. He demonstrated a unique ability of honokiol to suppress hyperglycemia and weight gain, which turns this compound into an interesting natural product with a wide range of applications as a dietary supplement.

The use of energy restriction mimetic agents (ERMAs) was introduced by Professor Stéphane Flament (Université de Lorraine, France) as cliglitazone derivatives, namely delta 2 troglitazone and thiazolidinedione independently triggered endoplasmatic (ER) stress prior to apoptosis as the result of an energy restriction mimetic action.

The p53-induced protein TIGAR plays an important role in cancer cell metabolism as discussed by Professor Guido Bommer (Université Catholique de Louvain, Belgium). Bommer identified and re-evaluated the chemical function of TIGAR by demonstrating that fructose 2,6-bisphosphate (F26BP) does not represent a physiologic substrate for TIGAR, and its catalytic activity is 400-fold lower than for 2,3-bisphosphoglycerate (2,3-BPG), which suggest that 2,3-BPG might play a yet unrecognized function in metabolic control.

Professor Lina Ghibelli (University of Roma Tor Vergata, Italy) focused on the activity of sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPases (SERCA) related to glycolysis in damage-induced apoptosis. Ghibelli concluded that an ongoing glycolytic flux is necessary to maintain the activity of SERCA during the commitment phase of damage-induced apoptosis, and to attain the full finalization of the intrinsic apoptotic pathway.

Professor Sergio Giannattasio (University of Molise, Campobasso Italy) discussed an interesting experimental model based on yeast acetic acid-induced programmed cell death (AA-PCD) related to mitochondrial functions. Yeast grown in raffinose instead of glucose favors mitochondrial respiration and exhibits AA-PCD resistance that is decreased in both ROS production and cytochrome c release in comparison to glucose-grown AA-PCD cells. Giannattasio concluded that constitutive activation of the mitochondrial retrograde (RTG) signaling pathway inhibits AA-PCD in response to mitochondrial respiration de-repressed by low glucose levels: cellular metabolism determines cell stress response *via* RTG pathway activation.

Deregulation of cellular metabolism was a topic introduced by Professor Marie-Clotilde Alves-Guerra (Université Pairs Descartes, Paris, Frances). She focused on mitochondrial uncoupling protein 2 (UCP2) which play a role in tumor development by modulation of cellular energy metabolism and ROS production. Cells over-expressing UCP2 shift their metabolism from glycolysis toward oxidative phosphorylation; moreover, UCP2 overexpression activated adenosine monophosphate-activated protein kinase (AMPK) signaling concurrent with a downregulation of HIF expression thus UCP2 controls metabolic reprogramming in cancer cells.

Lastly, Professor Yong Sang Song (Seoul National University, College of Medicine, South Korea) investigated clinical implications by addressing metabolic interactions between cancer cells and its microenvironment in ovarian cancer. He pointed out that energy-rich metabolites produced by epithelial tumor cells are used in oxidative phosphorylation in adjacent cancer cells by promoting tumor growth. Specifically for ovarian cancer, targeting cancer-associated fibroblasts (CAFs) might be an effective therapeutic strategy as many evidence support the critical role of CAFs in relation to the reciprocal cancer-stromal communication in the development and progression of ovarian cancer.

In conclusion, the meeting "Metabolism 2014: Alterations of metabolic pathways as therapeutic targets" provided an excellent overview describing specific metabolic traits of cancer cells as well as pharmacological and clinical trials targeting the cancer cell metabolism. Exclusive traits of cancer cell metabolism discussed in this meeting will improve future cancer therapy and generate synergistic effects with established cancer drugs. We are at the beginning of a new challenging era in cancer research and diverse efforts to renew interest on cancer cell metabolism might contribute to better define this therapeutic target.

1. Meeting information

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

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Reference

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