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VIEW ON NEWS

The metabolic switch of cancer
From the 2016 Sino-US Symposium on Cancer Metabolism, Chongqing, P.R. China, October 10–11, 2016

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Abstract Although remarkable progress has been made in oncology research, cancer is still a leading cause of death worldwide. It is well recognized that cancer is a genetic disease, yet metabolic alterations or reprogramming are the major phenotypes associated with the (epi-) genetic modifications of cancer cells. Thus, understanding the metabolic changes of tumor cells will facilitate the diagnosis of cancer, alleviate drug resistance and provide novel druggable targets that can lead to cures for cancer. The first Sino-US Symposium on Cancer Metabolism was held in Chongqing on October 10th and 11th, with the theme of "cancer metabolism and precision cancer therapy". The symposium brought about a dozen keynote speakers each from the US and mainland China, as well as one hundred delegates with an interest in cancer metabolism. This short article will briefly summarize the advances reported during this meeting.

Stress-responsive machinery regulates cancer metabolism

Fast-proliferating malignant cells require an excessive supply of energy and resources; thus, they are sensitive to environmental fluctuations. Ribosome biogenesis is an energetically-demanding process that controls protein synthesis and cell growth. Professor Yanping Zhang, from the University of North Carolina at Chapel Hill, USA, reported that perturbations of this process can trigger an acute stress response, in which several ribosomal proteins inhibit the E3 ubiquitin ligase, MDM2, leading to p53 activation and cell cycle arrest. However, cancer cells can also develop various tactics to adapt to unfavorable microenvironments. Upon nutrient deprivation, the ribosomal protein-MDM2-p53 pathway acts as a critical regulator of energy expenditure, as well as an essential stress sensor. Besides acting as a tumor suppressor, p53 also facilitates hepatic lipid partitioning and fatty acid oxidation by inducing malonyl-CoA decarboxylase (MCD). Importantly, the discovery of an MDM2-p53-mediated metabolic switch has potential diagnostic, prognostic, and therapeutic applications for hepatocellular carcinoma, as well as other cancer types.

Transcriptome changes reflect the impact of environmental changes. In addition to alterations in the gene expression profile, non-protein coding transcripts, including microRNAs and long non-coding RNAs (lncRNAs), can also be modulated by stress conditions. Professor Mian Wu, from the University of Science and Technology of China, Hefei, PR China, reported his latest discovery regarding a lncRNA-mediated pro-survival mechanism for tumor cells. Wu's group discovered a novel p53-inducible lncRNA9, which is

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primate-conserved and specifically upregulated in response to oxygen and glucose deprivation. Mechanistically, LncRNA9 binds to and destabilizes STRAP (Serine/Threonine Kinase Receptor Associated Protein), which in turn inhibits the glucose synthase kinase-3 beta (GSK-3b)-NF-kB mediated necrotic pathway. Interestingly, p53-mediated upregulation of TRINGS (Tp53-regulated inhibitor of necrosis under glucose starvation) occurs only under glucose starvation, but not serum, serine or glutamine deprivation. Moreover, the upregulation of TRINGS by p53 was found to protect tumor cells, but not normal cells, from necrotic cell death.

In addition to nutrient deprivation-induced stress, living organisms often encounter oxidative stress from the reactive oxygen species (ROS) and nitrogen species generated from endogenous metabolism or exogenous toxicant exposure. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key transcription factor that regulates a wide array of genes encoding antioxidant and detoxification enzymes in response to oxidative and xenobiotic stress. In the normal state, Kelch-like ECH-associated protein 1 (Keap1) may bind to cytoplasmic Nrf2 and mediate Nrf2 ubiquitination and degradation. Upon oxidative stress, Nrf2 is translocated into the nucleus and initiates the expression of antioxidant response element (ARE)-dependent genes. Nrf2 agonists are usually considered cancer-preventive agents. Surprisingly, Professor Jingbo Pi, from China Medical University, Shenyang, PR China, reported that chronic activation of antioxidative responses can be detrimental and may lead to cancer development. Keap1$^{-/-}$−/− mice show neonatal death due to sustained Nrf2 activation. Oncogenes (such as Myc) can induce Nrf2 activation and promote tumorigenesis. In addition, Nrf2 expression was found to be significantly higher in neoplastic sites than peri-tumor tissues. Persistent activation of Nrf2 also reinforces the chemoresistance of tumor cells. Their work indicates that antagonizing Nrf2 may represent a potential therapeutic approach to sensitize cancers with elevated Nrf2 activity to chemotherapy and/or radiotherapy.

Even when the nutrient supply is sufficient, a lack of variety may also affect cancer progression. Professor Yongquan Chen, from Wake Forest University, USA, and Jiangnan University, Wuxi, PR China, described their work on the creation and analysis of a unique mouse strain, which is deficient for cholesterol efflux pump Abca1 and tumor suppressor PTEN, and which overexpresses fatty acid synthase (FASN). This strain shows a high incidence of prostate cancer. Augmenting the ratio of polyunsaturated fatty acid (PUFA) uptake (ω-6:ω-3; from 1:1 to 40:1) triggered chronic inflammation in the prostate, promoted cancer progression and shortened the overall animal survival. Interestingly, when ω-3 fatty acid desaturase Fat1 was overexpressed in these mice, high ω-6 dietary did not promote tumorigenesis in the mouse prostate. The tumor-protective effect of ω-3 PUFA depends on Bcl-2-associated death protein (BAD). They also demonstrated that the tumor-inhibitory role of ω-3 PUFA can be modulated by cytochrome c oxidases, COX1 and COX2, which exerted opposing effects. Taken together, their findings indicate that PUFA modulate prostate cancer development, at least partially through Bad-dependent apoptosis, which highlights the importance of gene—diet interactions in prostate cancer.

(Epi-)genetic modifications modulate tumor metabolism

Genetic modifications

It has been uncovered that tumor metabolism can be modulated at various levels. Chromosome 17p deletions are among the most common genetic abnormalities in various cancers and are associated with a dismal prognosis. However, the impact of 17p deletions has long been considered to be due to the inactivation of the tumor suppressor gene TP53. However, using a novel genetically-engineered mouse model that incorporates conditional deletion of chromosome 11B3, which is syntenic to the common deletion region on human 17p13, Professor Yu Liu, from West China Hospital, Sichuan University, Chengdu, China, discussed her group's identification of arachidonate lipoxygenases (ALOX) member Alox15B as a contributor to tumor development driven by 17p deletion. The loss of Alox15B correlates with an increase of its substrates, arachidonic acid (AA) and leukotriene. *Ex vivo* treatment with AA suppresses the apoptosis of lymphoma-origin pre-B cells.

Epigenetic modifications

Lymphocyte-specific helicase (LSH), a member of the ATP-dependent helicase in sucrose nonfermenting 2 (SNF2), is not only involved in DNA methylation, but also promotes RNA polymerase II stalling. Professor Yongguang Tao, from Xiangya Hospital, Central South University, Changsha, PR China, demonstrated that LSH can induce a cascade of epigenetic (methylation) changes and modulate tumor metabolism, which leads to IKKα recruitment to promoters of EMT (epithelial—mesenchymal transition)-related genes. They found that LSH not only promotes the growth, migration, and invasion of cancer cells *in vitro*, but also facilitates the EMT and colonization of metastatic cells *in vivo*. Furthermore, they showed that the TCA cycle intermediates and the ratios of α-KG/succinate and α-KG/fumarate are regulated by LSH via LSH-G9a (also known as euchromatic histone-lysine N-methyltransferase 2)-mediated repression of fumarate hydratase (FH) expression.

Autophagy is an evolutionarily-conserved protein degradation pathway in eukaryotes that plays a key role in many pathological conditions, including cancer. Understanding the mechanism(s) of autophagy will offer hope for the development of new therapeutic approaches for cancer. Professor Xiao-Feng Zhu, from the State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, PR China, summarized his group's studies on the roles of autophagy-associated proteins in tumor development and their prognostic potential in cancer patients. They found that patients with lower expression of Beclin 1 or ULK1 had a significantly shorter cancer-related survival and distant metastasis-free survival. Mechanistically, activation of the JNK pathway can phosphorylate c-Jun and promote c-Jun binding to the promoters of Beclin 1, LC3 and Sestrin 2 to upregulate their expression, which plays a key role in anticancer agent-induced autophagy in cancer cells. In addition,

Beclinacetylated by p300 at lysine residues 430 and 437, while the phosphorylation of Beclin 1 at S409 by CK1 is required for p300 binding and Beclin. Beclin 1 acetylation inhibits autophagosome maturation and endocytic trafficking by promoting the recruitment of Rubicon. In support of this finding, the expression of an acetylation site-specific mutant Beclin 1 led to enhanced autophagosome maturation and tumor growth suppression in an *in vivo* xenograft model, indicating that alterations of autophagy-related proteins via post-translational modifications are associated with tumor progression.

The NAD^+-dependent protein deacetylase SIRT1, a master regulator of chromatin structure and an important cellular metabolic stress sensor, has controversial roles in tumorigenesis. Professor Xiaoling Li from the National Institute of Environmental Health Sciences (NIEHS), National Institute of Health (NIH), USA, presented work performed in both immortalized mouse embryonic fibroblasts (MEFs) and human colorectal cancer cell lines carrying two copies (WT), one copy (Het), or no copy (KO) of the SIRT1 gene. They found that the SIRT1 Het cells displayed elevated proliferation in culture, increased colony formation on soft agar, and enhanced tumor formation in a nude mouse xenograft model, whereas SIRT1 KO cells exhibited reduced proliferation, colony formation, and cancer formation in comparison with the SIRT1 WT cells. Mechanistically, they showed that deletion of one copy of the SIRT1 gene is sufficient to activate NF-κB and induce c-Myc expression, promoting cell proliferation, autophagy, and stress resistance in a glutamine-dependent manner. On the other hand, deletion of both copies of the SIRT1 gene triggers cellular apoptotic pathways, leading to increased cell death, diminished autophagy, and reduced cancer formation. There results demonstrate a dose-dependent effect of SIRT1 in tumorigenesis, which highlights the importance of maintaining a suitable SIRT1 expression level for metabolic and tissue homeostasis.

Noncoding RNAs (ncRNAs) are emerging as new regulators of gene expression. Recent studies have revealed that a growing number of ncRNAs, especially microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), have crucial roles in metabolism and human diseases. Professor Xianghui Fu, from West China Hospital, Sichuan University, Chengdu, PR China, reported that miR-26a functions as a buffer to maintain normal cellular metabolism, thereby preventing the development of multiple human diseases, including cancer and metabolic diseases. They showed that miR-26a could maintain the tricarboxylic acid cycle of hepatocytes, thereby preventing cancer-related metabolic reprogramming and the development of liver cancer. With regard to metabolic disease, hepatic miR-26a was reduced in obese mice and humans. Overexpression of miR-26a in mice fed a high-fat diet improved their insulin sensitivity, decreased gluconeogenesis, and decreased fatty acid synthesis, thereby attenuating obesity-induced metabolic complications. Conversely, silencing of endogenous miR-26a led to the opposite effects. Collectively, their data revealed a novel function for miR-26a in metabolism and human diseases, including cancer and metabolic diseases.

Metabolic regulation and cancer treatment

Metabolite sensing

Professor Shimin Zhao from Fudan University found different mechanisms for metabolite-sensing. For example, acetyl-CoA was sensed by protein lysine acetylation, α-ketoglutarate was sensed by the α-ketoglutarate-dependent dioxygenase protein family, amino acids were sensed by tRNA synthetases, and their signals were transmitted via lysine aminoacylation. In this way, IDH1 mutations produced 2-hydroxyglutarate or FH, and SDH mutations led to the accumulation of fumarate and succinate. These mutations promoted tumorigenesis by either disrupting α-ketoglutarate sensing to alter the epigenetics or by promoting hypersuccinylation, which induces cancer-associated metabolism and resistance to apoptosis. These seminal discoveries provided new insights into altered cancer metabolism and provide opportunities for the development of new therapeutic strategies.

Drug resistance

Epidermal growth factor receptor (EGFR) inhibitors such as erlotinib are novel effective agents in the treatment of EGFR-driven lung cancer, but their clinical impact is often impaired by acquired drug resistance through the secondary T790M EGFR mutation. Mass spectrometry and NMR-based cancer metabolomics have witnessed exponential growth in the last decade. One discovery in this field was made by Professor Huiru Tang of Fudan University, who showed that reduced glutathione (GSH) biosynthesis contributed to EGFR T790M-driven erlotinib resistance in non-small cell lung cancer using ^{1}H-NMR-based metabolic flow analysis. They showed that decreased transcription of the GSH-synthesising enzymes (GCLC and GSS) was responsible for low GSH levels in resistant cells and was directly linked to the T790M mutation. Whereas, increasing intra-tumoral GSH levels with a small-molecule GST inhibitor Ethacrynic acid re-sensitised resistant tumors to erlotinib in mice. Their work demonstrated the power of NMR-based metabonomic profiling to discover alternative strategies to tackle drug resistance in lung cancer treatments.

EMT blockade

Reprogramming of the cellular metabolism is an important alteration that occurs during the metastatic transformation of cancer cells, leading to enhanced invasiveness and stem cell-like properties. Professor Binhua P. Zhou from the University of Kentucky, USA discovered that Snail-mediated fructose-1,6-biphosphatase (FBP1) repression provided basal-like breast cancer cells with metabolic advantages in the EMT. Using unbiased protein purification coupled with mass spectrometry analyses, they identified that Snail and Twist, two key EMT-inducing transcription factors, act as a transcriptional repressor (a "break") and activator (an "engine"), respectively. Because Snail is a labile protein and is subject to protein ubiquitination and degradation, it represents a potentially druggable target. Professor Zhou's

group also identified the protein kinase, phosphatase, ubiquitin E3 ligase and de-ubiquitinase involved in the regulation of Snail, which may provide new targets for the development of therapeutic drugs against metastatic breast cancer.

De novo nucleotide biosynthesis

De novo nucleotide biosynthesis is increased in tumors. However, it remains unclear how cancer cells obtain building blocks such as ribose-5-phosphate, glycine, glutamine, aspartate, and NADPH from glucose and glutamine metabolism to achieve enhanced *de novo* nucleotide biosynthesis. Professor Xuemei Tong from Shanghai Jiaotong University School of Medicine identified a novel role for the Mondo family transcription factors, including MondoA and ChREBP, in promoting *de novo* nucleotide biosynthesis. In addition, she reported that transketolase (TKT), a regulatory enzyme in the non-oxidative branch of the pentose phosphate pathway, played an important role in providing cancer cells with building blocks for *de novo* nucleotide biosynthesis.

Eukaryotic cells can sense glucose and evoke signaling pathways to regulate growth and development. Thioredoxin interacting protein (TXNIP), the product of an immediate glucose response gene, TXNIP, functions as a negative regulator of glucose uptake, and its expression is dysregulated in diabetes and cancer. Professor Faxing Yu demonstrated that MondoA and Max-like protein X (MLX) form a complex with the assistance of nuclear factor Y (NF-Y), which is recruited to the TXNIP promoter upon glucose stimulation. This, in turn, recruits general transcription factors and RNA polymerases to initiate gene transcription. MondoA/MLX activity and TXNIP expression are tightly correlated with the status of mitochondrial oxidative phosphorylation (OXPHOS), and inhibition of OXPHOS by drugs such as metformin can dramatically repress TXNIP transcription by inducing glycolytic flux. Moreover, the expression of TXNIP is induced by an array of adenosine-containing molecules, and these molecules function as amplifiers of glucose signaling.

Metabolic control of cancer-related inflammation

Glycolysis leads to acute inflammation, which will trigger a resolution phase, accompanied by lipid catabolism. If this phase is not well controlled, a chronic inflammation phase will appear that leads to cancer progression. Professor Tiefu Liu, from Fudan University, Shanghai, demonstrated that Sirtuins control tumorigenesis by regulating metabolite-mediated inflammation.

The impact of metabolites on the immune responses against tumors

It has been proven that mobilizing the immune system with immunotherapy is a promising strategy for cancer management. In addition, accumulating evidence suggests that the immune system is important for the success of chemotherapeutic interventions. Chemotherapy elicits stress responses in tumor cells, leading to the release of endogenous factors named "Cell Death-Associated Molecular Patterns (CDAMPs)". A series of CDAMPs have been reported to be indispensible for triggering an anti-tumor immune response. One of these, adenosine triphosphate (ATP), the central intermediate in energy metabolism, has been intensively investigated. Professor Yuting Ma from the Chinese Academy of Medical Sciences reported that anthracyclines could provoke autophagy, apoptosis and necroptosis pathways in tumor cells, which are critical for ATP release. ATP is essential for the recruitment of $CD11b^{+}CD11c^{+}Ly6C^{hi}$ cells to the tumor microenvironment and their further differentiation to dendritic cells for tumor antigen presentation. Chemotherapy also induces Annexin A1 release from stressed tumor cells, which engages formyl peptide receptor-1 (FPR1) on dendritic cells (DC). This signaling is crucial for the DC to approach and stably interact with dying tumor cells. ATP can engage the P2RX7 receptor on DC to trigger NLRP3 inflammasome activation and IL-1β secretion. IL-1β is crucial for the activation of anti-tumor effector cells, including $\gamma\delta$T and $CD8^{+}$T. These findings emphasize the impact of tumor metabolites on the tumor immune microenvironment.

Aside from the above four topics that mainly focused on metabolic regulation and altered metabolite sensing under stress conditions or during anti-cancer therapies and metastatic processes, several speakers also touched on other aspects related to cancer metabolism. For instance, Professor Fengming Lu from Peking University Medical Center presented his group's latest discovery related to doxorubicin-induced bile acid accumulation, which they found occurs via p53-mediated upregulation of NTCP (sodium taurocholate co-transporting polypeptide). They also reported its association with intolerance to doxorubicin therapy due to bile salt-induced skin irritation. Professor Jingke Chen from Shanghai Jiaotong University School of Medicine reported reciprocal interactions between Sirt3 and SUMO-specific protease (SENP) in the mitochondria, which link sumoylation with cancer. Professor Hongbing Zhang from Peking Union Medical College and the Chinese Academy of Medical Sciences discovered a role for the PI3K-AKT-TSC-mTOR pathway in regulating the Warburg effect, and described a way to target this pathway in tumor therapy. Last but not the least, metabolism-based imaging technologies for monitoring tumors are improving rapidly. Professor Mei Tian from the Second Affiliated Hospital of Zhejiang University School of Medicine outlined new metabolism-based technologies for tumor imaging and the importance of molecular imaging for personalized cancer therapy.

More than 20 lectures were given during the condensed two-day meeting, which highlighted the substantial advances in understanding the links between metabolism and cancer initiation and progression, as well as the potential clinical implications. In addition to these lectures, many short talks were also presented. We apologize to the many other excellent speakers and presenters whose work was not discussed here due to space constraints.

Conflict of interest

There is no conflict of interest by all coauthors.

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