Genes & Diseases (2017) 4, 12–15

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://ees.elsevier.com/gendis/default.asp

Selected Abstracts from The First Sino-US Summit & 2nd National Symposium on Cancer Metabolism

MECHANISM OF P53-INDUCED LNCRNA IN PRETECTING TUMOR CELL SURVIVAL DURING GLUCOSE STARVATION

Mian Wu
Hefei National Laboratory of Physical Science at Microscale School of Life Sciences, University of Science and Technology of China Hefei, Anhui 230027, China

Due to Warburg effect, cancer cells prefer to metabolize glucose through aerobic glycolysis, which results in low efficiency of ATP production. It is reasonable to believe that tumor cells will rely more heavily on glucose uptake to make up insufficient energy produced from glycolysis. It is expected that, under glucose starvation, cancer cells will subject to more cell death than normal cells. Yet, even those solid tumors that are intermittently or constantly exposed to glucose deprivation were shown to grow vigorously. How tumors successfully cope with the glucose stress remains unclear. Metabolic reprogramming can be one of the key strategies by which cancer cells stay healthy under stresses. Tumor suppressor p53 was found to be mutated in about 50% of the human cancers and whether WT p53 in the remaining 50% tumors is tumor-preventing or tumor provoking is as yet an unanswered question. Recently, some reports have shown that p53 promotes cell survival under glucose stress. In this regard, p53 no longer acts as a tumor suppressor, rather it become an "accessory" to help cancer cells to survive harsh environment. Moreover, besides protein factors, whether and how p53 regulated lncRNA(s) is (are) involved in cancer cell death regulation has (have) been less studied. Here, we report a new p53-regulated lncRNA, which we named TRINGS (Tp53-regulated inhibitor of necrosis under glucose starvation), and it protects cancer cells from necrosis. A detailed mechanism of how TRINGS protects cancer cell against necrosis had also been delineated in this study. Here, we show that under glucose starvation condition, p53 directly upregulates lncRNA-TRINGS that in turn binds to STRAP and inhibits STRAP-GSK3β-NFκB necrotic signaling axis, thus to protect tumor cells from necrotic cell death. Interestingly, TRINGS responses to glucose starvation, but not FBS-, serine- or glutamine-deprivation. Furthermore, its protective role is limited to tumor but not normal cells. Our finding reveals a p53-dependent, a long non-coding RNA TRINGS—mediated new necrotic pathway that contributes to survival of cancer cells harboring wild-type p53 under glucose stress.

http://dx.doi.org/10.1016/j.gendis.2016.10.005

MOLECULAR MECHANISMS OF METABOLITES SENSING AND SIGNAL TRANSDUCTION

Shimin Zhao
Institute of Biomedical Sciences, Fudan University, Shanghai 200433, China

The interconversion of metabolites provides the bases of the exchange of materials between organisms and their surroundings, and the connections among different physiologies. We found that metabolites are sensed through different mechanisms and deregulated metabolites-sensing contribute to pathology of various diseases. Acetyl-CoA, an indicator of both energy and nutrients, is sensed by protein lysine acetylation that regulates homeostasis of metabolites including glucose. α-Ketoglutarate is sensed by α-Ketoglutarate-dependent dioxygenases family proteins. IDH1 mutations produced 2-hydroxyglutarate or FH and SDH mutations accumulated fumarate and succinate promotes tumorigenesis through either disrupting α-Ketoglutarate sensing that alters epigenetics or promoting hypersuccinylation that induces cancerous metabolism and apoptosis resistance. Amino acids are sensed by tRNA synthetases and their signals are transmitted via lysine aminoacylation. The revealing of metabolites sensing and signal transmitting mechanisms is providing us opportunities to identify novel drugable targets.

http://dx.doi.org/10.1016/j.gendis.2016.10.006

ROLE OF DIETARY FAT IN CANCER

Yongquan Chen
Wake Forest University Baptist Medical Center, USA

Although a causal role of genetic alterations in human disease such as cancer is well established, it is still unclear whether dietary fat can modulate cancer risk in a predisposed population. Omega-3 and omega-6 polyunsaturated fatty acids (PUFA) are essential fatty acids: mammals can neither synthesize them de novo nor interconvert them; therefore, they have to be taken in from diet. Homo sapiens historical diet is estimated to have an omega-6:3 PUFA ratio of 1:1. Current Western diets, however, have omega-6:3 ratios of 20 and sometimes as high as 50. Diet has also been changing rapidly in Chinese population during the last three decades in terms of fat quantity and quality. Interestingly, prostate cancer occurs at a much higher frequency in the Western than Asian countries, whereas asymptomatic occult prostate cancer with genetic mutations has similar prevalence worldwide. We used transgenic/knockout animals and cell culture models to determine the influence of dietary fat on prostate cancer risk. We found that omega-3 PUFA suppresses and omega-6 accelerates prostate cancer progression and the ratio of omega-6 to 3 is important for effective tumor suppression. Modulation of prostate cancer development by PUFA is mediated in part through Bad-dependent apoptosis. Our study highlights the importance of gene-diet interactions in prostate cancer.

http://dx.doi.org/10.1016/j.gendis.2016.10.007

THE IMPACT OF ALOX CLUSTER LOSS IN CHROMOSOME 17P DELETIONS ON CANCER

Yu Liu [a], Chong Chen [a], Zhengmin Xu [a], Ting Niu [b], Scott Lowe [c]
[a]*State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University and National Collaborative Innovation Center, Chengdu, China*

[b]Department of Hematology, West China Hospital, Sichuan University, Chengdu, China
[c]Memorial Sloan Kettering Cancer Center, New York, USA

Chromosome 17p deletions are among the most frequent genetic abnormalities in various cancers and associated with a dismal prognosis. However, compared to comprehensive studies on individual gene mutations role in cancer biology, the impact of 17p deletions have long been simply considered as the inactivation of tumor suppressor gene TP53. Previous work in our laboratory identified additional tumor suppressor genes next to TP53, indicating that large deletions on 17p may contribute to cancer biology beyond their impact on eliminating wildtype TP53 allele. To explore this further, we generated a novel genetically-engineered mouse model that incorporates conditional deletion of chromosome 11B3, which is syntenic to the common deletion region on human 17p13. We found that besides p53, heterozygous deletion of linked genes on 11B3 not only promotes Myc-driven lymphomagenesis or Nf1; Mll3-defective leukemogenesis as seen by shorter tumor latency and overall survival than controls with only p53 loss, but also contributes to the poor outcome of chemotherapy treatments as shown by additional resistance to cyclophosphamide, vincristine and methotrexate. Furthermore, most lymphomas generated from heterozygous deletion of 11B3 have spontaneously missense or frame-shift mutations on the other wildtype p53 allele during the loss of p53 heterozygosity, which represents the major p53 configurations in human cancers. In contrast, no large deletion has been detected in lymphomas generated from current p53 mouse model with either deletion or mutation. Furthermore, to comprehensively understand the impact of individual 17p13 gene on tumorigenesis, we have performed a corresponding 17p13 shRNA library screening and identified several new tumor suppressors that is capable of promoting Eμ-Myc lymphoma development by its own or cooperating with p53 suppression in tumorigenesis. Moreover, three of them are clustered together, and all belong to arachidonate lipoxygenase (ALOX) family members, Alox15b-Alox12b-Aloxe3. Loss of Alox15b are found to be correlated with the cellular increase of its substrate, arachidonic acid, as measured by Lipid Chromatography-Mass Spectrometry (LC-MS). Additionally, in vitro extracellular arachidonic acid treatment suppresses the apoptosis of lymphoma-origin pre-B cells. Together, these results indicate that arachidonic acid metabolism pathway may contribute to the roles of 17p deletions in driving tumor. In summary, our results provide the new aspects of chromosome 17p deletions in cancer biology and may shed light on developing new therapeutic methods.

http://dx.doi.org/10.1016/j.gendis.2016.10.008

CHROMATIN REMODELING FACTOR LYMPHOID-SPECIFIC HELICASE AND METABOLISM IN CANCER

Yongguang Tao
Center for Medicine Research, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China

Cancer metabolism and epigenetic alteration, especially in chromatin remodeling, are two critical mechanisms for carcinogenesis, however, the dynamic interplay between them in tumors remains poorly understood. Lymphocyte-specific helicase (LSH), a member of the ATP-dependent helicase in sucrose nonfermenting 2 (SNF2), is not only involved in DNA methylation, but it also promotes RNA polymerase II stalling. Epithelial-mesenchymal transition (EMT) is thought to be activated in cancer cells, linked to their dissociation from the primary tumor and their intravasation into blood vessels. However, the effect of EMT in cancer progression, especially in chromatin remodeling, remains poorly understood. Oncoprotein latent membrane protein 1 (LMP1) encoded by Epstein-Barr virus (EBV) infects more than 90% of the global adult population and contributes to several malignancies, including nasopharyngeal carcinoma (NPC). We here provide robust evidence that LSH is highly expressed in NPC, where it is controlled by LMP1. Furthermore, we found that LSH does not only promote growth, migration, and invasion of NPC cancer cells in vitro, but also links with EMT, including cell migration, invasion, and tumor growth and colonization in vivo, indicating that LSH plays a critical role in tumor growth and metastasis through promoting transition from the epithelial stage to the mesenchymal stage. Then we found a repressive regulatory role of LSH in the expression of fumarate hydratase (FH) expression. a key component of the TCA cycle, catalyzes the hydration of fumarate to malate and is essential for cellular energy production and macromolecular biosynthesis. We confirmed that LSH is an important regulator of FH expression and down-regulates FH protein level in NPC derived from xenograft and clinical samples. We found that LSH was associated with the fh promoter; therefore, FH may serve as a direct target of LSH function. However, LSH may repress the fh promoter independent of DNA methylation, indicating that another mechanism is involved. G9a, also known as euchromatic histone-lysine N-methyltransferase 2, is an important epigenetic regulator, which monomethylates and dimethylates lysine-9. We provided the evidence of an interaction between LSH and G9a; the evidence of recruitment of G9a to the fh promoter in a LSH-dependent manner; and the evidence of subsequent chromatin modification leading to FH promoter repression, thus linking epigenetic regulation by LSH with suppression of the emerging tumor suppressor gene FH. Then, we found further that TCA cycle intermediates and the ratio of α-KG/succinate and α-KG/fumarate are regulated by LSH, However, we found no association between the EBV status and the intermediates of TCA cycles in NPC patients. Moreover, TCA intermediates promote cancer progression through the decrease of epithelial markers and the increase of mesenchymal marker expression. Finally, we demonstrate that the chromatin regulator and transcriptional activator inhibitor of nuclear factor kappa-B kinase alpha (IKKα) may be involved in the regulation of EMT markers, mediating the effect of LSH and TCA intermediates. LSH overexpression, as well as de-regulation of TCA intermediates, leads to IKKα recruitment to the promoters of EMT-related genes. In this way, LSH induces a cascade of epigenetic and metabolic changes that result in further epigenetic regulations via IKKα and EMT.

http://dx.doi.org/10.1016/j.gendis.2016.10.009

REGULATION OF DE NOVO NUCLEOTIDE BIOSYNTHESIS IN CANCER CELLS

Xuemei Tong
Shanghai Key Laboratory of Tumor Microenvironment and Inflammation, Shanghai Jiao Tong University School of Medicine, Shanghai 200240, China

Increased de novo nucleotide biosynthesis is required for cancer cell proliferation. However, it remains unclear how cancer cells obtain ribose-5-phosphate, glycine, glutamine, aspartate, and NADPH from glucose and glutamine metabolism to achieve increased de novo nucleotide biosynthesis. Mondo family transcription factors including MondoA and ChREBP play important roles in regulating glucose, lipid and amino acid metabolism. We recently identified a novel role of MondoA and ChREBP in promoting de novo nucleotide biosynthesis. In order to investigate the mechanism by which ChREBP and MondoA increased de novo nucleotide biosynthesis, we searched for target genes for ChREBP and MondoA which played critical roles in nucleotide biosynthesis. We found that transketolase (TKT), a target gene for Mondo family, could be important for nucleotide biosynthesis. TKT is a regulatory enzyme in the non-oxidative branch of pentose phosphate pathway and plays an important role in providing cancer cells with building blocks for de novo nucleotide biosynthesis.
We generated a liver specific TKT knockout mice strain by crossing TKTfl/fl mice with albumin (Alb)-Cre mice. 2-week old male mice were injected 25mg/kg diethylnitrosamine (DEN), followed by high fat diet (HFD) feeding from one-month postbirth. We found that about 100% TKT+/+ Alb-Cre and TKTfl/+ Alb-Cre mice developed liver cancer whereas the tumor incidence decreased to 40% in TKTfl/fl Alb-Cre mice at 9 month postbirth. Tumor number and size were significantly reduced in TKTfl/fl Alb-Cre mice when compared to control littermates. Intriguingly, TKT deficiency reduced NADPH levels while promoting R5P production. Notably, loss of TKT in liver not only attenuated DEN/HFD-induced hepatic steatosis and fibrosis, but also led to increased apoptosis, reduced cell proliferation and decreased expression of TNF-α, IL-6 and Stat3. Our study may provide new strategies for liver cancer prevention and therapy through transcriptional and metabolic regulation.

http://dx.doi.org/10.1016/j.gendis.2016.10.010

IMMEDIATE GLUCOSE RESPONSE

Faxing Yu [a], Yan Luo [b]
[a]Children's Hospital and Institutes of Biomedical Sciences, Fudan University, Shanghai 200433, China
[b]School of Basic Medical Sciences, Zhejiang University College of Medicine, Zhejiang 310058, China

Eukaryotic cells can sense glucose and evoke signaling pathways to regulate growth and development. An immediate response to glucose is the expression of a set of genes mediated by cis carbohydrate response elements