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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

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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.

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MOLECULAR MECHANISMS OF METABOLITES SENSING AND SIGNAL TRANSDUCTION

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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.

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ROLE OF DIETARY FAT IN CANCER

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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.

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

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