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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.

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CHROMATIN REMODELING FACTOR LYMPHOID-SPECIFIC HELICASE AND METABOLISM IN CANCER

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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.

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REGULATION OF DE NOVO NUCLEOTIDE BIOSYNTHESIS IN CANCER CELLS

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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.

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IMMEDIATE GLUCOSE RESPONSE

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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

(ChoRE) and their associated transcription factors MondoA and Max-like protein X (MLX). Thioredoxin interacting protein (TXNIP), the product of an immediate glucose response gene TXNIP, functions as a negative regulator for glucose uptake, and its expression is dysregulated in diabetes and cancer. We have observed that the ChoRE cis regulatory element is duplicated during vertebrate evolution, with one ChoRE in fish and two in mammals. In mammalian cells, both ChoREs are required for an optimal glucose response. With assistance by nuclear factor Y (NF-Y), MondoA/MLX complex is recruited to TXNIP promoter upon glucose stimulation, which in turn recruits general transcription factors and RNA polymerases to initiate gene transcription. In addition to glucose or its derived metabolites, MondoA/MLX activity and TXNIP expression is tightly correlated with 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, we have discovered that the expression of TXNIP is induced by an array of adenosine-containing molecules, and these molecules function as amplifiers of glucose signaling. Thus, MondoA/MLX complex serves as a hub integrating diverse upstream signals and a master regulator of glucose homeostasis.

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REGULATION OF SNAIL IN EPITHELIAL-MESENCHYMAL TRANSITION AND BREAST CANCER PROGRESSION AND METASTASIS

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Triple-negative Breast Cancer (TNBC) is associated with an aggressive clinical history, development of recurrence, distant metastasis and shorter patient survival. Intriguingly, TNBC has activated the epithelial-mesenchymal transition (EMT) program, which is a cellular de-differentiation process that provides cells with the increased plasticity and stem cell-like properties required during embryonic development, tissue remodeling, wound healing and metastasis. Using unbiased protein purification coupled with mass spectrometry analysis, we identified that Snail and Twist, two key EMT-inducing transcriptional factors, act as transcriptional repressor and activator, respectively. Snail is a labile protein and is subjected to protein ubiquitination and degradation, and we have identified the protein kinase, phosphatase, ubiquitin E3 ligase and de-ubiquitinase in the regulation of Snail. Interestingly, the protein stability of Snail and its interaction with these effectors are controlled by signals from the tumor microenvironment, resulting in the EMT induction and invasive phenotypes that commonly observed at the tumor-stromal boundary. Our study provides new insights and opportunities for the development of effective therapeutic approaches against metastatic breast cancer.

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WHY ARE RED HAIRED INDIVIDUALS SO PRONE TO DEVELOPING MELANOMA?

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Melanoma is a highly aggressive cancer with an alarmingly increasing incidence. A major question in melanoma biology is why are red-haired individuals at a high risk of developing melanoma. Polymorphisms in the melanocortin-1-receptor (MC1R) gene, encoding a trimeric G protein-coupled receptor activated by α-melanocyte-stimulating hormone (α-MSH), are frequently associated with red or blonde hair, fair skin, freckling and skin sensitivity to ultraviolet (UV) light, and several (RHC-polymorphisms) also associate with increased melanoma risk. However, some polymorphisms appear to affect melanoma risk independent of phenotype; using an in vivo model system we recently reported that some MC1R mutations synergize with UV to induce melanoma independently of their effects on melanogenesis. Understanding precisely how MC1R polymorphisms differentially affect melanoma biology is therefore a key issue. Importantly, we also found that UV irradiation triggered MC1R-interaction with and degradation of PTEN, leading to increased PI3K-signalling—driven senescence in melanocytes, but senescence bypass in BRaf mutant melanoma. Importantly, WT MC1R but not red-hair associated MC1R mutants could interact with PTEN. Furthermore, we used newly generated MC1R conditional RHC-polymorphism mouse models to dissect the tumor suppressive functions of MC1R in melanoma initiation in vivo and specifically its role in controlling PI3K signaling via PTEN degradation. Our studies identify intracellular molecular targets of MC1R in suppressing melanoma initiation that are directed towards identifying novel strategies for melanoma prevention and therapeutic intervention.

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CYSTEINE PROMOTION OF BREAST CANCER TUMORIGENESIS IS DEPENDENT OF THE SOLUTE CARRIER SLC3A1

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Cysteine as well as glutamine and alanine are critical substrates for synthesis of glutathione (GSH). Glutamine and alanine, but not cysteine, are most upregulated intermediate metabolites in cancer cells, suggesting cysteine uptake is increased. However, it's not clear how the uptake of cysteine is regulated. Here, we report that the cysteine carrier SLC3A1 is upregulated in breast cancer cells, and its expression levels are correlated with clinical stages and patients' survival. In breast cancer cells, overexpression of SLC3A1 accelerates the uptake of cysteine, which in turn increases the concentration of reductive GSH and the GSH/GSSH ratio and concomitantly decreases the cellular level of ROS (reactive oxygen species). Consequently, overexpression of SLC3A1 promotes the tumorigenesis of breast cancer cells, whereas knocking-down or inhibition of SLC3A1 decreases tumorigenesis of breast cancer cells in mice. Moreover, SLC3A1 inhibitor Sulfasazine suppressed tumor growth and abolished dietary NAC-promoted tumor growth. Mechanistically, our data manifest that ROS catalyzes thiol into sulfenic acid at the HC(X)4EXV motif of serine/threonine phosphatase PP2Ac which is similar as the ROS-induced sulfenylation at the HC(X)5RS/T motif of protein tyrosine phosphatases (PTPs); however, unlike PTPs, sulfenylation increases the stability and activity of PP2Ac rather than deactivating PTPs. SLC3A1 activates the Akt pathway through decreasing the sulfenylation and stability of protein phosphatase PP2Ac. Collectively, our data demonstrate that SLC3A1-mediated increase of cysteine uptake promotes the tumorigenesis of breast cancer cells, and SLC3A1 determines breast cancer cell response to antioxidant N-acetylcysteine, suggesting SLC3A1 is a potential therapeutic target for breast cancer.

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REGULATION OF CHREBP TRANSCRIPTION IN RESPONSE TO GLUCOSE

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Transcription factor carbohydrate responsive element binding protein (ChREBP) is abundant in liver and adipose tissues. ChREBP promotes glycolysis and lipogenesis in metabolic tissues and cancer cells. ChREBP-α and ChREBP-β are two isoforms of ChREBP transcribed from different promoters. Both ChREBP-α and ChREBP-β are transcriptionally induced by glucose. However, the mechanism by which glucose promotes ChREBP transcription remains unclear. Here we report that hepatocyte nuclear factor 4 alpha (HNF-4α) mediates transcription of ChREBP-α and ChREBP-β induced by glucose. Ectopic HNF-4α expression promoted ChREBP transcription while knockdown of HNF-4α reduced ChREBP mRNA levels in liver cancer cells and mouse primary hepatocytes. We found that the expression of HNF-4α and ChREBP was positively correlated by analyzing levels of ChREBP and HNF-4α in the liver of mice under fasting and feeding conditions. HNF-4α directly bound to an E-box-containing region in intron 12 of the ChREBP gene, in addition to directly binding to DR1 sites of the ChREBP-β promoter. Moreover, HNF-4α interacted with ChREBP-α and synergistically promoted ChREBP-β transcription. Interestingly, HNF-4α knockdown decreased glucose-dependent ChREBP induction in liver cancer cells. Glucose increased expression and nuclear abundance of HNF-4α and its binding to cis-elements of ChREBP gene, which contributed to glucose-induced ChREBP transcription in liver cancer cells.