(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.

http://dx.doi.org/10.1016/j.gendis.2016.10.011

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

Binhua P. Zhou
Madeline F. James Gardner Endowed Chair Co-leader, Genomic, Epigenetic and Metabolism Program Markey Cancer Center and Department of Molecular and Cellular Biochemistry University of Kentucky School of Medicine, USA

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.

http://dx.doi.org/10.1016/j.gendis.2016.10.012

WHY ARE RED HAIRED INDIVIDUALS SO PRONE TO DEVELOPING MELANOMA?

Rutao Cui
Department of Pharmacology and Experimental Therapeutics, Boston University Cancer Center, Boston University School of Medicine, Boston, MA 02118, USA

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.

http://dx.doi.org/10.1016/j.gendis.2016.10.013

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

Yuan Cao
Shanghai Jiaotong University School of Medicine, Shanghai 200240, China

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.

http://dx.doi.org/10.1016/j.gendis.2016.10.014

REGULATION OF CHREBP TRANSCRIPTION IN RESPONSE TO GLUCOSE

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

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.