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PhD Dissertation Defense

Entitled

Epigenetic modifications in metabolic syndrome: Identification and evaluation of early indicators using a rodent model system

by

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Abstract

It is increasingly realized that mechanisms of developmental plasticity rather than pathology independently facilitate the size of developing embryos during early development. Changes in the early developmental environment alter the metabolic traits resulting in diseases, including metabolic syndrome, which includes type 2 diabetes and obesity in adulthood. Molecular and epidemiological studies have documented an association between lower birth weight (LBW) and increased risk of developing metabolic syndrome. Henceforth, using birth weight as a marker, two groups of normal birth weight range rat pups, lower birth weight (LBW, 5th to 25th percentile) and average birth weight (ABW, 50th to 75th percentile) as determined by their uterine horn positions were established. In the LBW pups, metabolic signaling pathways, P13k/Akt, Pparγ, insulin metabolism and the genes regulating growth were significantly downregulated. The expression of DNA methyltransferase 1 (Dnmt1) an epigenetic regulatory enzyme involved in DNA methylation was increased and this correlated with the decrease in the expression of insulin through increased methylation in the promoter of the Ins II gene in the LBW pups. Dnmt1 also contributed to the LBW pups through the inhibitory complex formation with Hdac1, RB, and E2f1. This increase in the inhibitory complex by regulating the cell cycle check point slowed down the embryo's growth by retarding the progression of the cell cycle. In adulthood, the LBW pups are heavier in weight than ABW pups, also showed increased visceral fat accumulation, higher fasting glucose, increased LDL, triglycerides, and a decrease in HDL. Microarray analysis identified the expression of clustered Protocadherins was altered in LBW adults. In the skeletal muscle and liver, we found only Pcdha4 isoform was predominantly expressed.

We have further verified the association of clustered Protocadherin, Pcdhα4 in the development of obesity. Analysis using qPCR and western blotting showed down regulation of Pcdha4 in the skeletal muscle and liver of LBW adults. Methylation studies using Methylated DNA immunoprecipitation followed by qPCR showed increased methylation in the regulatory region of Pcdha4, which correlated with the decreased expression of Pcdhα4 seen by qPCR and western blotting. We also found this increased methylation affected the binding of transcription factors E2f2 and E2f3 on the regulatory region of Pcdha4, as evidenced by CHIP and EMSA analysis. Further analysis established the importance of Pcdha4 in forming a stable, functional complex involving Ret-Gdnf-Gdnfr alpha, which is altered in LBW adults. We also show that this stabilized complex regulates the genes involved in lipid metabolism including, Srebp1, Pparγ, C/ebpβ, C/ebpα. Our analysis identifies the factors which respond to changes in the developmental environment and establishes a role for Pcdha cluster in lipid metabolism.

Together our analysis identifies the factors which respond to changes in the developmental environment. We also identified some of the factors and pathways that regulate these factors and changes, leading to an increased risk of developing metabolic syndrome.

Keywords: Developmental plasticity, metabolic syndrome, Lower birth weight, DNA methylation, lipid metabolism, PCDHa cluster.