

GLOBAL DNA METHYLATION AND GENE EXPRESSION ANALYSIS IN PRE-B CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is a fast-growing cancer of lymphoblasts. Our complete understanding of all mechanisms responsible for ALL induction is inadequate. DNA methylation plays a significant role in hematopoiesis and malignant transformation. Therefore, the identification of altered DNA methylation on key regulatory regions of the genome is critical to gaining a better understanding of ALL pathogenesis. This dissertation identified the dynamic establishment of DNA methylation during normal B-cell development, and alterations of DNA methylation in the pathogenesis of ALL. First, a protocol to isolate the subsets of precursor B-cells from human umbilical cord blood (HCB) was developed. Using this protocol, we were able to isolate sufficient numbers of pro-B, pre-BI, pre-BII and naïve B-cells from a single HCB unit. Next, genome-wide DNA methylation profiles using the methylated CpG island recovery assay followed by next generation sequencing (MIRA-seq) were generated for each of the four subsets of precursor B-cells. We report for the first time that hypermethylated loci are associated with the transition of pro-B to pre-BI cells. Differentially methylated regions were identified and the majority of the loci were present within intronic and intergenic regions that harbor putative regulatory elements. The development of methylation profiles in normal precursor B-cells will aid in elucidating the role of altered DNA methylation in the pathogenesis of ALL. In order to identify epigenetic alterations in ALL, we next determined the differentially methylated regions (DMRs) between ALL and healthy precursor B-cells. Further, whole genome transcriptome analysis was performed to determine the regulatory potential of the DMRs. Our studies identified ALL specific epigenetically deregulated genes, novel putative enhancers, and biological pathways that showed concurrent DNA methylation and changes in gene expression during malignant transformation. These altered epigenetic marks could be used as prospective biomarkers for ALL and/or as potential targets to reset the altered DNA methylation in order to modify gene expression which may enhance the present treatment protocol for ALL and eventually improve patient outcome.