Public Abstract

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Title:Global DNA methylation and gene expression analysis in pre-B cell acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is a hematological cancer associated with precursor B-cells and is the most common cancer diagnosed in children under the age of 15. Our complete understanding of all mechanisms responsible for ALL induction is inadequate. DNA methylation is an epigenetic modification and is accountable for regulating gene expression and plays a significant role in hematopoiesis. In addition to genomic rearrangements and hyperdiploidy, other mechanisms like alteration of DNA methylation may be involved in ALL pathogenesis. 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. This method can be adapted for any type of cell present in HCB at any stage of differentiation. 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 gaining of DNA methylation in certain regions of genome were associated with the transition of pro-B to pre-BI cells. Differentially methylated regions were identified and the majority of the regions 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 revealing the role of altered DNA methylation in the pathogenesis of precursor B-cell related disorders including 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 genes expression 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.