

Hypermethylation Status of Promoter is an Epigenetic Change in Lymphoid Malignancies

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Alteration in methylation pattern of promoters is associated with tumorigenic events,(1, 2) and differentiation control,(3, 4) in several types of cells in humans. Specific hypermethylation in promoter region of some genes exist in different types of neoplastic cells.(5) DNA methylation indicates to the addition of a methyl moiety to the cytosine in a CpG dinucleotide. CpG dinucleotides tend to gather closely together in CpG islands, and are usually located in promoter region of genes.(6)

In cancerous transformation, there is a change in the methylation pattern of specific genes, by which hypermethylation of CpG islands in promoter region and hypomethylation of the noncoding regions occur.(7) Methylation of CpG islands in promoter region result in gene silencing, a phenomenon that has oncogenic potential when it arises in tumor suppressor genes.

The methylation status of several promoters has been analyzed in lymphoid malignancies. Roman-Gomez et al. evaluate the 39 genes involved in cell immortalization and transformation in 307 patients with acute lymphoblastic leukemia (ALL) by Methylation Specific PCR (MSP). Of 39 genes 23 genes showed hypermethylation status in promoter region of genes including: SMC1L2, NES1, ADAMTS1, PGR, sFRP1, CDH1, ADAMTS5, CDH13, LATS1, DKK3, WIF1, LATS2, REPRIMO, sFRP5, PARK2, PACRG, HDPR1, RIZ, APAF1, ARTS, ASPPI, DIABLO and sFRP4.(8) Dunwell et al. demonstrated frequent epigenetic inactivation of *THRB*, *BNCl*, *PPP2R3A*, *FBLN2* and *MSX1* in lymphoid malignancies including B-cell and T-cell ALL.(9) The recognition of hypermethylated genes in lymphoid malignancies showing epigenetic alterations will be useful in developing targeted epigenetic therapies.(10, 11, 12)

Also, Methylation changes of CpG islands in promoter region of the p57KIP2, p73, and p15 genes have been shown to have poor prognostic value in adult ALL patients with Philadelphia (Ph) chromosome-negative disease.(13) These methylation changes are stable in greater number of patients with ALL at the time of relapse. Therefore, they can be used as a marker for minimal residual disease (MDR) detection.(14)

Hence, epigenetic mechanism such as hypermethylation in promoter region of genes can play important role in pathogenesis, diagnosis, prognosis, relapse detection and therapy of ALL. Nonetheless other epigenetic mechanisms such as histone modifications and small non coding RNAs such as microRNAs may have role in lymphoid malignancies.

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