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Genomic vulnerability to LINE-1 hypomethylation is a potential determinant of the clinicogenetic features of multiple myeloma

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Abstract

Background: The aim of this study was to clarify the role of global hypomethylation of repetitive elements in determining the genetic and clinical features of multiple myeloma (MM).

Methods: We assessed global methylation levels using four repetitive elements (long interspersed nuclear element-1 (LINE-1), Alu Ya5, Alu Yb8, and Satellite-α) in clinical samples comprising 74 MM samples and 11 benign control samples (7 cases of monoclonal gammopathy of undetermined significance (MGUS) and 4 samples of normal plasma cells (NPC)). We also evaluated copy-number alterations using array-based comparative genomic hybridization, and performed methyl-CpG binding domain sequencing (MBD-seq).

Results: Global levels of the repetitive-element methylation declined with the degree of malignancy of plasma cells (NPC>MGUS>MM), and there was a significant inverse correlation between the degree of genomic loss and the LINE-1 methylation levels. We identified 80 genomic loci as common breakpoints (CBPs) around commonly lost regions, which were significantly associated with increased LINE-1 densities. MBD-seq analysis revealed that average DNA-methylation levels at the CBP loci and relative methylation levels in regions with higher LINE-1 densities also declined during the development of MM. We confirmed that levels of methylation of the 5′ untranslated region of respective LINE-1 loci correlated strongly with global LINE-1 methylation levels. Finally, there was a significant association between LINE-1 hypomethylation and poorer overall survival (hazard ratio 2.8, $P = 0.015$).

Conclusion: Global hypomethylation of LINE-1 is associated with the progression of and poorer prognosis for MM, possibly due to frequent copy-number loss.

Keywords: Multiple myeloma, Global hypomethylation, Common breakpoints, Repetitive elements, LINE-1

Background

Multiple myeloma (MM) is a malignant plasma-cell tumor characterized by various and frequent chromosomal aberrations. Representative examples of these aberrations are loss of chromosome 13, hyperdiploidy, and translocations involving the immunoglobulin heavy chain (IGH) locus situated at 14q32.33. Several studies have shown that these genetic changes are associated with the clinical features of MM, including its prognosis [1-7]. In addition to such genetic changes, recent studies have begun to shed light on the role of epigenetic alterations in the pathogenesis of MM. One of the earliest reports of epigenetic aberrations in MM was of DNA hypermethylation in the promoter CpG islands of p15 and p16 [8-10]. Tumor-specific hypermethylation has also been found in the promoter regions of various tumor suppressors and other tumor-related genes, including *BNIP3*, *DAPK* and *RASD1*, which are associated with prognosis and drug resistance in MM [11-14]. Unexpectedly, however, recent advances in genome-wide analysis revealed

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