ADAMTSL5 and CDH11: putative epigenetic markers for therapeutic resistance in acute lymphoblastic leukemia

ABSTRACT

Background and objectives: DNA hypermethylation has been linked to poor treatment outcome in childhood acute lymphoblastic leukemia (ALL). Genes differentially methylated in the chemoresponsive pre-B-ALL compared to chemoresistant pre-B-ALL cases provide potential prognostic markers. Methods: DNA methylation profiles of five B-ALL childhood patients who achieved morphological complete remission (chemoresponsive) and five B-ALL patients who did not (chemoresistant) after induction treatments as well as four normal controls were compared on 27 000 CpG sites microarray chips. Subsequently, methylation-specific polymerase chain reaction (MSP) on selected hypermethylated genes was conducted on an additional 37 chemoresponsive and 9 chemoresistant B-ALL samples and 2 normal controls. Results: Both methods were found to be highly correlated. Unsupervised principal component analysis showed that the chemotherapy-responsive and -resistant B-ALL patients could be segregated from one another. Selection of segregated genes at high stringency identified two potential genes (CDH11 and ADAMTSL5). MSP analysis on the larger cohort of samples (42 chemoresponsive, 14 chemoresistant B-ALL samples and 6 normal controls) revealed significantly higher rates of hypermethylation in chemoresistant samples for ADAMTSL5 (93 vs. 38%; $p = 0.0001$) and CDH11 (79% vs. 40%, $p < 0.01$). All control cases remained unmethylated. Conclusion: Chemoresistant B-ALL patients are associated with increased methylation in ADAMTSL5 and CDH11. These findings need to be validated in a larger group of patients, and the functional biological and prognostic significance of differential methylation needs to be studied further.

Keyword: Acute lymphoblastic leukemia (ALL); Epigenetic marker; Methylation