To the editor:

Lack of RPS14 promoter aberrant methylation supports the haploinsufficiency model for the 5q- syndrome

In the past few decades several groups have tried to identify the putative gene(s) responsible for the development of 5q- syndrome, a specific clinical, morphologic, and cytogenetic myelodysplastic syndrome (MDS) subtype characterized by a defect in erythroid differentiation.1,2 The more distal common deleted region (CDR) at 5q31-q32, containing around 40 genes, seems to be restricted to 50% in expression profiling analysis was consistent with a decrease close to impairment of the ribosomal subunit protein RPS14 recapitulated the characteristic phenotype of the 5q- syndrome in normal CD34+ human hematopoietic progenitor cells. Further, forced expression of RPS14 in patient-derived bone marrow cells was able to restore the normal erythroid differentiation pattern. Point mutation or cryptic biallelic deletions of RPS14 were excluded by sequencing and high density single nucleotide polymorphism analysis of samples of patients with del(5q) and gene expression profiling analysis was consistent with a decrease close to 50% in RPS14 expression.4

The presence of a putative CpG island in RPS14 promoter region makes this gene susceptible to inactivation through aberrant methylation. Although the data by Ebert and colleagues indirectly suggest the lack of epigenetic silencing of RPS14,4 no specific gene methylation analysis of RPS14 has been performed so far and, thus, that possibility cannot be definitely excluded. To assess whether aberrant methylation of the remaining allele of RPS14 gene was involved in loss of RPS14 function in the 5q- syndrome, we studied the methylation status of RPS14 in bone marrow samples of 23 MDS patients with del(5q) (5q- syndrome: 12; RAEB-I: 5 and RAEB-II: 6, according to World Health Organization [WHO] classification3). 9 patients with acute myeloid leukemia (AML) with del(5q), in 4 AML-derived cell lines (Kasumi1, KG1A, HL-60, and THP1) and in 20 MDS cases with normal karyotype by methylation-specific polymerase chain reaction after DNA bisulfite treatment.5 Briefly, bisulfite conversion was carried out with Epitext Bisulfite Kit (Qiagen, Hilden, Germany) according to the manufacturer’s instructions. Primer-specific sequences of the gene for the unmethylated and methylated reactions were designed with Methyl Primer Express software v 1.0 (Applied Biosystems, Foster City, CA). DNA from healthy donors was used as negative control and methylated control DNA (CpGenome Universal Methylated DNA; Seralogicals, Norcross, GA) was used as positive control. Approval for these studies was obtained from the Hospital Universitario La Fe Institutional Review Board. Informed consent was obtained in accordance with the Declaration of Helsinki.

The CpG island present in RPS14 promoter region was unmethylated in all the samples analyzed, including 5q- cases, MDS with normal karyotype, AML primary cells and derived cell lines, as well as healthy donors. These findings demonstrate that low expression of RPS14 is not due to promoter hypermethylation, further supporting the haploinsufficiency model suggested by Ebert et al5 for the 5q- syndrome. They also suggest that the use of hypomethylating agents (ie, azacitidine or decitabine) is unlikely to benefit this subset of MDS patients.

References

To the editor:

Patients’ age and BCR-ABL frequency in adult B-precursor ALL: a retrospective analysis from the GMALL study group

The frequency of BCR-ABL is higher in adults than in children with acute lymphoblastic leukemia (ALL). We analyzed data from a large number of patients obtained within the framework of the central diagnostics of various GMALL (German Multicenter ALL) study group trials between 1990 and 2007 (www.ClinicalTrials.gov: NCT00199069, NCT00199056, NCT00198991). Investigations were done primarily at the central diagnostic laboratory of the GMALL study group in Berlin and, from 1990 to 2000, also in part at the University of Heidelberg. Overall, 2544 primary cell samples from patients with B-precursor (pro-B, common, pre-B) ALL (age 15-74 years) were diagnosed and..
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Ana Valencia, Jose Cervera, Esperanza Such, Miguel A. Sanz and Guillermo F. Sanz