IDENTIFICATION OF A NOVEL MECHANISM OF NPM1 CYTOPLASMIC LOCALIZATION IN ACUTE MYELOID LEUKEMIA: THE RECURRENT GENE FUSION NPM1–HAUS1

Chromosomal aberrations and gene mutations are the most important prognostic determinants in acute myeloid leukemia (AML). While several genomic aberrations have been well studied in AML, some remain uncharacterized. The study of such alterations can yield important biological insights and generate clinically relevant information. Herein we describe the molecular characterization of the recurrent AML associated chromosomal translocation, t(5;18)(q35;q21). Through whole genome sequencing of a bone marrow sample of a patient harboring the aforementioned translocation we identified the chimeric gene NPM1-HAUS1 and demonstrated the presence of an in frame transcript harboring NPM1 exons 1-10 fused to HAUS1 exon 9. This chimeric gene biologically resembles the more commonly seen NPM1 mutations, in that both abnormalities generate putative proteins of the same size, with disruption of tryptophan 288 and 290 and the generation of a novel C terminal nuclear export signal motif (NES). Finally, we demonstrate that NPM1-HAUS1, like the mutated NPM1, are localized both in the nucleus and in the cytoplasm by a mechanism dependent on NES, suggesting that patients harboring the t(5;18)(q35;q21) (NPM1-HAUS1) have a form of AML that biologically resembles the provisional World Health Organization entity “AML with mutated NPM1”.