Long non coding RNA expression profile in cytogenetically normal acute myeloid leukemia identifies a distinct signature in NPM1-mutated patients

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ABSTRACT

In this study we sought to evaluate the long non coding RNA (lncRNA) expression profile of patients with cytogenetically normal acute myeloid leukemia (CN-AML). RNA sequencing of forty CN-AML patients allowed us to identify more than 8000 previously-undescribed lncRNAs. Using unsupervised analysis we observed a specific lncRNA expression profile dependent of the mutational status of the Nucleophosmin (NPM1) gene. Indeed, statistical analyses highlighted a minimal set of 12 differentially expressed lncRNA between NPM1-mutated and NPM1-wild type patients. These results were validated by RT-qPCR (Fluidigm) on an independent cohort composed of 134 new CN-AML patients.

Furthermore, we have specifically identified one putative biomarker, the lncRNA XLOC_109948 whose expression pattern predicts clinical outcome. Interestingly, low XLOC_109948 expression indicates a good prognosis especially for NPM1-mutated patients. Transient transfection of GapmeR against XLOC_109948 in NPM1-mutated AML cell line treated with Ara-C or ATRA enhances apoptosis suggesting a role of XLOC_109948 in drug sensitivity.

Moreover, among the 12 lncRNAs deregulated in NPM1-mutated patients, we observed that the expression of a newly described lncRNA called LONA (lncRNA overexpressed in NPM1-mutated AML patients) inversely correlates with its neighboring histone-coding genes. LONA interacts with SUZ12, a component of the Polycomb Repressive Complex 2 (PRC2), suggesting its contribution in the epigenetic repression of histone genes and therefore a potential impact on chromatin remodeling. We demonstrated that mutant NPM1 modulates the nuclear/cytoplasmic localization of LONA which could consequently regulate its cellular function. We showed that downregulation of LONA in NPM1-mutated AML cell line enhances myeloid differentiation and apoptosis which are deregulated in AML, suggesting an oncogenic role of LONA in the development of AML.

Altogether, these data suggest that lncRNA should be considered as strong prognostic biomarkers and emerged as key players in the pathogenesis of acute myeloid leukemia.