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

Morgane Gourvest1*, Etienne De Clara1*, Hanjing Ma2, François Vergez1-3, Marie Tosolini1, Sébastien Dejean2, Cécile Demur1-3, Eric Delabesse1-3, Christian Recher1-3, Christian Touriol1, Maria Paola Martelli5, Brunangelo Falini5, Pierre Brousset1 and Marina Bousquet1

1Cancer Research Center of Toulouse (CRCT), UMR1037 Inserm/Université Toulouse III Paul Sabatier, ERL5294 CNRS, Laboratoire d’excellence Toulouse Cancer (TOUCAN); 2BGI, China; 3 Laboratoire et service d’Hématologie, Centre Hospitalier Universitaire de Toulouse, Institut Universitaire du Cancer; 4Institut de Mathématiques de Toulouse, UMR 5219 Université de Toulouse Paul Sabatier / CNRS; 5Institute of Hematology, University of Perugia, Ospedale S. Maria della Misericordia, Perugia, Italy; 6Department of Pathology, Institut Universitaire du Cancer de Toulouse-Oncoopole and Centre Hospitalier Universitaire de Toulouse, France

Long non-coding RNAs (lncRNAs) have recently emerged as important actors in the regulation of multiple cellular processes, and their deregulation could contribute to diseases and cancer. But little is known about their implication in hematopoietic malignancies, especially in Acute Myeloid Leukemia (AML). In this study we sought to evaluate the 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.