P1000 INCREASED PLASMA LEVELS OF LNCRNAS ARE POTENTIAL PROGNOSTIC BIOMARKERS IN MYELOFIBROSIS

Topic: 15. Myeloproliferative neoplasms - Biology & Translational Research

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Background:

Myelofibrosis (MF) displays the worst prognosis among Philadelphia-negative myeloproliferative neoplasms and is characterized by megakaryocyte hyperplasia, progressive bone marrow fibrosis, extramedullary hematopoiesis and frequent transformation to acute myeloid leukemia.

Different therapeutic approaches are being used depending on the severity and the specific clinical manifestations of the disease in each patient. Unfortunately, no curative therapy is currently available for MF, except for bone marrow transplantation, which however has a consistent percentage of failure. There is therefore a great urgency to identify biomarkers correlated with the different stages of the disease and to treat patients with a more tailored treatment.

Long non-coding RNAs (IncRNAs) have been described as key mediators in the development of hematological malignancies. Moreover, circulating IncRNAs have already been proposed as a new class of non-invasive biomarkers for diagnosis and prognosis.

Aims:

The aim of this study was to identify circulating IncRNAs whose plasmatic concentration differs between MF patients and healthy donors (HDs). Subsequently, we evaluated their potential role as non-invasive disease biomarkers in MF.

Methods:

As a preliminary result we analyzed the expression of 38 IncRNAs in CD34+ cells collected from 83 MF patients and 26 HDs leading to the identification of 26 differentially expressed IncRNAs. To confirm these results and to move to a more accessible sample type we collected plasma from 143 MF patients and 65 HDs. RNA was extracted from

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these samples and the relative abundance of lncRNAs, including some of those deregulated in CD34+ cells or already described as involved in hematological malignancies and myeloid differentiation, was assessed using qRT-PCR. According to the plasmatic levels of each lncRNA patients were split into two groups (low- or high-) and this subdivision was used to unveil the potential correlation between the various lncRNAs and the clinical features of MF patients.

Results:

Our analysis identified 7 lncRNAs significantly upregulated in MF patients’ plasma compared to HDs. Among these, high levels of LINC01268, MALAT1 or GAS5 correlated with several detrimental clinical features of MF, such as high counts of leukocytes and CD34+ cells, a severe grade of bone marrow fibrosis and the presence of splenomegaly.

Strikingly, high plasma levels of LINC01268 (Log-rank p-value = 0.0018), GAS5 (Log-rank p-value = 0.0008) or MALAT1 (Log-rank p-value = 0.0348) were associated with a poor overall-survival (OS) while high levels of LINC01268 correlated also with a shorter leukemia-free-survival (LFS). Finally, multivariate analysis demonstrated that a high plasma concentration of LINC01268 was an independent prognostic variable for both OS (HR = 2.104; confidence interval (CI) = 1.08–4.12; p = 0.0297) and LFS (HR = 8.190; CI = 1.02–65.78; p = 0.0479).

Summary/Conclusion:

To our knowledge, this is the first study describing the expression profile of circulating lncRNAs in MF patients’ plasma and focusing on their putative role as biomarkers in clinical practice. In particular, our results demonstrated that increased levels of circulating LINC01268, GAS5 or MALAT1 are associated with disease detrimental features and correlate with an inferior OS in MF patients. Notably, multivariate analysis confirmed that LINC01268 plasma levels might improve the identification of patients with a poor prognosis. If the prognostic value of this lncRNA will be confirmed in independent patients’ cohorts it might be used to integrate contemporary prognostic models.