Abstract: P608

Title: THE EXPRESSION OF CYTOR LNCRNA HAS POOR PROGNOSTIC VALUE IN CLL PATIENTS AND IS ASSOCIATED WITH MICROENVIRONMENTAL STIMULI.

Abstract Type: Poster Presentation

Session Title: Chronic lymphocytic leukemia and related disorders - Biology & Translational Research

Background:

The lncRNA CYTOR has been described to have oncogenic roles and its expression be associated with poor prognosis in several solid cancers. Nevertheless, its biological functions and clinical impact are still poorly known in lymphoid neoplasms. Particularly in CLL, there is only one report pointing to its overexpression measured by qRT-PCR in a subset of patients but lacking any significant clinical value in a series of Binet A CLL samples.

Aims:

To determine the prognostic value of the lncRNA CYTOR in a large series of well characterized CLL samples both clinically and biologically. Furthermore, we wished to characterize its potential biological roles in the CLL pathogenesis as well as the possible origin of its overexpression in a subset of patients.

Methods:

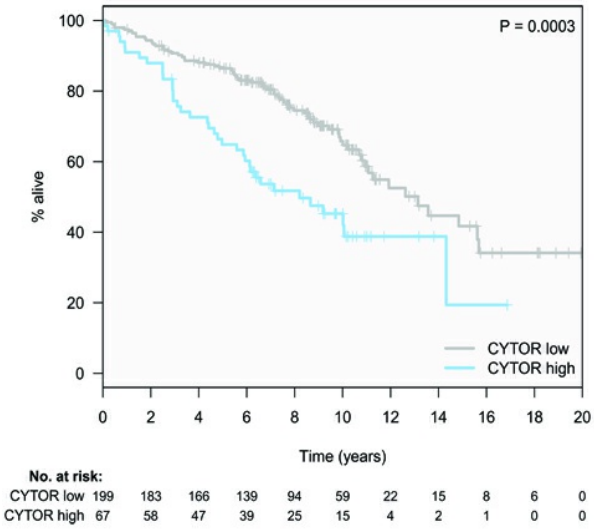
We analyzed CYTOR expression in RNA-seq data in CLL samples from the ICGC project (https://dcc.icgc.org). In addition, CLL purified cells from 8 patients were treated *ex vivo* with some factors mimicking the microenvironment stimuli in the LN (CpG-ODN+CD40L+IL10) and compared with the corresponding untreated controls. From their purified total RNA, 10 ng were used for transcriptomic analysis with Clariom D WT pico microarray platform and TAC software (Applied Biosystems). Pathway enrichment analysis was performed using GSEA on ranked list of coding genes according to Pearson correlation of each gene from CYTOR levels across the series of samples.

Results:

CYTOR expression showed a significant association with a shorter time-to-treatment and overall survival, both in in Binet A cases as the entire cohort. Furthermore, this clinical impact was found to be independent of other well-established prognostic factors in CLL (IGHV mutational status and epigenetic subtypes as Binet stage) in multivariate Cox models. Biologically, CYTOR expression showed a significant positive correlation with the proliferative drive score previously described to be a poor prognostic marker in CLL, orthogonal to other known prognostic biomarkers and biologically associated with increased lymphocyte doubling rate and response to pro-proliferative stimuli (PMID: 34423310). Moreover, several pathways known to be related to CLL pathogenesis and proliferative drive were significantly enriched among coding genes correlated with CYTOR in the studied ICGC series, also including genes previously known to be upregulated in CLL cells in the lymph nodes compared to peripheral blood. Concordantly, we found its expression significantly increased in CLL cells treated *ex vivo* with some factors mimicking the microenvironment stimuli in the lymph nodes. The coding genes correlated with CYTOR in these samples also showed a highly significant enrichment in signatures previously described to be induced by CpG-ODN treatment.

Summary/Conclusion:

All these results showed that CYTOR has poor prognostic value in CLL and could be biologically related with the degree of microenvironment stimulation in the lymph nodes and the previously described proliferative drive in CLL.



Keywords: Hematological malignancy, B cell chronic lymphocytic leukemia, Prognostic factor