HBZ-related dysregulation of circular RNAs (circRNA) expression in ATLL

Ladet J[1], Marie P[1], Marçais A[2], Forlani G[3], Accolla R[3], Mortreux F[1]

[1] Laboratory of Biology and Modelling of the Cell, Univ Lyon, ENS de Lyon, Univ Claude Bernard, CNRS UMR 5239, INSERM U1210, Lyon, France
[2] Department of Hematology, Necker Hospital, University of Paris Descartes, Paris, France.
[3] Laboratories of General Pathology and Immunology "Giovanna Tosi", Department of Medicine and Surgery, University of Insubria, Varese, Italy.

Background:
Besides transcriptional deregulations, alternative splicing modifications have been described in HTLV-1 infected cells *in vivo*, particularly at high abundance in ATLL cells, suggesting that altered splicing processes participate in leukemogenesis. Circular RNAs (circRNA) constitute a new class of single-stranded RNAs that are highly stable and covalently circularized by non-canonical back splicing events. circRNAs regulate gene expression and alternative splicing of linear RNAs by acting as miRNA or RNA-binding protein (RBP) sponges, as well as transcriptional regulators. Some circRNAs have been described in tumorigenesis and cancer development, thereby becoming of particular interest as potential new biomarkers or therapeutic targets.

Methods:
We carried out RNA-seq analysis of 56 ATLL and 8 donors with the pipelines CIRI and ClipStick for circRNA prediction.

Results:
ATL samples showed downregulation of circRNAs constitutively expressed in donors (1041/1722), including circRNA_FBXW7 and circRNA_SMARC5 which have been previously characterized as tumor suppressors. Gene ontology analysis, as well as in silico predictions of miRNA and RBP binding sites of circRNAs, suggest that such circRNA deregulation may affect functional pathways involved in RNA maturation, NF-κB and MAPK signaling, and cancer. Similar RNA-seq analysis of Jurkat cells expressing or not HBZ revealed a 96% overlap in circRNA identification between HBZ-expressing cells and ATLL samples, including 25 circRNAs that were absent in the control samples Jurkat and donors. Some circRNA deregulations were confirmed by back-splicing specific qRT-PCR. Mass spectrometry analysis of HBZ interactome permitted to identify 19 RBP already described in circRNA biogenesis. We confirmed interactions between HBZ and various RNA helicases including the back-splicing inhibitor DHX9. The impact of HBZ on RNA helicase-regulated back splicing events will be presented.

Conclusion:
Overall, our data show that HBZ affects back splicing processes in T cells, thereby explaining the large deregulations of circRNA expression profiles in ATLL.

Disclosure of Interest Statement:
Nothing to disclose.