29ème congrès du CHO
11 au 14 octobre 2023
Giens, Var, France

POSTER 3: CircRNA-PTPN22 in chemoresistance of anaplastic large cell lymphoma expressing the oncogenic tyrosine kinase ALK

Elissa Andraos[1], Loélia Babin[1], Steffen Fuchs[1], Chloé Bessière[1], Laurence Lamant[1], Stéphane Pyronnet[1], Fabienne Meggetto[1]

1 : CRCT, Inserm - Université de Toulouse Paul Sabatier - France

---

The Anaplastic large cell lymphoma (ALCL) is a pediatric aggressive lymphoma deriving from CD4 T lymphocytes mostly harbouring the t(2;5)/NPM-ALK translocation which fuses the tyrosine kinase domain of ALK protein to the dimerization domain of a chaperon protein, the nucleophosmin (NPM1). Oncogenic NPM–ALK signaling is mostly mediated by STAT3 pathway which play major roles in lymphomagenesis by controlling key cellular processes. Inspite of their responsivness to chemotherapy, 30% of the patients relapse with very bad prognosis. Thus, understanding the mechanisms responsible for the relapse and the discovery of new theragnostic biomarkers are crucial for treating relapsing patients. Circular RNAs (circRNAs), a new class of non-coding RNAs, have emerged as biomarkers for drug resistance in cancers. CircRNAs derived from back-spliced exons have been widely identified as being co-expressed with their linear counterparts.

We performed whole transcriptome deep sequencing on 9 reactive healthy lymph nodes and 39 primary biopsies of NPM-ALK (+) ALCL including 18 patients with early relapse and 21 patients without relapse. Using circRNA prediction algorithm and differential analysis, we identified overexpression of 9 circRNAs in the relapsed group compared to the non-relapsed and reactive lymph nodes samples. Among them, 3 circRNAs deriving from *PTPN22* gene which encodes a tyrosine phosphatase known to inhibit the TCR signaling pathway. Since previously we published that *PTPN22* gene is overexpressed in resistant NPM-ALK (+) ALCL patient (*Daugrois et al, Cancers, 2021*), we decided to investigate the involvement of both coding and non-coding PTPN22 RNA in NPM-ALK (+) ALCL resistance to treatment. Based on RNAseq data analysis, we noted that the PTPN22 expression is anti-correlated to the NPM-ALK expression level and the aggressiveness of the disease. The inhibition of STAT3 (siRNA)

or NPM-ALK activity (crizotinib (an ALK inhibitor) or siRNA) induced a clear increase in PTPN22 RNA suggesting a PTPN22 regulation through NPM-ALK/STAT3 axis. Divergent primers spanning the back-splice junction (BSJ) were designed to explore the 3 circPTPN22 isoforms. The full-length sequences and BSJ were validated by Sanger sequencing. RNase R and actinomycin D resistance analysis showed that the 3 circPTPN22 isoforms were more stable than linear PTPN22 mRNA suggesting their circular form. Cytoplasmic and nuclear fractionation experiments showed that the 3 circRNA isoforms were mainly localized in the cytoplasm, suggesting a potential role as miRNA and RBP sponges. Currently using different approaches, we are modulating the expression level of PTPN22 in order to explore and understand their role in the progression of the disease.