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New technologies and multiomics analysis

MULTI-OMICS ANALYSIS UNRAVELS NEW BIOMARKERS OF RELAPSE RISK IN ADULT PHILADELPHIA-POSITIVE B-ALL

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Introduction: The management and long-term outcome of adults with Philadelphia-positive Acute Lymphoblastic Leukemia (Ph+ B-ALL) improved since the introduction of tyrosine-kinase inhibitors (TKIs). With the administration of a chemo-free strategy combining second or third generation TKIs with Blinatumomab, hematological relapses occur in about 10% of cases (Foà. et al, 2024, Kantarjian et al, 2024). Nevertheless, mechanisms underlying relapse in Ph+ B-ALL still need to be clarified. In this context, the study of circular RNAs (circRNAs), single-stranded closed RNAs, adds a new layer to leukemic cells deciphering. In this study, we obtained a multi-omics characterization of Ph+ B-ALL using integrative data analysis to extract the molecular feature linked to an increased risk of relapse.

Methods: Total RNA sequencing (RNA-seq) was performed on 17 diagnostic samples of Ph+ B-ALL patients (phase III GIMEMA ALL2820 trial), 10 without relapses (NR) and 7 who experienced a relapse (R). Genes and circRNA expression were quantified using CirComPara2. Differential expression (DE) analysis was done using DESeq2 (Adj.p-<0.01) and logistic regression extracted the DE features more linked to relapse. CircRNA quantification was obtained by qRT-PCR with divergent primers followed by Sanger sequencing to confirm backsplice junctions. R library clusterProfiler was used to perform gene set enrichment analysis (GSEA). Integration of genes and circRNAs expression profiles was performed by the DIABLO mixOmics framework. RNA-call and STAR-fusion pipelines were used to identify expressed oncogenic variants and fusions genes, respectively.

Results: We observed a different expression profile of R and NR Ph+ B-ALL, with 18 DE circRNAs and 218 DE genes between the two patient groups. Several non-coding RNAs were DE. According to GSEA, genes were significantly enriched in specific pathways (including MYC targets, E2F targets and G2M checkpoint) activated in R cases. Most classifying DE genes and circRNAs were selected using a logistic regression algorithm and validations are ongoing, as well as integrative analyses of genes and circRNA data with DIABLO. Genetic profiling was performed to detect oncogenic variants and gene fusions, and beyond *BCR::ABL1*, unique lesions of or more frequent in R cases were disclosed.

Conclusions: We are providing an integrative multi-omics characterisation of relapsed Ph+ B-ALL patients, defining unique molecular signatures linked to disease relapse, including oncogenic variants, fusion genes and specific associations of genes and circRNA expression patterns. We discovered that R cases present a proliferative phenotype and activation of other oncogenic pathways. The identification of circRNAs linked to relapse provides new candidate biomarkers. Validations of selected DE circRNAs will be extended to consolidate findings.