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POSTER ABSTRACTS

618.ACUTE LYMPHOBLASTIC LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

3D Genome Organization and Single-Cell Characterization of Pediatric Intrachromosomal Amplification of Chromosome 21 (iAMP21) B-Cell Acute Lymphoblastic Leukemia

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B-cell Acute Lymphoblastic Leukemia (B-ALL) is the most frequent childhood cancer, and around 2% of these cases are associated with intrachromosomal amplification of chromosome 21 (iAMP21). The iAMP21 cases represent one of the high-risk but least understood sub-group of B-ALL. The sub-group also has a significantly low survival rate and a higher risk of relapse than non-iAMP21 cases. Recent studies suggest that structural variations in iAMP21 are linked to complex rearrangements such as a chromothripsis event on chromosome 21. The consequences of chromothripsis by which it drives the tumorigenesis are still unclear. Given the limited knowledge of chromothripsis and its impact on the epigenetic landscape in pediatric iAMP21 cases, we aim to systematically provide a critical understanding of the causes and consequences of such complex genomic rearrangements.

We conducted an in-depth analysis of 9 iAMP21 and 10 non-iAMP21 pediatric patient samples associated with B-ALL using different sequencing techniques. These included whole genome sequencing (WGS), long-read sequencing, RNA-sequencing, and 3D genome organization. The WGS analysis revealed that iAMP21 cases had more genomic rearrangements compared to the non-iAMP21 group. Interestingly, iAMP21 subtypes displayed a unique feature - the presence or absence of the chromothripsis signature on chromosome 21. However, all patients shared a common characteristic - amplified and frequently deleted regions on chromosome 21, suggesting these genetic changes are a key aspect of the iAMP21 subtype, regardless of chromothripsis. Genomic rearrangements, a crucial element in oncogenesis, also modify the 3D structure of the human genome, and iAMP21 is no exception. Our Hi-C data analysis showed the devastating effect of chromothripsis on the 3D organization of chromosomes in iAMP21 patients. We observed a significant reconfiguration of the genomic compartments, along with changes in cis- and trans-acting regulatory elements such as enhancers and promoters. These changes disrupt the delicate balance of gene expression profile. To better understand the impact of these genomic rearrangements on the transcriptional landscape, we examined global gene expression patterns in iAMP21 subtypes, identifying distinct upregulated and downregulated genes. Our comparison between iAMP21 and non-iAMP21 groups identified a unique set of 186 upregulated and 174 downregulated genes in iAMP21 patients. Further, tumor diversity can greatly influence cancer diagnosis and treatment responses. Therefore, analyzing gene expression at the single-cell level is essential to uncover this diversity and identify unique cellular characteristics. Our analysis provided clear evidence of iAMP21 subclones within individual patient samples, resulting from differences in genomic rearrangements in each cancer cell.

The iAMP21 cases with complex chromosomal rearrangement make it a high-risk and poorly characterized subtype of pediatric ALL. We hypothesize that even though related to worse outcomes, investigating the chromosomal rearrangement and the epigenetic landscape in iAMP21 may expose specific vulnerabilities of cancer cells in these patients allowing for targeted therapies and devising new therapeutic strategies. While our findings so far are preliminary, they offer valuable insights that can guide the formulation of hypotheses for further detailed experiments and data analysis. The project has already amassed a wealth of genomic data and a consistent approach to data analysis, addressing the challenging task of identifying relevant prognostic and predictive molecular factors in patients battling aggressive forms of cancer.

Disclosures Chandra: *Thermo Fisher Scientific:* Current Employment.

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