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617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Detection of Cryptic Gene Fusion and Chimeric RNA Variants in Relapsed/Refractory Acute Myeloid Leukemia Patients Diagnosed with KMT2A/Afdn Chromosomal Translocation

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Chromosomal rearrangements, such as translocations, play a significant role in creating chimeric genes and oncofusion proteins initiating leukemogenesis in 52% of acute myeloid leukemia (AML) patients, and are associated with an adverse prognosis. Currently, there are limited targeted therapies available for AML patients with chromosome rearrangements primarily due to a lack of accurate molecular and genetic characterization of the mechanism of leukemic progression along the treatment course. In our study, we investigated the pathological landscape of treatment resistance and relapse in AML patients with KMT2A-rearranged gene fusions (previously known as mixed lineage leukemia, MLL gene, 11q23), which is one of the most common gene rearrangements in AML with a dismal prognosis. Our approach included chromosome analysis, fluorescence in situ hybridization (FISH), transcriptomic analyses (RNA-seq), polymerase chain reaction (PCR), DNA-sequencing and quantitative PCR (qPCR) were applied to monitor RNA- and genome-wide changes among newly diagnosed, refractory and relapsed AML patients.

Bone marrow samples of seven AML patients with different chromosome were obtained and two samples were found to possess the chromosomal translocation t(6;11)(q27;q23) which leads to KMT2A/AFDN gene fusion. In these patients, RNA-seq identified a cryptic CCDC32 (15q15.1) /CBX3 (7p15.2) gene fusion in both newly diagnosed and relapsed samples, which is previously unreported in KMT2A/AFDN-rearranged AML patients. Quantitative gene expression measurement by qPCR demonstrated that CCDC32/CBX3 gene fusion significantly affected the expression of wild-type genes of CCDC32 (essential for embryonic development) and CBX3 (an oncogene for solid tumors) during the relapse, suggesting the potential oncogenic role for the CCDC32/CBX3 chimera in AML development. Our result is consistent with a previous study showing multiple breakpoints in AML patients with KMT2A/AFDN translocations.

KMT2A rearrangements are known to have an unfavorable prognosis in AML and the specific t(6;11)(q27;23) translocation in AML patients leads to a median overall survival of only 12 months. Our novel findings also suggest that one reason for the adverse outcomes of KMT2A chromosomal rearrangements is their complex ability to generate chimeric variants and more aggressive subclones to elude the treatment.

Our study implies that standard cytogenetic analyses and emerging NGS are not sufficient to fully diagnose a patient with chromosome rearrangement. Particularly, short-read RNA-seq presents problems because it cannot detect gene fusions with

low expression level, like the KMT2A/AFDN gene fusion that was undetected in patient 7 by our short-read RNA-seq. Instead, long-read RNA-seq, combined with cytogenetics and molecular profiling through PCR/Sanger DNA-sequencing, should be utilized to identify complex fusion transcripts and different chimeric variants of multiple gene fusions.

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