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POSTER ABSTRACTS

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

The XPO1-FOXC1-HOX Functional Axis Opens New Therapeutic Avenues to Treat DEK-NUP214 AML Patients

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Introduction: t(6;9)(p23;q34.1)/DEK-NUP214 patients represent a discrete group of younger AML patients recognised as a separate disease entity in the World Health Organization classification of myeloid neoplasms. They typically display a dismal prognosis, higher relapse rate and a striking co-occurrence with *FLT3*-ITD mutations in > 70% of cases. DEK is a nuclear factor that has been attributed multifunctional roles, including gene regulation, while its fusion partner, NUP214, plays a pivotal

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role in nuclear export by interacting with transport receptors such as XPO1. However, the precise mechanism by which DEK-NUP214 drives leukaemia remains unclear.

Aims: Application of a multi-omics profiling to understand the oncogenic mechanisms underlying DEK-NUP214 fusion protein and identify potential therapeutical vulnerabilities.

Methods: A comprehensive multi-omics screening (whole genome sequencing, targeted sequencing, transcriptomics, (phosphor)proteomics, mass cytometry (CyTOF) and *in vitro* drug screening) was conducted on 57 untreated primary AML samples from cytogenetically poor-risk AML, including four cases with t(6;9) translocation (complex karyotype (n=20), -7/del(7) (n=15), KMT2A rearrangements (not including t(9;11)) (n=12), t(6;9) (n=4) and other poor-risk karyotypes (inv(3), -5/del(5), t(3;12)/+8 or -17/del(17)) (n=6)). The t(6;9)/DEK-NUP214 cell line FKH-1, was utilised as a model for *in vitro* experiments and compared with other AML cell lines (OCI-AML3, KASUMI-1, THP-1, P31-FUJ, MV4-11 and K562). *In vitro* drug treatments were conducted in the cell lines and patient samples using Cell-Titer&Glo, and transcriptional changes were evaluated using qPCR and RNA-seq. To examine the function of selected target genes of DEK-NUP214, we used lentiviral shRNA system followed by cell cycle, apoptosis, differentiation, and cell proliferation assays.

Results: An integrative RNA-seq analysis of our cohort and a separate series of 691 AML cases that included three additional t(6;9) cases (Leucegene, https://leucegene.ca/) revealed 128 genes significantly upregulated and 74 downregulated in t(6;9) patients compared to other AML samples. The overexpressed genes included some known leukaemia mediators *(FOXC1, HOXA* and *HOXB* genes), the genes previously reported in t(6;9) patients *(EYA3, SESN1* and *PRDM2)* and novel genes with roles in haematopoiesis or cancer cell survival that showed the most significant differences *(NFIX* and *GGT5)*. The significant overexpression of these genes was also confirmed in the t(6;9) FKH-1 cell line. *In vitro* drug screening of 527 licenced or investigational drugs allowed us to identify the compounds that were most effective and selective for t(6;9) patients in comparison with other AML cytogenetic groups. The two XPO1 inhibitors (Selinexor and Eltanexor) included in our drug panel were within the four top-ranked compounds. Of note, qPCR and RNA-seq analyses in the cell lines and primary patient samples showed that inhibition of XPO1 resulted in significant downregulation of the expression of *FOXC1, NFIX, EYA3, HOXA* and *HOXB* genes, highlighting a functional axis linking these target genes, XPO1 and the fusion. In line with this finding, silencing of *FOXC1* in the FKH-1 cells led to an increase in apoptosis, lower cell proliferation and reduced clonogenic capacity, accompanied by a concomitant downregulation of *HOXA* and *HOXB* genes. Collectively, these findings support a key role of *FOXC1* in DEK-NUP214-driven AML.

Conclusion: This study offers valuable insights into the molecular and pathological mechanisms underlying t(6;9)-AML, revealing a functional interaction between DEK-NUP214, XPO1 and FOXC1, and providing evidence to consider XPO1 inhibition as a potential new avenue to treat these patients.

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