

Literature review

Dissecting poor-risk acute myeloid leukemia with *DEK::NUP214*

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Introduction

Acute myeloid leukemia (AML) arises from the malignant transformation of myeloid progenitor cells with excessive clonal proliferation, differentiation blockage and apoptosis resistance, underpinned by genetic abnormalities and epigenetic aberrations.¹⁻³ Regarding the World Health Organization (WHO) classification of myeloid neoplasms⁴ and the European Leukemia Net (ELN) risk stratification of AML⁵, the chromosomal abnormalities and genetic mutations play a crucial role in prognostic significance. Additionally, they lead to creating personalized treatment by risk-adapted strategy and targeted therapy in a particular patient with AML.

Among recurrent genetic abnormalities of AML, the t(6;9)(p23;q34.1) is a translocation between the short arm of chromosome 6 and the long arm of chromosome 9, resulting in the chimeric fusion gene *DEK::NUP214*. This AML subtype represents about 1% of all AML cases and is classified in the adverse risks of AML because of a significantly lower complete remission (CR) rate (65-81% after standard high intensity chemotherapy), higher relapse and poor overall survival.⁶ Studies of *DEK::NUP214*-driven AMLs revealed some specific clinical characteristics such as relatively younger age of onset with a median of 34.5 years (range 2 to 76 years), bone marrow basophilia of about 40% and dysplastic features in around two thirds of cases. Five-year estimated survival was only 10 to 38%, with median overall survival (OS) of 14 months.^{7,8} Furthermore, *Fms*-like tyrosine kinase 3 (*FLT3*) with an internal tandem duplication (*FLT3*-ITD) mutation was also detected in over 70%⁹, significantly elevated compared with the general AML population where *FLT3*-ITD underpins AML among 25 to 30% of patients.^{10,11} However, the

presence of t(6;9) was associated with poor outcomes regardless of *FLT3*-ITD status.¹² Allogeneic hematopoietic stem cell transplantation in AML with t(6;9)(p23;q34.1)/*DEK::NUP214* demonstrated improvements in survival, especially when patients received the transplantation after achieving the first complete remission from high intensity chemotherapy.^{8,13-16} Additionally, the longitudinal monitoring of measurable residual disease (MRD) with real-time quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR or RQ-PCR) of *DEK::NUP214* fusion transcripts should be applied in clinical practice to improve the treatment outcomes by tailored therapy regarding the results of MRD positive or MRD negative.¹⁷

DEK

DEK, encoding the 43-kDa DEK protein, is located on human chromosome 6p23. The DEK protein structurally consists of the scaffold attachment factor A/B-Acinus-Pias (SAP) domain on the N-terminal and second DNA binding regions on the C-terminal with multiple putative functions and plays a role as a transcription factor.¹⁸ It has the ability to bind DNA, affecting gene expression and the cellular function.^{19,20} The binding specificity between DNA and the DEK protein is influenced by chromatin sequence and structure;^{21,22} thus, one possibility is that DEK may play a role in chromatin architecture.²³ DEK also interacts with the Serine-Arginine (SR) proteins and U2AF2/3 splicing complexes that remain attached to the exon product RNA after splicing, influencing splice site selection during mRNA processing.^{24,25} Moreover, the DEK protein is also distributed throughout the genome and ubiquitously accumulated at transcription start sites of highly expressed genes across different cell types and tissues, especially in regulatory regions

enriched for PU.1 and SP1 motifs, critical regulators of myeloid cell development.²⁶ *DEK* expression is generally high in rapidly proliferative cells but decreases in differentiation, maintaining the long term stemness of hematopoietic stem cells. Additionally, the DEK protein plays a role as a senescence inhibitor and anti-apoptotic factor by reducing replicative senescence and promoting the transcriptional activity of the MCL-1 anti-apoptotic protein, respectively.^{27,28} Furthermore, the DEK protein acts also as a cofactor of DNA damage repair machinery, regulating genomic stability.²⁹

NUP214

NUP214 (formerly called the *CAN* gene) is located in the human chromosome 9q34.1. It encodes the 214-kDa nucleoporins 214 (NUP214) protein, one of the components of the nuclear pore complex (NPC) anchored at the cytoplasmic domain forming a subcomplex with nucleoporin NUP88.^{30,31} NPC is a transversely embedded protein complex in the nuclear membrane consisting of more than 30 proteins. It plays an essential role in bidirectional transport between the nucleus and cytoplasm. NPC allows small molecules (ions and polypeptides) to pass through by diffusion and macromolecules (> 40 kDa) by active transport mediated by carrier proteins and transport factors, collectively called karyopherins (importins, exportins and transportin).³² The NUP214 protein is structurally composed of three domains: an N-terminal b-propeller domain, two central coiled-coil motifs that mediate NUP88 interaction and anchored to the NPC and a C-terminal FG (Phenylalanine-Glycine) repeats domain that can be detected on both sides of the NPC.^{33,34} The FG-repeat motifs exert interaction binding with the highest affinity for the nuclear transporter named chromosomal maintenance 1 (CRM1)^{35,36}, also known as exportin 1 (XPO1), able to recognize proteins with leucine-rich nuclear export signal (NES) and use RanGTP as a cofactor to export those proteins to the cytoplasm.³⁷⁻⁴⁰ Moreover, the NUP214 protein also interacts with the main mRNA export factor, NXF1. The interaction of

NXF1 and the ATP-dependent DEAD-box helicase 19 (DDX19), is stabilized by NUP214 at the cytoplasmic ring of NPC to both inhibiting and activating DDX19 activity. Although, NUP214's role in mRNA export is not completely understood⁴¹, either depletion or overexpression of the NUP214 protein can induce intranuclear accumulation of proteins and poly(A⁺) RNA, causing cell cycle arrest without affecting NPC architecture.^{42,43}

DEK::NUP214

The *DEK::NUP214* fusion gene caused by t(6;9) (p23;q34.1), results in the fusion of exon 2 of *DEK* and exon 6 of *NUP214* with the juxtaposition of amino terminus of NUP214, containing FG repeats, fused in frame to carboxyl terminus of DEK (Figure 1). This fusion gene encodes a 165-kDa of DEK::NUP214 chimeric protein¹⁹ interacting with XPO1, preventing its exporter activity and resulting in the nuclear accumulation of its cargoes (Ran-binding protein 1: RanBP1) and nuclear export signal (NES) proteins (nuclear factor-kappa B (NF- κ B) signaling proteins, cyclin B).⁴⁴ Furthermore, the deregulation of DEK from the DEK::NUP214 fusion protein could increase histone hypoacetylation leading to excessive inhibition of histone acetyltransferase (HAT), p300, the CREB-binding protein (p300/CBP), p300/CBP associated factor (PCAF); and therefore, a possible downregulation of genes involving lineage commitment and hematopoietic differentiation.^{45,46} Additionally, the DEK::NUP214 protein seems to activate the mammalian target of rapamycin complex 1 (mTORC1) and the eukaryotic translation initiation factor 4E (eIF4E), resulting in increased protein synthesis, a shift of glucose metabolism from glycolysis to oxidative phosphorylation and enhanced cellular proliferation.^{47,48} Also, a mouse model expressing *DEK::NUP214* AML revealed significantly high expression of *HOXA* and *HOXB* genes.⁴⁹ According to the role of *HOXA/B* genes in regulating differentiation, proliferation, self-renewal of hematopoietic stem and progenitor cells⁵⁰, as well as leukemic transformation^{51,52}, the abnormal upregulation of these genes caused by

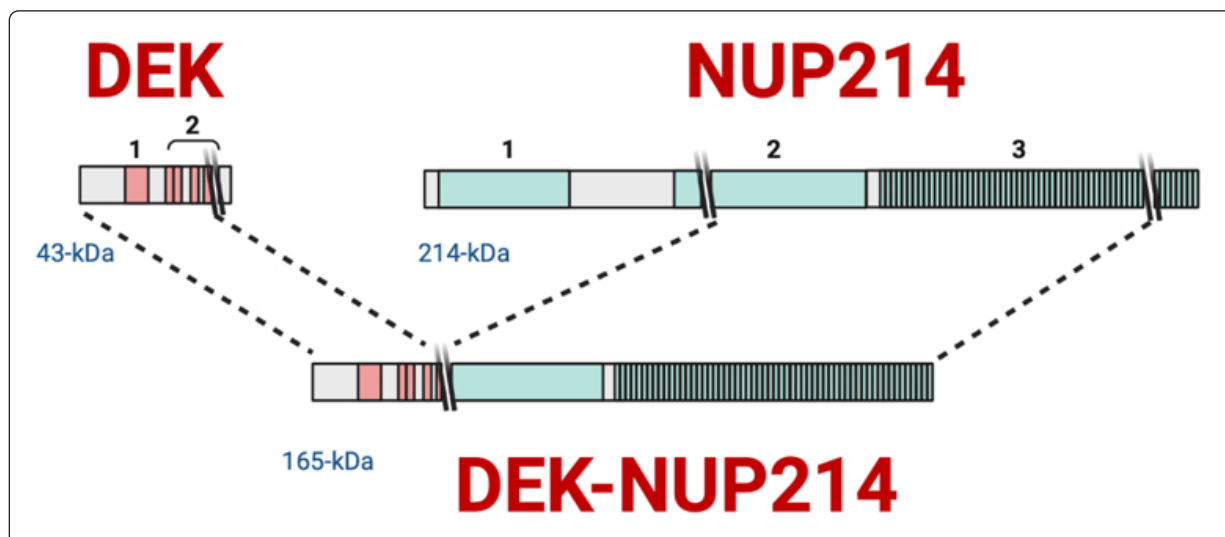


Figure 1 DEK::NUP214 chimeric protein. DEK encodes the DEK protein containing 1-SAP and 2-DNA binding domains. NUP214 encodes the NUP214 protein including 1- b-propeller domain, 2-coiled-coil motifs and 3-FG repeats. The DEK::NUP214 fusion gene, caused by t(6;9)(p23;q34.1), encodes the 165-kDa DEK::NUP214 fusion protein³² [created by BioRender].

DEK::NUP214 could play a role in leukemogenesis. Furthermore, in a study comprising 62 patients with AML and the DEK::NUP214 rearrangement, the upregulated expression of a specific gene including *HIST2H4*, *EYA3*, *SESN1* and *PRDM2/RIZ* was also demonstrated.¹⁵ *HIST2H4* encodes a member of the histone H4 family with an unknown mechanism of leukemogenesis. *EYA3* encodes a member of the 'eyes absent' protein family, involving DNA repairing and cell survival in response to damaging signals in organogenesis.⁵³ *SESN1* encodes a member of the sestrin family, a TP53 target and exerts a tumor suppressor function.⁵⁴ *PRDM2*, also known as RIZ, encodes RIZ1 and RIZ2 proteins with the function of tumor suppressor by its methyltransferase activity and proto-oncogenic property, respectively.^{55,56} Moreover, concurrent *FLT3*-ITD mutation in DEK::NUP214 AML, occurring in > 70% of cases⁹, may contribute to myeloid differentiation blockage and to the particular poor prognosis associated with these patients.⁵⁷ The summary of the *DEK*, *NUP214* and *DEK::NUP214* fusion genes including protein structure and functions are provided (Table 1).

The multi-omics study and the future of DEK::NUP214 AML

The center for Cancer Genomics and Computational Biology (GCB) of the Barts Cancer Institute (BCI) have completed a multi-omics profiling program in more than 50 primary poor-risk AML samples combining genomics (whole genome sequencing (WGS, 60X for tumor and 30X for germ-line controls), targeted sequencing of 54 myeloid loci, and total RNA-seq (100 million reads per bulk sample), mass spectrometry proteomics and phosphoproteomics (with > 6,000 proteins and > 25,000 phosphorylation sites detected and quantified), mass cytometry (CyTOF, 39 markers), drug screening (ranging from 200 to 500 approved or investigational compounds). The cohort of patients with AML was analyzed, including four cases with t(6;9)/DEK-NUP214 and the multi-omics analysis validated the upregulation of *SESN1*, *EYA3*, *PRDM2* and *HOX* genes as well as revealed a significant overexpression of the nuclear factor 1 X-type (NFIX), forkhead box C1 (FOXC1) and gamma-glutamyltransferase 5 (GGT5) in t(6;9) AMLs compared to other poor risk AML.⁵⁸ NFIX belongs to

Table 1 Summary of *DEK*, *NUP214*, *DEK::NUP214* fusion gene, proteins and function

Gene	<i>DEK</i>	<i>NUP214</i>	<i>DEK::NUP214</i>
Chromosome	6p23	9q34.1	t(6;9)(p23;q34.1)
Protein	DEK	NUP214	DEK::NUP214
(Molecular weight)	(43-kDa)	(214-kDa)	(165-kDa)
Protein structure	- SAP domain - DNA binding domain	- b-propeller domain - Coiled-coil motifs - FG repeats	- SAP domain - DNA binding region - Coiled-coil motifs - FG repeats
Function	- Transcription factor - Splice site selection - Senescence inhibition - Anti-apoptosis - DNA damage repair	- NPC component - Protein export - mRNA export	- Prevent XPO1 exporter activity - Increase histone hypo-acetylation - Increase protein synthesis - Increase oxidative phosphorylation of glucose

SAP, Scaffold attachment factor A/B-Acinus-Pias; FG, Phenylalanine-Glycine; NPC, nuclear pore complex; XPO1, exportin 1

the family of CCATT-binding transcription factors with an important role in HSPC survival and myelopoiesis regulation. *FOXC1* encodes an essential transcription factor in AML.⁵⁹ GGT5 is a key factor in glutathione homeostasis by supplying substrates for its synthesis and a mediator of cancer cell survival and drug resistance.⁶⁰ From the *in vitro* drug sensitivity screening of over 500 compounds, XPO1 inhibitors (selinexor and eltanexor) also showed selectively sensitivity in t(6;9) AMLs compared with other cytogenetic risk groups. XPO1 inhibitors covalently bind to cysteine-528 in the cargo-binding groove of XPO1, preventing NES loading of proteins and export to the cytoplasm^{61,62}, leading to lethal nuclear stress of AML cells and antileukemic activity. The XPO1 inhibition is currently being explored for acute myeloid leukemia treatment. The phase 1 studies of relapsed or refractory AML with single-agent selinexor and combining selinexor with high intensi-

ty chemotherapy or tyrosine kinase inhibitor against *FLT3*-mutated AML showed an overall response rate of 14% and up to 39 to 70%, respectively.⁶²⁻⁶⁶ Importantly, the only t(6;9) patient included in a selinexor clinical trial in AML, achieved complete remission.

Conclusion

Although the ontological relationship of t(6;9)/DEK-NUP214 with the development of AML has been established, the molecular etiology for this subtype of AML remains unclear. The genomics study of *DEK::NUP214* AML will shed light to determine the new targeted treatment, resulting in improving this poor risk AML in the future.

Conflict of interest statement

The author declare they have no conflict of interest.

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