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Review

Nucleoporins and nucleocytoplasmic transport in hematologic malignancies

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ABSTRACT

Hematologic malignancies are often associated with chromosomal rearrangements that lead to the expression of chimeric fusion proteins. Rearrangements of the genes encoding two nucleoporins, NUP98 and NUP214, have been implicated in the pathogenesis of several types of hematologic malignancies, particularly acute myeloid leukemia. NUP98 rearrangements result in fusion of an N-terminal portion of NUP98 to one of numerous proteins. These rearrangements often follow treatment with topoisomerase II inhibitors and tend to occur in younger patients. They have been shown to induce leukemia in mice and to enhance proliferation and disrupt differentiation in primary human hematopoietic precursors. NUP214 has only a few fusion partners. DEK-NUP214 is the most common NUP214 fusion in AML; it tends to occur in younger patients and is usually associated with FLT3 internal tandem duplications. The leukemogenic activity of NUP214 fusions is less well characterized. Normal nucleoporins, including NUP98 and NUP214, have important functions in nucleocytoplasmic transport, transcription, and mitosis. These functions and their disruptions by oncogenic nucleoporin fusions are discussed.

1. Introduction

Hematologic malignancies are often associated with chromosomal rearrangements that lead to the expression of chimeric fusion proteins [1] (Fig. 1). Among the proteins that are known to be part of such oncogenic fusions, are two nucleoporins, NUP98 and NUP214. Nucleoporins are protein components of the nuclear pore complex (NPC). In conjunction with soluble shuttling carrier proteins (karyopherins), they play important roles in the nucleocytoplasmic transport of macromolecules [2–6]. Components of the nucleocytoplasmic transport machinery also play pivotal roles in other cellular processes such as mitosis and transcription [2–6].

Oncogenic nucleoporin fusions have been described in several types of hematologic malignancies, most commonly acute myeloid leukemia (AML), but also including myelodysplastic syndromes (MDS) and T-cell acute lymphoblastic leukemia (T-ALL). AML is a malignant proliferation of myeloid precursors characterized by failure of myeloid differentiation with accumulation of primitive cells (blasts) in the bone marrow and blood [7]. Myeloid malignancies associated with NUP98 fusions often arise as a complication of prior chemotherapy with topoisomerase II inhibitors [8]. Nucleoporin-associated malignancies tend to occur at a younger age and have a poor clinical outcome [8–27].

2. Oncogenic NUP98 fusions

At least 29 NUP98 fusions have been reported in hematopoietic malignancies, mostly AML, but also including T-ALL and MDS [8–22,28–30] (Table 1). In most cases the breakpoints occur in introns 11–13 of *NUP98*, resulting in fusion of the N-terminal region of NUP98 that is rich in phenylalanine–glycine (FG) repeats to one of 29 different proteins [30]. Many of the NUP98 fusion partners are transcription factors of the homeobox family; the prototype of such fusions is NUP98-HOXA9 [31,32]. The overall incidence of NUP98 fusions is not clear and there is evidence that it may vary by geographical region [30]. For example, the vast majority of NUP98-HOXA9 fusions have been reported in patients from the Far East [8,26,33,34]. NUP98-NSD1 has been reported in 16.1% of pediatric and 2.3% of adult cytogenetically normal AML [35]. NUP98-JARID1A was identified in 10.5% of cases of pediatric acute megakaryoblastic leukemia (a subset of AML) [36]. A study from Taiwan identified NUP98-HOXA9 in 2.23% of adult AML patients [26].

NUP98 fusions cause aberrant differentiation and increased proliferation when expressed in primary human hematopoietic

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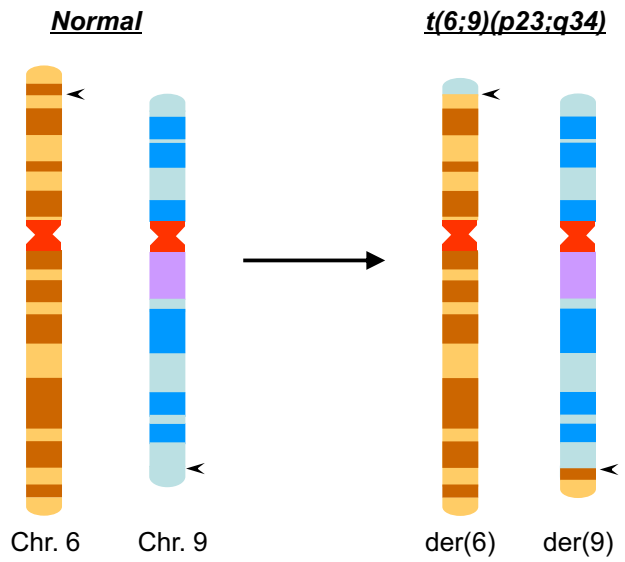

Fig. 1. Schematic of the t(6;9)(p23;q34) chromosomal rearrangement that results in the DEK-NUP214 oncogenic fusion. On the left are normal chromosomes 6 and 9; the Giemsa banding pattern is shown in brown and blue, respectively. The centromeres are shown in red and the non-centromeric heterochromatin of chromosome 9 is shown in pink. On the right are shown the derivative chromosomes 6 and 9 that result from the t(6;9)(p23;q34) chromosomal rearrangement. The arrowheads indicate the chromosomal breakpoints.

Table 1
Nucleoporin gene rearrangements in hematologic malignancies. AML = acute myeloid leukemia, CML-BC = chronic myelogenous leukemia in blast crisis, MDS = myelodysplastic syndrome, t-AML = therapy-related acute myeloid leukemia, t-MDS = therapy-related myelodysplastic syndrome, APL = acute promyelocytic leukemia, T-ALL = T-cell Acute lymphoblastic leukemia, B-ALL = B-cell acute lymphoblastic leukemia, and AUL = acute undifferentiated leukemia.

Rearrangement	Fusion transcript	Disease
NUP98		
t(7;11)(p15;p15)	NUP98-HOXA9	AML/MDS, t-AML/MDS, CML
t(7;11)(p15;p15)	NUP98-HOXA11	CML-BC
t(7;11)(p15;p15)	NUP98-HOXA13	AML, MDS
t(11;12)(p15;q13)	NUP98-HOXC11	AML
t(11;12)(p15;q13)	NUP98-HOXC13	AML
t(2;11)(q35;p15)	NUP98-HOXD11	Pediatric AML
t(2;11)(q31;p15)	NUP98-HOXD13	AML, t-AML
t(1;11)(q23;p15)	NUP98-PMX1	AML, t-MDS/AML
t(9;11)(q34;p15)	NUP98-PRRX2	t-AML
t(10;11)(q23;p15)	NUP98-HHEX	AML
inv(11)(p15;q22)	NUP98-DDX10	AML, MDS, CML
t(11;20)(p15;q11)	NUP98-TOP1	AML, t-MDS
t(9;11)(p22;p15)	NUP98-PSIP1	AML, MDS
t(5;11)(q31;p15)	NUP98-NSD1	Pediatric AML
t(8;11)(p11.2;p15)	NUP98-NSD3	AML
t(3;11)(p24;p15)	NUP98-TOP2B	AML (Monoblastic)
Complex (12p13)	NUP98-JARID1A	AML (Megakaryoblastic)
t(11;17)(p15;p13)	NUP98-PHF23	AML
Complex (3p25)	NUP98-ANKRD28	MDS/AML
t(6;11)(q24.1;p15.5)	NUP98-CCDC28A	AML (Megakaryoblastic), T-ALL
Complex (3q29)	NUP98-IQCG	Biphenotypic T-ALL/AML
t(11;18)(p15;q12)	NUP98-SETBP1	Pediatric T-ALL
t(4;11)(q21;p15)	NUP98-RAP1GDS1	Adult T-ALL
t(10;11)(q25;p15)	NUP98-Adducin 3	T-ALL
t(X;11)(q28;p15)	NUP98-HMGB3	t-AML
t(3;11)(q12;p15)	NUP98-LOC348801	AML
inv(11)(p15q23)	NUP98-MLL	AML
t(11;12)(p15;q13)	NUP98-RARG	APL
t(3;11)(p11;p15)	NUP98-POU1F1	t-AML
NUP214		
t(6;9)(p23;q34)	DEK-NUP214	AML
del(9)(q34)	SET-NUP214	T-ALL, AML, AUL
der(5)t(5;9)(q35;q34)	SQSTM1-NUP214	T-ALL
Amplified episomes	NUP214-ABL1	T-ALL, B-ALL

cells [37–40]. When introduced into mice by transplantation or transgenically, they cause myeloproliferation, MDS and AML with relatively long latency and variable penetrance, suggesting that additional cooperating oncogenic events are needed for the development of full-blown leukemia [16,41–49]. This notion is supported by clinical data as well as *in vivo* studies in mice. NUP98 rearrangements have been described in patients with BCR-ABL1-positive chronic myelogenous leukemia who developed blast crisis, which is a form of AML, suggesting that NUP98 fusions can cooperate with BCR-ABL1 in causing AML [50]. Further, patients with hematologic malignancies associated with NUP98 fusions have an increased incidence of additional mutations such as FLT3 internal tandem duplications (FLT3-ITD), KIT, WT1 and KRAS [26,35,51]. Several mouse studies have shown that oncogenes, including *Meis1*, *FLT3*, and *BCR-ABL1*, can cooperate with NUP98 fusions and enhance their leukemogenic potential [41,42,47,52–58].

3. Oncogenic NUP214 fusions

NUP214 was the first nucleoporin to be implicated in the pathogenesis of hematologic malignancies [59]. The translocation t(6;9)(p23;q34) (Fig. 1) results in a DEK-NUP214 fusion and defines a specific subcategory of AML under the most recent World Health Organization classification of AML [23]. This subtype of AML is characterized by basophilia, poor clinical outcome, and a high incidence of FLT3-ITD [23,60–62]. The breakpoints always occur within the same introns of both *DEK* and *NUP214*, resulting in an invariant fusion protein that includes the C-terminal FG repeat region of NUP214 [25,63]. SET-NUP214 is a fusion between exon 7 of *SET* and exon 18 of *NUP214* that results from del(9)(q34). It is associated with T-ALL and less frequently with AML and acute undifferentiated leukemia [64–70]. Most reported cases in the literature are from the Far East [64–70]. Fusion SQSTM1-NUP214 has been reported in a patient with refractory T-ALL [71].

Recently, a NUP214-ABL1 fusion was described in a series of patients with T-ALL [72,73]. This fusion is cytogenetically cryptic and is often located on amplified episomes. In contrast to other NUP214 fusions, NUP214-ABL1 fusions contain an N-terminal portion of NUP214 that includes some but not all of the FG repeats. This fusion has also been described in B cell acute lymphoblastic leukemia [74,75]. In T-ALL, NUP214-ABL1 is usually associated with rearrangement and/or overexpression of TLX1 or TLX3 and/or deletion of the tumor suppressor CDKN2a [72,76]. In some patients there are more cells with abnormalities of these genes than with NUP214-ABL1, suggesting that the latter is a secondary mutation [76].

In transduction/transplantation studies, DEK-NUP214 induced AML in mice with low penetrance and long latency; the penetrance was enhanced and the latency shortened by enriching the transduced population for long-term hematopoietic stem cells [77]. Conflicting data have been reported on the effects of DEK-NUP214 in human myeloid cell lines. In one study DEK-NUP214 caused mild growth inhibition in the myeloid cell line U937 [78], whereas in a subsequent study DEK-NUP214 was found to enhance proliferation of U937 and another myeloid cell line, PL-21, through upregulation of the mTOR pathway [79]. SET-NUP214 transgenic mice showed some abnormalities in hematopoietic differentiation and expansion of early precursors but no clear-cut leukemic phenotype [80,81].

4. Subcellular localization of nucleoporin fusions

Normally, NUP214 is present primarily on the cytoplasmic face of the NPC [59], whereas NUP98 is present on both the nuclear and cytoplasmic sides of the NPC as well as within the nucleus [82–84].