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Review Article

Nucleoporin Gene Fusions and Hematopoietic Malignancies

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Nuclear pore complexes (NPCs) are the sole gateways between the nucleus and the cytoplasm of eukaryotic cells and they mediate all macromolecular trafficking between these cellular compartments. Nucleocytoplasmic transport is highly selective and precisely regulated and as such an important aspect of normal cellular function. Defects in this process or in its machinery have been linked to various human diseases, including cancer. Nucleoporins, which are about 30 proteins that built up NPCs, are critical players in nucleocytoplasmic transport and have also been shown to be key players in numerous other cellular processes, such as cell cycle control and gene expression regulation. This review will focus on the three nucleoporins Nup98, Nup214, and Nup358. Common to them is their significance in nucleocytoplasmic transport, their multiple other functions, and being targets for chromosomal translocations that lead to haematopoietic malignancies, in particular acute myeloid leukaemia. The underlying molecular mechanisms of nucleoporin-associated leukaemias are only poorly understood but share some characteristics and are distinguished by their poor prognosis and therapy outcome.

1. Introduction

1.1. Nuclear Pore Complexes. The nuclear envelope (NE) serves as a boundary that separates nuclear and cytoplasmic compartments to protect the genome. This compartmentalization necessitates the transport of RNAs and proteins across the NE and this bidirectional macromolecular trafficking occurs through nuclear pore complexes (NPCs) [1, 2]. NPCs are large multiprotein assemblies, which both in vertebrates and yeast consist of ~30 different proteins, known as nucleoporins or Nups, [3–5]. Nucleoporins assemble into repetitively arranged subcomplexes to form NPCs with the pseudo-8-fold rotational symmetry [6–10]. In total, NPCs are estimated to be formed from about 500–1000 individual proteins [10, 11], which account for a molecular weight of about 110 MDa in vertebrates, according to scanning transmission electron microscopy and proteomic analyses [4, 10, 12].

The principle structural organization of the NPC has been determined by distinct electron microscopy (EM) approaches, including cryo-EM tomography, mainly in *Xenopus laevis* oocyte nuclei, but also in yeast, amoebozoa, plants, and human and appears as evolutionary conserved [6, 9, 10, 13–19]. Overall, NPCs are characterized by a roughly tripartite architecture: a central framework (also known as spoke complex, spoke-ring complex, or scaffold-ring complex) that is decorated with eight cytoplasmic filaments and a nuclear basket, which, in turn, is formed from eight filaments that join into a distal ring (Figure 1(a)). The central framework consists of eight spokes (i.e., the scaffold or the spoke-ring) that are flanked by the cytoplasmic and nuclear ring moieties and it encloses a central pore (or central channel), which accomplishes the nuclear-cytoplasmic exchange [1, 2]. The central, hour-glass shaped pore of the NPC has a diameter of 60–80 nm at its cytoplasmic and nuclear periphery and ~40–45 nm in the midplane of the NE (Figure 1(b)) [9, 10, 14, 15, 19–21]. Macromolecules with a diameter up to ~39 nm can pass the central pore in a signal-, receptor-, and energy-dependent manner, while smaller molecules up to ~9 nm in diameter can diffuse between the nucleus and the cytoplasm [21–24]. Despite an overall resemblance in the 3D architecture, NPCs from different species show significant variance in their protein density, most likely due to variations in nucleoporin sequence, position, and number, in their linear dimensions, and in the overall number of NPCs per nucleus in distinct species [4, 16, 25–27].

On the molecular level, NPCs are built of the about 30 different nucleoporins. Nucleoporins fall into three some groups with respect to their amino acid sequence and

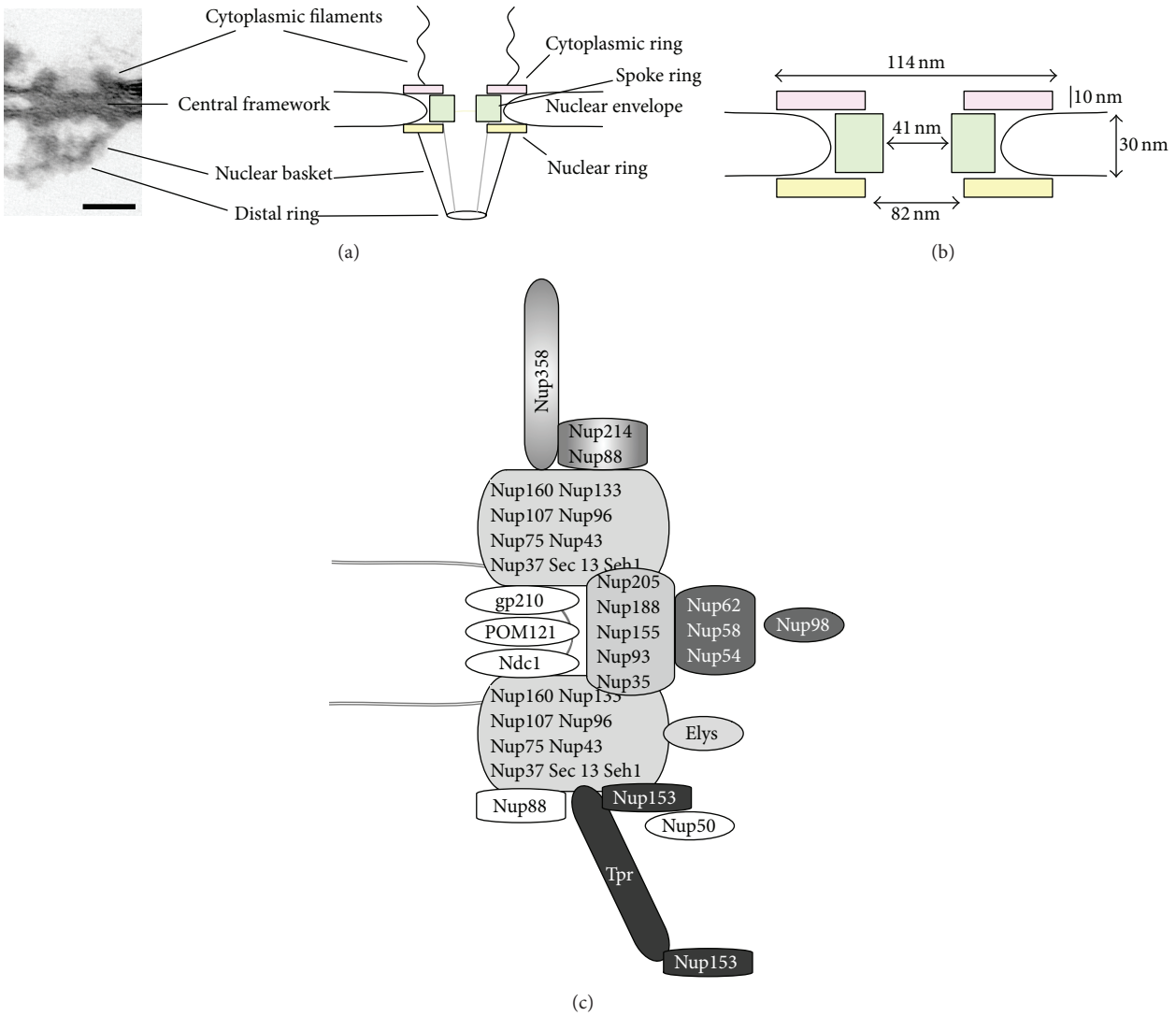

Figure 1: Schematic representation of nuclear pore complex (NPC) architecture, subcomplex composition, and localization within the NPC. (a) *Xenopus* oocyte nuclei have millions of closely packed NPCs and a cross-section along an embedded nuclear envelope from these nuclei offer side views of NPC architecture that can be visualised by transmission electron microscopy. Shown are a selected NPC in side view (left) and a schematic diagram of the main structural components of NPCs (right). Scale bar, 100 nm. (b) Linear dimensions of the central framework of the human NPC. Numbers are according to [10]. (c) Nucleoporins can be classified in different subgroups depending on their structural motifs and their localization: transmembrane proteins (white), scaffold nucleoporins (light grey), nucleoporins of the cytoplasmic filaments (gradient), central channel nucleoporins (middle grey), and nuclear basket nucleoporins (dark grey). Nup153 has two anchoring domains at the nuclear basket, the N terminus close to the nuclear ring and a zinc-finger domain at the distal ring of the nuclear basket. Nup88 is also found in the proximity of the nuclear ring and Nup50 is a mobile nucleoporin associated with the nuclear basket.

predicted structural motifs [28, 29]. Accordingly, transmembrane proteins, which in metazoans are comprised of gp210, Ndc1, and POM121, anchor the NPC to the NE. These nucleoporins reside at the boundary between the central framework and the pore membrane (Figure 1(c)). The scaffold of the NPC is made of nucleoporins containing α-helical solenoid and β-propeller fold motifs. This group of nucleoporins includes the Nup107-160 complex, which represents the major constituent of the cytoplasmic and the nuclear ring moieties [10, 30, 31] as well as the Nup93 complex, which is located towards the central pore of the NPC (Figure 1(c)). The third group of nucleoporins is characterized by the presence of repetitive phenylalanine-glycine (FG) motifs and/or by coiled-coil motifs [28, 29]. Individual FG motifs are typically interspersed by hydrophilic linkers of variable length and composition and these FG-Nups are typically engaged in nucleocytoplasmic transport. The Nups of the third group can be further subdivided into nucleoporins of the cytoplasmic filaments, such as Nup358 and Nup214, nucleoporins of the central channel, such as Nup98 and the Nup62 complex, and the nuclear basket nucleoporins Nup153, Nup50, and Tpr (Figure 1(c)).

During interphase, nucleoporins exhibit multiple functions, not only as structural elements and facilitators of

nucleocytoplasmic transport, but also as key players in the regulation of gene expression [32–38]. At the onset of mitosis, NPCs disassemble along with the NE. During this disassembly stage, nucleoporins frequently stay in their subcomplexes, some of which associate with mitotic structures, such as kinetochores or the mitotic spindle. As a consequence, the function of these nucleoporins has been linked to mitotic processes like spindle formation, kinetochore function, and the spindle assembly checkpoint (SAC) [39–41]. Nucleocytoplasmic transport, gene expression, and mitosis are highly specific and tightly regulated processes that are important aspects of normal cellular function. Not surprisingly, nucleoporin dysfunction has been linked to human pathologies, including various forms of cancer. Of particular interest in this context are the three nucleoporins Nup98, Nup214, and Nup358, which are recurrent targets for chromosomal translocations leading to human hematopoietic malignancies, in particular acute myeloid leukaemia.

1.2. Acute Myeloid Leukaemia. Leukaemias are a biologically and clinically heterogeneous group of malignant disorders that are grouped into chronic and acute leukaemia, among which the acute leukaemias are having the more aggressive presentation. Among the acute leukaemias, ~80% are acute myeloid leukaemia (AML) and ~20% acute lymphoblastic leukaemia (ALL). AML represents a genetically and phenotypically highly heterogeneous disease characterised by blocked differentiation and uncontrolled proliferation of haematopoietic precursor cells, which coincides with an increase in their self-renewal capacities [42, 43]. Based on WHO classification, AML falls into four main groups: AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related AML and MDS, and AML that does not fit into any of these groups. The origin of AML is associated with two classes of mutations: class 1 mutations enhance proliferation signalling pathways, such as Flt3 kinase and NRas/KRas signalling, whereas class 2 mutations target the transcription machinery coinciding with impaired haematopoietic differentiation conferring the self-renewal ability of haematopoietic precursor cells. A frequent target for transcriptional misregulation in AML is the *HOXA* locus [43]. *HOX* genes are expressed sequentially during embryonic development and in haematopoiesis. Expression of *HOXA7*, *HOXA9*, and *HOXA10* promotes stem cell self-renewal, and downregulation of these gene clusters coincides with terminal differentiation [44]. In 70–80% of human AML, *HOXA7*, *HOXA9*, and *HOXA10* are overexpressed, together with one of the Hox cofactors, Meis1 (myeloid ectropic insertion site) or PBX (pre-B-cell leukaemia) [43, 45]. *HOXA* gene aberrations alone, however, are not sufficient to initiate leukaemogenesis [46, 47] and are therefore often accompanied by class I mutations (see above), by aberrant formation of complexes with histone-modifying enzymes, such as the histone deactelyase complex (HDAC), as well as by modifications in DNA methylation and micro-RNAs [48, 49].

Recurrent chromosomal translocations found in AML are t(8;21)(q22;q22) resulting in *AML1-ETO* and t(15;17)(q22;q12) resulting in *PML-RARα*, rearrangements involving the *MLL1* (mixed lineage leukaemia) gene on 11q23, and also the nucleoporins Nup98, Nup214, and Nup358. AML with t(8;21) and t(15;17) have a relatively good prognosis, MLL translocations typically an intermediate prognosis [50], whereas AML associated with nucleoporins often have a poor prognosis [51, 52]. One reason for the poor prognosis might be the upregulation of *HOXA9*, which is highly correlated with worst treatment outcome and disease relapse and which is frequently coinciding with Nup98 and Nup214 translocations [43, 53]. However, *HOXA9* activation is a prevalent but not a uniform hallmark of nucleoporin-associated haematopoietic malignancies.

2. Nucleoporins in Leukaemia

2.1. The Nucleoporin Nup98. Nup98 is a rather mobile FG nucleoporin, which dynamically associates with NPCs in a transcription-dependent manner [54, 55]. The *NUP98* gene is located on human chromosome 11 and it encodes two major transcripts: *NUP98* and *NUP98-NUP96* [56, 57]. Both give rise to protein precursors, which are cleaved into a 98-kDa N-terminal and an 8-kDa C-terminal peptide and Nup98 and Nup96, respectively (Figure 2(a)). The mature cleaved proteins are generated by autoproteolytic cleavage of Nup98, which is critical for its correct targeting to NPCs [56, 58, 59]. Based upon its amino acid sequence Nup98 is comprised of two major domains (Figure 2(b)): an N-terminal GLFG (glycine-lysine-phenylalanine-glycine) domain and a C-terminal autoproteolytic domain [59]. Different forms of FG-domains are found in approximately one-third of the nucleoporins and Nup98 is the sole vertebrate GLFG-nucleoporin. FG domains mediate the interaction of nucleoporins to soluble nuclear transport receptors and Nup98 binds the nuclear protein export factor CRM1 [60, 61] as well as the mRNA export factor TAP/NXF1 [62, 63]. The repeat domain of Nup98 contains a distinct region, the Gle2-binding sequence (GLEBS), which provides binding sites for its partner Rae1/Gle2 [64, 65]. The GLFG region further associates with the CREB-binding protein CBP/p300, which acts as transcriptional coactivator [66]. The C-terminal domain of Nup98 provides the binding site for Nup88 [67], a nucleoporin which is found overexpressed in various human tumours [68, 69]. Nup98's C terminus further contains a so-called nucleoporins RNA-binding motif (NRM), which is, however, most likely not binding RNA [58, 70], and it harbours the autoproteolytic cleavage site (Figures 2(a) and 2(b)).

The localization of Nup98 is typically restricted to the nucleus and two nuclear pools have been described: one at NPCs and a second one in the nucleoplasm [34, 54, 60]. In a few cases, however, an extranuclear localization of Nup98 has been observed: in *C. elegans*, it was also found in the cytoplasm in association with P granules, but not P bodies, and in mice Nup98 was detected in germ granules [71]. Within NPCs, the anchoring C-terminal domain is tethering Nup98 to the centre of the NPC [72, 73], whereas the FG domain can be seen on both the cytoplasmic

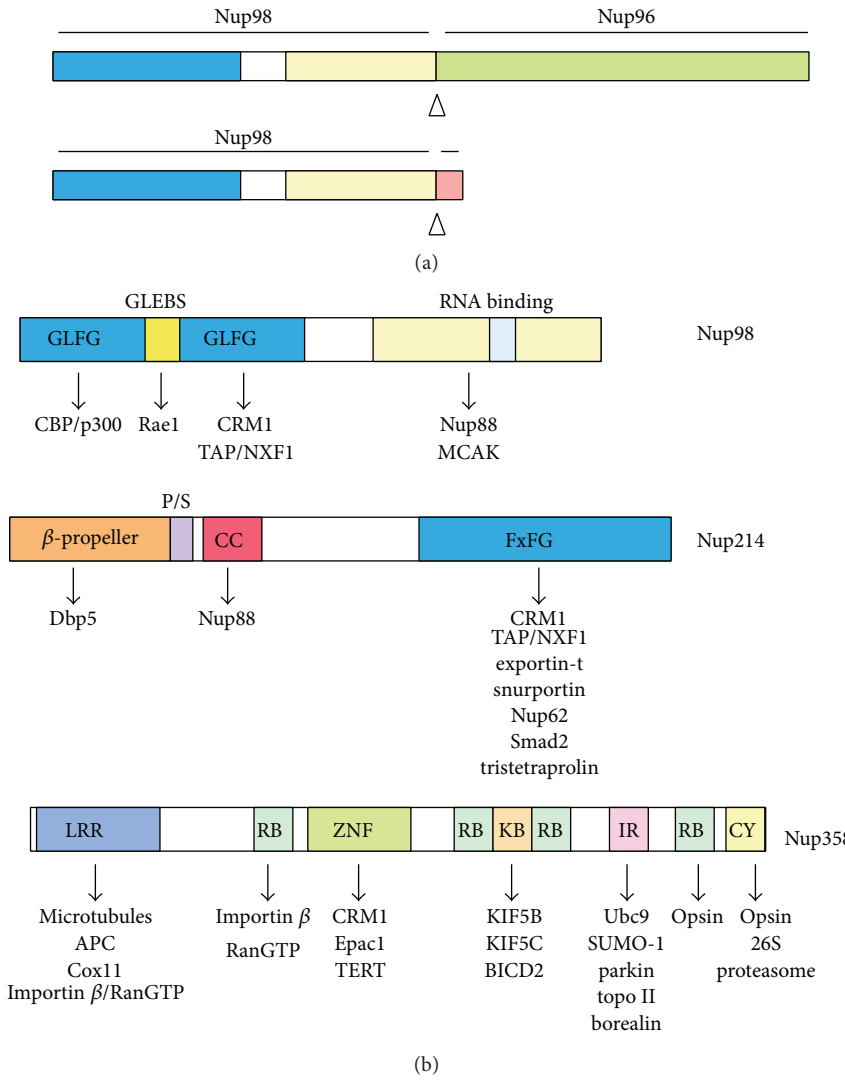

FIGURE 2: Molecular features of nucleoporins. (a) Nup98 is generated by autocleavage of the Nup98-Nup96 and Nup98 precursor, respectively. Cleavage occurs due to an intrinsic peptidase activity (indicated by the white arrow heads). (b) Schematic representation of Nup98, Nup214, and Nup358 domain organization and their binding partners. P/S: proline-serine rich; CC: coiled-coil; LRR: leucine-rich region; RB: Ran-binding domain; ZNF: zinc-finger domain; KB: kinesin-binding domain; IR: internal repeats (E3 ubiquitin ligase domain); CY: cyclophilin A homology domain.

and the nuclear periphery of NPCs. FG domains have little secondary structure and are considered as disordered [74–78], which assures a high structural flexibility of these domains and alternating locations within the NPC [6, 73, 79–82].

Nup98 is an important player in nucleocytoplasmic transport and exhibits multiple roles in RNA export from and protein import into the nucleus [62, 83–89]. Moreover, it serves as a mobile cofactor for the protein export factor CRM1, in concert with the CRM1-cofactor RanBP3 [60]. Consistent with its tethering to the centre of NPCs, Nup98 acts as the major constituent of the NPC's permeability barrier [90], which assures the selectivity of nucleocytoplasmic transport.

Modulating gene expression is another important function of Nup98. It was first noticed in *Drosophila* that the intranuclear fraction of Nup98 is localized to promoters of developmentally regulated genes [36, 91]. More recently, Nup98 was shown to bind to developmentally regulated genes that are active during differentiation of human embryonic stem cells [35]. Interestingly, genes that are active during early developmental stages bind to Nup98 at NPCs, whereas genes active at later stages associate with the intranuclear pool of Nup98 [35]. Nup98 is furthermore promoting epigenetic transcriptional memory for interferon-γ-inducible genes. Typically, interferon-γ-inducible genes are more rapidly and strongly activated in cells that have been treated with interferon-γ before as compared to untreated cells and this transcriptional memory is lost in cells lacking Nup98 [92]. The recently expressed promoters exhibit a persistent histone H3 lysine 4 dimethylation (H3K4me2) and are poised with

RNA polymerase II (pol II). In cells lacking Nup98, pol II does not remain associated with promoters, and the H3K4me2 mark is lost, just as the transcriptional memory. The role for Nup98 in promoting epigenetic transcriptional memory for inducible genes appears conserved from yeast to humans [92].

Beyond transcription, Nup98 affects gene expression also posttranscriptionally: Nup98 prevents p21 mRNA degradation by the exosome, likely due to a role in p21 mRNA export [93]. Nup98 binds directly to the 3′ UTR of p21, a key effector of the p53 pathway, but not to several other p53 targets. As p21 is an important inhibitor of cell death under stress conditions, liver cells depleted for Nup98 are prone to camptothecin-induced apoptosis, while they have a reduced capability for undergoing cellular senescence [93]. Interestingly, Nup98-dependent downregulation of p21 appears to be a hallmark in a significant fraction of hepatocellular carcinomas (HCC): Nup98 is largely reduced in an HCC mouse model as well as in patients with HCC [93]. The downregulation of Nup98 in patients was associated with a reduction in p21 levels. Beyond NCT and gene expression, roles in DNA replication in *Xenopus* reconstituted nuclei [85] and in DNA damage response in *Aspergillus nidulans* [94] have been assigned to Nup98. During mitosis, Nup98 regulates mitotic spindle assembly due to a direct association with microtubules and the depolymerizing kinesin MCAK [95]. In addition, Nup98, in association with the mRNA export factor and nucleoporin Rae1 (also known as Gle2) [65], is impacting the timing of mitotic exit by preventing securin degradation by the anaphase promoting complex [96, 97].

2.2. Chromosomal Translocations Involving NUP98. The *NUP98* gene, located on chromosome 11p15, is frequently involved in balanced chromosomal translocations that juxtapose the N-terminal GLFG domain of Nup98 to the C terminus of a partner gene. The breakpoint in *NUP98* is in most cases between intron 11 and 13. In contrast to Nup98, the fusion proteins do not associate with NPCs but are found in the nucleoplasm, often in a very distinctive pattern (see, e.g., [98]). The GLFG domain of Nup98 needs to be intact for cellular transformation and it can act as both transcriptional coactivator and corepressor [66]. The first identified as well as most frequent and best-studied chimera is *NUP98-HOXA9* [51, 99, 100] and since its discovery in 1996 about 30 distinct partner genes for *NUP98* have been identified. *NUP98* rearrangements are primarily associated with *de novo* and therapy-related acute myeloid leukaemia (AML), and also with myelodysplastic syndrome (MDS), chronic myelogenous leukaemia (CML), and T cell acute lymphoblastic leukaemia (T-ALL) [51, 101–103]. Nup98-associated leukaemias are rare but recurring and characterised by their aggressiveness and disappointing treatment outcome [51, 101, 103]. Compared to other AML patients, patients with *NUP98* translocations are younger and have a poorer overall and a poorer relapse-free survival [104, 105].

The partner genes of *NUP98* can be roughly divided into two groups: 10 homeobox domain (HD) genes and ~20 non-HD genes (Table 1). HD proteins are transcription factors that play crucial roles during development and haematopoiesis and they are characterized by their DNA-binding HD domain [106]. The non-HD partners of Nup98 often contain histone "reading" and "writing" domains, such as PHD fingers and SET domains; the partners are RNA helicases and DNA topoisomerase, and about one-third of the Nup98 partners lack any RNA, DNA, or histone binding activity but are harbouring protein-protein interaction motifs and coiled-coil domains (Table 1) [51]. In contrast to the variety in the C-terminal partner, the presence of the N-terminal GLFG domain of Nup98 is a mutuality of all fusion proteins and their expression is driven by the *NUP98* promoter [51]. How the fusions of Nup98 with so many different partners can cause similar disease phenotypes and drive leukaemogenesis has remained largely elusive.

Malignant cells in AML are characterised by continuous proliferation and aberrant differentiation. The impaired differentiation of hematopoietic precursor cells is attributed to the activation of the *HOXA9* locus, which in fact is frequently coinciding with Nup98 chimeras [45, 107–113]. *HOX* activation is controlled by the trithorax proteins, whereas their silencing is regulated by polycomb proteins [42]. Spreading of polycomb proteins and silencing of the *HOXA* locus appear to be prevented by binding of PHD fingers adjacent to the *HOXA7* and *HOXA9* locus, which maintains methylation of histone H3 at lysine 4 and lysine 36, respectively, and histone acetylation, at least for Nup98 fusions containing PHD fingers, such as Nup98-NSD1 and Nup98-JARID1A [45, 113]. *HOXA* gene aberrations alone, however, are not sufficient to initiate leukaemogenesis [46, 47], and consequently in about 90% of *NUP98*-associated leukaemia an internal tandem duplication of the Flt3 kinase (FLT3-ITD) or overexpression of KRas/NRas has been found, which may account for the uncontrolled proliferation of the leukaemic cells [114–116]. Importantly, HoxA9 expression is not required for myeloid immortalization by *NUP98-HOXA9* as shown in $HOXA9^{-/-}$ mice [107] and it is low or absent in Nup98 fusion to non-HD partners, for example, Nup98-NSD1, Nup98-RAP1GDS, Nup98-TOP1, and Nup98-MLL [115, 117, 118]. Therefore, the entire basis for the impaired differentiation of the haematopoietic precursors upon *NUP98* rearrangements remains to be seen.

The potential contribution of the GLFG domain of Nup98 to leukaemogeneis has enjoyed only scant attention, despite the fact that this is the invariable part to all fusion proteins. While Yassin and colleagues found evidence that the Nup98 moiety is also important to disrupt differentiation [119], it is primarily suggested that Nup98 translocation leads to aberrant nucleocytoplasmic transport, mitotic progression, and/or transcription. Aberrant localization of some CRM1 targets in cells expressing Nup98-HoxA9 [61], some mitotic abnormalities due to reduced levels of Rae1 [120, 121], and the recruitment of Nup98-HoxA9 and Nup98-PMX1 to kinetochores [98] indicate irregularities in both nucleocytoplasmic transport and mitosis. Whether this is important for leukaemogenesis, however, remains to be seen. Given that Nup98 by itself can bind chromatin [34–36, 91], it is very likely that translocations involving

Table 1: NUP98 fusion partners.

Nucleoporin gene	Partner gene	Translocation	Domain or partner function	Disease	Reference
NUP98	HOXA9	t(7; 11)(p15; p15)	HD	AML, MDS, CML, CMML	[99, 100, 104, 107, 108, 112, 214]
	HOXA11	t(7; 11)(p15; p15)	HD	AML, JMML	[215–218]
	HOXA13	t(7; 11)(p15; p15)	HD	AML	[215, 219]
	HOXC11	t(11; 12)(p15; q13)	HD	AML	[220, 221]
	HOXC13	t(11; 12)(p15; q13)	HD	AML	[222–224]
	HOXD11	t(2; 11)(q31; p15)	HD	AML	[223, 225]
	HOXD13	t(2; 11)(q31; p15)	HD	AML	[226–229]
	HHEX	t(10; 11)(q23; p15)	HD	AML	[110]
	PMX1	t(1; 11)(q23; p15)	HD	AML, MDS	[230–232]
	PMX2	t(9; 11)(q34; p15)	HD	AML	[233]
	POU1F1	t(3; 11)(p11; p15)	HD	AML	[234]
	GSX2	t(4; 11)(q12; p15)	HD	MDS	[235]
	PHF23	t(11; 17)(p15; p13)	PHD	AML	[236]
	JARID1A	t(11; 12)(p15; p13)	PHD	AML	[237, 238]
	NSD1	t(5; 11)(q35; p15)	PHD	AML, RA	[115, 116, 237, 239–244]
	NSD3	t(8; 11)(p11; p15)	PHD	AML	[245, 246]
	MLL	inv(11)(p15q23)	PHD	AML	[117]
	AF10	t(10; 11)(p12; p15)	AT hook	MDS, CML	[235]
	SETBP1	t(11; 18)(p15; q12)	AT hook	T-ALL	[247]
	HMGB3	t(X; 11)(q28; p15)	DNA binding, bending	AML	[248]
	TOP1	t(11; 20)(p15; q12)	DNA topoisomerase 1	AML, MDS	[249–253]
	TOP2B	t(3; 11)(p24; p15)	DNA topoisomerase 1	AML	[254]
	DDX10	inv(11)(p15q21–q23)	RNA helicase	AML, MDS, CML	[105, 255–258]
	RAP1GDS1	t(4; 11)(q21; p15)	RAS signalling	T-ALL	[259–261]
	ADD3	t(10; 11)(q25; p15)	Actin-binding, calmodulin-binding	T-ALL	[262]
	ANKRD28	t(3; 11)(p25; p15)	Ankyrin repeats	AML, MDS	[263]
	LEDGF	t(9; 11)(p22; p15)	PWWP domain	AML, CML	[223, 264–267]
	IQCG	t(3; 11)(q29q13; p15) del(3q29)	IQ motif, EF-hand binding	AML, T-ALL	[268]
	RARG	t(11; 12)(p15; q13)	Nuclear hormone receptor	AML	[269]
	CCDC28A	t(6; 11)(q24; p15)	Coiled-coil	AML, T-ALL	[270, 271]
	LOC348801	t(3; 11)(q12; p15)	Coiled-coil	AML	[272]

Nup98 lead to misregulation of Nup98 target genes and aberrant haematopoiesis. Moreover, with respect to the poor treatment response of the patients, the Nup98 moiety may be responsible for aberrant DNA damage response and in consequence aberrant apoptosis of the malignant cells [94, 122].

2.3. Nup214. The vertebrate nucleoporin Nup214, also called CAN, is an FG-repeat nucleoporin, which participates in both nuclear import and export [123–126], and is essential for embryonic development in mice [123], and localises to the cytoplasmic face of the NPC [80, 127–129]. Nup214 has been found in three different nucleoporin subcomplexes: together with the nucleoporin Nup88 and the nuclear export factor CRM1 [126, 130–133], as well as in complexes with Nup358 [134] and Nup62 [135], respectively. The Nup214 protein can be divided into three distinct regions (Figure 2(b)): a N-terminal domain containing a β-propeller [136], a central domain with a predicted coiled-coil region, and a C-terminal flexible and unstructured FG-repeat domain [80, 130]. The N-terminal domain of Nup214 binds to the RNA helicase and mRNA export factor Dbp5/Ddx19 [136–140], whereas the coiled-coil domain is required for binding Nup88 [130, 131].

The repeat domain of Nup214 mediates interactions to several nuclear export factors, in particular to the most abundant nuclear export factor CRM1 and also to the export factors for mRNA and t-RNA, TAP/NXF1, and to exportin-t, respectively [125, 126, 130, 132, 141–143]. The C-terminal domain of Nup214 provides further binding sites for Nup62 [135], as well as for the nuclear import adaptor snurportin 1 [144], Smad2 [145], and tristetraprolin [146]. Nup214 therefore appears to primarily act in nuclear export pathways but appears important in certain nuclear import pathways. In addition, Nup214 is a substrate of the JNK pathway in neurons [147] and target for adenoviruses to promote virus infection [148, 149].

2.4. Chromosomal Translocations Involving NUP214. The human *NUP214* gene locates to chromosome 9q34 and it is a target for chromosomal translocations associated with AML, MDS, acute undifferentiated leukaemia (AUL), and T-ALL [150, 151]. Four fusion partners have been identified for Nup214 (Table 2): the histone chaperone Set/Taf-1β, the chromatin binding factor DEK, the tyrosine kinase Abl1, and SQSTM-1 (sequestosome-1), a multifunctional protein that binds ubiquitin and regulates activation of NFκB [150–152]. These chromosomal translocations join almost the full-length Set and Dek, respectively, to the C-terminal region of Nup214, containing a portion of the coiled-coil domain and the entire FG domain, the N-terminal half of SQSTM1 to the C-terminal third of Nup214's FG domain, and the N-terminal domain of Nup214 with almost the entire Abl1 kinase, resulting in *SET-NUP214*, *DEK-NUP214*, *SQSTM1-NUP214*, and *NUP214-ABL1*, respectively (Figure 2(b)). Dek and Set are nuclear proteins and the resulting Nup214 fusion proteins are found in intranuclear foci, while Nup214-Abl1 locates to NPCs [153–156].

The mechanisms by which the Nup214 fusions lead to leukaemogenesis are unknown, but *SET-NUP214* and *DEK-NUP214* show some similarities to Nup98-associated leukaemia. In the *SET-NUP214* expressing cell line LOUCY, the *HOXA* cluster is upregulated and Set-Nup214 binds to promoter regions of *HOXA* genes, where it interacts with CRM1 and the histone methyltransferase DOT1L, indicating that epigenetic regulation keeps the *HOXA* locus active [157]. Targeted inhibition of Set-Nup214 abolished the expression of the *HOXA* genes, inhibited proliferation, and induced differentiation of LOUCY cells. However, this cell line has several other chromosome rearrangements, which may at least partially cooperate with *SET-NUP214*. *SET-NUP214* expression nevertheless consistently inhibits T-cell and myeloid lineage differentiation [157, 158], which may result in either AML or T-ALL [157, 159, 160].

Patients with a *DEK-NUP214* translocation have a poor prognosis and a high frequency of FLT3-ITD [52, 161]. The requirement of a cooperative lesion has also been seen in a *SET-NUP214* mice model, as these mice are not leukaemia prone [158]. Expression of Dek-Nup214 coincides with an increased global protein synthesis, which occurs due to increased translation rather than dysregulated transcription [162]. The rise in protein synthesis is restricted to the myeloid lineage and correlates with hyperphosphorylation of the translation initiation factor EIF4E. Expression of Dek-Nup214 cells in myeloid cells caused increased cellular proliferation, which coincided with an upregulation of the mTORC1 activity, without affecting mTORC2 [163]. Augmented proliferation is attributed to a symmetrical decrease of the major cell cycle phases and an upregulation of the mTORC1 protein, which is accompanied by elevated mTORC1 signalling [163]. Inhibition of mTORC1 selectively reverted the Dek-Nup214-induced proliferation.

A third fusion partner of Nup214 is the tyrosine kinase Abl1. *NUP214-ABL1* fusions are exclusively associated with T-ALL and they act as constitutively phosphorylated tyrosine kinase, although with a lower kinase activity than *BCR-ABL1*, the most frequent *ABL1* rearrangement [151, 154, 155]. Nup214-Abl1 fusion proteins respond to tyrosine kinase inhibitors, such as imatinib (Glivec), but patients have a poor prognosis [151, 164]. *NUP214-ABL* which is weakly transforming in haematopoietic and mouse bone marrow cells, similar to *SET-NUP214* and *DEK-NUP214*, has a multistep pathogenesis and it is associated with Hox11 and Hox11L2 expression, which is frequently found in T-ALL [151, 165]. Cooperative factors for Nup214-Abl1 are the SRC kinase LCK as well as the spindle checkpoint protein Mad2L, the nucleoporin Nup155, and the SMC4 subunit of the condensin complex [166].

NUP214-ABL contains the N-terminal part of *NUP214* with breakpoints between intron 23 and intron 34 and almost the entire *ABL1* gene with breakpoints mostly in intron 1, resulting in fusion proteins of 239–333 kDa (Dek-Nup214 in contrast ~165 kDa, Set-Nup214 ~155 kDa) [150, 151, 159]. The presence of the Nup214 N-terminal domain enables the recruitment of the fusion proteins to NPCs, where they interact with the Nup214-binding partners Nup88 and Nup62. *NUP214-ABL1* frequently delete the tumour suppressor genes *CDKN2A* and *CDKN2B* [151], while *SET-NUP214* have a recurrent deletion of *ABL1* (del (9)q31.11q34.13; [167]).

2.5. The Nucleoporin Nup358. Another nucleoporin linked to hematopoietic malignancies is Nup358 (also known as RanBP2), the largest vertebrate nucleoporin [168]. Nup358 is a multidomain protein (Figure 2(b)), which resides at the cytoplasmic filaments of the NPC [169, 170]. It is involved in numerous cellular processes that range from more general functions in nucleocytoplasmic transport [171–175], mitosis and chromosome segregation [176–179], and cellular signalling due to its E3 SUMO ligase activity [180–184] to more specialized functions, for example, in the translation of a subset of mRNAs encoding secreted and membrane-bound proteins [185] to tissue-specific functions, particularly in neurons and muscle cells [186–192]. With respect to nucleocytoplasmic transport, Nup358's depletion perturbs the nuclear import of specific cargoes but does not impair nucleocytoplasmic transport in general [169]. Known Nup358-dependent nuclear import cargoes are DMAP-1, a DNA methyltransferase 1-associated protein, the putative tumour suppressor DBC-1 (deleted in breast cancer 1), and TERT, the protein component of telomerase [173, 193]. DMAP-1 and DBC-1 are directly interacting with the N-terminal region of

Nup358 in an import receptor-independent manner, whereas importin 7 is mediating the binding of TERT to the zinc-finger domain of Nup358 [173, 193]. It is furthermore thought that Nup358 has a critical function in capturing RanGTP-importin β-complexes at the cytoplasmic filaments of NPCs to allow efficient recycling of importin β and in turn importin β-dependent nuclear import [175]. In this context, it likely promotes the formation of import complexes between DMAP-1 and DBC-1 and importin β at the NPC, thereby stimulating their nuclear import [173].

Due to its large size and its diverse domains, manifold functions have been attributed to Nup358. Via its N-terminal, leucine-rich domain (Figure 2(b)), Nup358 is capable of binding interphase microtubules (MTs), which is augmenting MT bundling and stability in CHO cells, whereas depletion of Nup358 is impairing polarized cell migration and reducing the number of stable MTs [194]. Nup358 association with MTs depends on APC, the adenomatous polyposis coli tumour-suppressor protein, which is a MT plus-end binding protein [195]. APC interacts with both MTs and Nup358 and ectopic expression of its MT-binding domain is sufficient to recruit Nup358 to MT plus ends. The association between Nup358 and APC is important for APC's localization at the cell cortex and for centrosome reorientation during cell migration after wound-scratching [195].

Owing to their central location at the transit routes between the cytoplasm and the cell nucleus, nucleoporins often act as scaffold for proteins for cellular signalling pathways and Nup358 acts as negative regulator of the second messenger cyclic adenosine monophosphate (cAMP) signalling [196]. Epac1, a cAMP-regulated guanine nucleotide exchange factor (GEF) for Rap GTPases, binds directly to the zinc-finger (ZNF) domain of Nup358 (Figure 2(b)) in a phosphorylation-dependent manner. Epac1 functions in cellular processes ranging from exocytosis to cell-cell-junction formation and cell-extracellular matrix adhesion, and its activity is directly regulated by cAMP [197]. Binding to Nup358 mediates the anchoring of Epac1 to the NE during interphase and in turn inhibits the activity of Epac1 towards Rap GTPases. Depletion of Nup358 by RNAi is enhancing Epac1, and hence Nup358 functions as negative regulator of Epac1 by establishing an inactive pool of this Rap GEF at NPCs [196].

Nup358 furthermore has tissue-specific functions, in particular in retinal neurons. Nup358 acts specifically as a chaperone for red/green opsin, to which it binds via its Ran-binding domain (RBD) 4 and cyclophilin-like domain (Figure 2(b)) in *Drosophila*, human, and bovine cells [198, 199]. In mice, Nup358 acts as a chaperone for the mitochondrial metallochaperone Cox11 [200]. Nup358 and Cox11 are copurified from retina extracts and colocalize to mitochondria in several classes of neurons, including photosensory neurons and neurons of the central nervous system (CNS). Nup358 is suppressing the inhibitory activity of Cox11 over hexokinase I (HKI), the major regulator of glycolysis [200]. Haploinsufficiency in Nup358 causes the delocalization of mitochondria in the photosensory neurons and defects in glucose clearance and the electrophysiological response of photosensory and postreceptoral neurons, the latter likely due to a pronounced decrease of HKI and ATP levels in the CNS [200, 201]. Nup358 further associates with kinesin KIF5B and KIF5C in the cytoplasm via its kinesin-binding domain and the Ran-binding domains 2 and 3 (Figure 2(b)) [148, 189, 202]. Nup358 binds leucine-rich heptad repeats in the C-terminal coiled-coil domain of the kinesin heavy chain [188, 189, 201, 202]. In the presence of MTs and ATP, binding of Nup358 enhances the low intrinsic ATPase activity of KIF5B. A disruption of the interaction between Nup358 and the KIF5s results in perinuclear clustering of mitochondria, deficits in the mitochondria membrane potential, and cell shrinkage, further supporting the role of Nup358 in mitochondria transport and function [201].

By a mechanism that is not understood, haploinsufficiency of Nup358 in aged mice safeguards neurons against light-induced oxidative stress [186, 187]. Neurodegeneration of photoreceptors by apoptosis is induced by prolonged light exposure, and aged Nup358$^{+/-}$ mice have suppressed apoptosis and reduced membrane dysgenesis in central retina regions when exposed to light stress [187]. The reduced light-induced oxidative stress and the suppression of apoptosis in haploinsufficient Nup358 cells appears to be due to reduced levels of free fatty acids, the upregulation of the orphan transmembrane tyrosine kinase receptor ErbB2, and the suppression of ubiquitylation [186, 187]. Together these studies point to a determinant role for Nup358 in glucose, energy, and lipid homeostasis in neurons of the CNS and the retina and implicate Nup358 (and its binding partners) as key player in neuropathic and neurodegenerative diseases [200].

2.6. Chromosomal Translocations Involving NUP358. Nup358 is located on chromosome 2p12 and is found in chromosomal translocations with the fibroblasts growth factor receptor 1 (FGFR1), a tyrosine kinase receptor, and the anaplastic lymphoma kinase (ALK) (Table 2). *Nup358-FGFR1* fusion results in myeloproliferative/myelodysplastic syndrome [203]. Three fusions of *NUP358* exon 20 with *FGFR1* exon 9 have been identified, which preserves the LRD of Nup358 and the two tyrosine kinase domains of FGFR1. Nup358-FGFR1 is not further characterized, but *FGFR1* is known to be fused to different recurrent gene partners and its translocation typically leads to its constitutive activation. FGFR1-associated malignancies are rare, aggressive myeloproliferative syndromes that rapidly progress into AML and are associated with a bad prognosis [203].

The *NUP358-ALK* fusion is associated with several human malignancies ranging from inflammatory myofibroblastic tumours (IMT) to large B cell lymphoma and MDS/AML and is associated with a poor patient prognosis [204–211]. ALK is a receptor tyrosine kinase and hyperactivated in the fusions, which may coincide with the hyperphosphorylation of cooperative factors, such as STAT3 [205]. The fusion points are consistently composed of exon 19 of *NUP358* and exon 20 of *ALK*, which maintains the LRD of Nup358 and the tyrosine kinase domain of Alk and results in a fusion protein of 1430 amino acids that resides at the nuclear membrane [206–208]. The molecular bases for the diseases are unknown, but the expression of Nup358

Table 2: NUP214 and NUP358 fusion partner.

Nucleoporin gene	Partner gene	Translocation	Partner function	Disease	Reference
NUP214	SET	del(9)(q34)	Apoptosis, cell cyle, migration, nucleosome assembly, inhibitor of PP2A	T-ALL, AML	[150, 153, 156–158, 160, 167, 273, 274]
	DEK	t(6; 9)(p22; q34)	DNA-binding, transcription	AML, MDS	[150, 156, 159, 161, 162, 274, 275]
	ABL1	Amp(9q34)	Tyrosine kinase	T-ALL	[151, 154, 155, 158, 164–166, 276–278]
	SQSTM1		NFκB activation	T-ALL	[152]
NUP358	ALK	inv2(p23; q13)	Kinase	AML, MDS, IMT	[204–211]
	FGFR1	t(2; 8)(q12; p11)	Tyrosine receptor kinase	MDS	[203]

chimeras commonly lead to the presence of large nucleoli. Moreover, IMT tumours are massive and the incidence for IMT is significantly higher in male with a male to female ratio of 10 : 1 [205, 209].

3. Conclusion

Three nucleoporins, Nup98, Nup214, and Nup358, are targets for rare but recurrent chromosomal translocations, which by the majority lead to AML. *NUP98* and *NUP214* rearrangements share some common characteristics, such as *HOXA* activation and cooperation with the FLT3-ITD kinase, which may account for the impaired differentiation of the haematopoietic precursor cells and their uncontrolled proliferation. *NUP214* and *NUP358* fusion partners are on the other hand often kinases, which become constitutively activated and may stimulate proliferation. The basis for impaired differentiation to myeloid cells has remained elusive. Commonly malignancies associated with Nup98, Nup214, and Nup358 come along with a poor prognosis for the patients and a poor treatment outcome. As Nup98, Nup214, and Nup358 are all somewhat important for protein and/or mRNA export, it will be interesting to see if their rearrangements lead to similar defects in nuclear export, which may account for the marked similarities in the clinical features in the hematopoietic malignancies associated with these three nucleoporins. Of particular interest in this context might be their link to the nuclear export receptor CRM1, which appears to play an important role in the aetiology of AML. CRM1 is mediating the nuclear export of tumour suppressor proteins and cell cycle regulators, such as p53 and nucleophosmin (NPM) [212]. Mutations in NPM account for about one-third of AML cases in adults and the mutations lead to an enhanced nuclear export of NPM. Novel, selective CRM1 inhibitors are currently tested *in vitro* and *in vivo* in preclinical and clinical trials to treat NPM-related AML [213]. These CRM1 inhibitors are inhibiting proliferation and inducing cell-cycle arrest, apoptosis, and differentiation, they cause decreased CRM1 protein levels and accumulation of CRM1 targets (including p53 and NPM) in the nucleus, and they also cause a downregulation of FLT3 and FLT3-ITD [213]. These promising results indicate that CRM1 might be a therapeutic target to treat AML and it will be highly interesting to see whether or not this also holds true for nucleoporin-associated AML.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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