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The role of Nup98 in transcription regulation in healthy and diseased cells

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Abstract

Nuclear pore complex (NPC) proteins are known for their critical roles in regulating nucleocytoplasmic traffic of macromolecules across the nuclear envelope. However, recent findings suggest that some nucleoporins (Nups), including Nup98, have additional functions in developmental gene regulation. Nup98, which exhibits transcription-dependent mobility at the NPC but can also bind chromatin away from the nuclear envelope, is frequently involved in chromosomal translocations in a subset of patients suffering from acute myeloid leukemia (AML). A common paradigm suggests that Nup98 translocations cause aberrant transcription when they are recuited to aberrant genomic loci. Importantly, this model fails to account for the potential loss of wild type (WT) Nup98 function in the presence of Nup98 translocation mutants. Here we examine how the cell might regulate Nup98 nucleoplasmic protein levels to control transcription in healthy cells. In addition, we discuss the possibility that dominant negative Nup98 fusion proteins disrupt the transcriptional activity of WT Nup98 in the nucleoplasm to drive AML.

Keywords

Nup98; Nup96; nuclear pore complex; chromatin; transcription; chromosomal translocation; acute myeloid leukemia

The NPC is composed of scaffold and peripheral nucleoporins

The NPC is one of the largest and most intricate protein complexes in the cell. It is composed of multiple copies of approximately 30 proteins that regulate nuclear-cytoplasmic transport of macromolecules larger than ~40 kD [1–3]. The NPC is formed by two ring structures, which are composed of the scaffold nucleoporins (Nups) of the Nup107-160 complex on the cytoplasmic and nuclear faces of the nuclear envelope bridged by the Nup93-205 complex (Figure 1) [3–5]. A variety of peripheral Nups associate with the NPC scaffold to form the nuclear basket and cytoplasmic filaments, which regulate transport between the two cellular compartments (Figure 1) [6–8]. In addition, a subset of Nups which contain phenylalanine-glycine (FG) repeats interact with the NPC core to form a meshwork in the central channel of the pore and are important for regulation of the permeability barrier (Figure 1) [9–15].

Recent studies have demonstrated that core NPC complexes are among the most stable protein assemblies in the cell that are not turned over in postmitotic cells [16–18]. Concomitantly, scaffold Nups are transcriptionally downregulated in postmitotic cells, whereas peripheral Nups are still expressed. These observations have important implications

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for aging cells because NPCs become prone to deterioration that occurs when core Nups are lost during aging resulting in the deterioration of the nuclear permeability barrier [16].

In contrast to scaffold Nups, which are shown to have NPC residence times >20 h, peripheral Nups cycle off the pore more quickly with NPC occupancy ranging from 20 seconds to a few hours [19]. In principal, this dynamic behavior allows peripheral Nups to affect cellular functions at off-pore sites including mRNA/protein export and transcription regulation [19–22]. Interestingly, knockout or disruption of many nucleoporins gives rise to tissue-specific defects. For example knockout of Nup96 or Nup133, two components of the Nup107-160 complex, gives rise to selective alterations of the immune system and defects in neurogenesis in mice, respectively [23,24]. In addition, mutation of Nup155, a member of the Nup93-205 complex, has been shown to cause atrial fibrillation [25]. Finally, depletion or overexpression of Nup210, a transmembrane Nup, inhibits or enhances differentiation of mouse C2C12 cells, respectively [26].

Peripheral Nups have also been linked to tissue-specific defects as Nup62, TPR, Nup153, and Nup210 were shown to be autoantigen targets in patients suffering from primary biliary cirrhosis [27]. Moreover, peripheral Nups (Nup98, Nup214, TPR, and Nup358) are involved in chromosomal translocations that are linked to tumorigenesis [28]. The most studied Nup translocations are those that involve the Nup98 gene locus on human chromosome 11 with various other chromosomal loci. The resulting translocation fuses the N-terminal half of the Nup98 protein in-frame with the C-terminal fragment encoded by numerous other genes [28,29]. Nup98 translocations have been identified as potent transcription factors that induce acute myeloid leukemia (AML) with a particularly poor patient prognosis [29]. Here we focus on Nup98 function in normal and diseased cells and propose a model for how Nup98 translocations might trigger the onset of leukemic phenotypes.

Nup98-Nup96 coexpression and relevance to disease

With the exception of plants [30], Nup98 is expressed in eukaryotes as bicistronic fusion consisting of the Nup98 gene directly upstream of the Nup96 gene [31]. The Nup98-Nup96 polypeptide undergoes autoproteolysis by a mechanism that closely resembles the self-splicing inteins, hedgehog, and NTN protein families (Figure 2a) [31,32]. Why are a peripheral and a scaffold Nup coexpressed from the same mRNA? Perhaps it could serve as a way to regulate Nup98 interaction with the NPC. Interestingly, the crystal structure of the Nup98-96 autoproteolytic site revealed that cleavage of the Nup98-96 linkage actually enhances the interaction between the two proteins. Moreover, imaging studies showed that autoproteolysis promotes localization of Nup98 and Nup96 to the NPC [31–33]. Thus, it seems likely that an evolutionary advantage is conferred by expressing Nup98 and Nup96 in stoichiometric amounts. However, it is important to note that an alternative splice variant of Nup98 exists, which expresses only the Nup98 portion of the Nup98-96 mRNA (Figure 2a, right pathway). In HeLa cells the short Nup98 mRNA can be detected, but its expression is very low compared to that of the Nup98-96 mRNA [31]. Although these data do not address how the Nup98-96 mRNA is spliced in relevant tissues, it does suggest that a strong preference for coexpression of Nup98 and Nup96 could exist.

Despite the fact that Nup98 and Nup96 interact at the NPC, at a glance they seem like two unrelated proteins. Nup96 is a member of the Nup107-160 complex and thus is predicted to have an NPC residence time on the order of years in postmitotic cells [18]. In dividing cells, Nup96 protein levels are tightly regulated during mitosis. After NPC disassembly at the onset of mitosis, Nup96 levels are reduced by approximately 50% through ubiquitination and degradation by the proteasome, and are subsequently replenished during interphase [34].

It is currently unclear why Nup96 levels are reduced during mitosis; however, there must be a purpose for this because overexpression of Nup96 does cause delays in the cell cycle [34].

In contrast to Nup96, Nup98 is a relatively dynamic Nup that has been shown to cycle off the NPC. Thus, at least two pools of Nup98 exist; an NPC-bound fraction and an intranuclear fraction [35,36]. Recent studies in *Drosophila* showed that the intranuclear fraction of Nup98 could localize to promoters of genes that have important roles in processes such as development [20,21]. Knockdown of Nup98 resulted in robust suppression of target genes, suggesting that Nup98 has important functions as a transcription factor in *Drosophila* salivary glands and tissue culture [20,21]. One important unanswered question is how are Nup98's on- and off-pore protein pools regulated. One possibility is that all Nup98 molecules are inherently the same, and they simply cycle off the pore to find cargoes or regulate gene expression. Alternatively, two or more different populations of Nup98 might exist that have exclusive functions either at the NPC or in the nucleoplasm. In support of the latter possibility, Nup98 has a relatively long residence time at the pore (~3 h) compared to other dynamic Nups, which could be too slow to support the rapid response one would expect is required to perform multiple functions in two different cellular locations [19]. Perhaps alternative splicing of the Nup98-96 transcript to create the short Nup98 isoform leads to production of Nup98 protein with low affinity for Nup96 at the NPC, and thus produces a nucleoplasmic protein pool (Figure 2b; red sphere). Moreover, production of the large Nup98-96 transcript, which yields high affinity Nup98-96 interactions [32], might enrich the NPC-bound pool of Nup98 (Figure 2b; grey sphere). Interestingly, a HeLa cell clone has been isolated with an unusually high amount of endogenous intranuclear Nup98 [37], but whether the increase in off-pore Nup98 correlates with an increase in alternative splicing of the Nup98 short isoform remains to be seen.

Another possibility for how the two Nup98 populations are regulated is through post-translational modifications. Many Nups are phosphorylated throughout the cell cycle, especially during mitosis [38]. It has recently been shown that phosphorylation of Nup98 causes it to release from the pore at the onset of prophase to promote NPC disassembly [39]. Although it has not been formally tested, it is possible that regulated phosphorylation/dephosphorylation of Nup98 during interphase could promote Nup98 cycling to and from the NPC.

Coexpression of a dynamic Nup and a scaffold Nup with very different turnover rates poses an interesting problem when considering postmitotic expression of the Nup98-96 transcript. Nup96 is predicted to be extremely long lived in postmitotic tissues because NPCs are not turned over. Thus, one can assume that any new Nup96 protein that is expressed in postmitotic cells could be mislocalized and cause damage to the cell [16,18]. By contrast, Nup98 is rapidly turned over and needs to be constantly replenished during the lifetime of the cell [16,18]. Thus, how can cells replenish Nup98 protein levels without overexpressing Nup96? One possibility is that postmitotic cells switch exclusively to expression of the short Nup98 isoform. Alternatively, an uncharacterized mechanism could exist to degrade the extra Nup96 protein that is predicted to be located off the pore in postmitotic tissues. A third possibility is that Nup96 has additional functions in postmitotic cells that might require higher Nup96 expression. These questions should be explored because they have important implications for cycling cells during interphase as well as in aging postmitotic cells.

Nup98 is a transcriptional regulator

The first evidence that WT Nup98 might function as a transcription factor came when it was shown that Nup98 could interact directly with histone-modifying enzymes CBP/p300 and histone deacetylases (HDACs) through its unique GLFG (glycine-leucine-phenylalanine-

glycine) repeats [40,41]. Later it was determined that Nup98 translocation mutants, which promote the onset of AML, do so through a mechanism that requires the GLFG domain of Nup98 [41]. Finally, two recent studies showed that Nup98 can bind to promoter regions of intranuclear genes in *Drosophila* salivary glands and tissue-culture cells [20,21]. These studies showed that Nup98 primarily serves as an activator with a preference for promoters of genes involved in development, cell signaling, and cell cycle related processes.

How does Nup98 activate transcription? It is currently unclear how Nup98 interacts with DNA because it lacks a bona fide DNA-binding domain. Thus, one might predict that other unidentified adapter proteins cooperate with Nup98 to promote its interaction with chromatin (Figure 2b, blue spheres). Then Nup98 recruits other transcription factors like CBP/p300 through the GLFG domain (Figure 2b, gold spheres). Interestingly, the GLFG domain promotes the localization and cycling of intranuclear Nup98 to and from distinct foci in the nucleoplasm termed GLFG bodies [33,35] (Figure 2b). What role GLFG bodies play in the regulation of intranuclear Nup98 is currently unclear. Notably, transcriptional inhibitors prevent the dynamic behavior of Nup98 in GLFG bodies; however, it is unlikely that GLFG foci serve as sites of transcriptional regulation because active RNA polymerase II does not localize there [35]. Rather, GLFG bodies might be storage centers from which Nup98 can rapidly cycle to transcription start sites when needed.

Several lines of evidence suggest that GLFG bodies are the result of elevated Nup98 levels because they have only been observed in cells such as the unique HeLa-C cell line that highly expresses Nup98, or in cells that overexpress exogenous Nup98 [35,37]. Although GLFG bodies can only be observed under certain experimental conditions, they have provided important information about the status of intranuclear Nup98 under various cellular conditions, suggesting that Nup98 protein in GLFG bodies behaves in a similar manner to diffuse Nup98 in the nucleoplasm [35].

Nup98 fusions cause leukemia

The Nup98 gene has been observed in translocations with the C-terminal fragment of approximately 30 genes in patients suffering from AML, and the list continues to grow longer and more diverse [29]. The chimeric Nup98 protein that results always contains the intact N-terminal GLFG repeats of Nup98 and the C-terminal domain of another protein. How do so many Nup98 fusions involving drastically different proteins cause similar leukemic phenotypes? The most common model suggests that aberrant transcription occurs when a Nup98 translocation is targeted to hematopoietic specific genes by a C-terminal partner gene [29]. Indeed, many Nup98 translocation mutants do contain a DNA-binding domain capable of targeting Nup98 to DNA [29]. For example, Nup98–homeodomain fusions such as Nup98–HoxA9 contain a characteristic DNA-binding domain commonly found in many transcription factors that regulate development [42] (Table 1). In addition, several fusion partners contain chromatin interaction domains such as SET, PWWP, and PHD or other DNA-binding domains such as an AT-Hook domain [29] (Table 1). However, although most of the fusions mentioned are predicted to bind to DNA, they likely do so at different loci and affect chromatin differently.

To date, only two translocation mutants have been studied at the mechanistic level. In the first study, it was shown that the Nup98–Nsd1 fusion could induce an AML-like phenotype in mice and inhibit differentiation while promoting proliferation in cells [43]. A closer look at the mechanism revealed that Nup98–Nsd1 interacts with the developmentally crucial Hox locus at multiple promoter sites to reinforce H3K36 methylation and acetylation. This fixes the Hox cluster in an active state to prevent deactivation by silencing factors and promotes leukemogenesis [43]. In another study, it was shown that the Nup98–JARID1A fusion could

use the PHD finger in JARID1A to bind to and lock hematopoietic-specific promoters in a constitutively active H3K4-trimethylated state [44]. In a similar manner to the Nup98–Nsd1 fusion, this prevents differentiation because repression of genes like Hox, Meis1, Pbx1, and others promotes a progenitor cell state [45].

While these studies give some insight into how Nup98 translocations with chromatin binding domains cause leukemia, they do not explain how Nup98 fusions that lack DNA-binding activity might cause the same phenotype as the Nup98–Nsd1 and Nup98–JARID1A fusions. For example, the Nup98–DDX10 fusion triggers the onset of AML through aberrant activation of many of the same genes that are misregulated in cells expressing Nup98–Nsd1 or Nup98–HoxA9 [43,46]. Surprisingly, the DDX10 protein does not appear to possess DNA-binding activity, but instead contains an RNA helicase domain that is required for the Nup98–DDX10 fusion to cause leukemia [46]. Another non-DNA-binding Nup98 translocation partner, RAP1GDS1, is a guanine exchange factor that regulates effectors of the Ras pathway [47] (Table 1). It is currently unclear where the Nup98–RAP1GDS1 protein localizes; however, it seems unlikely that the fusion directly mis-regulates hematopoietic-specific genes by binding to their promoters. Other Nup98 fusion partners, which cause AML but are not predicted to directly regulate transcription, have been identified including ADD3 (actin-binding protein) and LNP1, as well as IQCG, CCDC28, and ANKRD23, which are proteins of unknown function [28,29] (Table 1).

A role for WT Nup98 in hematopoiesis?

The current model for how Nup98 fusion proteins cause leukemia fails to explain how such a broad range of functionally different proteins can bring about similar AML phenotypes. We postulate that Nup98 is a potent transcriptional regulator during hematopoiesis under normal conditions. When a translocation occurs, the cell becomes heterozygous for Nup98 activity, which likely reduces the ability of Nup98 to regulate its target genes. Moreover, the Nup98 fusion protein uses the C-terminal domain provided by the translocation partner to bind to an anchor point, while the N-terminal GLFG domains tether the remaining WT Nup98 protein away from its normal genomic binding sites (Figure 3; right). If the C-terminal fragment happens to be from a transcriptional regulator such as Nsd1, HoxA9, or JARID1A the translocation causes transcriptional misregulation in addition to what is observed with WT Nup98 disruption. This model would explain why a variety of heterogeneous translocation partners can trigger AML, and would explain why the activity of a C-terminal fusion partner, such as DNA binding and RNA unwinding, would need to be intact to provide an anomalous anchoring site for endogenous Nup98. In addition, this model could offer an explanation as to why the GLFG domain of Nup98 is important for leukemia – the GLFG domain, which is essentially a self-aggregation domain, promotes the interaction between the Nup98 fusion and WT Nup98 (Figure 3) [37].

The reported role of Nup98 in direct transcriptional regulation of developmentally-specific genes supports the possibility that Nup98 could regulate genes that are important for hematopoiesis [20,21]. Furthermore, a recent study showed that the Nup98–IQCG fusion could interact with WT Nup98 through the GLFG domains of both proteins [48]. Another study demonstrated that the Nup98–HoxA9 and Nup98–PMX1 fusion proteins could mislocalize WT GFP–Nup98 away from GLFG bodies to foci that are unique to the Nup98–HoxA9 or Nup98–PMX1 proteins, respectively [37]. Taken together, these studies support the idea that mutant Nup98 can tether WT Nup98 to unnatural sites in the cell. Finally, an inspection of other non-Nup98 leukemic translocations reveals that most proteins that cause leukemia when translocated are themselves important for hematopoiesis in healthy cells. Future studies should focus on identifying the role of WT Nup98 in hematopoiesis, as this

could provide a big breakthrough in our understanding of the mechanism of how Nup98 translocations cause leukemia.

Concluding remarks

Nup98 is a multifunctional protein that plays important roles on and off the NPC. While the role of Nup98 in macromolecular export has been studied extensively, relatively little is known about Nup98's off-pore function. Specifically, we have almost no understanding of how broadly the transcriptional role of Nup98 extends, especially in mammals. In addition, we do not yet understand how the levels of the Nup98 nucleoplasmic pool are regulated to provide the proper expression of target genes without unwanted crosstalk occurring with other pathways such as mRNA export and NPC homeostasis. It is hard to envision how one protein could faithfully conduct so many tasks. Thus, the future will be an exciting time for the study of Nup98 that will provide many important answers to these disease-relevant questions (Box 1).

Box 1

Outstanding questions

- How is Nup96 regulated in postmitotic cells? Is Nup96 degradation accelerated or is alternative splicing of the small Nup98 transcript enhanced?
- Does the splicing of Nup98-96 regulate Nup98 on-pore versus off-pore population? Or does one population of Nup98 perform both pore functions and intranuclear functions?
- What genes does Nup98 regulate in mammalian cells? Is Nup98 important for transcriptional regulation during development? If so, what role does Nup98 play during hematopoietic differentiation?
- Do Nup98 translocation mutants interact with endogenous Nup98? If so, are Nup98 fusions able to mislocalize WT Nup98 from its normal transcriptional binding sites to aberrant binding sites? What is the effect on Nup98 target genes and the new gene mistargeted by Nup98?
- How much of the phenotypes observed in AML patients can be attributed to the transcriptional misregulation by Nup98 fusions and how much is caused by loss of endogenous Nup98 function.

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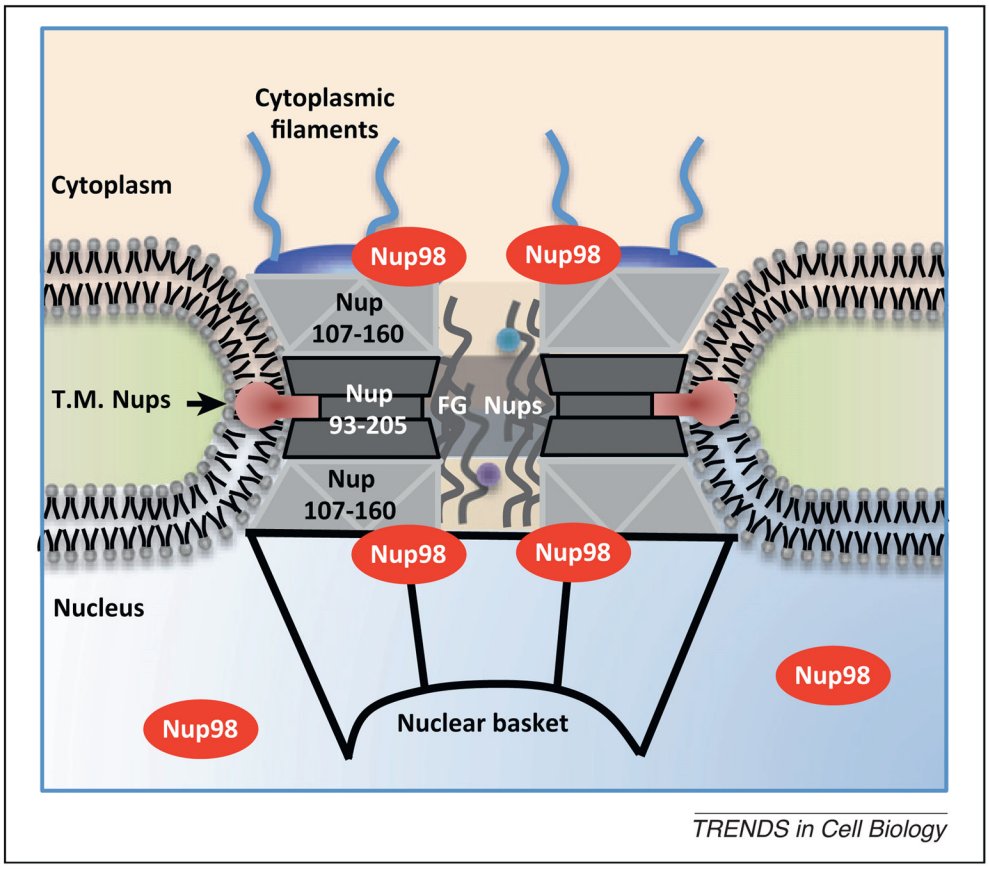

Figure 1.

The nuclear pore complex (NPC). The core structure of the NPC is maintained by the Nup93-205 complex (black) and the supporting structures of the Nup107-160 complex (grey) on the nuclear and cytoplasmic faces of the pore. The cytoplasmic filaments (blue) and the nuclear basket (black) allow the pore to sense the cytoplasmic and nuclear compartments, respectively, and regulate transport of macromolecules through the NPC via binding sites on FG Nups (grey lines) in the barrel of the pore. The entire pore is anchored to the nuclear envelope by protein–protein contacts between transmembrane Nups (pink) and the NPC scaffold. Nup98 is found on the nuclear and cytoplasmic faces of the pore (red) as well as in the nucleoplasm.

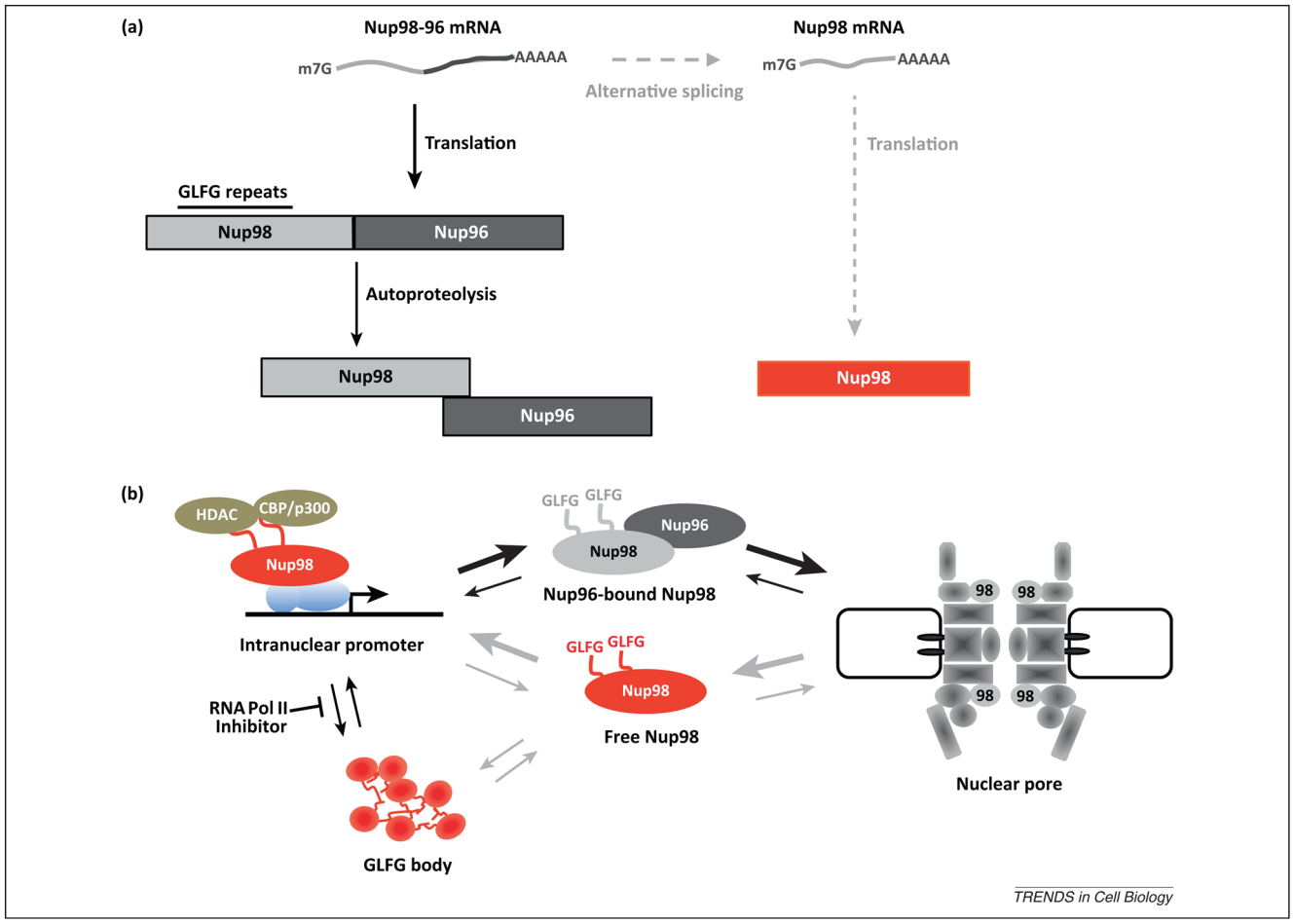

Figure 2.

Model for regulation of Nup98 levels on and off the NPC. **(a)** Nup98 and Nup96 are expressed from one mRNA. Following translation, autoproteolytic cleavage separates the two proteins but promotes the interaction between the C-terminus of Nup98 and the N-terminus of Nup96 (left pathway). Alternatively, Nup98 can be spliced as a short mRNA that does not encode Nup96 (right pathway). Therefore, this Nup98 protein pool could exist in a complex that does not contain Nup96 (red rectangle). Notably, the short Nup98 mRNA is much less abundant, and thus free Nup98 probably only contributes a small amount to the Nup98 protein pool (portrayed with semitransparent grey arrows). **(b)** If Nup98 exists in two different protein pools, one is predicted to be bound to Nup96 (grey sphere) and the other is not (red sphere). Nup96 should promote localization of Nup98 to the NPC (thick black arrow pointing to NPC) and inhibit localization to the nucleoplasm (thin black arrow pointing away from NPC). Without coexpression of Nup96, Nup98 has a lower affinity for the pore and localizes to the nucleoplasm where it can bind to promoters to regulate transcription via its GLFG domains (represented by thick grey arrows). When nucleoplasmic Nup98 is in excess, it can aggregate into GLFG bodies in a transcription dependent manner (see arrow inhibited by ‘RNA Pol II inhibitor’).

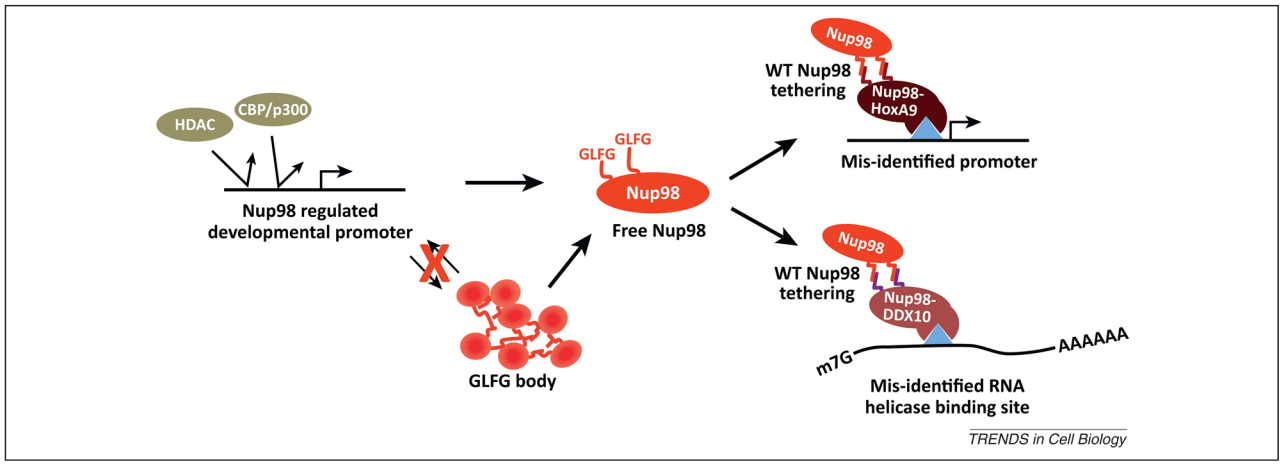

Figure 3.

Model for misregulation of wild type (WT) Nup98 in cells expressing Nup98 fusion proteins. Nup98 fusion proteins use C-terminal domains to bind to aberrant sites in the cell such as promoters (top right) and RNA modification sites (bottom right). The production of the Nup98 fusion represents a 50% loss of WT Nup98 protein. The other 50% can interact with Nup98 fusions at aberrant sites though the GLFG domains in each protein. This shifts the equilibrium of nucleoplasmic Nup98 (center red sphere) towards aberrant binding sites (thick black arrows) and away from important developmental transcription sites. As a result, histone-modifying enzymes like CBP/ p300 and HDACs can no longer bind and modify important developmental genes involved in hematopoiesis and GLFG bodies are dispersed (left).

Table 1

Nup98 translocation partners[a]

Partner gene	Partner gene function	Domain type
Known role in transcription		
HOXA9,11,13	Transcription	Homeodomain
HOXC11,13	Transcription	Homeodomain
HOXD11,13	Transcription	Homeodomain
PMX1,2	Transcription	Homeodomain
HHEX	Transcription	Homeodomain
PHF23	?	PHD
JARID1A	Histone demethylase	PHD
NSD1,3	Histone methyltransferase	PHD, SET
MLL	Histone methyltransferase	PHD, SET
LEDGF	Transcription	PWPP, AT Hook
RARG	Retenoic acid receptor	DNA binding domain
HMGB3	Transcription	HMG box
SETBP1	SET binding protein	–
No known role in transcription		
RAP1GDS1	Guanine exchange factor	–
ADD3	Actin binding protein	–
DDX10	RNA helicase	Helicase
TOP1	DNA topoisomerase	–
TOP2B	DNA topoisomerase	–
LNP1	?	–
CCDC28	?	–
ANKRD28	?	Ankyrin
IQCG	?	–

[a]?, not known; –, absent.