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Review

Gene Regulation by Nucleoporins and Links to Cancer

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Nuclear pore complexes (NPCs) composed of ~30 individual nucleoporins form huge macromolecular assemblies in the nuclear envelope, through which bidirectional cargo movement between the nucleus and cytoplasm occurs. Beyond their transport function, NPCs can serve as docking sites for chromatin and thereby contribute to the organization of the overall topology of chromosomes in conjunction with other factors of the nuclear envelope. Recent studies suggest that gene-NPC interactions may promote both transcription and the definition of heterochromatin-euchromatin boundaries. Intriguingly, several nucleoporins were linked to cancer, mostly in the context of chromosomal translocations, which encode nucleoporin chimeras. An emerging concept is that tumor cells exploit specific properties of nucleoporins to deregulate transcription, chromatin boundaries, and essential transport-dependent regulatory circuits. This review outlines new mechanistic links between nucleoporin function and cancer pathogenesis.

Introduction

Nucleocytoplasmic transport, intrinsically tied to eukaryotic gene expression, occurs exclusively through the nuclear pore complexes (NPCs). These nuclear import and export pathways utilize shuttling transport receptors, which are either members of the importin-β superfamily (karyopherins) requiring the small GTPase Ran (Stewart, 2007a) or another type of transporters unrelated to karyopherins (e.g., the mammalian mRNA exporter TAP-p15/yeast Mex67-Mtr2; Köhler and Hurt, 2007). NPCs are ~40–60 MDa macromolecular assemblies with an overall octagonal symmetry. They are composed of distinct building blocks such as the spoke-ring complex, the cytoplasmic pore filaments, and the nuclear basket (Brohawn et al., 2009; Tran and Wente, 2006). Despite its enormous size, the NPC is built from a comparatively small number (~30) of different nucleoporins, which exist in multiple copies per NPC. The nucleoporins are categorized into three major classes. About one-third of the nucleoporins contain phenylalanine-glycine (FG)-rich repeat sequences, which are intrinsically disordered and fill up the active transport channel (Figure 1, light-blue region). Shuttling transport receptors pass through the meshwork of FG nucleoporins by transient interactions with FG repeats (Peters, 2009). A second class of nucleoporins is devoid of FG repeats and is thought to provide a scaffold for NPC architecture. Only a few nucleoporins have transmembrane domains to anchor the NPC in the nuclear envelope. Whereas the majority of nucleoporins are symmetrically located on both sides of the nuclear membrane, a small number of them exhibit an asymmetric NPC distribution (e.g., at the nuclear basket or the cytoplasmic pore filaments). Genetic, biochemical, structural, and bioinformatic approaches have established a rough model of nucleoporin interactions and their localization within the NPC framework (Figure 1).

Because traffic through the NPC is highly selective and regulated, it provides an important means to control gene expression, signaling networks, and cell homeostasis (Kaffman and O'Shea, 1999). In principle, transport can be controlled at the level of the cargo, the transporter, and the NPC itself. The recognition of specific nuclear import (NLS) or export signals (NES) by the cognate transport receptor is modulated by elaborate mechanisms, which involve posttranslational modifications and masking of signal motifs (Poon and Jans, 2005). Moreover, individual nucleoporins seem to mediate specific transport pathways. Tissue-specific expression of nucleoporins (Uv et al., 2000) and cell-cycle adjusted changes in nucleoporin abundance (Chakraborty et al., 2008) can add another layer of complexity to the regulation of NPC transport. Significantly, several nucleoporins were identified as factors that expand their reach into chromatin organization and gene expression by their ability to physically recruit gene expression and DNA repair machineries to the NPC. In light of these developments, we discuss emerging models of nucleoporin-based gene and chromatin regulation and analyze the intriguing interplay between NPC malfunction and cancer. We do not comprehensively cover examples in which NPC transport of oncogenes and tumor suppressors is disrupted in cancer cells (for a review, see Kau et al., 2004). For a general overview of NPC-related human diseases, the reader is referred to Cronshaw and Matunis (2004) and Capelson and Hetzer (2009).

Roles of Nucleoporins in Gene Expression and Chromatin Organization

The eukaryotic nucleus is highly compartmentalized and dynamic. Studies in various model organisms revealed that gene positioning relative to the nuclear periphery (i.e., inner nuclear membrane), other genes, and various nuclear subcompartments can favor either transcriptional activation or repression (Fraser and Bickmore, 2007). In the following section, we consider the NPC as a structural entity that regulates transcription, genome partitioning, and genome stability and aids in repairing damaged DNA.

Classically, the nuclear periphery was believed to exert no more than a repressive role on gene expression. Contrary to this, studies in yeast suggested that physical association between genes and NPCs can regulate the levels of transcription,

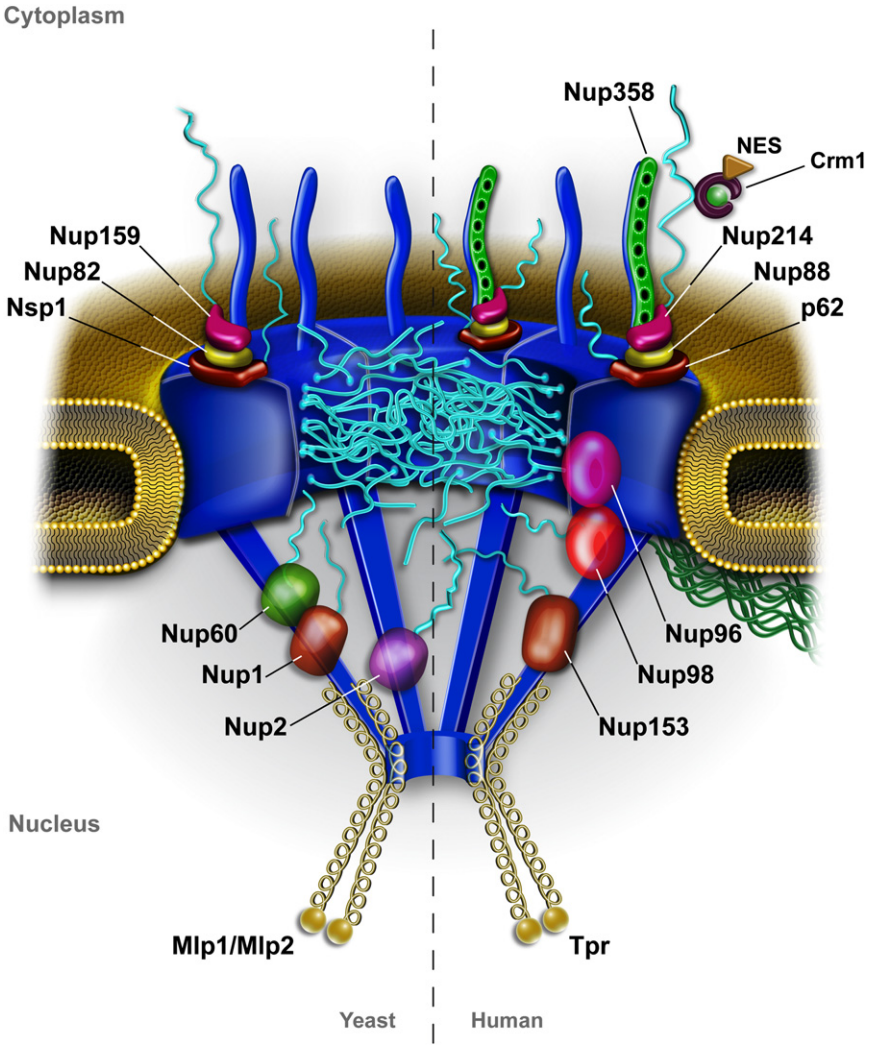

Figure 1. Scheme of the NPC Highlighting Nucleoporins with a Link to Chromatin Interaction and Cancer

Schematic drawing of the NPC embedded in the double nuclear membrane and consisting of an octagonal structural core with attached cytoplasmic pore filaments and the nuclear basket (dark blue). Nucleoporins with FG repeat domains protrude in the central pore channel, forming a meshwork of natively unfolded filaments (light blue) through which active nucleocytoplasmic transport occurs. (Right) NPC model with schematically drawn human nucleoporins that are implicated in cancer (see text), including Nups at the cytoplasmic pore filaments (Nup358, Nup214, and Nup88), Nups at the nuclear basket (Nup153 and Tpr), and the Nup98-Nup96 pair located at the NPC ring, which is generated by autoproteolytic cleavage of a large nucleoporin precursor. Also shown is the Crm1:RanGTP:NES complex attached to the FG repeats of Nup214. (Left) NPC with yeast nucleoporins that are related to the depicted human nucleoporins.

increase the efficiency of mRNA processing and export, and support rapid reactivation of inducible genes (for reviews, see Akhtar and Gasser, 2007; Brown and Silver, 2007). Adaptor proteins that mediate an interaction between chromatin and the NPC were identified. An important example of a linker device is chromatin-bound SAGA, a transcriptional coactivator that harbors two chromatin-modifying activities: a histone acetyltransferase (Gcn5) and a histone deubiquitinase (the Ubp8-Sgf73-Sgf11-Sus1 module) (Baker and Grant, 2007). In yeast, SAGA was shown to interact with the nuclear basket protein Mlp1 (Luthra et al., 2007) and the NPC-associated TREX-2 complex (Sac3-Thp1-Cdc31-Sus1) (Rodríguez-Navarro et al., 2004). TREX-2 is an NPC-bound complex with roles in mRNA export and transcription elongation (Köhler and Hurt, 2007). SAGA and TREX-2 share a common and conserved factor, Sus1, which was implicated to fulfill an integrative function in chromatin-NPC tethering and transcription-coupled mRNA export (Rodríguez-Navarro et al., 2004; Cabal et al., 2006; Köhler et al., 2008; Pascual-García et al., 2008). Consistent with this possibility, *Drosophila* E(y)2 (a Sus1 ortholog) in conjunction with the TREX-2 component Xmas-2 (a Sac3 ortholog) regulate mRNA expression, export, and perinuclear positioning of the *hsp70* gene cluster in flies (Kurshakova et al., 2007a). Because human cells contain a homologous SAGA complex and the Sac3-related GANP protein, it is likely that the chromatin-NPC connection for gene activation is broadly conserved across eukaryotes.

The physical link between TREX-2 and the NPC requires Sus1 and the nucleoporin Nup1, which exhibits an exclusive location at the nuclear side of the NPC (i.e., nuclear basket; Fischer et al., 2004; Köhler et al., 2008; Jani et al., 2009). Moreover, the nucleoporins Nup2, Nup60, and Mlp1 (homolog of metazoan Tpr; see below), which are all constituents of the NPC basket, were reported to be involved in gene-NPC interactions (Casolari et al., 2004; Schmid et al., 2006; Luthra et al., 2007). In *Drosophila melanogaster*, upregulation of the male X chromosome (dosage compensation) requires the nuclear basket proteins Nup153 and Tpr/Mtor (Mendjan et al., 2006). Deletion of these nucleoporins eliminates hypertranscription of the male X chromosome, implicating *Drosophila* NPCs in transcriptional activation. Thus, nucleoporins of the NPC basket are ideally positioned to mediate a direct contact between the NPC and the genome and/or the gene expression machinery (Figure 1). Of note, a recent study in yeast reported the formation of gene loops, which interacted with NPCs in an Mlp1-dependent manner. Gene loops, which are thought to join promoter and terminator regions at their base, were proposed to facilitate rapid reinduction of genes and confer a cellular memory of recent transcriptional activity (Tan-Wong et al., 2009). The ability to tether gene loops significantly expands the repertoire of NPC-associated functions and could aid in creating distinct topological chromatin domains in

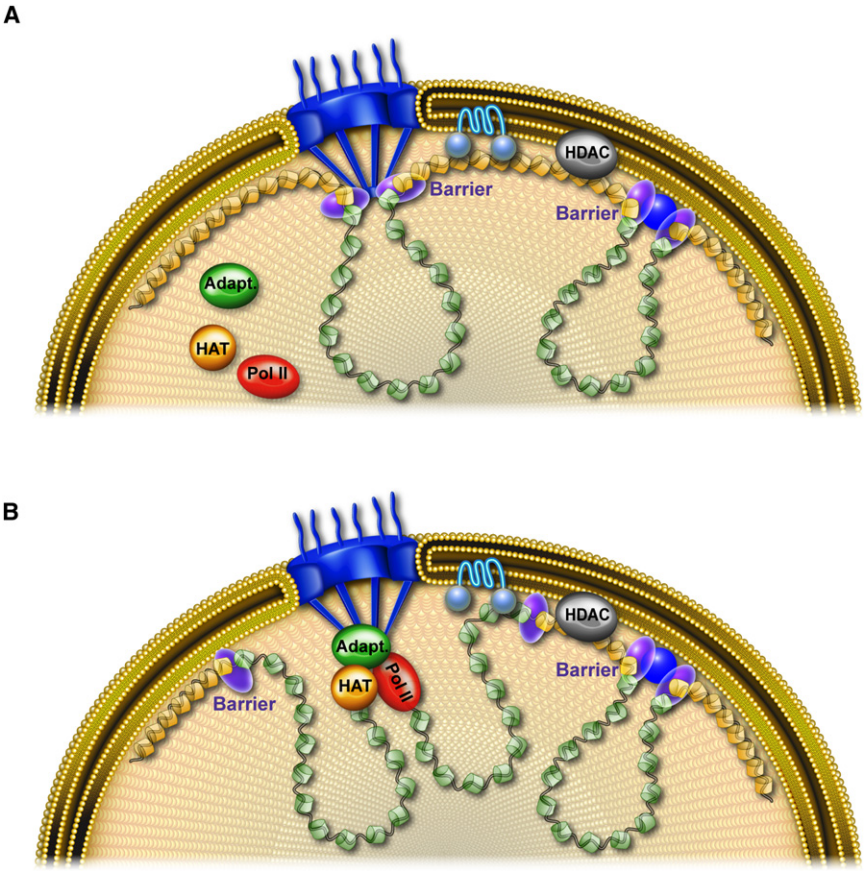

Figure 2. Model for the Function of Nuclear Pores as Chromatin Insulators and Transcription Platforms

(A) Hypothetical model shows partitioning of the chromatin fiber into distinct heterochromatic (yellow) and euchromatic regions (green). NPCs and other tethering stations at the NE (dark blue) organize the chromatin fiber into distinct topological domains by gene loop formation and by establishing various forms of chromatin barriers to prevent the spread of heterochromatin factors. Histone deacetylases (HDAC), inner nuclear membrane (INM) proteins (light blue), and other factors contribute to keeping NE-tethered chromatin in a repressed state.

(B) Repositioning of activated genes to the NPC involving adaptor proteins (e.g., TREX-2), HAT activities (e.g., SAGA transcriptional coactivator), and RNA polymerase II (Pol II). Transcription at the NPC is postulated to also affect euchromatin-heterochromatin boundaries, which may expose INM proteins to a permissive transcriptional environment (e.g., Src1 in yeast or lamina-associated factors in metazoa).

conjunction with DNA loops formed at other nonpore sites of the nuclear envelope (NE) (Noma et al., 2006) (Figure 2).

Until recently, it was unclear whether NPCs in human cells would also contribute to regulating gene expression. Brown et al. (2008) demonstrated that the human genome indeed exhibits specific interactions with NPCs when probing genome-wide interactions of the core nucleoporin Nup93. Surprisingly, Nup93 interacted mostly with heterochromatic regions of HeLa nuclei. However, global histone acetylation induced by a histone deacetylase (HDAC) inhibitor resulted in Nup93 association with euchromatic regions. These data indicate that NPCs can interact with both active and repressed chromatin (either sequentially or simultaneously) and that dynamic chromatin reorganization occurs at NPCs in response to altered histone acetylation patterns.

A possible implication of this and earlier reports in yeast is that NPCs may interact with DNA at boundaries, which separate active from repressed chromatin domains. Consistent with this idea, physically tethering components of the nucleoplasmic transport machinery to chromatin in yeast prevents the spread of transcriptional activation or repression between flanking genes, a function operationally defined as boundary activity (Ishii et al., 2002). Crucial for NPC-mediated boundary activity was the nuclear basket component Nup2. Nup2 was later found to interact with chromatin-bound Prp20 (Ran-GEF) (Dilworth et al., 2005). Histone modification patterns of Prp20-associated nucleosomes exhibited a mixture of active and repressive chromatin marks in support of a model of NPC interactions at or near chromatin boundaries (Figure 2).

How could NPCs play an active role in establishing or maintaining discrete boundaries between active and silenced chromatin domains, a classical function of so-called insulators? In general, chromatin insulators partition the genome by either acting as barrier insulators or enhancer-blocking insulators (Gaszner and Felsenfeld, 2006). Barrier elements antagonize heterochromatin spreading, for example, by recruiting chromatin-modifying/remodeling activities or through formation of higher-order chromatin loops. In contrast, enhancer-blocking elements interfere with enhancer-promoter interactions when placed between them. Recruitment of histone acetyltransferases to NPCs may not only activate transcription (see above), but more generally establish a barrier to heterochromatin invasion at gene boundaries (Figure 2). For example, Nup93 was shown to interact with the histone acetyltransferase (HAT) CBP in mammalian cells (Ryan et al., 2006). Moreover, SAGA HAT activity is recruited via Mlp1 and Nup1 (see above), and various SAGA subunits were identified as barrier elements in genome-wide screens (Oki et al., 2004). On the other hand, the mammalian nuclear periphery contains the deacetylase, HDAC3, which associates with the lamin-binding protein LAP2β to induce histone deacetylation (Somech et al., 2005). In fact, a balance of HAT and HDAC activity is essential for the maintenance of proper boundaries between active and repressed chromatin (Kimura et al., 2002; Suka et al., 2002), and insulator proteins recruit HATs to prevent the advance of inactivating modifications from heterochromatic regions (West et al., 2004). Of interest, a recent report described recruitment of Ada2, a subunit of the SAGA transcriptional coactivator to yeast telomeres and a barrier function to

heterochromatin spreading. Thus, SAGA factors appear to participate in both transcriptional activation and repression (Jacobson and Pillus, 2009). Furthermore, the SAGA/TREX-2 component Sus1 operates as a chromatin insulator in conjunction with Su(Hw) in *Drosophila* (Kurshakova et al., 2007b). Specific mechanisms for NPC-based insulator functions remain to be determined, and there may, in fact, be multiple ways to establish chromatin barriers at the pore.

At present, it is unclear how many genes utilize the NPCs as docking sites to regulate their expression, and the functional relevance of this phenomenon in different organisms needs to be better defined. In the long run, gene-NPC associations will also have to be analyzed in pathological states. Distinctive changes to the nuclear structure are hallmarks of many cancers. Intriguingly, breast cancer tissues were recently found to exhibit disease-specific gene-repositioning events, which are apparently not caused by genome instability or by a general cellular response to disease (Meaburn et al., 2009). It was suggested that altered interphase gene positioning patterns may even provide diagnostic tools to detect cancerous tissues. Whether gene repositioning in cancer cells reflects (in part) the formation or dissolution of gene-NPC interactions remains to be addressed in the future.

Nucleoporins with a Link to Cancer

Blobel and colleagues reported in 1994 that the CAN protein, a putative oncogene product of 214 kDa involved in leukemogenesis (von Lindern et al., 1992a), was actually a nuclear pore protein: Nup214 (Kraemer et al., 1994). This unexpected finding opened new avenues for a molecular understanding of leukemia and oncogenesis in general. Subsequently, additional nucleoporins (Nup98, Nup358, and Tpr) were reported to produce protein chimeras with other cellular proteins as a result of chromosomal translocations in cancer cells (for a review, see Xu and Powers, 2009). Moreover, some nucleoporins (Nup88) were found to be highly overexpressed in tumors (Martínez et al., 1999). At present, there is no unifying theory to explain how NPC components can cause cancer; in fact, different nucleoporins operate differently, and cause-effect relationships are oftentimes unclear. However, in light of a growing perception of the NPC as a dynamic, potentially tissue-specific hub for the integration of chromatin regulation and transport (see above), new models of NPC-driven oncogenesis are emerging. In the following, we recapitulate the normal function of these "guilty" nucleoporins and describe possible mechanisms of how they contribute to cancer in an "oncogenic liaison." For a comprehensive inventory of nucleoporin chimeras, the reader is referred to Xu and Powers (2009).

Nup98 Fusion to Chromatin Factors Dysregulates Gene Boundaries

The evolutionary conserved Nup98 is essential for NPC structure and function (Tran and Wente, 2006; Griffis et al., 2003). Due to differential splicing, Nup98 can be synthesized in two forms: either Nup98 is connected to a short C-terminal tail or it is synthesized as a Nup98-Nup96 fusion protein. Nup98 harbors an intrinsic autoproteolytic activity, which cleaves both variants to produce either Nup98 alone (plus an 8 kDa tail) or to generate both Nup98 and Nup96 (Fontoura et al., 1999; Hodel et al., 2002). Nup98 harbors a number of GLFG-type repeats, which mediate direct contact to shuttling nuclear transport receptors and the selective NPC passage of cargo. In vivo, Nup98 together with its interacting partner Rae1 perform a specific role in nuclear RNA export (Pritchard et al., 1999).

A possible link between Nup98 and cancer emerged when Nup98 was encountered in chromosomal translocations of acute myeloid leukemia (AML) (Nakamura et al., 1996; Borrow et al., 1996). The largest group of *NUP98* translocations produces gene fusions between the GLFG repeats of NUP98 and homeodomain transcription factors. In the case of the original Nup98-HoxA9 translocation, which is under the control of the *Nup98* promoter, this chimera consists of the nearly entire Nup98 GLFG domain and the Rae1-binding site that is fused to the DNA-binding homeodomain of the HoxA9 transcription factor. The Nup98-HoxA9 fusion protein dissociates from the NPC and localizes to nucleoplasmic foci (Kasper et al., 1999). Homeodomain proteins are transcription factors and master regulators of development and differentiation (Argiropoulos and Humphries, 2007), and the human genome contains several clusters of homeobox genes (*HOXA-D*). Many *HOX* genes are initially expressed in hematopoietic stem cells but must be downregulated during differentiation to mature hematopoietic cells. Other homeobox genes, like *Pbx1* and *Meis1*, act as Hox cofactors during hematopoiesis. Subsequent to the *Nup98-HoxA9* translocation, *Nup98* was identified in chromosomal translocations with a remarkably wide array of partners (for overview, see Romana et al., 2006; Xu and Powers, 2009). In all cases, the chimeric proteins carry Nup98's GLFG domain of variable length fused to various partners, including topoisomerases, histone methyltransferases, transcriptional coactivators, RNA helicases, and several proteins of unknown function.

How can different Nup98-carrying fusion proteins elicit a common disease pathway? As a first hint, the GLFG repeat domain of Nup98 was reported to directly interact with the HAT CBP/p300 (Kasper et al., 1999) or with the histone deacetylase HDAC1 (Bai et al., 2006). In the case of the Nup98-HoxA9 fusion, the Nup98 FG repeats could be functionally replaced by the FG repeats of Nup153 or Nup214 to recruit CBP/p300. Furthermore, Nup98 is a "mobile nucleoporin" found both at the NPC and in the nucleoplasm, where it exhibits dynamic, transcription-dependent movements into nuclear foci (GLFG bodies) (Daigle et al., 2001; Griffis et al., 2002). This raised the possibility that FG repeats contain a cryptic HAT-interaction motif, which could misallocate HAT activities when fused to other chromatin-modifying factors in cancer cells.

Two recent publications have suggested a specific mechanism for the involvement of Nup98 in leukemogenesis. Wang et al. (2007) demonstrated that fusion between Nup98 and the histone methyltransferase NSD1, as found in AML, could indeed upregulate expression of the proto-oncogenes *HoxA7*, *HoxA9*, *HoxA10*, and *Meis1* and induce malignancy. During normal hematopoiesis, expression of *HoxA7*, *HoxA9*, and *HoxA10* promotes stem cell self-renewal, and the subsequent downregulation of *Hox* genes by polycomb proteins triggers terminal differentiation. Nup98-NSD1 was found to bind genomic elements adjacent to *HoxA7* and *HoxA9* genes and to maintain high levels of histone H3-Lys36 (H3K36) methylation and histone

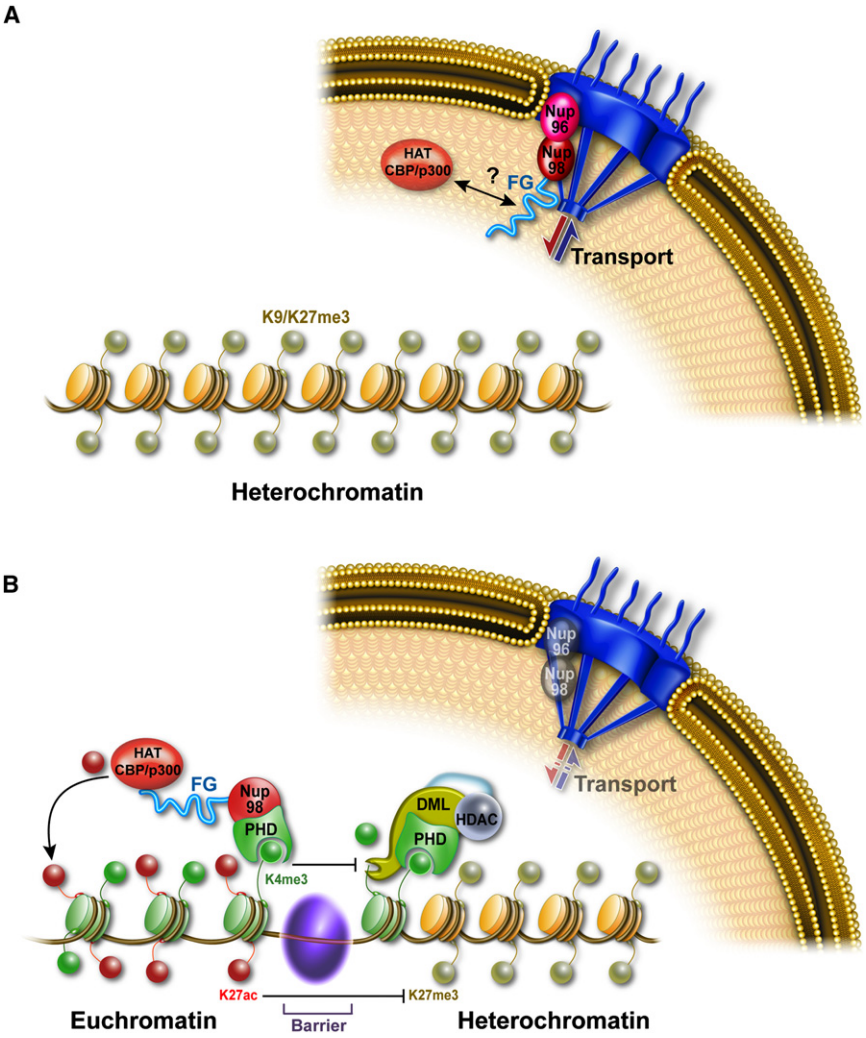

Figure 3. Misinterpretation of Histone Marks by an Oncogenic Nup98-PHD Chimera at Developmentally Critical *HOX* Gene Loci

(A) Model depicting a normally silenced state (K9/K27 trimethylated histone H3) of *HOX* gene loci during hematopoiesis. These loci exhibit low levels of H3K4me3 and H3 acetylation due to polycomb factor-mediated histone demethylation and deacetylation. Although speculative, the CBP/p300 histone acetyltransferase is shown to interact in a different nuclear compartment with the FG repeats of Nup98. This interaction may also occur in the nucleoplasm with free Nup98 (not shown).

(B) An oncogenic mechanism is initiated by the aberrant "capping" of the H3 K4me3 mark (green) through the Nup98-fused PHD finger. This protects the active K4me3 mark from removal by polycomb-associated demethylases (DML) like JARID1, which normally contain the Nup98-fused PHD finger. The Nup98 FG repeat portion of the chimera recruits histone acetyltransferases (HAT) to chromatin to aberrantly acetylate histone H3 at K27 (red). This active mark competes with K27me3 and antagonizes polycomb-associated deacetylase activity (HDAC). In effect, the Nup98 fusion acts as a barrier that prevents the normal spreading of polycomb factors from adjacent silenced *HOX* genes. Furthermore, translocation-dependent depletion of full-length Nup98 and its splicing variant Nup96 from the NPC could disrupt specific mRNA transport of critical cell-cycle regulators (broken arrows).

acetylation. Deletion of the Nup98 GLFG repeat domain, which is responsible for recruiting CBP/p300 HAT activity, or mutations in NSD1-inactivating H3K36 methyltransferase activity both abolished *HoxA* gene activation and leukemogenesis. These data imply that the Nup98 chimera could generate aberrant "active" chromatin marks within the developmentally important *Hox* gene cluster, which perturbs its polycomb-mediated transcriptional repression.

Furthermore, Allis and colleagues recently demonstrated that the fusion of Nup98 to a PHD (plant homeodomain) finger was indeed sufficient to cause AML in a murine model (Wang et al., 2009). In this case, leukemogenesis relied on the specific recognition of the histone H3 trimethyl mark by the PHD finger. Similar to the Nup98-NSD1 fusion, Nup98-PHD induced upregulation of developmentally important transcription factors that were either targets of polycomb factors or exhibited a "bivalent" chromatin pattern with both repressive (H3K27me3) and active (H3K4me3) histone marks. Nup98-PHD chimeras were enriched at these "bivalent sites" that are typically found at euchromatin-heterochromatin boundaries. Significantly, PHD point mutations, which abrogated binding to histone H3 trimethyl marks, also failed to induce leukemia. Thus, locking the Nup98-PHD fusion onto the H3K4me3 mark could have antagonized the spreading of the repressive H3K27me3 mark, a function of polycomb proteins. Consistent with this, gene loci occupied by Nup98-PHD failed to efficiently recruit repressive polycomb factors and exhibited increased levels of CBP/p300-induced acetylation (Figure 3).

Taken together, both reports suggest that a Nup98-dependent manipulation of the "histone code" contributes to leukemogenesis. Thus, these types of leukemia may recapitulate a possible function of Nup98 as a transcription factor and chromatin boundary element. It remains to be shown whether Nup98 via its FG repeats can indeed recruit HAT activities in normal cells (either as a mobile nucleoporin or as part of the NPC) and how Nup98 would be targeted to specific genes.

Another Nup98 effect in cancer cells could stem from its unusual biogenesis pathway. Of note, due to the autoproteolytic generation of Nup96 from the long *NUP98* splice variants, a chromosomal translocation is expected to lower Nup96 production. Surprisingly, Nup96 expression levels oscillate in synchronization with the cell-cycle and appear to influence cell proliferation by differentially regulating export of specific mRNAs, including those of key cell-cycle regulators (Chakraborty et al., 2008). Such effects may further aggravate the dysregulation of the cancer cell transcriptome by altering specific nuclear transport pathways (Figure 3). In summary, our current

knowledge about *Nup98* translocations suggests a two-fold mechanism of cellular dysregulation in which both transcription and nuclear transport could be perturbed. It will be important to study other Nup98 chimeras in order to reveal common themes and specific differences between the many existing Nup98 fusion proteins.

Tpr Provides a Molecular Zipper for Kinase Activation

Studies on a chromosomal translocation that fused the nucleoporin translocated promoter region (Tpr) (Figure 1) and the Met kinase have revealed a general mechanism for receptor tyrosine kinase-derived oncogenes. Under normal conditions Tpr is a key structural element of the nuclear basket (Krull et al., 2004). It is a conserved 265 kDa nucleoporin that forms long coiled-coil filaments reaching into the nucleoplasm. Nup153 is required for Tpr attachment to the NPC (Frosst et al., 2002; Krull et al., 2004). Tpr operates in nuclear RNA and protein export but has additional functions, e.g., in the mitotic spindle checkpoint as a binding partner and regulator of Mad1/Mad2 (Lee et al., 2008). A perplexing array of functions are attributed to the yeast Tpr orthologs, Mlp1 and Mlp2. These include RNA quality control and mRNA export, DNA repair, telomere positioning and length control, anchorage of activated genes, tethering of desumoylating enzymes, and spindle pole body assembly (Lewis et al., 2007 and references therein). Conceivably, these long filamentous proteins provide an extensive surface for interactions with different nuclear machineries.

The *Tpr-Met* chimera was first isolated after treating a sarcoma cell line with a carcinogen. The resulting chromosomal translocation fused the N terminus of Tpr to the kinase domain of the Met proto-oncogene (Cooper et al., 1984). Tpr consists mostly of heptad repeats (coiled-coil domains) followed by a short C-terminal domain with NLS activity (Byrd et al., 1994). In the Tpr-Met fusion, two Tpr heptad repeats are joined to the cytoplasmic tyrosine kinase domain of Met, and a zipper-like dimerization through the heptad repeats leads to constitutive Met activation in the absence of a ligand (Park et al., 1986). Since then, numerous other receptor tyrosine kinase-derived fusion proteins have been identified in human tumors.

Under normal conditions, Met is the cell surface receptor for hepatocyte growth factor (HGF). Met regulates a program of invasive epithelial growth through the coordination of cellular proliferation and survival, cell migration, and morphogenesis. Altogether, these processes are important during embryogenesis and for the repair of adult tissues (reviewed in Peschard and Park, 2007). In the chromosomal translocation, the extracellular ligand-binding transmembrane and juxtamembrane domains of Met are lost, which renders the Tpr-Met kinase resistant to downregulation and causes sustained activation of downstream signaling pathways (Lai et al., 2009).

Tpr is also found translocated with *NTrk1* (*TrkA*), the receptor tyrosine kinase for nerve growth factor (reviewed in Pierotti and Greco, 2006). In analogy to *Tpr-Met*, the *Tpr-NTrk1* translocation dysregulates NTrk1 signaling and causes tumorigenesis. In summary, the Tpr fusion proteins are examples of the effects of shuffling out structural NPC domains into a different protein context, wherein their ability to promote dimerization disrupts specific events in a signaling pathway.

Translocations Involving Nucleoporins of the Cytoplasmic Pore Filaments: Nup214/CAN and Nup358

Nup214 is an essential FG repeat nucleoporin that is exclusively located to the cytoplasmic face of the NPC and together with Nup358 (see below), a constituent of the cytoplasmic pore fibrils (Figure 1) (Walther et al., 2002 and references therein). Nup214, like its yeast ortholog Nup159, harbors an N-terminal β-propeller domain, which recruits the Dbp5 helicase. Dbp5 and its cofactors are thought to terminate mRNA export and release the mRNA into the cytoplasm (Stewart, 2007b). Nup214 contains numerous FG repeats, which provide binding sites for shuttling nuclear transport receptors. Importantly, Nup214 interacts with the general export receptor Crm1 (Fornerod et al., 1997), and this property may generally dysregulate export pathways upon Nup214 malfunction (Saito et al., 2004). Of interest, Nup214 also exposes a docking site for the nucleocapsids of large viruses (e.g., adenovirus) independent of soluble transport receptors to facilitate entry of the viral genome into the nucleus (Trotman et al., 2001). Nup214 forms a subcomplex with Nup88 and possibly p62 (Fornerod et al., 1997) that is related to an orthologous yeast assembly, the Nup159-Nup82-Nsp1 complex (Bailer et al., 2001). The tight biochemical interaction between Nup214 and Nup88 and the functional consequences of its disruption will be further considered below.

The *Nup214/CAN* locus was initially identified in leukemia-associated chromosomal translocations, which joined it to either the *DEK* or *SET* genes (von Lindern et al., 1992a, 1992b). This situation yields chimeras of almost full-length Dek or Set protein fused to the C-terminal part of Nup214, which are mainly localized in the nucleoplasm (Fornerod et al., 1995). Set and Dek are both involved in chromatin regulation. Set is a bona fide histone chaperone, a class of factors involved in chromatin assembly/disassembly during transcription, DNA replication, and repair (Muto et al., 2007). Set is required for transcription of chromatin templates by RNA polymerase Pol II (Pol II) in vitro (Gamble and Fisher, 2007). Mechanistically, Set together with the NAD^+-dependent PARP1 enzyme are needed to poly(ADP-riboysyl)ate and displace Dek from chromatin. With regards to histone modifications, Set (also known as INHAT) was initially proposed to inhibit CBP/p300-dependent histone acetylation (Seo et al., 2001), possibly by masking the histone tails. Though further work is required to precisely understand the different levels of Set function in vivo, Set and Dek seem to have opposing effects on chromatin accessibility and regulation. It can be hypothesized that the fusion of either SET or DEK to NUP214 would perturb a functional balance. The identification of target genes, which are (dys-)regulated by the NUP214-SET-DEK-PARP1 network, could generate further insights into leukemogenesis.

A third type of *CAN* translocation generates a fusion between Nup214 (β-propeller, coiled-coil region plus variable amounts of the FG repeats) and the SH2, SH3, and tyrosine kinase domains of *ABL*. The Nup214-Abl protein is an active tyrosine kinase (Graux et al., 2004). It associates with the NPC via Nup214's coiled-coil domain, which interacts with Nup88. Because Nup214-Abl is commonly overexpressed, it may replace endogenous Nup214 from the NPC and juxtapose Nup214-Abl molecules within the octagonal NPC array. This unique topology was proposed to

activate the Abl kinase activity by cross-phosphorylation (De Keersmaecker et al., 2008). As a result, activated Nup214-Abl chimeras tethered to the cytoplasmic pore fibrils could have access to cytoplasmic kinase substrates or substrates passing through the NPC and deregulate Abl signaling pathways.

A chromosomal translocation involving a further nucleoporin of the cytoplasmic pore filaments is the *Nup358-anaplastic lymphoma kinase* (*ALK*) chimera (Ma et al., 2003). Of interest, Nup358-ALK appears to localize to the NPC, and it was speculated that the N-terminal domain of Nup358 promotes oligomerization and activation of the ALK protein kinase domain.

Altogether, translocations involving nucleoporins of the cytoplasmic pore filaments can have very diverse cellular effects. A noteworthy finding is that some nucleoporin fusions are incorporated into the NPC, where they can potentially disrupt signaling pathways. Moreover, the idea that nup-chimeras in cancer cells may recapitulate a normal function of nucleoporins to regulate chromatin is supported by recent findings from three different labs, revealing that specific nucleoporins can indeed function inside the nucleoplasm as transcriptional regulators independent of their association with the NPC (Kalverda et al., 2010; Capelson et al., 2010; Vaquerizas et al., 2010).

Tumor Marker Nup88 Is Overexpressed in High-Grade Tumors

Nup88 is a non-FG nucleoporin located exclusively at the cytoplasmic side of the NPC (Figure 1). As outlined above, Nup88 forms a complex with the FG repeat nucleoporin Nup214 but also interacts with Nup358 (Bernad et al., 2004). The Nup214-Nup88 complex is an adaptor for the assembly and docking of nuclear import complexes, but its major role lies in Crm1-mediated export (Roth et al., 2003; see above). Accordingly, the Nup214-Nup88 complex targets Crm1 to the cytoplasmic side of the NPC (Figure 1). In yeast, the analogous Nup159-Nup82-Nsp1 complex (Figure 1) is essentially involved in mRNA export (Köhler and Hurt, 2007), suggesting an analogous role of mammalian Nup214-Nup88. Although Nup88 is a key structural constituent of the NPC, it is expressed in a tissue-specific manner in *Drosophila* (Nup88/members only) (Uv et al., 2000).

Unexpectedly, an antibody raised against *Candida albicans* cross-reacted with human Nup88, a finding that led to the discovery of Nup88 overexpression in a variety of malignant tumors (Martínez et al., 1999). Nup88 dosage does not correlate with a concomitant overexpression of its interacting partner Nup214, suggesting a rather selective nucleoporin dysregulation (Gould et al., 2002). Nup88 staining in tumor tissues is prominent in the cytoplasm and often appears as granular dots. The degree of Nup88 overexpression generally correlates with tumor grade and is most pronounced in advanced tumors and at their invasive periphery (Agudo et al., 2004).

How could Nup88 overexpression possibly influence tumorigenesis? A main function of Nup88 in normal cells is to anchor Nup214 to the NPC (Roth et al., 2003) and to recruit Crm1 to cytoplasmic pore filaments, which promotes Crm1 recycling back inside the nucleus for another round of export. This mechanism may, in consequence, facilitate NES-mediated nuclear export and thereby modulate signaling pathways. For instance, in mammals and flies, Nup88 was shown to be required for nucleocytoplasmic transport of NF-κB (Takahashi et al., 2008; Xylourgidis et al., 2006), a ubiquitous transcription factor involved in immune responses, apoptosis, and cancer. Moreover, overexpression of the Nup214-Nup88 complex trapped Crm1 and the Rel protein *Dorsal* to cytoplasmic foci and inhibited protein export and immune response activation (Roth et al., 2003). In another study, Nup88 was shown to participate in the expression of osmoprotective genes by regulating the nucleocytoplasmic transport of a specific transcription factor (Andres-Hernando et al., 2008). In plants, Nup88 is required for nuclear accumulation of defense regulators, thereby playing an important role in innate immunity (Cheng et al., 2009).

Taken together, Nup88 overexpression in cancer cells could mislocalize Nup214, which, in turn, would reduce Crm1 concentration at the NPCs and cause its trapping in cytoplasmic foci. Because many developmental signaling pathways rely on the selective Crm1-dependent translocation of transcriptional regulators, Nup88 overexpression may ultimately affect cancerogenesis by perturbing the fine-tuning of these signaling pathways. It remains to be determined whether this represents a cause or consequence of tumor formation.

Conclusions

The contribution of nucleoporin malfunction to cancer offers unique opportunities to understand disease mechanisms and the specialized function of distinct nucleoporins. The NPC-cancer link cannot be rationalized in simple concepts to date, but we expect that further research in this area will uncover interesting novel aspects of NPC biology. In particular, a growing perception of the NPC as a regulator of transcription and chromatin organizer may pave the way for a deeper understanding of how cancer transcriptomes are perturbed. This line of research will likely intersect with an analysis of how the spatial positioning of genes in cancer cells is perturbed, which, in turn, requires a deeper understanding of the machinery that targets and tethers genes to the NPC in normal cells. A major challenge for NPC research at present is the fact that integrated approaches are required to understand the complexity of the nuclear pore, whose function lies far beyond transport alone. Moreover, nucleoporins appear to be related to a bewildering array of other diseases, including neurological disorders (Basel-Vanagaite et al., 2006; Neilson et al., 2009), neuroendocrine disorders such as triple A syndrome (Cronshaw and Matunis, 2004), cardiac disorders (Zhang et al., 2008), and a number of autoimmune diseases (Enarson et al., 2004). In general, these diseases could offer valuable model systems for future NPC studies.

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