The Nuclear Pore Complex as a Transcription Regulator

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The nuclear pore complex (NPC) is a highly conserved channel in the nuclear envelope that mediates mRNA export to the cytosol and bidirectional protein transport. Many chromosomal loci physically interact with nuclear pore proteins (Nups), and interactions with Nups can promote transcriptional repression, transcriptional activation, and transcriptional poising. Interaction with the NPC also affects the spatial arrangement of genes, interchromosomal clustering, and folding of topologically associated domains. Thus, the NPC is a spatial organizer of the genome and regulator of genome function.

Eukaryotic cells spatially organize their genomes in a nonrandom fashion that both reflects and facilitates transcription regulation (Misteli 2020). Electron micrographs of metazoan nuclei show that heterochromatin associates with the nuclear lamina at the nuclear periphery in many cell types (Fig. 1; Jost et al. 2012). While it is true that heterochromatin is primarily positioned near the nuclear lamina or chromocenters, this can vary with cell type and organism (Zykova et al. 2018; Falk et al. 2019). While some organisms lack lamins, all eukaryotic nuclei are punctuated by hundreds to thousands of nuclear pore complexes (NPCs) that facilitate exchange between the nucleoplasm and cytoplasm. These structures also physically interact with specific sites in the genome, impacting their positioning and their expression.

NPCs act as a gate between the cell's two major compartments: the cytoplasm and the nucleus. Ubiquitous and essential, pores facilitating the transfer of material across the nuclear envelope were discovered at a time when there was still an ongoing debate about the existence of an organized nuclear membrane (Callan and Tomlin 1950; Watson 1955). Work over the intervening decades has revealed NPC function, organization, mechanism, and structure (Gall 1967; Goldberg and Allen 1992; von Appen and Beck 2016). Approximately 30 unique proteins make up the core eightfold radially symmetrical channel, with subcomplexes that extend from its cytoplasmic and nucleoplasmic faces, comprising additional proteins. NPC subunits with access to the nucleoplasm physically interact with chromatin and can impact their transcriptional regulation.

Based on electron micrographs showing that chromatin near NPCs was less condensed than adjacent, lamin-associated heterochromatin, Günter Blobel hypothesized that positioning of active genes near NPCs would enhance mRNA

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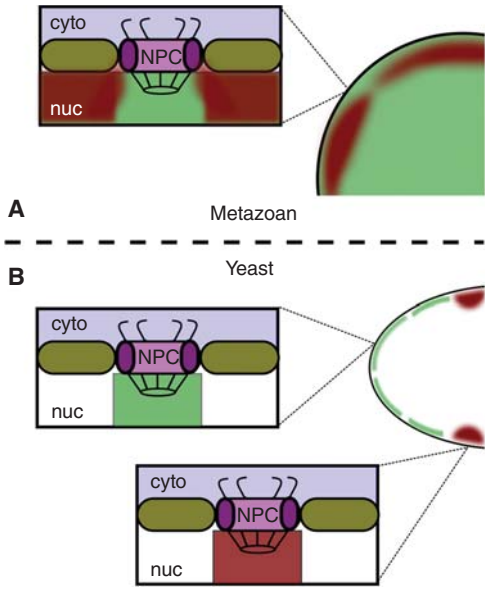

Figure 1. Spatial organization of nuclear pore complex (NPC) component interactions with chromatin. (*A*) (*Right*) Portion of metazoan nucleus where green represents euchromatin and red denotes heterochromatin. (*Left*) Peripheral chromatin adjacent to the nuclear lamina (red) and the NPC (green). (*B*) (*Right*) Portion of a *Saccharomyces cerevisiae* nucleus. Color indicates the space where NPC–chromatin interactions can occur (telomere silencing interactions in red, euchromatin transcription initiation in green). (*Left*) *Insets* show that the effects on transcription only occur at the nucleoplasmic face of the nuclear pore.

export (Blobel 1985). Years later, work from several systems confirmed that the NPC physically associates with active genes, impacting the spatial organization of genes and gene expression (Brickner and Walter 2004; Casolari et al. 2004; Guglielmi et al. 2020). To date, a convincing role for this interaction in promoting efficient mRNA export has not been established. However, data from yeast, flies, and mammals suggests that nuclear pore protein (Nup) interaction can alter gene expression to improve viability during stress conditions, maintain epigenetic memory of previous expression states, and promote tissue differentiation (Brickner and Walter 2004; Brickner et al. 2007; Liang et al. 2013a).

Here we review multiple, evolutionarily conserved ways the NPC regulates transcription. Widening our collective understanding of how the NPC regulates gene expression will help guide future research in epigenetics and transcriptional mechanisms.

MOLECULAR MECHANISM OF INTERACTION WITH THE NPC

Repositioning and interaction of active genes with the yeast NPC requires both nucleoplasmic nuclear pore proteins such as Nup1, Nup2, Nup60, Mlp1, and Mlp2 (Cabal et al. 2006; Luthra et al. 2007; Ahmed et al. 2010; Light et al. 2010). Furthermore, interaction with the NPC requires binding of sequence-specific DNA-binding transcription factors (TFs) to *cis*-acting DNA sequences near promoters (Schmid et al. 2006; Ahmed et al. 2010; Randise-Hinchliff et al. 2016). The binding sites of such transcription factors function as DNA zip codes; they are both necessary and sufficient to mediate repositioning to the periphery and interaction with Nups (Ahmed et al. 2010; Brickner et al. 2012). Of course, the NPC interacts with many complexes involved in transcription initiation, elongation, and RNA maturation. TFs, Nups, and complexes involved in mRNA export (i.e., TREX2 and Mex67) and transcription (Mediator, SAGA histone acetyltransferase) are required for targeting the nuclear periphery (Dieppois et al. 2006; Ahmed et al. 2010; Jani et al. 2014). However, several experiments argue that TFs and Nups play a direct role, while the others do not. Conditional inactivation of TFs and Nups, but not TREX-2, Mex67, Mediator, or SAGA, leads to rapid loss of peripheral localization (Brickner et al. 2019). Furthermore, tethering a TF at an ectopic site leads to peripheral localization and physical interaction with Nups but does not lead to chromatin binding with Mediator, TREX-2, or Mex67. Finally, for Gcn4-targeted genes, TF overexpression bypassed the requirement for SAGA and Mediator component null mutants for targeting chromatin to the nuclear periphery but still required Nup2 (Brickner et al. 2019). These results suggest that TFs and Nups play a

direct role in targeting genes to the nuclear periphery.

This is a common function of TFs: when tethered to a chromosomal locus, most yeast TFs can induce Nup-dependent peripheral localization (Brickner et al. 2019). Importantly, these TFs include activators, repressors, and chromatin factors, suggesting that the interaction with the NPC may impinge upon transcription and chromatin structure in more than one way.

THE NPC AND GENE SILENCING

The chromosomal position of a gene can impact its expression; genes near centromeres or telomeres show reduced recombination and transcription, a phenomenon known as "position effect" (Weiler and Wakimoto 1995). Position effects often reflect the spreading of silencing factors from sites of recruitment (Gottschling et al. 1990). For example, in budding yeast, telomeres and adjacent sequences are transcriptionally silenced by the recruitment of Rap1, and the silencing factors Sir2, Sir3, and Sir4 (Fig. 2A; Gotta et al. 1996). Rap1 is a sequence-specific DNA-binding protein that binds to telomeres and recruits Sir2, Sir3, and Sir4. The Sir proteins deacetylate histones and spread down the chromosome arms into subtelomeric regions, establishing and maintaining silenced chromatin. Telomeres localize at the nuclear periphery, and nuclear envelope membrane proteins such as Esc1 and Mps4, as well as Nups like those that make up the inner and outer ring subcomplexes (i.e., Nup170, Nup145, and Nup60) as well as nucleoplasmic TPR homologs (Mlp1 and Mlp2; Galy et al. 2000), act as a physical anchor to recruit and stabilize the Rap1/Sir3/Sir4 complex with chromatin and maintain telomere positioning at the nuclear periphery (Van de Vosse et al. 2013; Lapetina et al. 2017). Loss of these nuclear pore proteins leads to a defect in the silencing of telomeres and the silent mating-type loci (Feuerbach et al. 2002). In this way, the nuclear envelope and Nups contribute to both the spatial organization and transcriptional silencing of yeast telomeres.

In metazoan cells, genes interact with both NPC-associated Nups at the nuclear periphery and soluble Nups localized throughout the nucleoplasm (Griffis et al. 2002; Capelson et al. 2010; Kalverda et al. 2010; Liang et al. 2013b). At the fly NPC, active and silent genes interact with distinct Nups (Nup107 and Nup93, respectively; Gozalo et al. 2020). Polycomb repressive complexes (PRCs) catalyze methylation of H3K27 to establish and maintain facultative heterochromatin (Fig. 2A). More than a third of Polycomb-associated domains also physically interact with Nup93. Compared to other Polycomb domains, those that interacted with Nup93 had increased PRC presence and were more likely to be positioned at the nuclear periphery (Gozalo et al. 2020). Finally, Nup93 contributes to transcriptional silencing of these regions. Thus, interaction of Nups can also promote transcriptional silencing and heterochromatin formation in animals.

Interaction of Nups with the genome can also impact chromosome folding. Boundary elements and the chromatin architectural proteins that localize to them (CTCF and cohesin) interact with Nup153 to stabilize their organization in physical space and enhance insulation between TADs (Fig. 2B; Kadota et al. 2020). Knockdown of Nup153 leads to improper TAD formation and ectopic enhancer function across boundary domains. Embryonic stem cells are insensitive or slow to respond to epidermal growth factor following Nup153 knockdown. Likewise, looping of promoters with certain enhancers is stimulated by Nup98 in *Drosophila* (Pascual-Garcia et al. 2017). Finally, Nups are implicated in the formation of senescence-associated heterochromatin foci (SAHF) during oncogene-induced senescence (Boumendil et al. 2019). During this process, the heterochromatin reorganizes from the periphery to coalesce in the nucleoplasm, followed by cell cycle arrest and secretion of inflammatory cytokines. Knockdown of TPR blocks SAHF formation and reorganization of heterochromatin and cytokine secretion, suggesting that TPR influences the position and expression of heterochromatin.

The NPC and Transcriptional Activation

The NPC can also positively affect transcription. In budding yeast, genome-wide chromatin im-

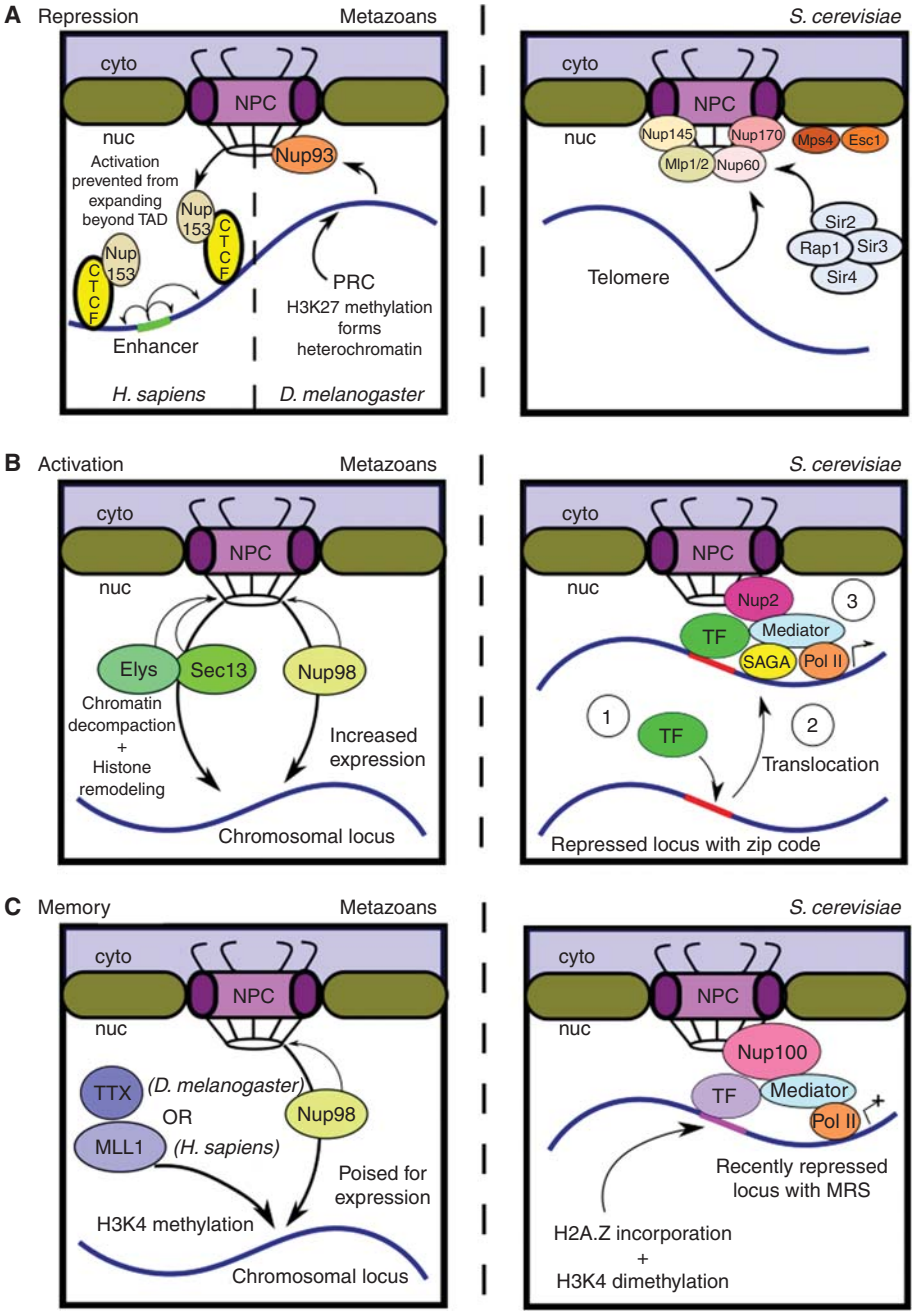

Figure 2. Nuclear pore complex (NPC) proteins affect transcription. (*A–C*) Schematic of metazoan nucleus (*left*) or yeast nucleus (*right*). (*A*) Nup-mediated transcriptional repression. (*Left*) Soluble Nup153 interacts with CTCF at topologically associated domain (TAD) boundaries in *Homo sapiens*. Heterochromatin at the nuclear periphery interacts with Nup93 and maintains Polycomb repressive complex (PRC) histone modification in *Drosophila melanogaster*. (*Right*) Telomere recruitment to the *Saccharomyces cerevisiae* NPC facilitates binding of chromatin silencing Sir factors. (*B*) Nup-mediated transcriptional activation. (*Left*) Chromatin decompaction by recruitment of Nups and transcriptional activation by recruitment of Nup98. (*Right*) Transcription factor (TF)- and Nup-dependent stimulation of transcription in *S. cerevisiae*. (*C*) Nup-dependent transcriptional poising. (*Left*) Nup98 recruitment can both enhance promoter–enhancer looping and, potentially, through recruitment of specific histone methyltransferases. (*Right*) Schematic of a Nu100-dependent chromatin changes leading to transcriptional poising during memory in *S. cerevisiae*. (MRS) Memory recruitment sequence.

munoprecipitation studies showed that hundreds of transcriptionally active loci interact with Nups (Casolari et al. 2004, 2005) and inducible genes reposition from the nucleoplasm to the nuclear periphery upon activation (Brickner and Walter 2004; Casolari et al. 2004). Likewise, in flies and mammals, thousands of chromosomal sites, including many euchromatic, transcriptionally active regions, interact with nuclear pore proteins (Brown et al. 2008; Capelson et al. 2010; Kalverda et al. 2010; Liang et al. 2013a; Jacinto et al. 2015; Pascual-Garcia et al. 2017). These interactions enhance transcription and increase the rate of expression; disrupting the interaction with nuclear pore proteins reduces the rate and extent of transcriptional induction of many genes in budding yeast and animals (Brickner et al. 2007, 2012, 2019; Ahmed et al. 2010; Capelson et al. 2010; Light et al. 2010, 2013; Liang et al. 2013a; Jacinto et al. 2015; Pascual-Garcia et al. 2017). Moving a DNA zip code from upstream of the promoter to downstream of the coding sequence had an interesting effect. Such a locus was targeted to the periphery but was still defective for transcription (Ahmed et al. 2010), suggesting that the physical interaction with the promoter is critical for promoting transcription. However, tethering of inducible genes to the nuclear envelope or the NPC is not sufficient to cause transcriptional activation (Brickner and Walter 2004; Green et al. 2012; Texari et al. 2013).

How do Nups promote transcription? Single molecule RNA FISH experiments suggest that disrupting the interaction with the yeast NPC reduces the fraction of cells expressing the *GAL1* gene (Brickner et al. 2016). For the subset of cells that express *GAL1*, the level of expression is normal. Because transcription occurs through stochastic bursts, mRNA output is the product of burst frequency, burst duration, and burst amplitude (Rodriguez and Larson 2020). This observation suggests that interaction with Nup2 quantitatively increases transcription by increasing the burst frequency or burst duration, without affecting burst amplitude. Because enhancers have been implicated in burst frequency, while core promoter strength has been implicated in burst amplitude (Tunnacliffe et al. 2018; Larsson et al. 2019), this suggests that Nups stimulate enhancer function.

An additional hint into the role of yeast Nups in transcriptional activation comes from structure–function analysis of the Gcn4 TF. Gcn4 is essential for both transcriptional activation and NPC interaction of many target genes (Hope and Struhl 1985; Rawal et al. 2018; Brickner et al. 2019). Tethering Gcn4 to a nucleoplasmic locus is sufficient to target that locus to the nuclear periphery, allowing identification of a minimal portion of Gcn4 that is necessary and sufficient to promote interaction with Nups. This strategy identified a *positioning domain* within the Gcn4 TF (PD_{GCN4}), a 27 amino acid peptide, separable from the activation domains. Mutation of three amino acids within this sequence disrupts interaction of Gcn4 target genes with the NPC and results in a global defect in transcriptional activation of Gcn4 target genes (Brickner et al. 2019). Tethering of the PD_{GCN4} to an ectopic locus led to interaction with Nup2, but not with coactivators like SAGA or Mediator. These results argue that Nup interaction can enhance activator domain-dependent transcription, but cannot activate transcription in the absence of an activator domain.

Interaction with metazoan Nups can also positively regulate transcription (Fig. 2B). Knockdown of Nups in flies leads to widespread decrease in transcription (Capelson et al. 2010). Likewise, loss of Nup98 in embryonic stem cells impacts transcription and developmental potential (Liang et al. 2013a) and loss of the tissue-specific Nup210 inhibits proper muscle cell gene expression and differentiation (D'Angelo et al. 2012; Raices et al. 2017). Although Nups interact throughout the genome, they bind strongly at super-enhancers (Ibarra et al. 2016). These effects correlate with impacts on chromatin folding and structure. Interaction with Nups facilitates recruitment of cohesin and formation of topologically associated domains (TADs) as well as promoter–enhancer looping (Pascual-Garcia et al. 2017; Kadota et al. 2020). Tethering of Nups such as Sec13 or Elys to polytene chromosomes in *Drosophila* leads to chromatin decondensation (Fig. 2B; Kuhn et al. 2019). The tethered Nups recruit PBAP/Brm and GAGA, which are required for decondensation (Kuhn

et al. 2019). Thus, the role of Nups in animals in promoting transcription may relate to their effects on chromatin folding and condensation.

The NPC's role in interacting with chromatin to modulate transcription has also been explored in plants. In *Arabidopsis thaliana*, tethering of the Nup Seh1 to a reporter transgene caused positioning at the nuclear periphery and stimulated transcription (Smith et al. 2015). Likewise, *Arabidopsis* Nup1 is necessary for pollen and ovule development, and loss of Nup1 leads to a significant decrease in the expression of gametogenesis genes, although it is unknown whether these genes physically interact with the NPC (Bao et al. 2019). Also, the chlorophyll a/b gene locus undergoes light-dependent repositioning from the nuclear interior to the nuclear periphery upon transcriptional activation (Feng et al. 2014). However, a connection to the NPC has not been explored and this repositioning requires a set of proteins not implicated in yeast or metazoan gene positioning, raising the possibility that other mechanisms impact localization to the nuclear periphery in plants.

THE NPC AS A REGULATOR OF EPIGENETIC MEMORY

Nups interact with both active and silent loci and can promote both transcription and repression. But Nups also play a conserved role in a type of epigenetic poising following specific expression states. In yeast, the *INO1* locus is targeted to the NPC both when active and when recently repressed (Brickner et al. 2007). This latter state is called "transcriptional memory" and is inherited for several generations. The molecular mechanism for targeting (i.e., the TFs, the *cis*-acting zip codes, and the Nups required) of active *INO1* and recently repressed *INO1* are different (Fig. 2C; Light et al. 2010). Whereas active *INO1* is targeted to the NPC by the gene recruitment sequences GRS1 and GRS2 and the TFs Put3 and Cbf1, recently repressed *INO1* is targeted to the NPC by the memory recruitment sequence (MRS), which binds the Sfl1 TF.

Furthermore, memory requires chromatin modifications and Nup100, both of which are not required for recruiting active *INO1* to the periphery (Brickner et al. 2007; Light et al. 2010; D'Urso et al. 2016). This suggests that there are at least two mechanisms by which genes interact with the NPC in yeast, one that requires Nup100 and one that does not. This conclusion is bolstered by the finding that, while tethering of 121 yeast TFs to a chromosomal site is sufficient to cause Nup2-dependent targeting to the nuclear periphery, only 76 of those TFs also require Nup100 (Brickner et al. 2019).

Transcriptional memory leads to changes in the chromatin state of the promoter, allowing the recruitment of a poised form of RNA polymerase II preinitiation complex (RNAPII PIC). This poised state of the promoter is activated more rapidly than it would be otherwise, presumably providing an adaptive fitness advantage. In the case of the *INO1* gene, loss of Sfl1, the MRS, or Nup100 blocks memory, leading to slower reactivation. Thus, the same locus can be targeted to the NPC by two distinct mechanisms, producing two distinct outcomes, depending on the state and history of the cell.

The phenomenon of yeast transcriptional memory is widespread. In yeast, many genes exhibit an enhanced activation rate if previously expressed, which can enhance adaptive fitness (Sood and Brickner 2017). Furthermore, memory is generally associated with changes in chromatin modifications (H2A.Z incorporation, H3 lysine 4 dimethylation [H4K4me2]) and recruitment of a novel, poised RNA polymerase II preinitation complex (Fig. 2C; D'Urso et al. 2016; Sood et al. 2017). However, it does not always require interaction with the NPC, suggesting that the interaction with the NPC regulates a core memory mechanism involving chromatin changes and promoter poising.

Nup-dependent memory has also been observed in metazoan cells. In HeLa cells, genes induced by interferon γ (IFN-γ) interact with Nup98 (the Nup100 homolog) upon removal of IFN-γ, and this interaction persists for >4 days. These genes show faster/more robust expression if cells are exposed to IFN-γ again. Promoters of such poised genes are marked with H3K4me2 and bind RNA polymerase II. Transient knockdown of Nup98 during memory led to a loss of H3K4me2 and RNA polymerase II from promot-

ers and disrupted the faster rate of reactivation (Light et al. 2013). Thus, Nups have an ancient, conserved role in controlling chromatin states that facilitate epigenetic transcriptional regulation.

In flies, ecdysone-induced genes also interact with Nup98 and exhibit transcriptional memory. Brief exposure of S2 cells to ecdysone leads to Nup98 binding and poises target genes for induction (Pascual-Garcia et al. 2017). The knockdown of Nup98 specifically disrupts this effect, leading to no memory. The effect of Nup98 in this system (and perhaps others) is to stabilize a promoter–enhancer loop. This loop is strengthened by previous treatment with ecdysone and by binding to Nup98, suggesting that Nup98-dependent chromatin folding can facilitate the establishment and inheritance of epigenetic states.

The impact of Nups on chromatin and transcription also has important effects on human health. Chromosomal translocations that lead to translational fusions of Nup98 with several proteins such as HOXA9, HOXD13, Top1, and Nsd1 lead to acute myeloid leukemia (AML) (Franks et al. 2017). Why? Nup98 is associated with H3K4 methylation in flies and humans and interacts with the H3K4 methyltransferases Trithorax and MLL1, respectively (Fig. 2C; Kaltenbach et al. 2010; Gough et al. 2011; Pascual-Garcia et al. 2014). This led to the hypothesis that AML is due to excessive H3K4 methylation of target genes induced by ectopic recruitment of Nup98 at those loci (Franks et al. 2017). Indeed, the Nup98-Nsd1 fusion protein expressed in myeloid cells from AML patients binds to Wdr82, a component of the H3K4 methyltransferase Set1A/B-COMPASS. Forming this aberrant complex results in transcription-associated histone modifications at Nsd1 target genes, such as the HOXA locus, and leads to an increase in expression (Michmerhuizen et al. 2020). These findings show the critical role of Nup98/Nup100 in epigenetic regulation in regulating normal and pathogenic transcription.

CLOSING REMARKS

The NPC is an ancient structural component of eukaryotic cells. In addition to mediating nucleocytoplasmic trafficking, a role for nuclear pore proteins in regulating transcription and chromatin structure is now appreciated. Additionally, the interaction of the NPC with the genome impacts its spatial arrangement. Specific interactions between genes and Nups are associated with transcriptional silencing, transcriptional activation, transcriptional poising, changes in chromatin modifications and changes in chromatin folding. While the field is still exploring the precise molecular nature of these roles, it is clear that the NPC impacts genome function and gene expression and multiple levels.

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