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## Nuclear Pore Complexes and Regulation of Gene Expression

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### Abstract

Nuclear pore complexes (NPCs), are large multiprotein channels that penetrate the nuclear envelope connecting the nucleus to the cytoplasm. Accumulating evidence shows that besides their main role in regulating the exchange of molecules between these two compartments, NPCs and their components also play important transport-independent roles, including gene expression regulation, chromatin organization, DNA repair, RNA processing and quality control, and cell cycle control. Here we will describe the recent findings about the role of these structures in the regulation of gene expression.

### Introduction

In 1950, Callan and Tomlin used *Xenopus laevis* oocytes to perform the first electron microscopy studies of the nuclear envelope (NE) and observed that it was perforated by many large pores [1]. This was the first description of nuclear pore complexes (NPCs). Our understanding of NPCs has come a long way since that initial observation. Thanks to a momentous amount of work performed by many different groups over the last six decades we now know that NPCs are giant multiprotein channels of about 110MDa in mammals that represent the sole gateway into the nucleus. At the structural level, NPCs have an eight-fold rotational symmetry, and consist of a core ring embedded in the NE, two outer rings, one cytoplasmic and one nuclear, and eight filaments attached to these rings [2]. The nuclear filaments are also joined in a distal ring assembling a structure known as the nuclear basket. Despite being one of the largest protein complexes of eukaryotic cells these structures have a rather simple composition and are built by the repetition of roughly 30 different proteins known as nucleoporins [3,4]. Recent studies combining structural information from the NPC itself and from individual nucleoporins has resulted in an unprecedented resolution of this structure [5–7].

In addition to their main function as mediators of nucleocytoplasmic molecule exchange, increasing evidence shows that NPCs regulate multiple cellular processes in a transport-

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independent manner [2]. Probably the most studied so far, and the focus of this review, is their role in genome organization and gene expression regulation.

## Gene expression regulation by NPCs in yeast

The first evidence for a role of nuclear pore complexes in the regulation of gene expression came from studies in *Saccharomyces cerevisiae*. Though the initial observations of NPCs association with repressed telomeric and subtelomeric chromatin fueled the idea that the nuclear periphery was always associated with gene silencing, [8,9], Menon *et al* were the first ones to show that the Nup84 scaffold subcomplex of the NPC could act as transcriptional activator by itself [10]. Two other later studies showed that many more nucleoporins were associated with transcriptionally active genes [11,12]. These findings supported a potential role for NPCs in active gene expression. In the decade following this discovery, several groups have confirmed the role of NPCs in the positive regulation of gene expression in yeast. Many different genes, including *CTT1* [13], *FIG2* [14], *GAL* (*GAL1*, *GAL2*, *GAL7* and *GAL10*) [15–20], *HIS4* [21], *HSP104* [15], *HXX1* [17,22], *INO1* [18,19,23,24], *PRM1* [21], *STL1* [13,25], *SUC2* [26], and *TSA2* [24] have been shown to relocalize from the nuclear interior to NPCs upon activation (Figure 1). In most cases NPC association is not required for activation, but results in a more efficient gene expression and enhances transcriptional memory of some of these genes [20,22,23], although the relocation of the *GAL* locus (*GAL7*, *GAL10*, and *GAL1*) to the nuclear periphery has also been associated with repression post-induction under specific conditions [16].

In the last few years there have been major advances in our understanding of the molecular mechanisms that mediate gene-pore association and gene regulation at the nuclear periphery. Targeting to the nuclear periphery for several yeast genes has been shown to rely on cis-DNA sequences in their promoters known as Gene Recruitment Sequences (GRSs) (recently reviewed in [27]) (Figure 1). Interestingly, several GRSs have been shown to represent binding sites for transcription factors which ultimately mediate gene-relocation [21]. For *INO1* it was identified that NPC-tethering is mediated by the transcription factors Put3 [28] and Cbf1 [27], which do not directly regulate the activity of this gene. Conversely, the Ste12 and Gcn4 transcription factors required for repositioning of *PRM1* and *HIS4* also regulate the activity of these genes [21]. Yet, the activation domain of Gcn4 is dispensable for gene repositioning [27]. These findings indicate that the transcription factors involved in gene positioning not necessarily need to regulate the expression of the gene, separating the processes of gene positioning and transcriptional regulation. Notably, genes that contain the same GRS sequences cluster together at the nuclear periphery [28]. Interestingly, Brickner *et al* showed that the molecular mechanisms that control NPC targeting are different from the ones controlling interchromosomal clustering and that both processes are regulated through the cell cycle [21,28,29].

GRS sequences are sufficient to artificially induce the relocation of an unrelated gene to the nuclear periphery. For example insertion of GRS I and GRS II sequences that mediate *INO1*-NPC association [24] into the *URA3* promoter results in the repositioning of this intranuclear gene to NPCs. But differently from the repositioning of endogenous *INO1*, the GRS-mediated association of *URA3* with NPCs is constitutive (note that *INO1* gene

localizes to the periphery only when activated by inositol starvation). This indicates that GRS activity is modulated by additional factors that can control repositioning in a stimuli-dependent manner. For *INO1*, relocation is negatively modulated by the histone deacetylase complex Rpd3(L) which is recruited to the *INO1* promoter by transcriptional repressors and blocks binding of Put3. [21]. On the other hand, NPC-relocation mediated by Ste12 and Gcn4 transcription factor binding sites is regulated independently of DNA binding. Mitogen-activated protein kinase phosphorylation of the Dig2 inhibitor induces its dissociation from Ste12 and allows the relocation of *PRM1*, while Gcn4-dependent targeting is up-regulated by increasing Gcn4 protein levels [21]. The different speeds at which, cell signaling (Ste12), chromatin remodeling (*INO1*) and transcription factor abundance (Gcn4) occur, might explain the different kinetics observed for the NPC-association of different genes [21].

Most of the studies investigating gene repositioning to NPCs have centered their analysis on specific genes without determining if the association with NPCs involved larger chromatin domains. Recent, work from the Weis lab has shown that during activation, the association of the GAL locus with the NPC involves large genome rearrangements that position several chromosomal domains in close proximity to the nuclear envelope [30]. The authors propose that this association likely results from multiple independent anchoring sites. Moreover, using a genome-wide screen, they identified a novel role for histone deacetylases in chromatin association with the nuclear periphery and provided further evidence for the previously described role of the transcriptional coactivator SAGA complex in peripheral gene repositioning in response to galactose activation [30].

### **SAGA and TREX complexes in NPC-gene tethering and gene expression regulation**

The SAGA complex, and the TREX-2 and THO-TREX complexes, which couple transcription to mRNA export (reviewed in [31]), were the first factors shown to mediate the interaction of chromatin with NPCs [32–37] (Figure 1). In yeast, the SAGA and TREX-2 complexes have been shown to interact with the nuclear basket of the NPC, [32,34,38,39]. Through a common partner, Sus1, these complexes tether genes that are being actively transcribed to NPCs and coordinate transcription with nuclear export [33,36,37,40,41]. Work by Schneider *et al* recently showed that the Mediator complex plays a critical role in connecting RNA Polymerase II to TREX-2 at NPCs [42]. By analyzing the re-positioning of *GAL1* and *HXK1* in Mediator mutant yeast strains or in mutants that affect the interaction between TREX-2 and Mediator, this group showed that both complexes are required for the NPC-targeting of these inducible genes. Moreover, they revealed that the TREX-2/Mediator-interacting surface is important for mRNA export [42]. Considering that Mediator is an important regulator of RNA Pol II during transcription initiation, this complex would provide the NPC-associated TREX-2 complex with access to the core transcription machinery (Figure 1). The NPC-associated SUMO protease Ulp1 is another factor required for the repositioning of *GAL1* to the nuclear periphery and for its efficient activation in response to galactose [20]. Texari *et al* showed that Ulp1 facilitates the derepression of *GAL1* at the nuclear periphery by desumoylating the transcriptional repressors Tup1 and Ssn6 and proposed that this modification could induce conformational changes that allow the interaction with coactivators such as the SAGA and Mediator complexes [20].

### NPC-gene tethering and transcriptional memory

The association of some genes, including *INO1*, *GAL* and *HXK1*, with NPCs has been linked to their transcriptional memory (reviewed in [43]). Upon activation these genes move from the nuclear interior to NPCs as described above. Once repressed, they are maintained at NPCs for several generations where they are poised for transcription and will reactivate faster in response to a second induction (transcriptional memory). *HXK1* and *GAL1* transcriptional memory depends on the formation of NPC-associated gene loops that require the nuclear basket nucleoporin Mlp1 [17]. Transcriptional memory of *INO1*, on the other hand, requires association with Nup100 [18,44]. Interestingly, even though *INO1* is recruited to NPCs through GRSI and II during activation [24], its maintenance at NPCs in the repressed state depends on a different cis-DNA element named Memory Recruitment Sequence (MRS) [44]. Binding of the transcription factor Sfl1 to MRS during memory is required for the maintenance of *INO1* at the nuclear periphery and binding of Mediator is needed for efficient reactivation [45]. Transcriptional memory for *INO1* also requires chromatin modifications mediated by the Set1/COMPASS and SET3C complexes [45].

### Gene expression regulation by NPCs in metazoans

Our knowledge of NPC-mediated regulation of gene expression in metazoans is considerably more limited than in yeast. The first connection of NPC components with chromatin modulation/gene expression regulation was described in *Drosophila melanogaster* with the identification of two nucleoporins, mTor/TPR and Nup153, as partners of the MSL dosage compensation complex [46]. This work showed that both nucleoporins were required for the localization of the MSL complex to the X chromosome and for the transcription of dosage compensation genes [46]. A year later, the SAGA/Eny-2(Sus-1) complex was shown to mediate the association of the *HSP70* loci with NPCs [47]. Although NPC-anchoring of *HSP70* was activation-independent, the association was necessary for efficient gene transcription and mRNA export [47]. More recently, CHIP-on-chip experiments and DamID assays have shown that the nucleoporin Nup98 binds to many actively transcribed sequences, mostly developmental and cell cycle genes [48,49] (Figure 2). Interestingly, the binding of these active genes takes place inside the nucleus and Nup98 was shown to be required for their proper expression [48,49]. NPC-associated Nup98, on the other hand, was described to bind a small subset of predominantly non-active genes [49]. Recently, Nup98 was also found to bind and regulate the expression of genes critical for the anti-viral response in *Drosophila*, but whether this association takes place inside the nucleus or at the nuclear periphery has not been investigated [50]. Other nucleoporins that were also found to bind active genes inside the nucleus include Nup50, Nup62, Sec13 and Nup153 [48,49,51] (Figure 2). Interestingly, Nup153 was identified to bind ~25% of the genome in Nucleoporin-Associated Regions (NARs) of 10–500 kb in length that are enriched in markers for active transcription [51].

In most cases, the molecular mechanisms through which nucleoporins regulate gene expression in *Drosophila* are still unknown. Recently, it was reported that Nup98 physically associates with the histone-modifying complexes MBD-R2/NSL and Trx/MLL, and that MBD-R2 mediates the recruitment of Nup98 to several active genes, including Hox genes

[52] (Figure 2). These findings link Nup98 to epigenetic modulation. Notably, the chromatin domains associated with NPC-associated Nup98 at the nuclear periphery are enriched in the insulator protein Su(Hw), further suggesting a potential role for this nucleoporin in chromatin organization [53]. The function of Nup98 in controlling chromatin organization might vary depending on its location/environment being different at the pore, where Nup98 binds inactive genes, and at the nuclear interior, where it associates with highly transcribed genes.

Mammalian Nup98 has also been shown to bind genes both in the nuclear interior and at NPCs. A study of Nup98 dynamics during embryonic stem cell differentiation showed that this nucleoporin is associated with developmentally regulated genes, which is consistent with the findings in *Drosophila*. Interestingly, this study identified that genes induced during the early stages of differentiation associate with Nup98 at NPCs, while genes that are highly activated bind Nup98 in the nucleoplasm [54]. Nup98 has also been shown to associate with INF- $\gamma$  regulated genes inside the nucleus [55]. Consistent with the role of its yeast homologue Nup100 in transcriptional memory, Nup98 is critical for the transcriptional memory to INF- $\gamma$  induction [55]. However, in mammalian cells, the transcriptional memory function of Nup98 is independent of NPCs. Interestingly, a soluble variant of the transmembrane nucleoporin Pom121 (sPom121) that arises from alternate transcription initiation was recently discovered to interact with nucleoplasmic Nup98 at the promoters of many target genes to co-regulate their activity [56] (Figure 2), though its role in the regulation of developmental or INF- $\gamma$  genes has not yet been studied. Like Nup98, Nup153 has also been shown to bind several developmental genes in embryonic stem cells. But differently from Nup98, Nup153 mediates the recruitment of the polycomb-repressive complex 1 (PRC1) silencing these genes to maintain stem cell pluripotency [57] (Figure 2).

In *Caenorhabditis elegans*, the *HSP-16* gene was recently shown to associate with NPCs upon heat shock induction [58]. Similar to yeast genes, the association with NPCs requires a transcription factor, HSF-1, and the Sus1 homologue Eny-2 suggesting that repositioning might be mediated by the SAGA-THO/TREX complexes. *C. elegans* nuclear pore complex components have also been described to associate with RNA Pol III transcribed genes [59]. In this case, nucleoporin association is not required for transcriptional regulation but plays a critical role in the processing of small nucleolar RNAs (snoRNAs) and tRNAs. Whether RNA processing takes place inside the nucleus or at NPCs remains to be investigated, but in yeast, tRNA genes have been shown to associate with NPCs during M-phase [60].

## Conclusions

Since the discovery of the first Nucleoporin-gene interactions just 10 years ago, it has become clear that the NPC and its components play a pivotal role in the regulation of gene expression in multiple organisms. In this review, we have mostly focused in the positive regulation of gene expression by these proteins, but NPCs and nucleoporins have also been shown to associate and regulate silent/inactive chromatin [8,26,57,61–65]. Understanding how NPCs contribute to modulating these two chromatin environments (active/silent) and further dissecting the molecular mechanism of transcriptional regulation are two foreseeable challenges for the next decade.

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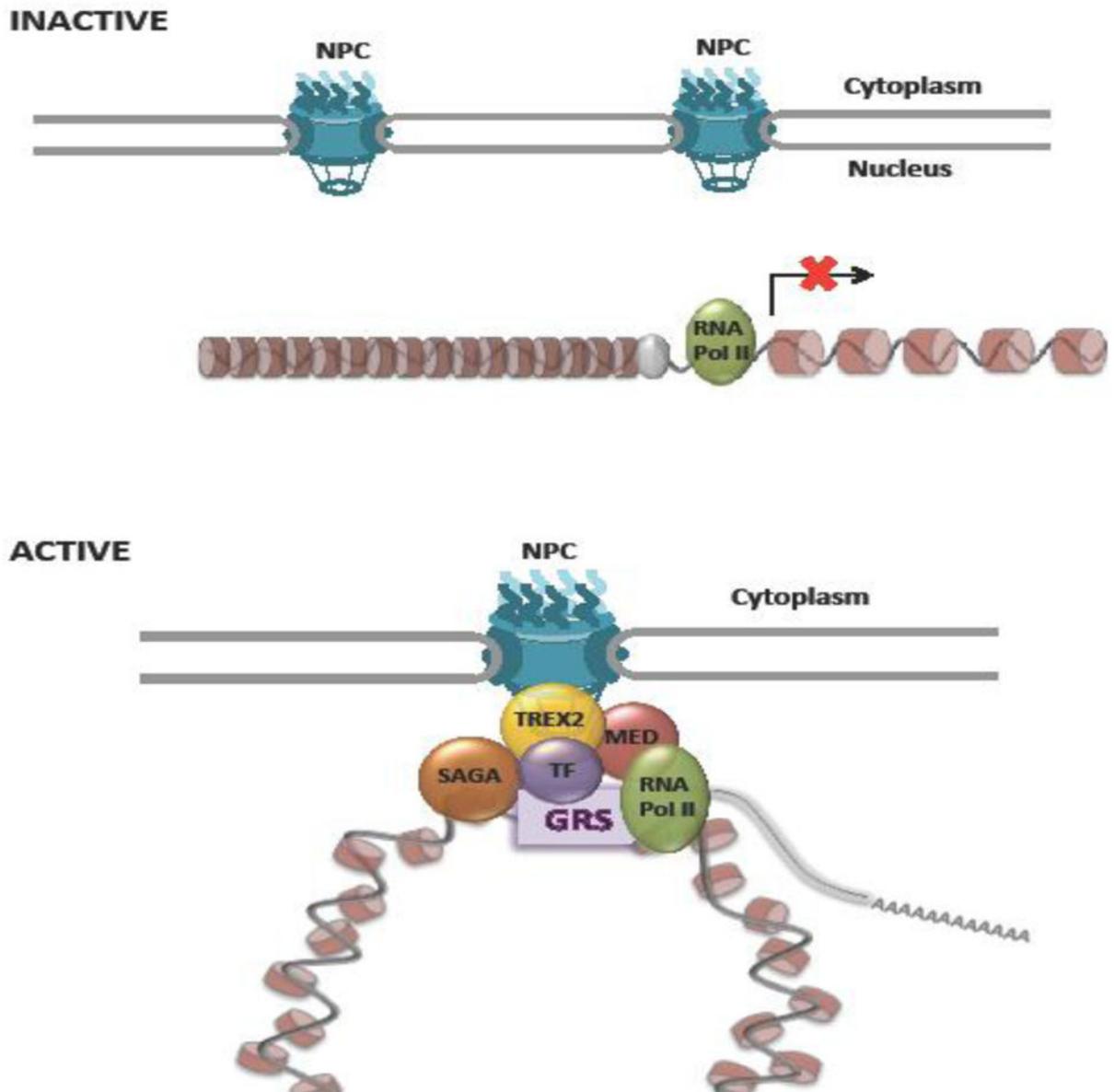
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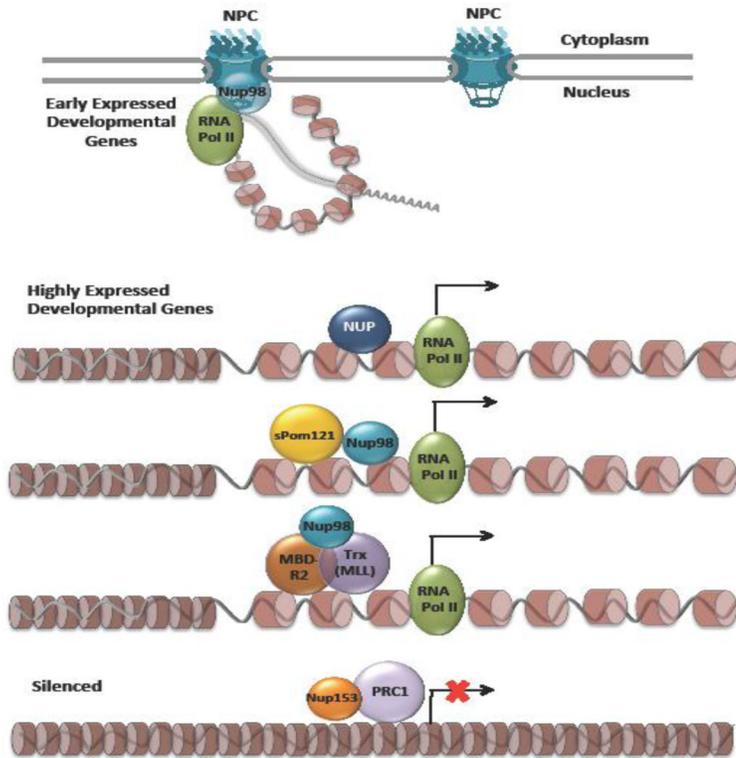
**Highlights**

- Nuclear pore complexes and nucleoporins have many transport-independent functions
- Nuclear pore complexes play key roles in gene expression regulation
- In yeast, the activity of many inducible genes is regulated at nuclear pore complexes
- In metazoans, many nucleoporins regulate gene expression inside the nucleus and away from nuclear pore complexes



**Figure 1. NPC-gene association in yeast**

Upon activation several inducible yeast genes re-localize to nuclear pore complexes. Factors involved in NPC tethering include nucleoporins (Mlp1, Mlp2, Nup1, Nup2, Nup42, Nup60, Nup100, Nup116, Nup157, Gle2), cis-DNA elements or Gene Recruitment Sequences (GRS), transcription factors (TF) including Put3, Cbf1, Gcn4, Ste12, Gal4, Sfl1, chromatin modulators (SAGA, HDACs), transport export complexes TREX-2/THO-TREX (TREX) and Mediator.



**Figure 2. Gene regulation by nucleoporins and NPCs in metazoans**

In *Drosophila* and mammalian cells, several nucleoporins regulate gene expression inside the nucleus and independent of NPCs. Nup98, Nup62, Nup50, and Sec13 (NUP) have been shown to bind and regulate developmental and cell cycle genes. A soluble form of the transmembrane nucleoporin Pom121 (sPom121) binds many target genes together with Nup98. Nup98 also interacts with the histone-modifying complexes MBD-R2/NSL and Trx/MLL. MBD-R2/NSL is required for Nup98 recruitment to its target genes. Nup153 on the other hand recruits the polycomb complex PRC1 to gene promoters repressing the activity of developmental genes.