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Nuclear pore interactions with the genome

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Within the nucleus, chromatin is functionally organized into distinct nuclear compartments. The nuclear periphery, containing Nuclear Pore Complexes (NPCs), plays an important role in the spatial organization of chromatin and in transcriptional regulation. The role of Nuclear Pore Proteins (Nups) in transcription and their involvement in leukemia and viral integration has renewed interest in understanding their mechanism of action. Nups bind to both repressed and active genes, often in a regulated fashion. Nups can associate with chromatin both at the NPC and inside the nucleoplasm. These interactions are guided by evolutionarily conserved mechanisms that involve promoter DNA elements and *trans*-acting factors. These interactions can also lead to interchromosomal clustering of co-regulated genes. Nups affect gene expression by promoting stronger transcription, by limiting the spread of repressed chromatin or by altering chromatin structure. Nups can promote epigenetic regulation by establishing boundary elements and poising recently repressed genes for faster reactivation.

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Introduction

The chromatin organization within the nucleus both reflects and impacts transcriptional regulation and can change in response to developmental or physiological signals [1,2]. The nuclear periphery is an important site to which both active and repressed genes are targeted [3,4]. Many transcriptionally inactive genes interact with the nuclear lamina at the nuclear periphery and relocalize to the nucleoplasm upon activation [4–7]. In addition, some active genes interact with components of the nuclear pore complex (NPC) [3]. These interactions involve transcription factor binding to *cis*-acting DNA 'zip codes' and occur both at the NPC and through binding of soluble nuclear porins in the nucleoplasm [8,9,10••]. The interaction of the genome with Nups has effects on chromatin structure, transcription and interchromosomal clustering of genes within the nucleus [1,2]. Here we review our current understanding of the molecular basis for gene targeting to the NPC or Nups and how this interaction impacts chromatin structure and transcription.

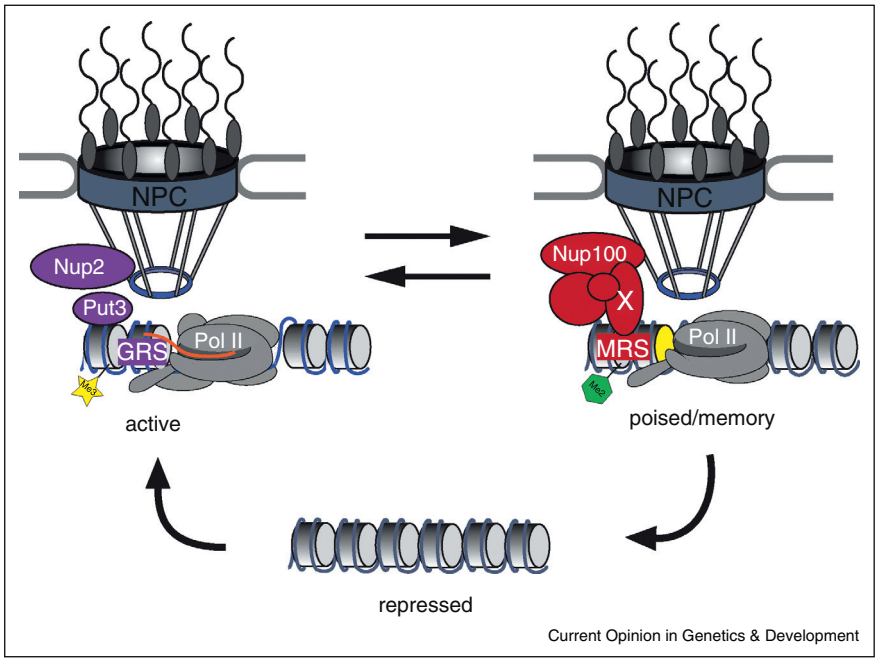
Active and repressed parts of the genome associate with nuclear pore proteins

The NPC is an evolutionarily conserved structure built from at least 30 nucleoporins (Nups) that penetrates the nuclear envelope [11,12]. In addition to its essential functions in regulating protein and RNA transport between the nucleus and the cytoplasm, the NPC has roles in cell division [13], transcriptional activation [14–17,18•,19] and epigenetically inherited transcriptional memory [20••,21,22].

Based on global chromatin immunoprecipitation (ChIP) and DamID experiments, Nups associate with many highly expressed genes in several species [23,24,25••,26••,27••]. In yeast, *Drosophila* and humans, interaction of several Nups with genes is positively correlated with transcription, suggesting an evolutionarily conserved link to transcription [17,23,24,25••,26••,27••]. Consistent with this notion, in electron-micrographs of the nuclear periphery, euchromatin tends to localize adjacent to NPCs and heterochromatin localizes adjacent to the nuclear lamina [28,29]. This association has been suggested as a function of the NPC-associated Tpr protein [30]. In yeast, highly expressed genes involved in glycolysis and ribosomal protein synthesis interact constitutively with the NPC as well as the Tpr homologues Mlp1 and Mlp2 [23,24]. Genes also bind to the NPC conditionally upon induction by environmental stimuli such as nutrient shifts (*GAL1*, *GAL2*, *INO1*, *HXK1*, *SUC2*) [14,15,31–33], heat shock (*TSA2*, *HSP104*) [31] and mating pheromone treatment (*FIG2*, *FUS1*) [23] (Figure 1). Although these interactions occur exclusively at the nuclear periphery in yeast, in higher eukaryotes, certain mobile Nups can interact with highly expressed genes inside the nucleoplasm (Figure 2a,b) [8,9]. For example, in *Drosophila*, nucleoplasmic Nup50 binds to developmental puffs and heat shock-induced puffs in the salivary glands of larva upon activation [25••]. Nucleoplasmic Nup98 preferentially binds to genes that are activated during embryonic development in *Drosophila* and during the differentiation of human embryonic stem cells into neurons [25••,27••].

Binding to Nups does not always correlate with high expression. In yeast, genome-wide binding of Nup84,

Figure 1



Yeast *INO1* association with NPC. Inducible genes like *INO1* associate with the components of nuclear pore complex (NPC) upon activation. The interaction with NPC requires *cis*-acting DNA 'zip codes' in the promoter called *G*ene *R*ecruitment *S*equences (GRSs), and nuclear pore proteins such as Nup2. The transcription factor Put3 binds to the GRS I element and is necessary for GRS I-mediated targeting to the NPC. After repression, *INO1* remains associated with NPC for 3–4 generations, poised for reactivation (transcriptional memory). The mechanism controlling interaction after repression is distinct from GRS-mediated NPC association and requires a *M*emory *R*ecruitment *S*equence (MRS) in the promoter and the nuclear pore protein Nup100. Transcriptional memory leads to incorporation of the histone variant H2A.Z and dimethylation of lysine 4 of histone H3 (Me2; yellow nucleosome). Transcriptional memory allows binding of a poised RNA polymerase II. The MRS and Nup100 are required for establishment of the chromatin modifications necessary for faster reactivation.

Nup100 and Nup145 is not correlated with expression levels [24]. Nup binding can even have repressive effect on active genes; binding of Nup1 to the *GAL1* gene leads to negative feedback, reducing expression [34], while Nup60, Nup145, Mlp1 and Mlp2 have been proposed to promote silencing of subtelomeric genes [35]. Several yeast genes interact with the NPC both while active and for several generations after repression [16,20••,21,36••]. Nup93 in HeLa cells and Nup88 in *Drosophila* larvae preferential bind repressed genes [26••,37]. Thus, nuclear pore proteins interact with both active and repressed regions of the genome.

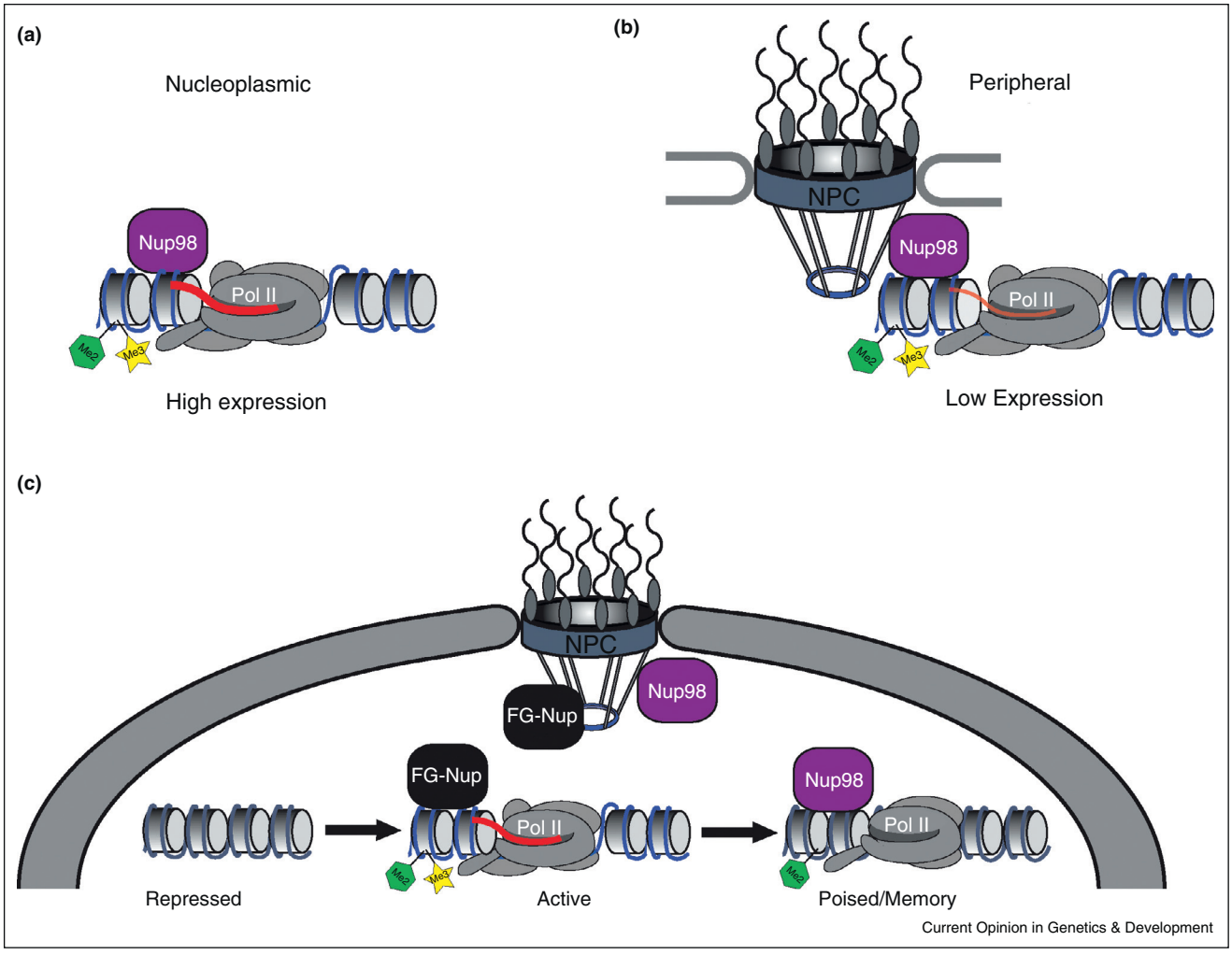
In human embryonic stem cells and flies, Nup98 binds both strongly and weakly expressed genes [25••,27••]. Each class correlates with a different position within the nucleus: binding of NPC-associated Nups correlates with poorer expression and repressive chromatin marks, whereas binding of nucleoplasmic Nups correlates with stronger expression [25••,27••] (Figure 2a). These poorly expressed regions are distinct from silenced, lamin-associated peripheral heterochromatic domains [25••]. Finally, developmentally regulated genes that are induced during neuronal development associate with NPC-Nup98 in neural precursor cells. These genes lose NPC-Nup98 binding when they are more strongly induced during differentiation to neurons [27••].

Mechanisms for NPC recruitment

The histone acetyltransferase SAGA, and the mRNA export factors Sac3-Thp1 play a conserved role in the interaction of genes with the NPC, in addition to their other roles [32,38–40]. In yeast, deleting a component of SAGA histone acetyltransferase (Ada2) or Sac3-Thp1 (Sac3) or a shared component between these complexes, Sus1, prevents *GAL1* gene association with the NPC [32,39,40]. In *Drosophila*, silencing of the homologs of these factors, *E(y)2* and *Xmas-2*, delocalizes the *HSP70* locus from the nuclear periphery [41].

The requirement for nuclear transport factors involved in mRNA export in the targeting of genes to the NPC is consistent with the idea that this may involve interaction of nascent RNAs with the NPC [23,42–45]. However, several studies suggest that NPC-association is guided by promoter DNA elements and does not require active transcription. The physical interaction of the *GAL1* gene with the NPC is centered over the promoter [46].

Figure 2



Metazoan nucleoporin binding to chromatin. Metazoan nuclear pore proteins (Nups) interact with genes both at the nuclear pore complex (NPC) and in the nucleoplasm. These may represent functionally distinct interactions. In the nucleoplasm, Nups such as Nup98 bind to highly expressed genes and promote expression **(a)**. At the NPC, Nups such as Nup98 bind to poorly expressed genes **(b)**. **(c)** Genes that exhibit transcriptional memory such as *HLA-DRA*, exhibit distinct Nup interactions during activation and transcriptional memory state. These interactions occur in the nucleoplasm and away from the NPC. Several FG-rich Nups, excluding the GLFG-rich Nup98, bind to the *HLA-DRA* promoter upon activation. Nup98 binds specifically after removal of interferon gamma to the promoters of genes that exhibit transcriptional memory. In the transcriptional memory state, the promoters are marked with a mitotically stable H3K4me2 modification and poised RNA polymerase II. Nup98 is required for the H3K4me2 modification, poised polymerase and faster reactivation.

Deleting the *GAL2* ORF does not affect association of active *GAL2* with the NPC [31]. Inactivation of RNA polymerase II does not affect targeting of *INO1* or *GAL1* to the NPC [16]. Two promoter DNA elements termed as Gene Recruitment Sequences (GRSI and GRSII) upstream of *INO1* gene are required for targeting to the nuclear periphery [18•] (Figure 1). A mutation that disrupts both of these elements blocks interaction with the NPC and leads to localization of *INO1* in the nucleoplasm. Importantly, when the isolated elements are inserted at an ectopic locus that normally localizes in the nucleoplasm (*URA3*), they are sufficient to lead to peripheral localization and interaction with the NPC [18•]. Thus, these sequences act as 'DNA zip codes' that can control interaction with the NPC. This is a general feature of gene targeting to the NPC. A GRS I element from the *TSA2* promoter is required for targeting of *TSA2* to the nuclear periphery [18•] and *HSP104* possesses a different DNA zip code (GRS III) in its promoter [10••].

We recently found that genes that share zip codes cluster together at the nuclear periphery upon activation [10••]. In diploid nuclei, the two alleles of *INO1* cluster together at the nuclear periphery when active, but do not cluster

together in the nucleoplasm when repressed. Active *INO1* also clusters with another endogenous GRS I-targeted gene, *TSA2*. Interchromosomal clustering is dependent on the GRS I zip code and the interaction with the NPC. Insertion of the GRS I zip code from the *INO1* promoter at the *URA3* locus (on a different chromosome) was sufficient to cause clustering of *URA3* with active *INO1*. Likewise, inserting the GRS III zip code from the *HSP104* promoter at *URA3* induces clustering of *URA3* with *HSP104* [10••]. Thus, DNA zip codes induce NPC-dependent interchromosomal clustering that may have important effects on the spatial and functional organization of the yeast nucleus.

It is still unclear precisely how DNA zip codes promote interaction with the NPC. The transcription factor Put3 binds to the GRS I zip code *in vivo* and is required for its ability to target loci to the nuclear periphery [10••] (Figure 1). Loss of Put3 blocks targeting of GRS I to the NPC and disrupts interchromosomal clustering of GRS I-containing genes. This suggests that transcription factors like Put3 play important roles in controlling the interaction of genes with the NPC. However, many questions remain. How does binding of transcription factors lead to targeting to the nuclear periphery? How does the function of Put3 in controlling gene localization relate to its function regulating transcription via the UAS_{PUT} element? Do transcription factors interact directly with the NPC or transport factors? How is zip code-mediated targeting regulated? How does targeting to the NPC lead to interchromosomal clustering? Does interaction with the NPC lead to targeting to a particular portion of the nuclear envelope? Answering these questions will be important to understand how transcription factors can regulate the spatial organization of the genome.

Nups promote transcription

How does the interaction of chromatin with Nups impact transcription? In yeast, NPC interaction is required for proper activation of *HXK1*, *INO1* and *TSA2* genes [15,16]. Tethering *INO1* or *HXK1* to the nuclear periphery promotes stronger expression [15,16]. Blocking the interaction of *INO1* or *TSA2* with the NPC by mutating the GRS elements reduces their expression [14–16]. Also, tethering of components of the Nup84 subcomplex stimulates expression of a reporter gene [19].

Nups are required for proper transcription of certain genes in metazoans as well. In *Drosophila*, Nup153 and MTOR bind to roughly 25% of the genome and silencing either Nup leads to reduced expression of the bound genes [17]. These Nups are also required to up-regulate the expression of genes on the X chromosome in male flies [47]. In salivary glands of *Drosophila* larvae, silencing of Sec13 or Nup98 reduces RNA polymerase II (RNAPII) recruitment to developmentally induced puffs, decreases puff size and down-regulates the expression of these genes [26••]. Nucleoplasmic Nup98 stimulates expression of bound genes in *Drosophila* embryos [25••] and S2 cells [26••]. Finally, in humans, Nup98 promotes expression of developmentally induced genes in embryonic stem cells and neuronal precursor cells. Over-expressing wild-type Nup98 increases expression of bound genes in neural precursor cells, while over-expressing a dominant negative allele of Nup98 down-regulates expression of a subset of these genes [27••]. Thus, the interaction of genes with Nups can promote stronger transcription.

Certain acute myeloid leukemias result from chromosomal translocations that fuse Nup98 with the HOXA9 DNA binding region [48]. Swapping Nup98 with VP16 transcriptional activator leads to a similar oncogenic transformation, thus suggesting that Nup98 is necessary and sufficient to activate transcription [48]. Nup98-mediated activation may involve the interaction with the histone acetyltransferase CBP-p300 [48].

Nups affect chromatin: boundaries and memory

Nups can also effect expression by affecting chromatin structure. When tethered to chromatin, Nups and NPC-associated factors induce a chromatin boundary that prevents the spread of chromatin-based silencing [49–51]. Consistent with a role for the NPC in regulating endogenous boundaries, loss of Nup2 leads to the spread of silencing from telomeres [50,51]. Furthermore, Nup-bound regions in yeast are enriched for the binding of the transcription factor Rap1, which also has boundary activity [52]. In a *Drosophila* embryonic cell line, NPC binding overlaps with the insulator protein, Suppressor of Hairy-wing [53]. Finally, in human ES cells, Nup98 binding sites are enriched for GAGA factor binding [27••], which exhibits boundary activity [54]. Therefore, binding of Nups can impact the local chromatin structure, which can impact transcriptional regulation.

Another example of the impact of Nups on chromatin structure is provided by the phenomenon of transcriptional memory. A diverse collection of inducible genes exhibit faster reactivation kinetics upon second exposure to the same stimulus, a phenomenon called transcriptional memory [55]. This phenotype is epigenetically inherited for several generations and involves evolutionarily conserved mechanistic features [36••]. The Nups play an important role in transcriptional memory in both yeast and humans.

In yeast, the nuclear basket protein Mlp1, is required for transcriptional memory of galactose-induced genes *HXK1* and *GAL1* [22]. A chromatin loop between the 5′ and 3′ end of these genes, which persists for several generations after repression, is essential for faster reactivation [22,56,57]. Mlp1 is required to stabilize these loops [22]. The SWI/SNF chromatin remodeler is also required

for *GAL1* transcriptional memory but not loop formation, suggesting that it functions downstream of looping [57,58].

The *INO1* gene possesses a distinct NPC-dependent form of transcriptional memory (Figure 1). After repression, *INO1* does not remain looped [22]. However, it remains associated with the NPC for several generations after repression and during this time, histone H3 in the promoter is dimethylated on lysine 4 (H3K4me2), H2A.Z incorporation into the promoter is altered and a poised form of RNAPII binds [20••] (Figure 1). Poised RNAPII is also found at the promoters of hundreds of genes in stationary phase yeast cells [59] and thousands of genes in G_0 lymphocytes [60]. The pre-initiation complex at recently-repressed *INO1* lacks TFIIK, TFIIS and Mediator and may bypass the rate-limiting step of RNAPII recruitment [36••,61]. This suggests that transcription can be regulated at (at least) three stages: RNAPII recruitment, initiation and, through promoter-proximal pausing, elongation.

The retention of recently-repressed *INO1* at the NPC is mediated by a distinct mechanism from the targeting of active *INO1* to the NPC [16,18•,20••]. Retention after repression does not require the GRS elements, but does require an 11 bp promoter-DNA element called the *M*emory *R*ecruitment *S*equence (MRS) [18•,20••] (Figure 1). Likewise, although the interaction of active *INO1* with the NPC is not dependent on Nup100, association of *INO1* with the NPC after repression does require Nup100 [20••]. Mutations in the MRS or loss of Nup100 leads to loss of the chromatin marks that are associated with transcriptional memory, loss of poised RNAPII after repression and slower *INO1* reactivation [20••,36••]. Thus, *INO1* exploits two independent mechanisms to interact with the NPC, each having different molecular requirements and different outputs (Figure 1).

Salt stress primes many genes for faster activation in response to H_2O_2 treatment. This effect persists for 3–4 generations and requires Nup42; in *nup42Δ* mutants, the rate of activation of these genes in H_2O_2 is unaffected by previous exposure to salt [21]. Interestingly, these genes are enriched for a promoter motif that is similar to the *INO1* MRS [21]. Therefore, the NPC has a general role in promoting epigenetic transcriptional memory.

In HeLa cells, previous exposure to interferon-gamma (IFN-γ) leads to faster reactivation of hundreds of genes during the second exposure [36••,62]. This effect persists for at least four cell divisions (~96 h). Nup98, a human homolog of yeast Nup100, binds to the promoters of genes that exhibit transcriptional memory for up to four generations after initial IFN-γ treatment. Knockdown of Nup98 leads to loss of transcriptional memory. The interaction between Nup98 and *HLA-DRA* occurs in the nucleoplasm in proximity to Promyelocytic Leukemia Bodies [36••,62]. As with *INO1* transcriptional memory in yeast, the *HLA-DRA* promoter exhibits H3K4me2 and binding of poised RNAPII. Therefore, Nup-dependent transcriptional memory represents a mechanism that has been conserved between yeast and humans.

Chromatin structure plays an essential and conserved role in transcriptional memory (Figures 1 and 2). *INO1* transcriptional memory requires the histone variant H2A.Z and the MRS element is both necessary and sufficient to promote H2A.Z incorporation [16,20••]. Dimethylation of histone H3 lysine 4 over the promoter of genes with transcriptional memory is observed in both yeast and humans [36••]. The MRS element is both necessary and sufficient to induce H3K4me2 [36••]. Loss of Set1 and Rad6, which are required for methylation of H3K4 [63], or Set3, a factor that recognizes H3K4me2 [64], leads to a loss of *INO1* memory [36••]. Loss of Nup100 in yeast or knockdown of Nup98 in HeLa cells leads to loss of H3K4me2 over promoters of genes that exhibit transcriptional memory. These effects suggest that transcriptional memory is related to other chromatin-based effects of Nups on repressed parts of the genome, such as boundary activity and poising genes for expression during differentiation [22,27••].

Transcriptional memory requires a persistent, heritable association of Nups with chromatin, but how are these contacts maintained and inherited? In the case of *INO1*, if memory is induced by binding of a transcription factor to the MRS then the activity or binding of this transcription factor may be regulated by previous expression of *INO1*. Consistent with this proposal, this regulation can function in *trans*: small fragments of the *INO1* promoter containing the MRS, when inserted at *URA3*, function as DNA zip codes only after previous expression of *INO1* [20••]. This suggests that a protein produced under activating conditions functions exclusively on the repressed promoter. Binding of an MRS binding protein specifically after repression could promote binding of Nups, chromatin alterations and binding of RNAPII. If such changes are mutually reinforcing, this might lead to a temporary, heritable state and the duration of this state would reflect the dilution and stability of the memory factors. Supporting this model, galactose-induced transcriptional memory is dependent on the very stable Gal1 protein being produced during the initial activation [65].

Conclusions

The roles of NPC components in promoting transcription and regulating chromatin structure have recently become apparent. How Nups mediate these effects remains to be elucidated. Understanding these mechanisms may illuminate the role of Nups in several leukemias [66] and integration of HIV in humans [67]. Therefore, future research in this area will provide important fundamental

insight into the regulation of gene expression and, potentially, strategies for biomedical applications.

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