# Nups Take Leave of the Nuclear Envelope to Regulate Transcription

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**Although components of the nuclear pore complex have been implicated in gene regulation independent of their role at the nuclear envelope, the evidence so far has been indirect. Capelson et al. (2010) and Kalverda et al. (2010) now reveal that certain nucleoporins are actively involved in transcription inside the nucleoplasm of *Drosophila* cells.**

It has been proposed that nuclear pore complexes (NPCs) may associate with active genes to facilitate the export of their mRNAs (Blobel, 1985). In support of this model, known as the "gene-gating" hypothesis, studies in yeast have found that some nucleoporins (Nups) associate with active genes and that certain genes are more frequently observed at the nuclear envelope upon activation (Casolari et al., 2004). However, arguing against this hypothesis is evidence from genome-wide analyses in human HeLa cells, which demonstrate that Nup93, a component of the NPC, predominantly associates at the nuclear envelope with chromatin domains enriched in repressive histone marks (Brown et al., 2008). Adding further complexity to this picture, several Nups associate dynamically with the NPC and exist in the nucleoplasm of mammalian cells (Rabut et al., 2004). In addition, an oncogenic protein produced by the fusion between the genes encoding Nup98 and homeobox PMX1 requires the Nup98 moiety to activate a number of genes in leukemia stem cells (Hirose et al., 2008). These findings suggest that Nups might interact with and regulate genes in the nucleoplasm away from the nuclear periphery. In this issue of *Cell*, the studies by Capelson et al. (2010) and Kalverda et al. (2010) provide fresh evidence that nucleoplasmic Nups are directly involved in the regulation of transcription in the fruit fly *Drosophila* (Figure 1).

Using a combination of experimental approaches, including genome-wide mapping of Nup-binding sites, Capelson et al. and Kalverda et al. determine which Nups associate with chromatin and, very importantly, distinguish between the Nup-chromatin interactions inside the nucleoplasm and those at the nuclear envelope. Several different Nups are present in distinct distribution patterns in salivary gland polytene chromosomes. Interestingly, the distribution patterns of Nups change with the developmental stage of the larvae, suggesting that binding of nucleoplasmic Nups to chromatin may correlate with changes in gene expression during cell differentiation. Nups found to interact with chromatin inside the nucleoplasm include the scaffold protein Sec13, Nup98, Nup62, Nup50, Nup88, and mAb414-positive FG-repeat-containing Nups. These observations clarify the long-standing issue of whether or not Nup-chromatin interactions occur exclusively at the nuclear periphery. Most Nups tested associate preferentially with active chromatin, except Nup88, an NPC filament protein located on the cytoplasmic side, which associates mainly with silenced chromatin. Genes enriched in Nup98 binding are overrepresented in the categories of developmental regulation and cell cycle.

What is the function of nucleoplasmic Nups at their target genes? Though some nucleoporins, such as Trp/Megator and Nup153, have been suggested to be required for dosage compensation in *Drosophila* (Mendjan et al., 2006), and the Nup98 FG domain fused to the NSD1 methyltransferase has been shown to be necessary for the abnormal activation of the Hox-A locus during differentiation (Wang et al., 2007), until now there has been no direct evidence for a role of Nups in transcription. The results of Capelson et al. and Kalverda et al. directly shed light on this issue. Nup98 is present at 841 genes in S2 cells; Nup50 and Nup62 associate directly with a similar set of genes. These genes are highly transcribed and their expression decreases in cells in which Nup98 or Nup50 are downregulated by RNA interference (RNAi). In addition, overexpression of a nucleoplasmic version of Nup98 led to preferential upregulation of the same set of genes where this protein is found. Using ecdysone treatment, heat shock induction, and RNAi knockdown experiments, both groups show that the association of nucleoplasmic Nups with active chromatin correlates with active gene expression. An involvement of Nups in transcriptional activation is supported by their presence at highly transcribed puff regions of polytene chromosomes and at sites where the active phosphorylated form of RNA polymerase II (RNAP II) is located and where histone modifications characteristic of active chromatin, such as H3K4me2 and H4K16Ac, are present. Thus, the authors establish a direct correlation between the association of Nups with chromatin and the activity of their target genes.

When investigating the association of different Nups with active or silent gene domains, Capelson et al. find that the levels of Sec13, Nup50, and Nup98 and the active form of RNAP II show an inverse correlation: sites with high levels of these Nups contain low levels of RNAP II and vice versa. These three Nups are recruited to ecdysone-inducible genes before RNAP II is recruited, suggesting

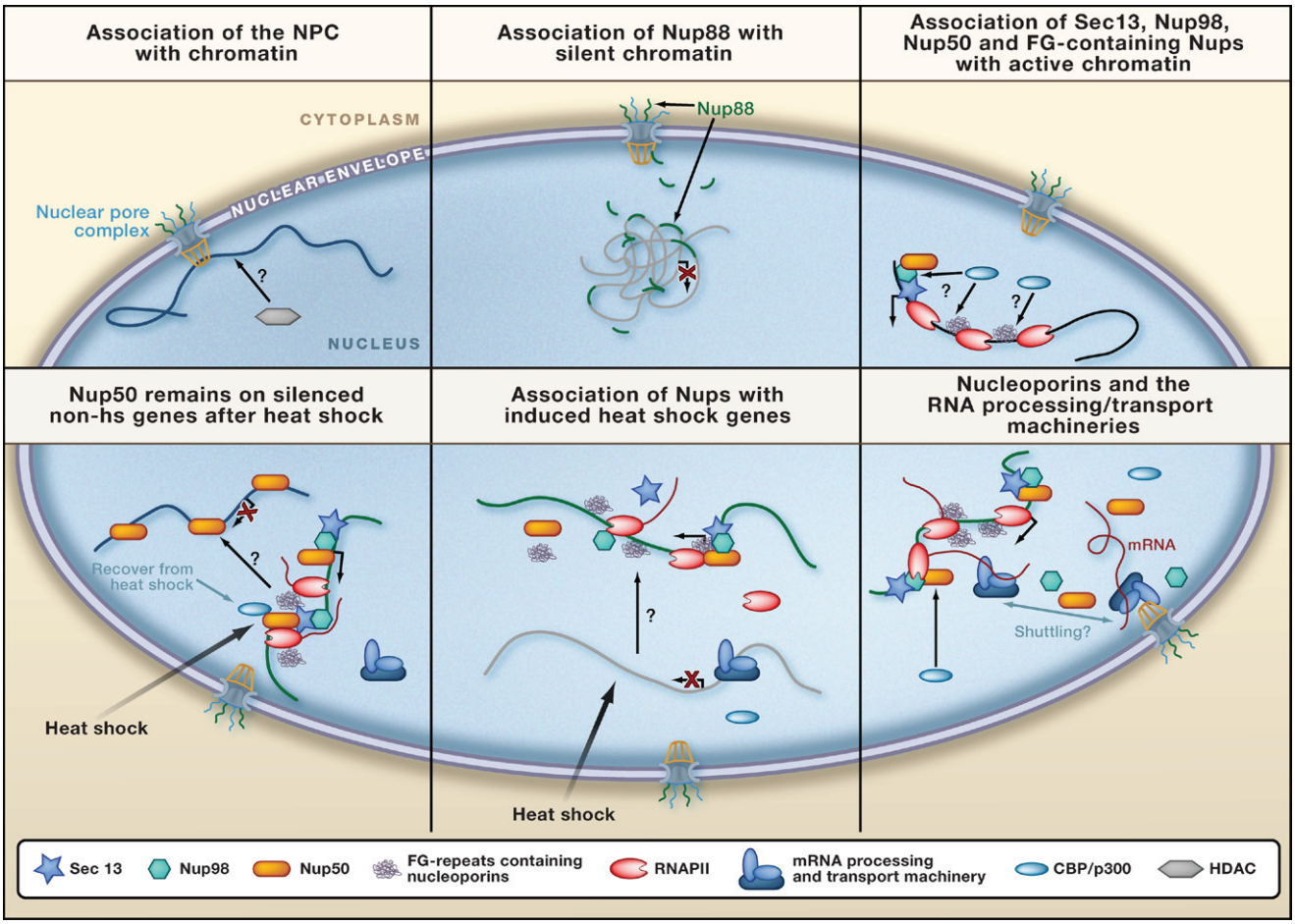


**Figure 1. Processes by which Nucleoporins Regulate Gene Expression**

Depicted are the established and putative interactions between nucleoporins (Nups) and various components of the nucleus, including DNA, mRNA, RNA polymerase II (RNAP II), RNA processing and export machineries, histone-modifying enzymes; some of these relationships are illustrative and require further confirmation. In *Drosophila* cells, nucleoporins (Sec13, Nup98, Nup62, Nup50,and mAB414-positive FG-Nups are sequentially recruited to genes undergoing activation and are required for distinct steps of transcription initiation and elongation). Nup88, a nuclear pore complex (NPC) filament protein located on the cytoplasmic side, associates mainly with silent chromatin. NPCs associate preferentially with a subset of genes expressed at a low level. Nucleoporins may also act as a shuttle to bridge transcription and mRNA transport between the inside of the nucleus and the nuclear periphery. During the heat shock response nucleoporins may be required for activation of the heat shock genes and for the transcriptional recovery of silenced but previously transcribed genes.

that they are involved in the early stages of transcription initiation. In agreement with this conclusion, downregulation of Sec13 and Nup98 leads to impairment in the recruitment of RNAP II. On the other hand, mAb414-positive FG-containing Nups are recruited at the same time as RNAP II, suggesting a function downstream from the initiation event. The dual role of these two classes of Nups in the transcription process is supported by the finding that inhibitors of P-TEFb (positive transcription elongation factor b) affect recruitment of FG-containing Nups whereas Sec13 and Nup98 are unaffected. The distinct roles of Nups in transcription activation are also manifested by the fact that Sec13 is not present at all heat shock genes during the heat shock response and Nup98 is present at heat shock loci different from those at which Sec13 is present. Both proteins are present at many loci in the process of reactivation of transcription of silenced genes during recovery from heat shock.

The process by which Nups are recruited to chromatin is poorly understood. Capelson et al. find that Nup98 recruitment depends on Sec13, whereas Kalverda et al. find that Nup98 is required for Nup50 recruitment. This suggests an ordered recruitment in which Sec13 recruits Nup98, which would then likewise bring Nup50 to target genes. Nevertheless, Kalverda et al. notice that Nup50 remains on polytene chromosomes when transcription of non-heat shock genes is repressed during the heat shock response, which might suggest that Sec13 and Nup98 should also be present at these genes. However, Capelson et al. find that Sec13 and Nup98 are actively recruited to previously silenced genes during recovery from heat shock, which is consistent with the observation that these Nups associate with genes during activation of transcription but not with silenced genes. These conflicting observations may suggest a complex relationship between Nups during their recruitment to chromatin.

Whether the nuclear periphery is a permissive or repressive environment for transcription has been debated for years.

The finding of a role for nucleoplasmic Nups in transcription provides an important advance in our knowledge of the basic role of nucleoporins in gene regulation. Contrary to their proposed function in the "gene-gating" model, nucleoplasmic Nups directly participate in the activation of transcription away from the NPCs on the nuclear envelope. Some Nups are highly dynamic and rapidly shuttle between NPCs and the nucleoplasm. If these Nups are involved in both transcription inside the nucleoplasm and trafficking at the NPCs, it would be tempting to speculate that they may bridge two fundamental cellular processes taking place in the inside of the nucleus and at the periphery. This finding challenges the conventional views of how the constituents of NPCs regulate gene expression at the nuclear periphery and also potentially excludes the necessity of bringing chromatin to the NPCs in order to affect transcription.

Half a century after first unveiling the existence of the NPCs (Watson, 1959), the work of Capelson et al. and Kalverda et al. places a new cornerstone in nuclear biology upon which to build a better understanding of the role of nuclear transport components in transcription regulation. Like all key discoveries, these studies raise many additional questions. Most of the Nups lack structural motifs suggestive of a DNA-binding function. Therefore, it will be of interest to elucidate how nucleoplasmic Nups associate with chromatin and how they selectively bind to distinct subsets of genes involved in different biological processes. Due to the strict requirement of NPCs for directional transport between the cytoplasm and the nucleoplasm, it will be important to understand whether this additional function of the Nups will affect NPC activity under physiological conditions that require active transport of proteins and mRNAs. Elucidation of the molecular mechanisms by which the Nups participate in gene regulation may give new insights into the interplay among different nuclear compartments in the activation of eukaryotic genes.

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# USP10: Friend and Foe


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**The tumor suppressor protein p53, a crucial player in the DNA damage response, is regulated in many ways, most notably through ubiquitination. In this issue, Yuan et al. (2010) identify the deubiquitinating protease USP10 as a new regulator of p53 in the DNA damage response and tumor development.**


Many oncogenic alterations in cellular genomes may never result in tumors: rather than boosting cell proliferation, these mutations lead to replication stress, DNA damage, and a DNA damage response. The DNA damage response is a network of pathways that rapidly modulates many aspects of cellular metabolism, particularly following the induction of cytotoxic lesions such as DNA double-strand breaks. A central part of the DNA damage response is the activation of p53, which results in cell-cycle arrest, apoptosis, or senescence. These responses are important barriers to tumor progression and malignancy. Indeed, p53's tumor suppressor activity is believed to be attenuated in human tumor cells, either by inactivating mutations in the *TP53* gene encoding p53 or by altered expression of p53 modulators and effectors. In unstressed cells, p53 is kept at low levels through its continuous degradation via the ubiquitin-proteasome pathway, whereas upon DNA damage p53 degradation is attenuated (Figure 1). The primary regulator of DNA damage-induced p53 stabilization is the nuclear protein kinase ATM (ataxia-telangiectasia mutated),