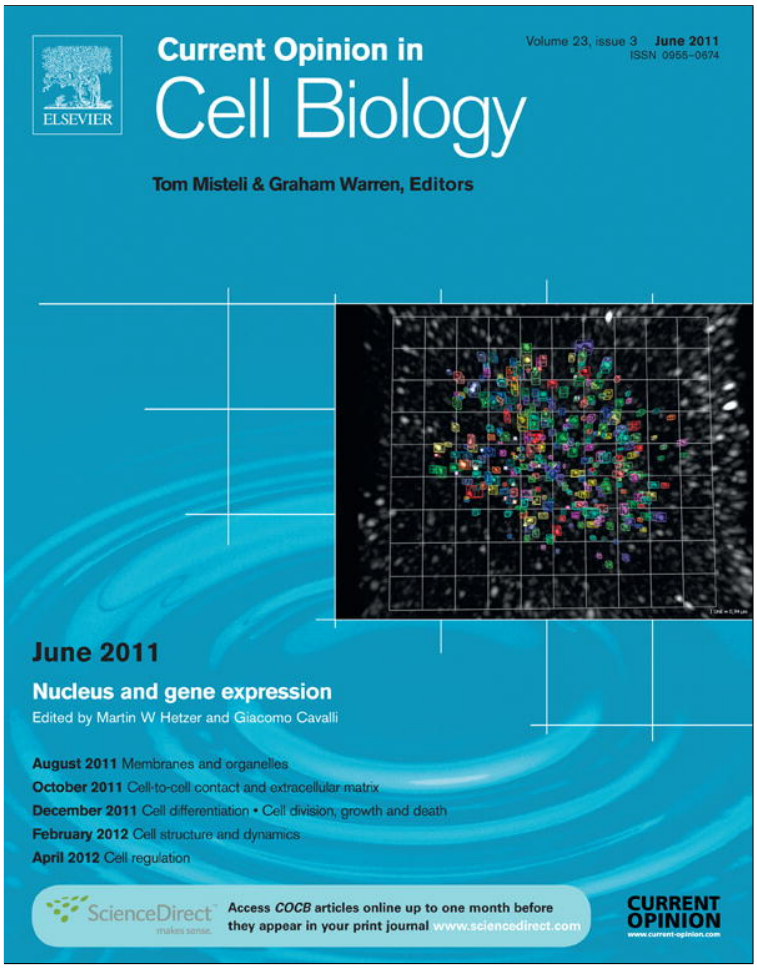


Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Cell Biology

Multiple facets of nuclear periphery in gene expression control

Ghislaine Arib and Asifa Akhtar

Nuclear pore complexes play a central role in controlling the traffic between the nucleus and the cytoplasm. Progress during the last decade has highlighted nuclear periphery components as novel players in chromatin organization, gene regulation, and genome stability. For instance, lamins associate with repressive chromatin while nuclear pores tend to associate with active chromatin. Interestingly, nucleoporins (Nups) act not only at the nuclear periphery but also in the nucleoplasm. Here we provide an overview of the latest findings and discuss the functional importance of nucleoporin association with specific genes, their role in transcriptional memory, the coupling of transcription and mRNA export, and genome integrity.

Address
Max-Planck-Institute of Immunobiology und Epigenetics, Stübeweg 51,79108 Freiburg im Breisgau, Germany

Corresponding author: Akhtar, Asifa (akhtar@immunbio.mpg.de)

Current Opinion in Cell Biology 2011, **23**:346–353

This review comes from a themed issue on
Nucleus and gene expression
Edited by Martin W Hetzer and Giacomo Cavalli

Available online 15 January 2011

0955-0674/$ – see front matter

DOI 10.1016/j.ceb.2010.12.005

Introduction

Chromosomes are highly organized within the nucleus and reside in specific functional subnuclear compartments in interphase cells [1]. These compartments are not membrane delimited and instead arise from the clustering of DNA regions with specific proteins, creating microenvironments that can favor or impede particular cellular processes such as transcription regulation or replication. Thus, the three-dimensional (3D) nuclear architecture provides a fundamental level for the regulation of gene expression (for review see [2,3]).

The nuclear envelope (NE) surrounds and defines this complex nuclear architecture. It consists of two membrane bilayers, perforated by nuclear pores, which control the traffic in and out of the nucleus. The NE is also associated with perinuclear proteins including membrane-associated or transmembrane proteins and the nuclear lamina. In higher eukaryotes, the inner nuclear membrane is associated with a network of intermediate filament proteins called lamins, which help to maintain the spherical geometry of nuclei. These play an important role in many fundamental processes such as NE assembly/disassembly during mitosis, gene expression, DNA replication and nuclear pore complex (NPC) positioning (for review see [4]).

The overall structure of the NPC is evolutionarily conserved and is a large protein complex of about 60 MDa embedded in the NE [5–7]. The primary function of the NPC is to mediate selective bidirectional transport between the nucleus and the cytoplasm [8,9]. NPCs are composed of approximately 30 different nucleoporins (Nups) [9,10] that fall into two broad categories: firstly, scaffold Nups and secondly, peripheral Nups. The scaffold Nups form the NPC core. On the other hand, the peripheral Nups, many of which contain phenylalanine-glycine (FG) repeats, are responsible for establishing the permeability barrier [11] and mediating nuclear trafficking [12]. Interestingly, several Nups are mobile and dynamically shuttle between the nucleoplasm and the NPC [13–15]. In this review, we highlight the role of nuclear periphery components in transcriptional control (Table 1).

Gene silencing at the nuclear periphery

Classical cytological studies revealed that heterochromatin has a tendency to associate with the nuclear periphery, raising the possibility that proximity to the NE facilitates silencing (for review see [16]). In *Saccharomyces cerevisiae*, for example, telomeres form clusters at the nuclear periphery [17]. Although tethering to the nuclear periphery has been shown to promote silencing, moving to the nuclear periphery is neither necessary nor sufficient for silencing [18,19].

Observations in higher eukaryotes also suggest a repressive role of the NE. For example, in human cells, gene-poor chromosomes tend to localize at the nuclear periphery as well as the inactive X chromosome or Barr body [20,21]. Several loci were found to localize near the NE in their inactive state and to change their nuclear localization upon induction of transcription. For example, the *IgH* locus moves away from the nuclear periphery in B cells concomitant with the initiation of V(D)J recombination [22]. Similarly, when the CFTR (cystic fibrosis transmembrane conductance regulator) gene is inactive, it preferentially associates with the nuclear periphery while in its actively transcribed state it associates with euchromatin in the nuclear interior [23].

Table 1

Summary of nucleoporins implicated in transcription regulation and genome stability.

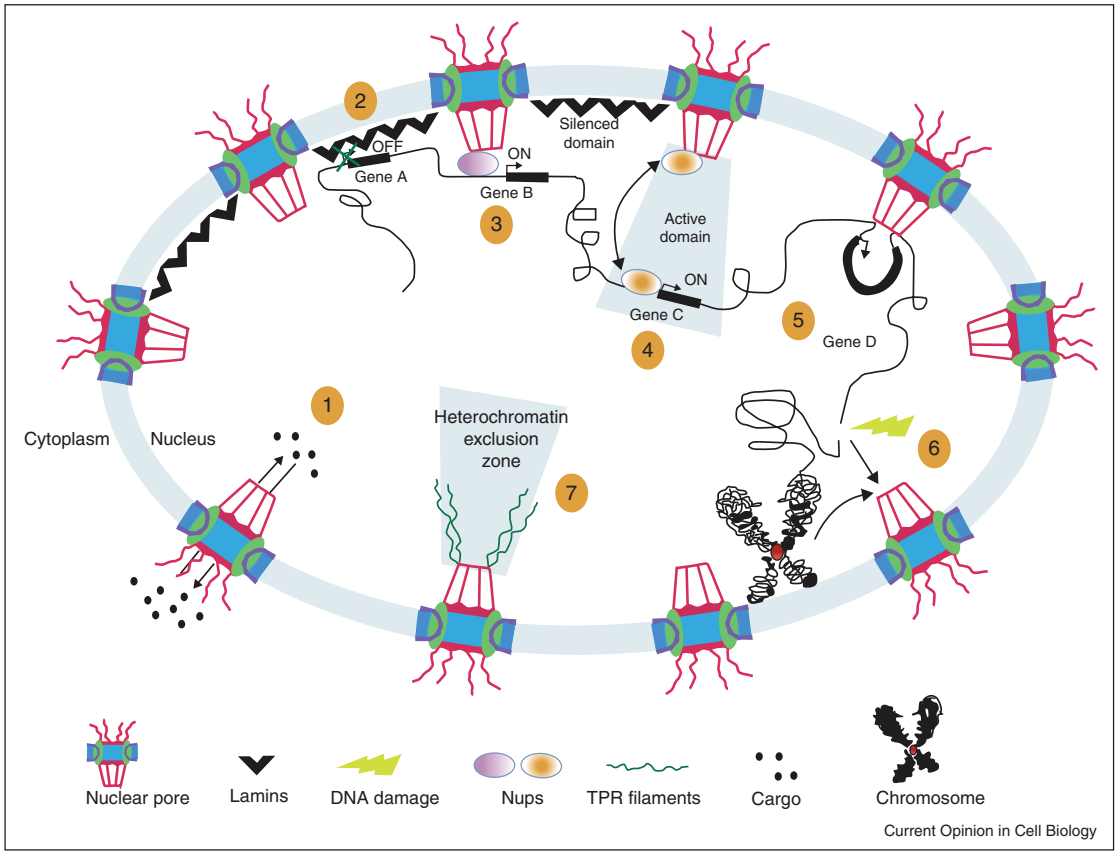
Yeast	Flies	Mammals	Location	Functions
Mlp1 Mlp2	Megator (Mtor)	TPR	Nuclear basket	Mtor is also present in the nuclear interior [80] Associates with active genes [28,39,40••] Mlp1/2 play a role in control quality of exported mRNA [81] TPR functions in the mitotic spindle checkpoint [82] Mlp1p is implicated in transcription memory [57••] TPR is required for the formation of heterochromatin exclusive zones [53••]
	Nup153	NUP153	Nuclear basket	Mobile nucleoporin [46] NUP153 mobility depends on ongoing transcription [15] Associates with active genes at the pore and off-pore [39,40••]
Nup145N Nup100 Nup116	Nup98	NUP98	Nuclear basket	Mobile nucleoporin [14,46] NUP98 mobility depends on ongoing transcription [14,15] Role in cancer [50] Drosophila Nup98 associates with active genes in the nuclear interior [47••,48••] Nup100 associates with genes that are not highly transcribed [28] Nup116 associates with active genes [28]
	Nup50	NUP50	Nuclear basket	Mobile nucleoporin [46,83] Drosophila Nup50 associates with active genes [48••]
Nup1			Nuclear basket	Phosphorylation of Nup1 is required for peripheral targeting of active *INO1* and *GAL1* genes [63]
Nup2			Nuclear basket	Mobile nucleoporin [84] Role in chromatin boundary [27] Associates with active genes [28]
Nup60			Nuclear basket	Associates with active genes [28]
Nup170	Nup154	NUP155	Core	Drosophila Nup154 does not associate with chromatin [48••]
Nic96	CG7262	NUP93	Core	Nic96 associates with transcribed genes [28] Mammalian NUP93 interacts with inactive chromosomal regions [52]
Nsp1	Nup62	NUP62	Central channel	Nsp1 associates with genes that are moderately transcribed [28] *Drosophila* Nup62 associates with active genes [48••]
Nup84	Nup107	NUP107	Core	Nup84 associates with genes that are moderately transcribed [28] Nup84 subcomplex mediates transcriptional activation [85] Nup84 subcomplex acts as a coordinator of SUMO-dependent repair pathway [74•].
Nup145C	Nup96	NUP96	Nuclear ring	Nup154c associates with genes that are not highly transcribed [28]
Nup82	Nup88/Mbo	NUP88	Cytoplasmic filaments	Drosophila Nup88 associates with inactive genes [47••]
Pom152	Gp210	GP210	Trans-membrane	Dynamic nucleoporin [46] Drosophila Gp210 does not associate with chromatin [48••]

Genome-wide studies performed both in *Drosophila melanogaster* and in human cells have revealed that lamin-bound genes are generally transcriptionally silent, late replicating and lack active histone marks. Interestingly, lamin-associated genes can be released from lamins upon transcriptional activation suggesting that perinuclear association promotes silencing [24•,25•]. All together these findings support the long-standing classical view of heterochromatin domains residing close to the nuclear membrane, and that the interaction of genes with lamins generally leads to gene repression (Figure 1).

Gene activation at the nuclear periphery

Several lines of evidence indicate that the nuclear periphery has a dual role in gene regulation, since it is not only involved in creating a repressive compartment but also promotes high levels of gene induction (Table 1). Already in 1985, the 'gene gating' hypothesis suggested

Figure 1



Nuclear periphery as a platform for integrating multiple cellular pathways. Schematic representation depicting various roles associated with the components of the nuclear periphery. Within the nuclear envelope, the NPCs are the major gateways for import and export between nucleus and cytoplasm (1). Nuclear lamina harbors a zone for gene repression (2). In contrast, the NPC is associated with gene activation. Transcription regulation can be mediated by both NPC bound pool (3) and soluble pools of nucleoporins (4). Components of the NPC have been shown to be involved in gene looping (5). DNA repair pathways also converge at the nuclear pore complexes (6). Nuclear pore component TPR in involved in creating heterochromatin exclusion zone (7).

that active genes associate with NPCs to increase the efficiency of nuclear export of transcribed RNA [26]. Support for this hypothesis comes from several studies done in *S. cerevisiae*. Among the first reports linking the NPC to gene activity showed that nucleoporin Nup2p functions as a boundary and blocks the spreading of heterochromatin into a reporter gene. Importantly, the insulation of the reporter gene from the surrounding heterochromatin involved its physical tethering to the NPC via Nup2 [27]. Later a genome-wide (ChIP-on-chip) approach demonstrated that Nups associate preferentially with transcriptionally active genes [28]. Nups have also been shown to associate with promoters of active genes [29]. Furthermore, a number of inducible genes including *INO1*, *GAL1*, *HXK1* or *HSP104* are targeted to the nuclear periphery (NPCs) upon activation [28,30,31] (Figure 1). One explanation is that gene–NPC association might be particularly important for inducible genes such as galactose and heat shock controlled promoters, which require rapid and high expression levels and export, which could be facilitated by their positioning closer to the NPCs. The chromatin remodeling complex SAGA controls expression of stress inducible genes and is connected to the mRNA export machinery by one of its components Sus1 that binds to the NPC [32].

What is the functional significance of NPCs–gene interaction? In yeast, targeting of certain genes to the nuclear periphery seems to involve nascent RNA transcripts [33–35]. However, since *GAL1* or *HSP104* gene association with the NPC can be disrupted without affecting expression levels, perinuclear localization of these genes may be a consequence rather than a cause of transcriptional activation [30,35]. Therefore, a model has been proposed where the *GAL1* gene is first activated and then is 'gated' at the nuclear periphery [30]. In contrast, targeting of the *INO1* gene to the nuclear periphery is not dependent on transcription [36], but is instead

controlled by DNA 'zip codes' in the promoter that enhance transcription [37••].

Given that most of the current evidence supporting 'gene gating' has been obtained in budding yeast, it leads one to question the evolutionary conservation of this phenomenon. In *Drosophila* the scenario appears more complex. For example in Schneider (SL-2) cells, *Hsp70* genes not only localize nonrandomly at the nuclear periphery under nonheat shock conditions but their position also remains peripheral upon induction [38]. This peripheral localization is lost upon Xma-2 or E(y)2 depletion, however, Hsp70 mRNA levels are only reduced by 50% indicating that the peripheral localization of Hsp70 genes is not necessary for their expression. As further evidence for the role of the nuclear pore components in the regulation of active chromatin, Nup153, and Megator (Mtor) have been found to copurify with MSL complex members, which participate in the X chromosome transcriptional hyperactivation during dosage compensation in *D. melanogaster* [39]. The male X chromosome was shown to be enriched in nucleoporin associated regions (NARs) that frequently reside closer to the nuclear periphery [40••]. Future studies will reveal how general functions of these proteins impact on specific processes such as X chromosome regulation.

In vertebrate cells, the DNaseI sensitive chromatin localizes preferentially at the nuclear periphery [41]. More recently it was shown that at the time of activation, the β globin locus is localized at the nuclear periphery and only moves into the nuclear interior at a later time point [42]. Support for this model comes from the study of repositioning of the Th2-specific transcription factor loci during Th1 differentiation [43]. Furthermore, the IFNγ locus is positioned at the nuclear periphery even under induced conditions, arguing strongly that the nuclear periphery cannot be an indiscriminately repressive environment.

Role of nuclear pore components off the pore

The spatial restriction of chromatin movement in the interphase nucleus [44,45] makes it highly unlikely that all genes need to relocalize to the NPC to be activated. Therefore, the coupling of transcription and export might be conserved in metazoan Nups at intranuclear active sites, where they can serve as a platform for coregulated assembly of transcription machinery and mRNA export factors. Support for this hypothesis comes from the fact that some Nups are mobile and that the dynamics of mammalian NUP98 and NUP153 is dependent on active transcription [14,15,46], possibly establishing a functional connection between sites of production of mRNAs and NPCs. One important question is therefore whether the chromatin–Nup interaction reported in yeast to happen at the NE can also take place in the nuclear interior.

Using polytene chromosome stainings, it has been reported that various *Drosophila* Nups, including Nup98, Sec13, Nup50, and mAb414-positive Nups, associate with active loci that often localize in the nucleoplasm whereas Nup88 associates preferentially with inactive loci [47••,48••]. Furthermore, Nup153 and Mtor bind large domains (NARs) of about 10–500 kb called NARs that demarcate regions of open chromatin and active transcription [40••]. NARs were shown to be at the nuclear periphery as well as in the nucleoplasm [40••]. These findings support the idea of a NPC duality in gene regulation and suggest that Nups could target different sets of genes based on their transcriptional state [47••]. Since some Nups are found associated with the pore or located in the nucleoplasm, an alternative possibility is that different pools of the same Nup may exhibit different functions depending on their subnuclear location. Nup98 and Nup50 have been shown to be associated with both expressed and moderately transcribed genes [48••]. The bound-expressed genes generally localize inside the nucleus whereas the bound-poorly expressed genes localize at the periphery. Therefore, it has been proposed that nucleoplasmic NPC components activate the expression of internally localized genes whereas DNA–NPC interaction leads to gene silencing [48••]. These observations support a role of Nups in nuclear compartmentalization for gene expression regulation also in the nucleoplasm (Figure 1).

Nucleoporins as regulators of the transcription process

Several chromosomal translocations in acute myeloid leukemia (AML) result in fusion proteins containing the FG repeat part of NUP98 and members of the homeobox transcription factor family such as HoxA9. These oncogenic fusion proteins are able to activate or repress target genes within the nucleoplasm [49–51]. Interestingly, a genome-wide study of NUP93-chromatin association in vertebrate cells revealed changes in NPC–chromatin interactions based on histone modification status of chromatin [52].

The observations that the absence of some Nups such as Nup98 and Sec13 abolishes the recruitment of RNA PolII on target genes [47••], that the mobility of NUP98 and NUP153 is closely associated with ongoing transcription [14,15], and that loss of Nup153, Mtor or Nup98 affects global gene expression [40••,48••] indicate that Nups might function as direct or indirect regulators of the transcription process possibly by delivering transcriptional activators to genes that are expressed. Interestingly, in mammalian cells, TPR, a component of the nuclear basket, is required for the formation and maintenance of heterochromatin exclusive zones (HEZs) that could facilitate the access of large cargo, including transcription or transport associated complexes, to the NPC [53••] (Figure 1).

Furthermore, Nups have been implicated in different steps of transcription. For example, Nup98 and Sec13 recruitment precedes or coincides with RNA pol II recruitment on target genes. Their down-regulation leads to impairment in the recruitment of RNA pol II suggesting that these Nups are involved in the early stages of transcription initiation [47••]. This finding is in agreement with a previous yeast study that reports interaction between genes promoters and Nup2 and propose that contact with pores may be a general feature of gene activation [29]. Interestingly, Nup binding sites have also been mapped on the body of active genes [28]. These studies suggest that Nups may also regulate transcription elongation or the recycling of polymerases to the promoters for reinitiation [47••]. Future work will be instrumental in unraveling the possible molecular mechanisms by which Nups could influence transcription.

Nucleoporins facilitating transcriptional memory

In yeast, formation of a gene loop between the 5′ and 3′ end of a gene has been shown to play an important role in transcriptional regulation termed 'transcriptional memory' that enables past events to be 'remembered' [54,55]. Gene loops are dynamic structures whose formation is dependent on active transcription and components of the RNA processing machinery [54,55].

Tethering of genes at the NPC is reported to facilitate transcriptional memory [56] (Figure 1). Interestingly, Mlp1, a NPC component, plays a role in the maintenance of the gene loop structure [57••]. Consistent with this, Mlp1 displays a 5′/3′ distribution pattern on the *HXK1* gene at time points coincident with gene loop formation [57••]. Therefore, one possible mechanism of how NPC localization could enhance gene expression is by inducing or stabilizing loop formation [57••]. Looping appears not to be a unique feature in yeast. The HIV provirus forms a loop between the 5′ long terminal repeat (LTR) and poly(A) signal, also in a transcription-dependent manner [58]. Dynamic promoter-terminator loops have been described for the breast cancer BRCA1 gene [55], and at the gene encoding the immunohistological marker CD68 in mammalian cells [59]. In *D. melanogaster*, looping of the HOX genes correlates with their repression and involves CTCF [60]. It is tempting to speculate whether Mtor (closest functional homologue of Mlp1) could also enhance gene expression by contributing to gene looping in *Drosophila*.

One player implicated in transcriptional memory is the histone variant H2A.Z. This factor has been shown to be required for the association of recently shut-off genes with nuclear periphery indicating that the chromatin state also plays a role in gene–NE interactions [36]. However, a recent study attributes the H2AZ function in general to *GAL1* gene regulation rather than to transcriptional memory [61]. Interestingly, a DNA sequence called memory recruitment sequence (MRS) has been identified in the promoter of the budding yeast *INO1* gene which mediates *INO1* association with the NPC after transcriptional shut-off. The MRS is required for the incorporation of the histone variant H2A.Z, which is also necessary for *INO1* transcriptional memory [37••,62]. Future studies will reveal whether sequence-dependent tethering could also be utilized by genes in other organisms.

Factors contributing towards gene dynamics

Multiple factors have been implicated in the relocation of active genes to the NPC, including transcriptional activators, mRNA processing and export factors, and distinct NPC subunits. The mechanisms allowing gene movement remain unclear. It is possible that intranuclear chromatin-binding Nups shuttle between genomic sites and the nuclear periphery thus acting as transport factors to target genes from one location to another.

Progression through the cell cycle is an important factor contributing to chromatin. In yeast active *INO1* and *GAL1* genes localize at the nuclear periphery during G1 and G2/M, but move to the nucleoplasm during S phase. Furthermore, phosphorylation of Nup1, a component of the NPC, by the cyclin dependent kinase (Cdk1) has shown to be necessary for targeting active *INO1* and *GAL1* to the nuclear periphery [63]. These findings suggest that post-translational modification of Nups could also play an important role for dynamic NPC–DNA interactions during the cell cycle.

Nuclear actin and myosin, as well as myosin-like and actin-related proteins have been proposed as candidates that could contribute to the organization of transcription in the interphase nucleus. Indeed, actin is found not only as part of the filamentous cytoskeleton, but also in various large chromatin modifying complexes that are exclusively nuclear [64–66]. Furthermore, actin-related proteins are also components of chromatin remodelers and are conserved from yeast to human [67]. Interestingly, actin-related protein Arp6, which is also a component of the chromatin remodeling complex SWR1, was recently shown to mediate localization of ribosomal protein genes to the nuclear periphery [68].

Interestingly, a recent genetic screen performed to comprehensively assess the role of essential factors in NPC localization, structure, and assembly into the NE has led to the identification of multiple components of the RSC chromatin remodeling complex including the essential ATPase catalytic subunits Sth1, RSC8, RSC58, and ARP9 in *S. cerevisiae* [69]. Consistently, several earlier reports also observed a link between NPCs and RSC [70,71].

These studies not only provide a functional link between the chromatin remodeling complexes and the nuclear

periphery but also highlight the complexity and connectivity between different pathways leading to gene regulation.

Nuclear periphery playing a role in genome stability

Repair of chromosomal breaks induced due to environmental insult or endogenous cellular metabolism is central to cell survival and genome integrity. Non-homologous end joining (NHEJ) is one of the major cellular repair pathways that eliminate chromosome double strand breaks (DSBs). Interestingly, mutations in components of a Nup subcomplex (Nup84, Nup120, Nup133, and Nup60) rendered yeast cells hypersensitive to DNA damaging agents and loss of the Nup84 complex was shown to be synthetic lethal with mutations that impair homologous recombination [72,73,74•,75,76]. Furthermore, it was recently demonstrated that damaged DNA is recruited to the nuclear pore to be repaired using a SUMO-dependent E3 ligase SlX5/Slx8 [74•].

Telomeres are unique nucleo-protein structures that facilitate replication at the ends of linear eukaryotic chromosomes and protect the ends against untimely erosion and recognition by the DNA damage machinery. Telomere length decreases each generation owing to the inherent inability of the conventional replication machinery to fully replicate the end of chromosomal DNA. The erosion of telomeric DNA resulting from replication can be compensated for by a variety of mechanisms involving recombination and telomerase-catalysed reverse transcription. Recent data indicate that the NE protects telomeric repeats from recombination [77,78]. Furthermore, it has been shown that eroded telomeres change their subnuclear location to the nuclear pore during DNA damage response [79]. All together these studies highlight that components of the nuclear periphery not only play a role in transcription control but are also implicated in genome integrity (Figure 1).

Concluding remarks

Recent progress has shed new light on the role of nuclear periphery components beyond nucleocytoplasmic transport. It appears that the nuclear pore components play an integral role in nuclear architecture, gene expression and genome stability by providing a supporting platform for tethering various molecules. This multifunctional platform serves to ensure the efficient control of gene expression at the transcriptional and post-transcriptional levels. Future studies will provide a better understanding of how components of the NPC execute their function on and off the pores.

Acknowledgements

We thank Juan M. Vaquerizas and the lab members for critical reading of the manuscript and very helpful comments and suggestions. This work was supported by Humboldt fellowship awarded to GA and DFG "SPP1129' to AA.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Cremer T, Cremer C: **Chromosome territories, nuclear architecture and gene regulation in mammalian cells**. *Nat Rev Genet* 2001, **2**:292-301.
2. Misteli T: **Beyond the sequence: cellular organization of genome function**. *Cell* 2007, **128**:787-800.
3. Spector DL: **The dynamics of chromosome organization and gene regulation**. *Annu Rev Biochem* 2003, **72**:573-608.
4. Dechat T, Pfleghaar K, Sengupta K, Shimi T, Shumaker DK, Solimando L, Goldman RD: **Nuclear lamins: major factors in the structural organization and function of the nucleus and chromatin**. *Genes Dev* 2008, **22**:832-853.
5. Alber F, Dokudovskaya S, Veenhoff LM, Zhang W, Kipper J, Devos D, Suprapto A, Karni-Schmidt O, Williams R, Chait BT *et al.*: **The molecular architecture of the nuclear pore complex**. *Nature* 2007, **450**:695-701.
6. Cronshaw JM, Krutchinsky AN, Zhang W, Chait BT, Matunis MJ: **Proteomic analysis of the mammalian nuclear pore complex**. *J Cell Biol* 2002, **158**:915-927.
7. Rout MP, Aitchison JD, Suprapto A, Hjertaas K, Zhao Y, Chait BT: **The yeast nuclear pore complex: composition, architecture, and transport mechanism**. *J Cell Biol* 2000, **148**:635-651.
8. Gorlich D, Kutay U: **Transport between the cell nucleus and the cytoplasm**. *Annu Rev Cell Dev Biol* 1999, **15**:607-660.
9. Tran EJ, Wente SR: **Dynamic nuclear pore complexes: life on the edge**. *Cell* 2006, **125**:1041-1053.
10. Beck M, Forster F, Ecke M, Plitzko JM, Melchior F, Gerisch G, Baumeister W, Medalia O: **Nuclear pore complex structure and dynamics revealed by cryoelectron tomography**. *Science* 2004, **306**:1387-1390.
11. D'Angelo MA, Hetzer MW: **Structure, dynamics and function of nuclear pore complexes**. *Trends Cell Biol* 2008, **18**:456-466.
12. Weis K: **Nucleocytoplasmic transport: cargo trafficking across the border**. *Curr Opin Cell Biol* 2002, **14**:328-335.
13. Daigle N, Beaudouin J, Hartnell L, Imreh G, Hallberg E, Lippincott-Schwartz J, Ellenberg J: **Nuclear pore complexes form immobile networks and have a very low turnover in live mammalian cells**. *J Cell Biol* 2001, **154**:71-84.
14. Griffis ER, Altan N, Lippincott-Schwartz J, Powers MA: **Nup98 is a mobile nucleoporin with transcription-dependent dynamics**. *Mol Biol Cell* 2002, **13**:1282-1297.
15. Griffis ER, Craige B, Dimaano C, Ullman KS, Powers MA: **Distinct functional domains within nucleoporins Nup153 and Nup98 mediate transcription-dependent mobility**. *Mol Biol Cell* 2004, **15**:1991-2002.
16. Akhtar A, Gasser SM: **The nuclear envelope and transcriptional control**. *Nat Rev Genet* 2007, **8**:507-517.
17. Cockell M, Gasser SM: **Nuclear compartments and gene regulation**. *Curr Opin Genet Dev* 1999, **9**:199-205.
18. Andrulis ED, Neiman AM, Zappulla DC, Sternglanz R: **Perinuclear localization of chromatin facilitates transcriptional silencing**. *Nature* 1998, **394**:592-595.
19. Gartenberg MR, Neumann FR, Laroche T, Blaszczyk M, Gasser SM: **Sir-mediated repression can occur independently of chromosomal and subnuclear contexts**. *Cell* 2004, **119**:955-967.
20. Croft JA, Bridger JM, Boyle S, Perry P, Teague P, Bickmore WA: **Differences in the localization and morphology of chromosomes in the human nucleus**. *J Cell Biol* 1999, **145**:1119-1131.

21. Walker CL, Cargile CB, Floy KM, Delannoy M, Migeon BR: **The Barr body is a looped X chromosome formed by telomere association**. *Proc Natl Acad Sci U S A* 1991, **88**:6191-6195.

22. Kosak ST, Skok JA, Medina KL, Riblet R, Le Beau MM, Fisher AG, Singh H: **Subnuclear compartmentalization of immunoglobulin loci during lymphocyte development**. *Science* 2002, **296**:158-162.

23. Zink D, Amaral MD, Englmann A, Lang S, Clarke LA, Rudolph C, Alt F, Luther K, Braz C, Sadoni N *et al.*: **Transcription-dependent spatial arrangements of CFTR and adjacent genes in human cell nuclei**. *J Cell Biol* 2004, **166**:815-825.

24. • Guelen L, Pagie L, Brasset E, Meuleman W, Faza MB, Talhout W, Eussen BH, de Klein A, Wessels L, de Laat W *et al.*: **Domain organization of human chromosomes revealed by mapping of nuclear lamina interactions**. *Nature* 2008, **453**:948-951.
See annotation to Ref. [25•].

25. • Pickersgill H, Kalverda B, de Wit E, Talhout W, Fornerod M, van Steensel B: **Characterization of the *Drosophila melanogaster* genome at the nuclear lamina**. *Nat Genet* 2006, **38**:1005-1014.
Along with Ref. [24•], these papers provide genome-wide analyses of lamina interactions in human and *Drosophila* cells, respectively.

26. Blobel G: **Gene gating: a hypothesis**. *Proc Natl Acad Sci U S A* 1985, **82**:8527-8529.

27. Ishii K, Arib G, Lin C, Van Houwe G, Laemmli UK: **Chromatin boundaries in budding yeast: the nuclear pore connection**. *Cell* 2002, **109**:551-562.

28. Casolari JM, Brown CR, Komili S, West J, Hieronymus H, Silver PA: **Genome-wide localization of the nuclear transport machinery couples transcriptional status and nuclear organization**. *Cell* 2004, **117**:427-439.

29. Schmid M, Arib G, Laemmli C, Nishikawa J, Durussel T, Laemmli UK: **Nup-PI: the nucleopore-promoter interaction of genes in yeast**. *Mol Cell* 2006, **21**:379-391.

30. Cabal GG, Genovesio A, Rodriguez-Navarro S, Zimmer C, Gadal O, Lesne A, Buc H, Feuerbach-Fournier F, Olivo-Marin JC, Hurt EC *et al.*: **SAGA interacting factors confine sub-diffusion of transcribed genes to the nuclear envelope**. *Nature* 2006, **441**:770-773.

31. Taddei A, Van Houwe G, Hediger F, Kalck V, Cubizolles F, Schober H, Gasser SM: **Nuclear pore association confers optimal expression levels for an inducible yeast gene**. *Nature* 2006, **441**:774-778.

32. Rodriguez-Navarro S, Fischer T, Luo MJ, Antunez O, Brettschneider S, Lechner J, Perez-Ortin JE, Reed R, Hurt E: **Sus1, a functional component of the SAGA histone acetylase complex and the nuclear pore-associated mRNA export machinery**. *Cell* 2004, **116**:75-86.

33. Abruzzi KC, Belostotsky DA, Chekanova JA, Dower K, Rosbash M: **3′-end formation signals modulate the association of genes with the nuclear periphery as well as mRNP dot formation**. *EMBO J* 2006, **25**:4253-4262.

34. Casolari JM, Brown CR, Drubin DA, Rando OJ, Silver PA: **Developmentally induced changes in transcriptional program alter spatial organization across chromosomes**. *Genes Dev* 2005, **19**:1188-1198.

35. Dieppois G, Iglesias N, Stutz F: **Cotranscriptional recruitment to the mRNA export receptor Mex67p contributes to nuclear pore anchoring of activated genes**. *Mol Cell Biol* 2006, **26**:7858-7870.

36. Brickner DG, Cajigas I, Fondufe-Mittendorf Y, Ahmed S, Lee PC, Widom J, Brickner JH: **H2A.Z-mediated localization of genes at the nuclear periphery confers epigenetic memory of previous transcriptional state**. *PLoS Biol* 2007, **5**:e81.

37. •• Ahmed S, Brickner DG, Light WH, Cajigas I, McDonough M, Froyshteter AB, Volpe T, Brickner JH: **DNA zip codes control an ancient mechanism for gene targeting to the nuclear periphery**. *Nat Cell Biol* 2010, **12**:111-118.
This is the first report showing the importance of conserved DNA elements in tethering a locus to the nuclear periphery.

38. Kurshakova MM, Krasnov AN, Kopytova DV, Shidlovskii YV, Nikolenko JV, Nabirochkina EN, Spehner D, Schultz P, Tora L, Georgieva SG: **SAGA and a novel *Drosophila* export complex anchor efficient transcription and mRNA export to NPC**. *EMBO J* 2007, **26**:4956-4965.

39. Mendjan S, Taipale M, Kind J, Holz H, Gebhardt P, Schelder M, Vermeulen M, Buscaino A, Duncan K, Mueller J *et al.*: **Nuclear pore components are involved in the transcriptional regulation of dosage compensation in *Drosophila***. *Mol Cell* 2006, **21**:811-823.

40. •• Vaquerizas JM, Suyama R, Kind J, Miura K, Luscombe NM, Akhtar A: **Nuclear pore proteins nup153 and megator define transcriptionally active regions in the *Drosophila* genome**. *PLoS Genet* 2010, **6**:e1000846.
This study identifies nucleoporins as a major class of global regulators of gene expression in *Drosophila melanogaster*.

41. Hutchison N, Weintraub H: **Localization of DNAase I-sensitive sequences to specific regions of interphase nuclei**. *Cell* 1985, **43**:471-482.

42. Ragoczy T, Bender MA, Telling A, Byron R, Groudine M: **The locus control region is required for association of the murine beta-globin locus with engaged transcription factories during erythroid maturation**. *Genes Dev* 2006, **20**:1447-1457.

43. Hewitt SL, High FA, Reiner SL, Fisher AG, Merkenschlager M: **Nuclear repositioning marks the selective exclusion of lineage-inappropriate transcription factor loci during T helper cell differentiation**. *Eur J Immunol* 2004, **34**:3604-3613.

44. Chubb JR, Boyle S, Perry P, Bickmore WA: **Chromatin motion is constrained by association with nuclear compartments in human cells**. *Curr Biol* 2002, **12**:439-445.

45. Marshall WF, Straight A, Marko JF, Swedlow J, Dernburg A, Belmont A, Murray AW, Agard DA, Sedat JW: **Interphase chromosomes undergo constrained diffusional motion in living cells**. *Curr Biol* 1997, **7**:930-939.

46. Rabut G, Doye V, Ellenberg J: **Mapping the dynamic organization of the nuclear pore complex inside single living cells**. *Nat Cell Biol* 2004, **6**:1114-1121.

47. •• Capelson M, Liang Y, Schulte R, Mair W, Wagner U, Hetzer MW: **Chromatin-bound nuclear pore components regulate gene expression in higher eukaryotes**. *Cell* 2010, **140**:372-383.
See annotation to Ref. [48••].

48. •• Kalverda B, Pickersgill H, Shloma VV, Fornerod M: **Nucleoporins directly stimulate expression of developmental and cell-cycle genes inside the nucleoplasm**. *Cell* 2010, **140**:360-371.
This study and Ref. [47••] are the first reports, together with Vaquerizas *et al.* Ref. [40••], describing the role of nucleoporins in transcription regulation in the nucleoplasm.

49. Bai XT, Gu BW, Yin T, Niu C, Xi XD, Zhang J, Chen Z, Chen SJ: **Trans-repressive effect of NUP98-PMX1 on PMX1-regulated c-FOS gene through recruitment of histone deacetylase 1 by FG repeats**. *Cancer Res* 2006, **66**:4584-4590.

50. Kasper LH, Brindle PK, Schnabel CA, Pritchard CE, Cleary ML, van Deursen JM: **CREB binding protein interacts with nucleoporin-specific FG repeats that activate transcription and mediate NUP98-HOXA9 oncogenicity**. *Mol Cell Biol* 1999, **19**:764-776.

51. Wang GG, Cai L, Pasillas MP, Kamps MP: **NUP98-NSD1 links H3K36 methylation to Hox-A gene activation and leukaemogenesis**. *Nat Cell Biol* 2007, **9**:804-812.

52. Brown CR, Kennedy CJ, Delmar VA, Forbes DJ, Silver PA: **Global histone acetylation induces functional genomic reorganization at mammalian nuclear pore complexes**. *Genes Dev* 2008, **22**:627-639.

53. •• Krull S, Dorries J, Boysen B, Reidenbach S, Magnius L, Norder H, Thyberg J, Cordes VC: **Protein Tpr is required for establishing nuclear pore-associated zones of heterochromatin exclusion**. *EMBO J* 2010, **29**:1659-1673.
This report identifies TPR protein as an essential determinant of the perinuclear organization, with a direct role in forming a morphologically distinct nuclear sub-compartment and delimiting heterochromatin distribution.

54. Laine JP, Singh BN, Krishnamurthy S, Hampsey M: **A physiological role for gene loops in yeast**. *Genes Dev* 2009, **23**:2604-2609.

55. Tan-Wong SM, French JD, Proudfoot NJ, Brown MA: **Dynamic interactions between the promoter and terminator regions of the mammalian BRCA1 gene**. *Proc Natl Acad Sci U S A* 2008, **105**:5160-5165.

56. Brickner JH, Walter P: **Gene recruitment of the activated INO1 locus to the nuclear membrane**. *PLoS Biol* 2004, **2**:e342.

57. •• Tan-Wong SM, Wijayatilake HD, Proudfoot NJ: **Gene loops function to maintain transcriptional memory through interaction with the nuclear pore complex**. *Genes Dev* 2009, **23**:2610-2624.

Here, myosin-like protein 1 (Mlp1) is shown to be important for the formation of gene loop structures required for the transcriptional memory.

58. Perkins KJ, Lusic M, Mitar I, Giacca M, Proudfoot NJ: **Transcription-dependent gene looping of the HIV-1 provirus is dictated by recognition of pre-mRNA processing signals**. *Mol Cell* 2008, **29**:56-68.

59. O'Reilly D, Greaves DR: **Cell-type-specific expression of the human CD68 gene is associated with changes in Pol II phosphorylation and short-range intrachromosomal gene looping**. *Genomics* 2007, **90**:407-415.

60. Ferraiuolo MA, Rousseau M, Miyamoto C, Shenker S, Wang XQ, Nadler M, Blanchette M, Dostie J: **The three-dimensional architecture of Hox cluster silencing**. *Nucleic Acids Res* 2010, **38**:7472-7484.

61. Halley JE, Kaplan T, Wang AY, Kobor MS, Rine J: **Roles for H2A.Z and its acetylation in GAL1 transcription and gene induction, but not GAL1-transcriptional memory**. *PLoS Biol* 2010, **8**:e1000401.

62. Light WH, Brickner DG, Brand VR, Brickner JH: **Interaction of a DNA zip code with the nuclear pore complex promotes H2A.Z incorporation and INO1 transcriptional memory**. *Mol Cell* 2010, **40**:112-125.

63. Brickner DG, Brickner JH: **Cdk phosphorylation of a nucleoporin controls localization of active genes through the cell cycle**. *Mol Biol Cell* 2010, **21**:3421-3432.

64. Hofmann WA, Stojiljkovic L, Fuchsova B, Vargas GM, Mavrommatis E, Philimonenko V, Kysela K, Goodrich JA, Lessard JL, Hope TJ *et al.*: **Actin is part of pre-initiation complexes and is necessary for transcription by RNA polymerase II**. *Nat Cell Biol* 2004, **6**:1094-1101.

65. Philimonenko VV, Zhao J, Iben S, Dingova H, Kysela K, Kahle M, Zentgraf H, Hofmann WA, de Lanerolle P, Hozak P *et al.*: **Nuclear actin and myosin I are required for RNA polymerase I transcription**. *Nat Cell Biol* 2004, **6**:1165-1172.

66. Ye J, Zhao J, Hoffmann-Rohrer U, Grummt I: **Nuclear myosin I acts in concert with polymeric actin to drive RNA polymerase I transcription**. *Genes Dev* 2008, **22**:322-330.

67. Dion V, Shimada K, Gasser SM: **Actin-related proteins in the nucleus: life beyond chromatin remodelers**. *Curr Opin Cell Biol* 2010, **22**:383-391.

68. Yoshida T, Shimada K, Oma Y, Kalck V, Akimura K, Taddei A, Iwahashi H, Kugou K, Ohta K, Gasser SM *et al.*: **Actin-related protein Arp6 influences H2A.Z-dependent and -independent gene expression and links ribosomal protein genes to nuclear pores**. *PLoS Genet* 2010, **6**:e1000910.

69. Titus LC, Dawson TR, Rexer DJ, Ryan KJ, Wente SR: **Members of the RSC chromatin-remodeling complex are required for maintaining proper nuclear envelope structure and pore complex localization**. *Mol Biol Cell* 2010, **21**:1072-1087.

70. Damelin M, Simon I, Moy TI, Wilson B, Komili S, Tempst P, Roth FP, Young RA, Cairns BR, Silver PA: **The genome-wide localization of Rsc9, a component of the RSC chromatin-remodeling complex, changes in response to stress**. *Mol Cell* 2002, **9**:563-573.

71. Wilson B, Erdjument-Bromage H, Tempst P, Cairns BR: **The RSC chromatin remodeling complex bears an essential fungal-specific protein module with broad functional roles**. *Genetics* 2006, **172**:795-809.

72. Bennett CB, Lewis LK, Karthikeyan G, Lobachev KS, Jin YH, Sterling JF, Snipe JR, Resnick MA: **Genes required for ionizing radiation resistance in yeast**. *Nat Genet* 2001, **29**:426-434.

73. Loeillet S, Palancade B, Cartron M, Thierry A, Richard GF, Dujon B, Doye V, Nicolas A: **Genetic network interactions among replication, repair and nuclear pore deficiencies in yeast**. *DNA Repair (Amst)* 2005, **4**:459-468.

74. • Nagai S, Dubrana K, Tsai-Pflugfelder M, Davidson MB, Roberts TM, Brown GW, Varela E, Hediger F, Gasser SM, Krogan NJ: **Functional targeting of DNA damage to a nuclear pore-associated SUMO-dependent ubiquitin ligase**. *Science* 2008, **322**:597-602.

This study shows a functional and physical relationship between the nuclear pore complex and the DNA repair pathway.

75. Pan X, Ye P, Yuan DS, Wang X, Bader JS, Boeke JD: **A DNA integrity network in the yeast *Saccharomyces cerevisiae***. *Cell* 2006, **124**:1069-1081.

76. Therizols P, Fairhead C, Cabal GG, Genovesio A, Olivo-Marin JC, Dujon B, Fabre E: **Telomere tethering at the nuclear periphery is essential for efficient DNA double strand break repair in subtelomeric region**. *J Cell Biol* 2006, **172**:189-199.

77. Oza P, Jaspersen SL, Miele A, Dekker J, Peterson CL: **Mechanisms that regulate localization of a DNA double-strand break to the nuclear periphery**. *Genes Dev* 2009, **23**:912-927.

78. Schober H, Ferreira H, Kalck V, Gehlen LR, Gasser SM: **Yeast telomerase and the SUN domain protein Mps3 anchor telomeres and repress subtelomeric recombination**. *Genes Dev* 2009, **23**:928-938.

79. Khadaroo B, Teixeira MT, Luciano P, Eckert-Boulet N, Germann SM, Simon MN, Gallina I, Abdallah P, Gilson E, Geli V *et al.*: **The DNA damage response at eroded telomeres and tethering to the nuclear pore complex**. *Nat Cell Biol* 2009, **11**:980-987.

80. Zimowska G, Aris JP, Paddy MR: **A Drosophila Tpr protein homolog is localized both in the extrachromosomal channel network and to nuclear pore complexes**. *J Cell Sci* 1997, **110(Pt 8)**:927-944.

81. Galy V, Gadal O, Fromont-Racine M, Romano A, Jacquier A, Nehrbass U: **Nuclear retention of unspliced mRNAs in yeast is mediated by perinuclear Mlp1**. *Cell* 2004, **116**:63-73.

82. Lee SH, Sterling H, Burlingame A, McCormick F: **Tpr directly binds to Mad1 and Mad2 and is important for the Mad1–Mad2-mediated mitotic spindle checkpoint**. *Genes Dev* 2008, **22**:2926-2931.

83. Lindsay ME, Plafker K, Smith AE, Clurman BE, Macara IG: **Npap60/Nup50 is a tri-stable switch that stimulates importin-alpha:beta-mediated nuclear protein import**. *Cell* 2002, **110**:349-360.

84. Dilworth DJ, Suprapto A, Padovan JC, Chait BT, Wozniak RW, Rout MP, Aitchison JD: **Nup2p dynamically associates with the distal regions of the yeast nuclear pore complex**. *J Cell Biol* 2001, **153**:1465-1478.

85. Menon BB, Sarma NJ, Pasula S, Deminoff SJ, Willis KA, Barbara KE, Andrews B, Santangelo GM: **Reverse recruitment: the Nup84 nuclear pore subcomplex mediates Rap1/Gcr1/Gcr2 transcriptional activation**. *Proc Natl Acad Sci U S A* 2005, **102**:5749-5754.