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Current Opinion in Cell Biology

Genome–nuclear lamina interactions and gene regulation

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The nuclear lamina, a filamentous protein network that coats the inner nuclear membrane, has long been thought to interact with specific genomic loci and regulate their expression. Molecular mapping studies have now identified large genomic domains that are in contact with the lamina. Genes in these domains are typically repressed, and artificial tethering experiments indicate that the lamina can actively contribute to this repression. Furthermore, the lamina indirectly controls gene expression in the nuclear interior by sequestration of certain transcription factors. A variety of DNA-binding and chromatin proteins may anchor specific loci to the lamina, while histone-modifying enzymes partly mediate the local repressive effect of the lamina. Experimental tools are now available to begin to unravel the underlying molecular mechanisms.

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Current Opinion in Cell Biology 2010, **22**:320–325

This review comes from a themed issue on
Nucleus and gene expression
Edited by Ana Pombo and Dave Gilbert

Available online 3rd May 2010

0955-0674/$ – see front matter

DOI 10.1016/j.ceb.2010.04.002

Introduction

The cell nucleus is enclosed by a double lipid bi-layer with interspersed nuclear pore complexes (NPCs) that facilitate selective nuclear-cytoplasmic exchange of macromolecules. In metazoans, the nucleoplasmic surface of the inner nuclear membrane (INM) is structurally supported by the nuclear lamina (NL), a filamentous meshwork consisting of specialized intermediate filament proteins named lamins. There are two types of lamins: B-type lamins are found in all cell types, whereas the A-type lamins are found only in differentiated cells [1,2]. Lamins interact with many other proteins, some of which are integral components of the INM [1,3]. A wide spectrum of human disorders has been linked to mutations in lamins or lamin-interacting proteins [4], illustrating the importance of the NL.

For decades it has been thought that the NL may act as a surface for the anchoring of specific DNA sequences, thereby providing a scaffold for the folding of chromosomes inside the nucleus. In addition, the NL may play an active role in the regulation of gene expression. Recent microscopy studies, gene-tethering approaches and the mapping of genome–NL interactions at molecular resolution have yielded new insights into these processes. In this review we discuss the possible roles of the NL in chromosome organization and transcriptional regulation, with emphasis on new data reported over the past two years.

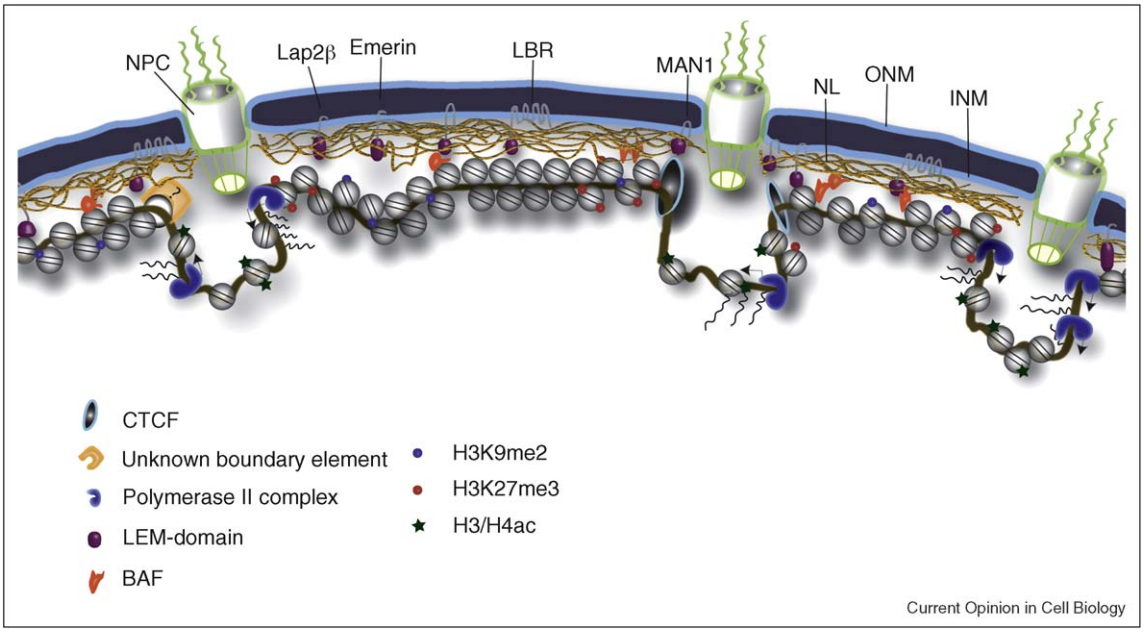
The genome in association with the NL and the NPC

Classic electron micrographs [5] and recent high-resolution light microscopy images of mammalian cell nuclei [6•] show that the NL tends to be in close contact with relatively compact chromatin, while NPCs are surrounded by much less, or decondensed, chromatin. Genome-wide mapping using the DamID technology has identified the regions of the genome that are in molecular contact with the NL in both human and fly cells [7,8•]. Human fibroblasts have more than 1300 of such genomic contact regions, which are named Lamina-associated domains (LADs). Human LADs are remarkably large genomic segments (0.1–10 Mb) and together harbor thousands of genes at a low gene-density. The vast majority of those genes have very low expression levels with only few active 'escaper' genes. Most LADs have sharp borders that are often marked by specific sequence elements, such as binding sites for the insulator protein CTCF [8•].

Recent data indicate that NPCs in metazoans also interact with specific genomic loci, as was previously found for budding yeast [9]. Molecular mapping studies have identified hundreds of sites in the *Drosophila* genome that are bound by NPC proteins [10–12]. In contrast to LADs, genes in association with NPCs are generally found active [9,10], or at least moderately transcribed [11]. Interestingly, a substantial pool of nuclear pore proteins freely diffuses and binds to genes located in the nuclear interior [11,12]. By a clever strategy with engineered NPC proteins, Kalverda *et al.* [11] managed to generate genome-wide maps that discriminate intranuclear interactions from NPC interactions at the nuclear periphery. This revealed that *bona fide* NPC-associated sequences are distinct from NL-associated regions, and primarily overlap with moderately active genes.

The molecular interaction maps for NL and NPC proteins offer an explanation for the sometimes confusing observations obtained by Fluorescence In Situ Hybridization (FISH) microscopy when correlating the nuclear

Figure 1



Cartoon model of genome–NL interactions in mammalian cells. NL-associated chromatin is mostly transcriptionally inactive and partially marked by specific histone modifications such as H3K9me2 and H3K27me3, while histone acetylation (H3/H4ac) and other 'active' modifications are depleted. LAD borders are demarcated by CTCF and possibly other specific proteins. NPCs form a microenvironment that is distinct from the NL. The LEM-domain is a protein domain shared by several transmembrane proteins of the INM. For simplicity, this cartoon leaves out much of the chromatin in the nuclear interior. Not all known NL-associated proteins are shown, and the cartoon is not to scale (LADs are typically larger than 100 kb). ONM, outer nuclear membrane.

radial position of genes to their expression status [13,14]. The molecular mapping results emphasize that NL and NPCs represent different microenvironments (Figure 1), which are difficult to resolve by conventional light microscopy. The possibility of NL 'microdomains' composed of different lamin subtypes [15] further emphasizes that the nuclear periphery is a heterogeneous structure.

Whether interacting with the NL or NPCs, loci that associate with the nuclear periphery typically do so in a stochastic manner. Even in a homogeneous cell population, the frequency of association is never found to be 100% [7,8•,11,14]. Partly, this may be attributed to intranuclear mobility of the chromatin fiber [16], and to some extent the folding of interphase chromosomes may have a stochastic component.

In addition, the organization of genes and chromosomes in the nucleus is dependent on the differentiation state of the cell. An extreme example of this are nuclei of rod cells in the retina of nocturnal animals. Here, the organization of chromatin is radially inverted, such that heterochromatin aggregates in the center of the nucleus and active euchromatin is located at the periphery. These inverted nuclei act as light-collecting lenses, thus enhancing the light sensitivity of rod cells [17••]. This fascinating anecdote illustrates the remarkable plasticity of nuclear architecture.

Mechanisms of genome–NL interactions

Do LADs adhere to the NL owing to specific biochemical interactions, or are they passively pushed towards the periphery because other chromosomal regions have a preference to be located in the nuclear interior? Interesting new computer simulations of chromosome polymer dynamics suggest that local differences in certain basic physical properties of the chromatin fiber, such as flexibility and thickness, may partly drive the peripheral location of heterochromatin by self-organization principles [18,19]. Yet, the NL does appear to play an active role in the nuclear organization of the genome by binding specific chromosomal regions. Indirect evidence comes from the observation that compacted chromatin is only touching the NL but not the neighboring NPCs [5,6•]. Passive brushing of chromatin against the NL is also difficult to reconcile with the sharply defined LAD structure and the presence of border elements that demarcate LADs [8•]. Furthermore, cells that lack Lamin B1 show abnormal positioning of some chromosomes [15,20], while cells from patients with a rare Lamin A mutation (causing Hutchinson Gilford Progeria Syndrome) have substantially reduced amounts of heterochromatin as judged from electron microscope images [21]. It is therefore likely that specific biochemical interactions between the NL and LADs help to organize chromosomes inside the nucleus.

A key question is how the NL interacts with specific genomic regions. Several DNA-binding factors physically interact with NL proteins [1,3,22] and are therefore good candidates to mediate specific genome–NL interactions. A notable candidate is the transcription factor Oct1, which binds to Lamin B1 and is present at the NL in a Lamin B1-dependent manner [23]. Oct1 recognition motifs are enriched within LAD sequences [8•], suggesting that Oct1 may help to tether LADs to the NL. Sequence-specific NL interactions are also illustrated by the recent identification of an 80 bp repeat sequence within a human subtelomeric region that is sufficient to localize an adjacent telomere to the NL in a CTCF and lamin A dependent fashion [24]. It is likely that additional sequence elements will be discovered that can be anchored to the NL via DNA-binding factors.

Besides 'hard-coded' sequence elements, local chromatin properties may also provide recognition sites for the NL. Lamins and INM proteins interact biochemically with histones and various chromatin proteins [1,3]. The histone modifications H3K9me2 and H3K27me3 in mammals are enriched at the nuclear periphery [14,25•] and are over-represented in LADs [8•,26]. However, microscopy studies of individual loci have so far not yielded direct evidence that these histone marks mediate NL interactions [25•,27], although more extensive investigation on this issue is needed. It is worth considering that the absence of activating histone marks (such as methylation of H3K4 and acetylation of several other histone lysines) may serve as a recognition cue for NL interactions. This notion is supported by the observation that treatment with trichostatin A, an inhibitor of histone deacetylases (HDACs), disrupts NL interactions genome-wide in *Drosophila* cells [7], and also dissociates some mammalian genes from the nuclear periphery [28].

Rebuilding genome–NL interactions after mitosis

During mitosis, phosphorylation of NPC-components and NL-components initiates the disassembly of the nucleus [29,30] and results into the dissociation of INM proteins and lamins from chromatin [31]. As cells need to progress through cell division for *de novo* NL–genome interaction to occur, the nuclear architecture is probably established during nuclear reassembly [32••,33••]. The molecular basis for the reassembly of the nuclear envelope at the end of mitosis is not understood in great detail, but a number of recent papers provide valuable insight in the order of events. At the onset of nuclear reassembly, BAF binds first to the telophase chromosomes at a distinct 'core-structure' followed by Lap2α and many – but not all – NL-associated proteins [34,35•]. Lamins bind to telophase chromosomes only after the core region is assembled. Lamin A binds to the core region, while Lamin B first localizes to the spindle pole to gradually associate with chromatin in a rather diffuse pattern [34,35•]. The core region itself stays devoid of the nuclear membrane until all NL-associated components have been docked to this structure [35•]. Many NL-associated proteins collectively contribute to reassembly of the nuclear envelope, as reducing the levels of individual components significantly slows down nuclear reassembly [36].

The recognition basis for the distribution of these components to telophase chromosomes is unknown, although non-specific DNA binding by NL-associated proteins appears to play a role [37]. It is unlikely that BAF recognizes the core-structure through sequence-specific DNA binding, as BAF binds to dsDNA in a sequence-independent manner [38]. Instead, BAF and other NL-associated components could be directed to the telophase chromosomes via interactions with distinct chromatin proteins. Given the rough similarities of the core region and interphase LADs (i.e., presence of NL-associated proteins and absence of most NPC components), it is tempting to speculate that the chromosomal regions in the telophase core region correspond to some LADs in interphase.

Gene regulation by the NL

Does the NL play an active role in gene regulation, or is it merely an innocent bystander? Microarray and *in situ* expression analyses have shown that the depletion of lamins and other NL proteins causes misregulation of hundreds of genes [20,23,39–41], as does expression of a lamin A mutant that causes premature aging in humans [42]. In *Drosophila*, the knockdown of the only B-type lamin causes derepression of a testis-specific gene cluster, together with the relocalization of this cluster towards the nuclear interior [43], strongly suggesting that the genes in this cluster are repressed via direct contact with the NL.

To investigate the impact of gene–NL interactions on transcription more directly, a number of laboratories have artificially tethered reporter genes (integrated in the genome) to the NL. While in two studies this resulted into partial repression of the reporter and some of the surrounding genes [33••,44••] virtually no effect on reporter expression was found in a third study [32••]. However, a similar set of tethering experiments in *Drosophila* by the Wallrath laboratory showed strong repression of one reporter gene in three different genomic integration sites, while a second reporter positioned in tandem was only repressed in two of the three integration sites (George Dialynas, Sean Speese, Vivian Budnik, Pamela K. Geyer and Lori L. Wallrath, personal communication[1], paper of special interest). Together, these studies indicate that

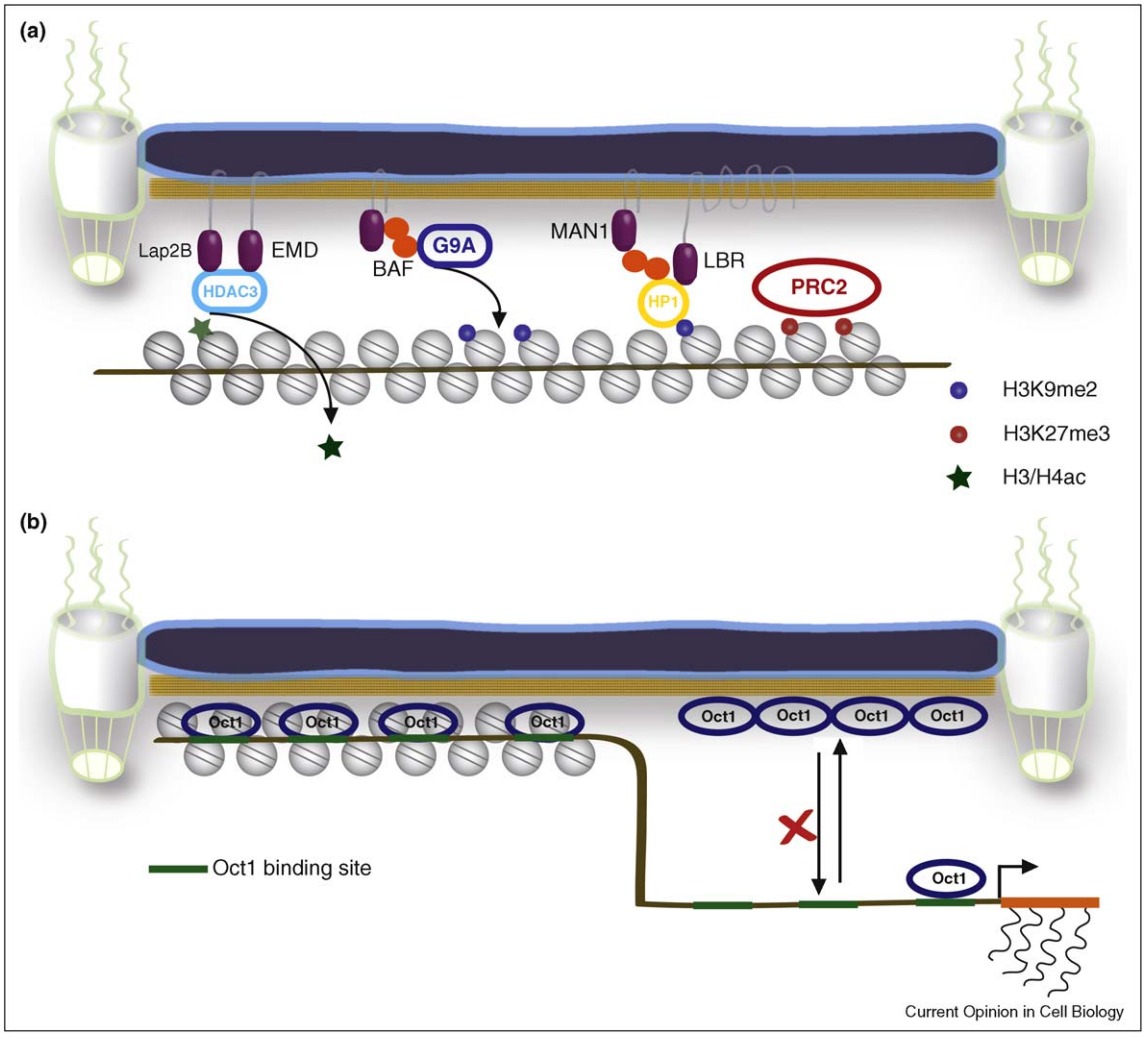
[1] This study reports, in analogy to mammalian laminopathies, that the expression of a N-terminal truncated form of Lamin A, causes muscle-defects in flies. Furthermore, the authors convincingly show, in an NL-targeting assay, that Lamin A is involved in gene-repression.

contact with the NL can contribute to gene silencing, yet the magnitude of the repressive effect depends on local chromatin context and regulatory sequences.

Interestingly, treatment with an HDAC inhibitor reverses the repression caused by NL-tethering [44••]. Histone deacetylation is therefore a likely contributor to gene repression at the NL. Consistently, histones in chromatin near the NL are normally hypo-acetylated [45], indicative of high local HDAC activity. Indeed, several NL-components interact with HDACs, including Lap2β and Emerin [46,47]. An attractive model, therefore is that the NL helps to repress genes in LADs partly by deacetylation of histones (Figure 2a).

A second histone modification that appears to be involved in gene regulation at the NL is H3K9me2. In human cells this modification was found to be enriched at the nuclear periphery [25•] possibly mediated by an interaction of BAF with G9a, the histone methyltransferase that is primarily responsible for dimethylation of H3K9 [48]. Chromatin immunoprecipitation data show that H3K9me2 occupies long stretches of the genome that substantially overlap with LADs [8•,26]. Knockout of G9a causes derepression of many late-replicating genes that tend to be positioned at the NL [25•]. Within the resolution of light microscopy, loss of G9a does not cause a significant relocation of the affected genes, suggesting that H3K9me2 is not required for genome–NL interactions, but

Figure 2



Models of regulatory interactions of the NL with chromatin and DNA-binding proteins. **(a)** Putative links between NL-associated chromatin and histone-modifying enzymes. G9a and HDACs interact with NL proteins [46–48] and may thereby locally dimethylate H3K9 and deacetylate histones in chromatin that is in close proximity, thus helping to repress gene activity near the NL. PRC2, Polycomb Repressive Complex 2, which methylates H3K27me3. **(b)** Hypothetical dual function of Oct1–NL interactions. Oct1 may anchor some LADs to the NL by binding simultaneously to Lamin B1 and to its binding motifs that are enriched in LAD sequences (*left*); at the same time, sequestering of Oct1 at the NL may prevent Oct1 from binding to its binding motifs at genes located in the nuclear interior (*right*) [23].

rather is needed for the repressive environment at the NL (Figure 2a).

The NL also contributes to gene regulation in indirect ways. For example, Oct1 can be sequestered away from its target genes by an interaction with Lamin B1. A number of genes involved in the oxidative stress response appear to be regulated through this mechanism. Both Oct1 and Lamin B1 null cells, show increased susceptibility to oxidative stress, which is probably due to the down-regulation of genes involved in this response [23]. Similar mechanisms involving sequestering by the NL have been reported for other transcription factors [22]. Note that Oct1 may have a dual partnership with the NL: on the one hand it may help to tether certain LADs to the NL, while at the same time the sequestration of Oct1 at the NL affects the expression of Oct1 target genes in the nuclear interior (Figure 2b).

Conclusions

The availability of new tools, such as molecular tethering methods, genome-wide mapping techniques, and subdiffraction light microscopy, has created exciting new opportunities to dissect the causal relationships among genome–NL interactions, interphase chromosome folding, and gene regulation in mammalian cells. A picture emerges in which the NL contributes to the spatial organization of the genome and helps to repress genes that are in close proximity. DNA-binding factors as well as chromatin components help to anchor LADs to the NL, and conversely the NL contributes to gene regulation by modulating chromatin and the activity of transcription factors.

Acknowledgements

We apologize to colleagues whose work we could not discuss owing to space constraints. We thank G. Filion, W. Meuleman, U. Braunschweig, and A. Pindyurin for helpful comments, and the M. Fornerod, M. Hetzer, A. Akhtar, and L. Wallrath labs for sharing unpublished results. Supported by an EMBO Long-term Fellowship to JK and an NWO-VICI grant to BvS.

References and recommended reading

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

- • of special interest
- •• of outstanding interest

1. Prokocimer M, Davidovich M, Nissim-Rafinia M, Wiesel-Motiuk N, Bar D, Barkan R, Meshorer E, Gruenbaum Y: **Nuclear lamins: key regulators of nuclear structure and activities**. *J Cell Mol Med* 2009, **14**:1059-1085.

2. 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.

3. Taddei A, Hediger F, Neumann FR, Gasser SM: **The function of nuclear architecture: a genetic approach**. *Annu Rev Genet* 2004, **38**:305-345.

4. Worman HJ, Fong LG, Muchir A, Young SG: **Laminopathies and the long strange trip from basic cell biology to therapy**. *J Clin Invest* 2009, **119**:1825-1836.

5. Belmont AS, Zhai Y, Thilenius A: **Lamin B distribution and association with peripheral chromatin revealed by optical sectioning and electron microscopy tomography**. *J Cell Biol* 1993, **123**:1671-1685.

6. • Schermelleh L, Carlton PM, Haase S, Shao L, Winoto L, Kner P, Burke B, Cardoso MC, Agard DA, Gustafsson MG *et al.*: **Subdiffraction multicolor imaging of the nuclear periphery with 3D structured illumination microscopy**. *Science* 2008, **320**:1332-1336.
Using three-dimensional structured illumination microscopy, the authors show, with unprecedented spatial resolution that the locale at the site of NPCs is devoid of lamins and heterochromatin.

7. 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.

8. • 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.
The authors show, at molecular resolution, that the genome in association with the NL is organized in remarkably large domains with sharp borders. These domains represent regions of very low transcriptional activity.

9. Akhtar A, Gasser SM: **The nuclear envelope and transcriptional control**. *Nat Rev Genet* 2007, **8**:507-517.

10. 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.

11. 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.

12. Capelson M, Liang Y, Schulate R, Mair W, Wagner U, Hetzer MW: **Chromatin-bound nuclear pore components regulate gene expression in higher eukaryotes**. *Cell* 2010, **140**:372-383.

13. Takizawa T, Meaburn KJ, Misteli T: **The meaning of gene positioning**. *Cell* 2008, **135**:9-13.

14. Luo L, Gassman KL, Petell LM, Wilson CL, Bewersdorf J, Shopland LS: **The nuclear periphery of embryonic stem cells is a transcriptionally permissive and repressive compartment**. *J Cell Sci* 2009, **122**:3729-3737.

15. Shimi T, Pfleghaar K, Kojima S, Pack CG, Solovei I, Goldman AE, Adam SA, Shumaker DK, Kinjo M, Cremer T *et al.*: **The A- and B-type nuclear lamin networks: microdomains involved in chromatin organization and transcription**. *Genes Dev* 2008, **22**:3409-3421.

16. Kumaran RI, Thakar R, Spector DL: **Chromatin dynamics and gene positioning**. *Cell* 2008, **132**:929-934.

17. •• Solovei I, Kreysing M, Lanctot C, Kosem S, Peichl L, Cremer T, Guck J, Joffe B: **Nuclear architecture of rod photoreceptor cells adapts to vision in mammalian evolution**. *Cell* 2009, **137**:356-368.
This remarkable study shows that the nuclear architecture of nocturnal rod photoreceptor cells is inverted, such that heterochromatin aggregates in the center of the nucleus and euchromatin is located at the periphery. These inverted nuclei act as light-collecting lenses, thus enhancing the light sensitivity of rod cells.

18. Cook PR, Marenduzzo D: **Entropic organization of interphase chromosomes**. *J Cell Biol* 2009, **186**:825-834.

19. de Nooijer S, Wellink J, Mulder B, Bisseling T: **Non-specific interactions are sufficient to explain the position of heterochromatic chromocenters and nucleoli in interphase nuclei**. *Nucleic Acids Res* 2009, **37**:3558-3568.

20. Malhas A, Lee CF, Sanders R, Saunders NJ, Vaux DJ: **Defects in lamin B1 expression or processing affect interphase chromosome position and gene expression**. *J Cell Biol* 2007, **176**:593-603.

21. Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB, Gruenbaum Y, Khuon S, Mendez M, Varga R *et al.*: **Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome**. *Proc Natl Acad Sci U S A* 2004, **101**:8963-8968.

22. Heessen S, Fornerod M: **The inner nuclear envelope as a transcription factor resting place**. *EMBO Rep* 2007, **8**:914-919.

23. Malhas AN, Lee CF, Vaux DJ: **Lamin B1 controls oxidative stress responses via Oct-1**. *J Cell Biol* 2009, **184**:45-55.

24. Ottaviani A, Schluth-Bolard C, Rival-Gervier S, Boussouar A, Rondier D, Foerster AM, Morere J, Bauwens S, Gazzo S, Callet-Bauchu E *et al.*: **Identification of a perinuclear positioning element in human subtelomeres that requires A-type lamins and CTCF**. *EMBO J* 2009, **28**:2428-2436.

25. • Yokochi T, Poduch K, Ryba T, Lu J, Hiratani I, Tachibana M, Shinkai Y, Gilbert DM: **G9a selectively represses a class of late-replicating genes at the nuclear periphery**. *Proc Natl Acad Sci U S A* 2009, **106**:19363-19368.
A conditional knockout of G9A in ESC and NPC cells, results in a loss of H3K9 dimethylation at the nuclear periphery and the derepression of generally late-replicating genes. Remarkably, derepression does not result in a change in replication timing, nor does it cause re-positioning of a small representative group of genes away from the nuclear periphery.

26. Wen B, Wu H, Shinkai Y, Irizarry RA, Feinberg AP: **Large histone H3 lysine 9 dimethylated chromatin blocks distinguish differentiated from embryonic stem cells**. *Nat Genet* 2009, **41**:246-250.

27. Williams RR, Azuara V, Perry P, Sauer S, Dvorkina M, Jorgensen H, Roix J, McQueen P, Misteli T, Merkenschlager M *et al.*: **Neural induction promotes large-scale chromatin reorganisation of the Mash1 locus**. *J Cell Sci* 2006, **119**:132-140.

28. 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.

29. Burke B, Ellenberg J: **Remodelling the walls of the nucleus**. *Nat Rev Mol Cell Biol* 2002, **3**:487-497.

30. Foisner R: **Cell cycle dynamics of the nuclear envelope**. *ScientificWorldJournal* 2003, **3**:1-20.

31. Prunuske AJ, Ullman KS: **The nuclear envelope: form and reformation**. *Curr Opin Cell Biol* 2006, **18**:108-116.

32. •• Kumaran RI, Spector DL: **A genetic locus targeted to the nuclear periphery in living cells maintains its transcriptional competence**. *J Cell Biol* 2008, **180**:51-65.
Positioning of a reporter to the NL leaves the transcription of a reporter-gene unaltered, thus providing evidence that the NL is not incompatible with transcriptional activity.

33. •• Reddy KL, Zullo JM, Bertolino E, Singh H: **Transcriptional repression mediated by repositioning of genes to the nuclear lamina**. *Nature* 2008, **452**:243-247.
Artificial tethering to the INM results in the accumulation of lamins and INM components to the site of a reporter construct and can result in transcriptional repression. Interestingly, re-positioning of the reporter requires a round of cell division.

34. Dechat T, Gajewski A, Korbei B, Gerlich D, Daigle N, Haraguchi T, Furukawa K, Ellenberg J, Foisner R: **LAP2alpha and BAF transiently localize to telomeres and specific regions on chromatin during nuclear assembly**. *J Cell Sci* 2004, **117**:6117-6128.

35. • Haraguchi T, Kojidani T, Koujin T, Shimi T, Osakada H, Mori C, Yamamoto A, Hiraoka Y: **Live cell imaging and electron microscopy reveal dynamic processes of BAF-directed nuclear envelope assembly**. *J Cell Sci* 2008, **121**:2540-2554.
This electron and light microscopy study reveals the presence of a core region at telophase chromosomes that consists of numerous NL-associated proteins. Intriguingly, this region is in close proximity and dependent on the spindle microtubules.

36. Anderson DJ, Vargas JD, Hsiao JP, Hetzer MW: **Recruitment of functionally distinct membrane proteins to chromatin mediates nuclear envelope formation in vivo**. *J Cell Biol* 2009, **186**:183-191.

37. Ulbert S, Platani M, Boue S, Mattaj IW: **Direct membrane protein–DNA interactions required early in nuclear envelope assembly**. *J Cell Biol* 2006, **173**:469-476.

38. Bradley CM, Ronning DR, Ghirlando R, Craigie R, Dyda F: **Structural basis for DNA bridging by barrier-to-autointegration factor**. *Nat Struct Mol Biol* 2005, **12**:935-936.

39. Frock RL, Kudlow BA, Evans AM, Jameson SA, Hauschka SD, Kennedy BK: **Lamin A/C and emerin are critical for skeletal muscle satellite cell differentiation**. *Genes Dev* 2006, **20**:486-500.

40. Vergnes L, Peterfy M, Bergo MO, Young SG, Reue K: **Lamin B1 is required for mouse development and nuclear integrity**. *Proc Natl Acad Sci U S A* 2004, **101**:10428-10433.

41. Tang CW, Maya-Mendoza A, Martin C, Zeng K, Chen S, Feret D, Wilson SA, Jackson DA: **The integrity of a lamin-B1-dependent nucleoskeleton is a fundamental determinant of RNA synthesis in human cells**. *J Cell Sci* 2008, **121**:1014-1024.

42. Scaffidi P, Misteli T: **Lamin A-dependent misregulation of adult stem cells associated with accelerated ageing**. *Nat Cell Biol* 2008, **10**:452-459.

43. Shevelyov YY, Lavrov SA, Mikhaylova LM, Nurminsky ID, Kulathinal RJ, Egorova KS, Rozovsky YM, Nurminsky DI: **The B-type lamin is required for somatic repression of testis-specific gene clusters**. *Proc Natl Acad Sci U S A* 2009, **106**:3282-3287.

44. •• Finlan LE, Sproul D, Thomson I, Boyle S, Kerr E, Perry P, Ylstra B, Chubb JR, Bickmore WA: **Recruitment to the nuclear periphery can alter expression of genes in human cells**. *PLoS Genet* 2008, **4**:e1000039.
This study reports that the artificial tethering of two genomic regions to the INM results in the suppression of some, but not all genes. Inhibition of histone deacetylation reverses the repressive effect indicating a role for HDACs in gene regulation at the NL.

45. Sadoni N, Langer S, Fauth C, Bernardi G, Cremer T, Turner BM, Zink D: **Nuclear organization of mammalian genomes. Polar chromosome territories build up functionally distinct higher order compartments**. *J Cell Biol* 1999, **146**:1211-1226.

46. Somech R, Shaklai S, Geller O, Amariglio N, Simon AJ, Rechavi G, Gal-Yam EN: **The nuclear-envelope protein and transcriptional repressor LAP2beta interacts with HDAC3 at the nuclear periphery, and induces histone H4 deacetylation**. *J Cell Sci* 2005, **118**:4017-4025.

47. Holaska JM, Wilson KL: **An emerin ''proteome'': purification of distinct emerin-containing complexes from HeLa cells suggests molecular basis for diverse roles including gene regulation, mRNA splicing, signaling, mechanosensing, and nuclear architecture**. *Biochemistry* 2007, **46**:8897-8908.

48. Montes de Oca R, Shoemaker CJ, Gucek M, Cole RN, Wilson KL: **Barrier-to-autointegration factor proteome reveals chromatin-regulatory partners**. *PLoS One* 2009, **4**:e7050.