



# THE UNIVERSITY *of* EDINBURGH

## Edinburgh Research Explorer

### The epigenetics of nuclear envelope organization and disease

**Citation for published version:**

Schirmer, EC 2008, 'The epigenetics of nuclear envelope organization and disease' Mutation research, vol. 647, no. 1-2, pp. 112-21. DOI: 10.1016/j.mrfmmm.2008.07.012

**Digital Object Identifier (DOI):**

[10.1016/j.mrfmmm.2008.07.012](https://doi.org/10.1016/j.mrfmmm.2008.07.012)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Peer reviewed version

**Published In:**

Mutation research

**General rights**

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

**Take down policy**

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.



## **The Epigenetics of Nuclear Envelope Organization and Disease**

**Eric C. Schirmer**

*Wellcome Trust Centre for Cell Biology, University of Edinburgh, Edinburgh, EH9 3JR, UK*

Corresponding author:

Eric Schirmer ([e.schirmer@ed.ac.uk](mailto:e.schirmer@ed.ac.uk))

Wellcome Trust Centre for Cell Biology

University of Edinburgh, Kings Buildings

Michael Swann Building, Room 5.22

Edinburgh, EH9 3JR, UK

Tel.: +441316507075

fax: +441316507360

### **Abstract**

Mammalian chromosomes and some specific genes have non-random positions within the nucleus that are tissue-specific and heritable. Work in many organisms has shown that genes at the nuclear periphery tend to be inactive and altering their partitioning to the interior results in their activation. Proteins of the nuclear envelope can recruit chromatin with specific epigenetic marks and can also recruit silencing factors that add new epigenetic modifications to chromatin sequestered at the periphery. Together these findings indicate that the nuclear envelope is a significant epigenetic regulator. The importance of this function is emphasized by observations of aberrant distribution of peripheral heterochromatin in several human diseases linked to mutations in NE proteins. These debilitating inherited diseases range from muscular dystrophies to the premature aging progeroid syndromes and the heterochromatin changes are just one early clue for understanding the molecular details of how they work. The architecture of the nuclear envelope provides a unique environment for epigenetic regulation and as such a great deal of research will be required before we can ascertain the full range of its contributions to epigenetics.

**Keywords:** nuclear envelope; lamin; inner nuclear membrane protein; epigenetics; position effect; heterochromatin.

### 1. Introduction

Structurally, the nuclear envelope (NE) is a double membrane system continuous with the endoplasmic reticulum (ER) [1]. The outer nuclear membrane, like the ER, is studded with ribosomes yet also appears to contain some unique proteins (Fig. 1). The membrane curves around the outside of the nuclear pore complexes (NPCs), which regulate directional transport of soluble macromolecules in and out of the nucleus [2]. The inner nuclear membrane (INM) contains a set of unique proteins and also some proteins common to other organellar membranes [3]. Directly underlying the membrane in higher eukaryotes (but not yeast) is a polymer of intermediate filament lamin proteins [4], which is connected to the membrane by several of the unique INM proteins (Fig. 1).

Functionally the NE first appeared over a billion years ago as the defining characteristic of eukaryotes. The obvious importance of its barrier function, protecting the genetic contents of the cell from the wide-ranging enzymatic activities in the cytoplasm, precluded thoughts of additional functions for many years. However, as for epigenetics, our view of the NE and its functions has evolved considerably in the past few years. A mechanical stability role for lamins in nuclear shape was recently given strong experimental support *in vivo* [5-8]. Lamins and INM proteins can also influence replication [9-11], transcription [12-14] and signaling cascades [15-18].

The many links between the NE and gene regulation complicate the task of discerning its role in epigenetic regulation. For example, in mammals, one characterized method of NE transcriptional regulation is sequestration of the retinoblastoma protein (pRb) by lamins: this prevents release of E2F-transcription factors from pRb, thus blocking activation of their targets. This does not qualify as an epigenetic mechanism, but such NE functions could be the true mechanism behind an effect that is misinterpreted as gene silencing at the periphery. Despite the many studies that will be discussed here, it remains unclear whether the nuclear envelope silences genes merely by bringing them into an environment rich with other silenced genes (position effect), by actively modifying peripheral chromatin to a silent configuration or by preferentially recruiting already silenced chromatin.

## Nuclear Envelope Epigenetics

It is also unclear in most cases whether genes and/ or modifying factors are directly tethered to the NE or simply in the environment of the periphery. Finally, it is important to keep in mind when thinking of these issues that while no data clearly demonstrate silencing through steric effects from tethering to the NE, no studies clearly show that this does not play a role in silencing.

### **2. Gene Silencing at the Nuclear Periphery**

Early studies of transcriptional activation in many organisms inferred a connection between inactive genes and the darker staining areas of dense chromatin observed under the electron microscope that was referred to as heterochromatin [19]. In particular the heterochromatin at the periphery of resting lymphocytes was noted to diminish upon activation [20]. Heterochromatin has now been re-defined in the context of epigenetics as inactive or silent chromatin based on histone and DNA modifications [21,22]. How well the denser chromatin observed by electron microscopy correlates with these epigenetic marks has not been investigated, but the amount of nucleic acid in the darker-staining chromatin is surprisingly variable [23], suggesting that in some cases the density is achieved with proteins. Dense chromatin is observed at centromeres and nucleoli in relatively standard amounts, while that at the NE has distinctive patterns and amounts in different cell types, suggesting that it may play a role in gene regulation throughout differentiation.

That chromatin is generally transcriptionally silent at the periphery was subsequently confirmed in a study that identified genes located at the periphery. Genes in contact with lamins in *Drosophila melanogaster* tissue culture cells were isolated using a trick where lamins were fused to the *Escherichia coli* DNA adenine methyltransferase (DAM) and the uniquely methylated DNA in contact with lamins was isolated, labeled and used to probe whole-genome microarrays. This revealed an enrichment of late replicating DNA lacking active histone modifications at the periphery [24]. This is consistent with previous observations that late-replicating DNA tends to be at the periphery from bromodeoxyuridine (BrdU) pulse chase experiments [25]. A subsequent study fusing DAM to Suppressor of

## Nuclear Envelope Epigenetics

Under-Replication (SuUR), a *Drosophila* protein associated with heterochromatin, found considerable overlap with the genes identified as associating with lamins [26].

Co-immunoprecipitation of proteins associated with other abundant NE proteins further confirms the bias at the periphery for heterochromatin. For example mass spectrometric analysis of chromatin associated with NPC protein nucleoporin 93 (Nup93) in yeast [27] and the INM protein lamin B-receptor (LBR) in mammalian cells [28] revealed principally heterochromatic/ silencing modifications.

### **3. Translocation of Genes To and From the Nuclear Periphery**

#### *3.1. Original studies in yeast*

Although yeast do not have visible heterochromatin by electron microscopy, they provided the first molecular observations supporting NE silencing in that the Sir silencing proteins exhibited partial concentration in telomeric foci at the nuclear periphery [29,30]. This followed on work showing that inserting genes close to yeast telomeres results in their silencing in a process involving Sir proteins [31,32]. Soon afterwards it was shown that tethering a reporter gene to a nuclear membrane protein resulted in silencing of the reporter [33]. Together these findings suggested a position effect model whereby targeting genes to the silencing factor-rich environment of the nuclear periphery results in their silencing.

Several focused studies in both yeast and mammalian cells on telomere tethering to the periphery appeared to support this model. Ku and Mlp proteins in yeast were found to be required for peripheral telomere localization [34-36] and mutations in these proteins resulted in derepression of silenced genes [35,37,38]. The Mlp proteins are homologs of the mammalian Tpr, which is the outermost nucleoplasmic component of the NPC and gave the same effect when knocked down [36]. This resulted in speculation that silencing at the periphery might be specifically mediated by NPCs; however in yeast Sir4 interacts with a nuclear membrane protein Esc1 in areas that are distinct from telomeres [39], indicating that silencing is a general property of the periphery.

## Nuclear Envelope Epigenetics

These studies also attempted to address the question of whether recruitment to the periphery silences chromatin in a heritable manner. Derepression of reporters in yeast upon deletion of NPC proteins involved in tethering telomeres argued that silencing required NE/NPC association [35,38]. However, deletion of the NPC proteins also resulted in a redistribution of Sir3p fused to green fluorescent protein [38]; thus derepression could be due to secondary consequences of NPC disruption, rather than simply relocation away from the periphery. Another report found that breaking the connection to the NE did not derepress the silent reporter [40], arguing that silencing results from changes to the reporter chromatin itself rather than being a consequence of the repressive environment of the periphery. As each study used different artificial experimental systems, this question remains unanswered in yeast and it may differ in mammalian cells.

### *3.2. Genes of higher eukaryotes undergo spatial regulation*

The yeast studies relied heavily on genetics and artificial reporters as the small size of the yeast nucleus does not allow high-resolution visual analysis. The larger nucleus of higher eukaryotes enables high-resolution analysis of nuclear positioning/ re-positioning. The relevance of nuclear positioning in gene regulation is underscored by observations of non-random localization of endogenous genes in *Drosophila* and mammalian nuclei and the influence of localization on their activity. In *Drosophila* several individual gene loci were observed to have conserved proximity to the NE [41]. Another interesting observation in *Drosophila* was that the suppressor of Hairy-wing [su(Hw)] protein that binds to the *gypsy* insulator and also the *gypsy* sequences themselves accumulate primarily at the nuclear periphery [42]. Insulators are DNA sequences that can protect a transgene from repression due to position effects if the transgene is inserted into a generally repressive environment. At the same time they can also block activity of an enhancer when inserted between it and the gene it activates [43]. Thus they can insulate a gene from propagation of surrounding epigenetic marks. The finding that *gypsy* and su(Hw) accumulate at the periphery was a major step in determining that NE positioning has a role in chromatin regulation.

## Nuclear Envelope Epigenetics

In mammalian cells chromosomes achieve defined positions within the 3D-framework of the nucleus: the relatively inactive gene-poor chromosome 18 tends to be located at the periphery while the much more active and gene-rich chromosome 19 tends to be internal [44]. Centromeres [45], and telomeres [46,47] have all been found at the NE in specific cell types and/ or cell cycle stages.

The number of individual genes whose intranuclear position has been determined by FISH is quite limited, but some of those tested appear to be regulated in part by positioning at the periphery. The immunoglobulin heavy chain *IgH* locus remains tethered to the nuclear periphery in early lymphocyte lineages but moves to the nuclear interior preceding the initiation of V(D)J recombination [48]. Among other genes regulated by peripheral association are the *Mash1* (*Ascl1*) gene that moves away from the periphery when it needs to be activated in neural development [49], a transcription factor locus in T helper cells that needs to be repressed during stages of differentiation [50] and the cystic fibrosis transmembrane conductance regulator (CFTR) gene [51]. In all cases what proteins tether the locus to the NE and how these connections are broken remains unresolved.

### 3.3. Directed localization of reporters to the NE in higher eukaryotes

It was expected that revisiting the artificial tethering of genes to the NE in mammalian cells would further elaborate on the mechanisms uncovered in yeast. However, the mechanisms may be distinct as higher eukaryotes differ from yeast in having a dense and highly stable filamentous lamin polymer connected to the INM that could in theory amplify a silencing position effect due to steric constraints. Indeed transgenes located near the nuclear periphery in mammalian cells have been shown to be less mobile than those residing in more internal positions [52], despite the fact that soluble molecules can travel quickly through such environments [53]. Furthermore, some of the chromatin is directly apposed to the lamina in both insect and mammalian cells [54,55] and associations are retained after extraction [56]. A role for specific lamins in tethering chromosome 18 to the periphery is supported by observations that the whole chromosome moves away from the periphery in lamin B1 knockout cells with resultant gene derepression [57].



## Nuclear Envelope Epigenetics

To get further at the molecular mechanism behind NE silencing, three elegant studies this year in mammalian cells used different systems for inducible tethering of genes directly to the NE [58-60]. All three studies used cell lines in which bacterial lac operator (LacO) repeat sequences were inserted into the mammalian genome in a locus that was not typically close to the NE and these cells were then transfected with lac repressor (LacI) fused to a reporter alone or to a reporter and different NE proteins (Fig. 2A): lamin B1 [59] and the INM proteins emerin [60] and the lamina-associated polypeptide LAP2 $\beta$  [58]. Two of the studies had a selectable marker inserted in the transgene array and both found that transcription of this reporter was reduced when the locus was at the periphery [58,60]. These systems allowed testing for the heritability of silencing as treatment of the cells with IPTG (isopropyl  $\beta$ -D-1-thiogalactopyranoside) disrupts the LacO-LacI binding and releases the locus from the periphery. The result of disrupting peripheral tethering was restoration of activity to the genes that had been silenced at the periphery in both studies [58,60]. One of the studies further found that many surrounding genes were repressed when the locus was at the periphery; however the pattern of gene regulation effected by the change in position was complex with some genes being downregulated and other genes unaffected [58]. If the environment of the periphery was generally repressive it could be due to a high concentration of general silencing factors or steric effects. For the environment of the periphery to repress only certain genes argues that a group of transcriptional repressors that have restricted targets are concentrated in this environment. The transcriptional repressors germ cell-less, Btf and Lmo7, each of which has target gene specificity, have been shown to bind variously to emerin and LAP2 $\beta$  [12,61-63]. Moreover germ cell-less was further shown to mediate specific repression of E2F-regulated genes when LAP2 $\beta$  was overexpressed [12,61]. Thus the use of emerin and LAP2 $\beta$  to mediate tethering to the periphery may have artificially repressed certain genes through recruitment of these transcriptional repressors. In one study the amino-terminus of emerin was deleted to minimize this criticism [60]; however the deleted region only partly overlaps with the binding site on emerin for germ cell-less [61], so this was probably not sufficient.

Gene repression was not observed in the third study when the locus was at the periphery; however the reporter system was quite different. In this case the reporter gene was under control of a strongly inducible promoter that could potentially overcome repressive effects of the periphery and a lamin B1-LacI fusion was used instead of the emerin and LAP2B fusions that, as noted above, could recruit transcriptional repressors [59]. Furthermore, the reporter gene contained MS2-binding sequences that allowed live visualization of its transcription with a fluorescent protein fusion to MS2 that bound to the mRNA [59]. Whether the locus was at the nuclear interior or the periphery the decondensation of the LacO spot and appearance of reporter-bound mRNA was the same, suggesting that gene repression did not occur. Therefore, the question of whether/ how tethering a locus to the periphery directly results in its repression remains unresolved.

### *3.4. Affinity tethering of chromatin to the NE*

In all three studies movement to the periphery was never observed during interphase, but required the cells to go through mitosis. During NE reassembly at the end of mitosis many INM proteins bind early to mitotic chromosomes [64,65]. Thus in the relatively mobile mitotic phase the chromosomes/ LacO array must sample their environment for higher affinity binding sites (LacI-NE protein fusions).

The use of higher affinity binding likely also functions to direct particular endogenous genes/ chromosomes to the periphery, but the proteins that tether them to the periphery have not been determined with the exception of Ku, Mlp/Tpr and SUN protein involvement in telomeric localization (shown in both yeast and mammalian cells) [34-36,46,47] and lamin B1 in chromosome 18 localization in human cells [57]. It is possible that both general and specific interactions are involved for different types of chromatin and for individual genes. Several nuclear envelope proteins interact with chromatin proteins in both yeast (see above) and mammalian cells (reviewed in [66]). In mammalian cells lamins bind histones H2A/H2B [67] while the INM protein lamin B receptor (LBR) can bind histones H3/H4 [68]. LBR can also bind heterochromatin, directly binding heterochromatin protein 1 (HP1) alpha and gamma [69] and preferentially binding histone H3 with the silent lysine 9 tri-

methylation (H3K9Me3) mark (Fig. 1) [28,68]. A higher affinity of HP1 for INM proteins compared to partners in other nuclear locations has not been directly tested, but might be inferred from observations that microinjected HP1 $\alpha$  accumulated at the periphery before eventually being distributed to other nuclear locations [70]. Barrier-to-autointegration factor (BAF), which binds several mammalian INM proteins [71,72], in turn binds to histone H3 and linker histone H1 [73]; however, it does not appear to show any preference for association with modified histones such as H3K9Me3 [74]. Nonetheless BAF might be considered an epigenetic regulator because it can crosslink DNA/histones [75] (Fig. 1).

The identification of specific histones as binding to lamins raises the question of whether other histone variants might have higher affinity for NE proteins. In yeast *INO1* and *GALI* genes were found to move to the periphery upon transcriptional inactivation. Concomitant with the relocalization was the replacement of histones with the histone variant H2A.Z, that is also found at promoters but has additionally been reported as a silencing factor [76]. This served as a mechanism for retaining memory of previous transcriptional activation as *GALI* at the periphery was activated faster than longer repressed *GALI* genes that were located in the interior of the nucleus. The tethering of *INO1* to the nuclear periphery required both H2A.Z [77] and the integral membrane protein Scs2p [78], suggesting that H2A.Z may have a higher affinity for Scs2p than other histones although this has not been tested. In this light it is interesting that unique peptides for histone H2A.Y and H1.5 were identified in proteomic studies of the mammalian NE, suggesting that these might have higher affinity for the lamina than other histone subtypes though this also has yet to be directly tested [79].

#### **4. Activation of Genes at the Nuclear Periphery**

While most studies have focused on NE silencing, association with the nuclear periphery has also been associated with transcriptional activation. As mentioned above (section 2) the amount of dense peripheral chromatin varies in different mammalian cell types. Brain cells tend to have very little dense peripheral chromatin and the proteolipid protein (PLP) gene undergoes the transition from inactive to active while remaining at the

## Nuclear Envelope Epigenetics

periphery during oligodendrocyte differentiation [80]. A similar effect was observed for the interferon- $\gamma$  locus [50] and the breast cancer ERBB-2 and osteogenesis collagen type 1 alpha 1 (COL1A1) loci are active when at the NE [81,82].

The yeast NE can also activate genes. Certain genes located proximal to NPCs are optimally activated at the periphery due to recruitment of transcription factors to these sites [83,84]. The ability of the NPC to both repress and activate genes may at least in part be due to interactions with insulator DNA sequences like the *Drosophila gypsy* sequences mentioned above (section 3.2). As genes flanked by such sequences are protected from the effects of nearby silencing or activating marks on chromatin, this function has also been referred to as “boundary activity”. Several NPC proteins were found to be able to function in insulator/boundary activity using a very creative assay system [85]. In the boundary assay (Fig. 2B) a transgene was constructed in which two reporter genes were placed within a partially depressed mating type locus with DNA sequences flanking that interact specifically with the DNA binding domain of the Gal4p transcription factor. Proteins were fused to the Gal4p DNA binding domain protein to screen for those that, when targeted to the specific flanking sequences, would be able to keep the reporter gene between them active when the second reporter was shut off due to propagation of silencing from the mating locus [85]. This screen identified the NPC-associated proteins Nup2p, Nup60p, Mlp1/2p and the Ran-GTP exchange factor Prp20p as being important for the formation of boundary activity in yeast [85,86]. Prp20p binds chromatin and in particular the H2A.Z (also called Htz1p) variant of histone H2A that is loaded by the SWR-C chromatin-remodeling complex and reported to be often associated with silenced chromatin [76]. Mass spectrometric analysis of nucleosomes associated with Prp20p and H2A.Z showed hypoacetylation on histone H4 at K5 and K8 considered to mark silent chromatin, but only moderately reduced acetylation (compared to total chromatin) at K12 and K16 that would be considered to mark active chromatin [87]. This combination of opposing epigenetic marks is consistent with an intermediate “poised” state and thus with boundary activity.

Consistent with the yeast role of NPCs in recruiting transcription factors and boundary elements, genome-wide analysis of DNA that had been co-immunoprecipitated with NPC components in yeast indicated an overall enrichment in transcriptionally active genes [88]. This contrasts with the favoring of silent marks on certain specific mammalian NPC proteins such as Nup93 [27], suggesting a division of labor within the NPC between silencing and activating functions, though there might also be differences between organisms.

### **5. De Novo Modification of Histones at the NE**

For the endogenous loci that have been shown to move between the periphery and interior of the nucleus, the chromatin modifications at the periphery differ from those in the interior. The *Mash1* locus involved in mammalian neurogenesis is located at the periphery in ES cells, replicates late and has some histone modifications characteristic of silenced chromatin and few active marks [49]. After *Mash1* moves to the interior in neurally committed cells the timing of locus replication switches to early and histone modifications consistent with active chromatin predominate (Table 1; [49]). However, as the movement in these systems is not subject to simple experimental regulation it is not possible to determine if the change in histone modifications is determined by the different environments or is a prerequisite for affinity-directed movement of the locus to the different environment.

This distinction was clear in the LacO systems as locus movement was directed by a purely artificial affinity mechanism. Differences in histone modifications were observed such that histone H4 acetylation was reduced when the locus was at the periphery [60]. Thus the more repressive environment at the periphery must contain enzymes that deacetylate histones. This was previously shown in the case of LAP2 $\beta$ , where a 2-hybrid screen identified histone deacetylase 3 (HDAC3) as a binding partner [13]. HDAC3 mediates H4 deacetylation, and is linked to heterochromatic, transcriptionally inactive genomic regions. Thus recruitment of HDAC3 to the periphery by LAP2 $\beta$  can silence genes that come into contact with the periphery [13]. Interestingly, treatment with HDAC3 inhibitors had little effect on NE-directed gene repression in the LacO system that used LAP2 $\beta$  to tether the locus to the

## Nuclear Envelope Epigenetics

periphery [58], suggesting that steric constraints at the periphery or specific repressors play a greater role than recruitment to an environment rich with silencing histone deacetylases.

NE proteins can directly modify histones for activation as well as repression. One of the proteins identified in a proteomic analysis of mammalian NEs, NET43/ hALP, is a histone acetyltransferase [79]. NET43/ hALP localizes to mitotic chromosomes in mammalian cells by binding to the INM protein SUN1 [89]. Depletion of SUN1 results in delayed chromosome decondensation and a reduction in histone H2B and H4 acetylation and these functions are mediated by NET43/ hALP [89]. Interestingly NET43/ hALP appears to be upregulated during lymphocyte activation when the large amount of dense peripheral chromatin of resting lymphocytes becomes decondensed (N. Korfali, L. Florens, and E. Schirmer, unpublished observations).

## 6. NE Diseases and Epigenetics

Twelve different NE proteins have now been linked to human disease (Table 2) [90-94]. Principle among them is lamin A, which with nearly 200 identified mutations has now been named the most mutated gene in the human genome. Lamin diseases affect many different tissues and include muscular dystrophies [95-97], lipodystrophy [98-100], neuropathy [101,102], cardiomyopathy [103], dermatopathy [104] and the aging disease progeria [105,106]. Several NETs and associated proteins also cause diseases or syndromes affecting muscle [107-110], bone [111,112], brain [113-117], skin [104] and immune cells [118]. Although each disease exhibits pathology preferentially in particular tissues, some patients have presented with overlapping pathologies. Recent observations suggest that in some cases affected individuals may harbor mutations in multiple proteins. For example one particularly debilitating case of Emery-Dreifuss muscular dystrophy is caused by mutations in both emerin and in desmin [119].

The three currently favored and partially overlapping mechanisms proposed to explain NE disease pathologies are: 1) cell damage due to mechanical instability of the nucleus, 2) disruption of signaling cascades through the NE affecting cell cycle progression,

## Nuclear Envelope Epigenetics

stem cell maintenance or differentiation, and 3) alteration of gene expression due to physical disruption of regulatory contacts at the NE.

The hypothesis that NE diseases involve genome misregulation is supported by observations that 1) lamin A-binding transcriptional regulators do not bind lamin mutants that cause disease, 2) microarray data from normal and NE mutation cells indicates a pattern of misregulation of myoD and Rb pathways in NE-related muscular dystrophies [120,121], and 3) cells from patients with NE diseases have abnormal distribution of dense peripheral chromatin. The first two observations are likely due to specific interactions with transcriptional regulators, but the alterations in chromatin are likely due to epigenetic misregulation. Specifically dense chromatin that is normally directly apposed to the NE redistributes away from the membrane in patients with lamin-related muscular dystrophy [122,123], progeria [124] and INM protein-related NE diseases such as emerin-linked muscular dystrophy [125-127]. Similar alterations in chromatin organization were observed in mouse lamin depletion models [128] and transgenic mice expressing lamin point mutants associated with cardiomyopathy [129]. Moreover, some differences in the overall positioning of chromosomes have also been observed in cells with specific lamin A mutations [92].

Progeria is caused by a lamin mutation that results in accumulation of an early pre-form with a farnesyl moiety [105,106]. Progeroid cells were analyzed for histone modifications associated with epigenetic regulation, finding that marks associated with silenced chromatin (histone H3 lysine 9 and lysine 27 methylation: H3K9Me3 and H3K27Me3) were reduced while a mark of active chromatin (histone H4 lysine 20 methylation: H4K20Me) was increased [130]. Moreover, in a female patient silencing marks on the inactive X chromosome decreased and lost their tight association with the periphery by fluorescence microscopy. A more striking effect was observed in immortalized tissue culture cells where H3K27Me3 strongly accumulated at the periphery with endogenous lamins, but dissipated in cells expressing a progeria mutation [130]. Moreover, an earlier pre-lamin A form lacking the farnesyl moiety accumulated HP1 $\alpha$  in abundance over farnesylated pre-lamin A [131]. These types of changes were recapitulated in normally aging cells [132].

## Nuclear Envelope Epigenetics

Moreover some of these heterochromatin defects could be reversed by treatment of cells with farnesyltransferase inhibitors (*i.e.* that reduce accumulation of the farnesylated form of lamin A that occurs in progeria) [133].

A further novel layer of epigenetic regulation may derive from nuclear structural organization at the level of nuclear shape. Nuclear lobulation is an aspect of neutrophil differentiation that increases the relative ratio of nuclear surface area to DNA [134]. This in theory would propagate silencing or activating effects from the NE over a much greater percentage of the genome. The differentiation program of neutrophils focuses most heavily on genes regulated by C/EBP, PU.1 and at later stages retinoic acid receptor (RAR) transcription factors [135] and unfortunately these genes have not been specifically mapped to determine their relationship to the periphery. Nonetheless, a recent study investigating global transcription in different blood cell lineages found that, though far fewer genes were expressed in neutrophils compared to progenitor cells, in both cases expression was concentrated in the nuclear interior [136]. Another particularly interesting observation is that terminally differentiated neutrophils withdraw completely from the cell cycle with complete silencing of E2F-mediated transcription [137]. In light of the repression of E2F-mediated transcription by overexpression of the INM protein LAP2 $\beta$  via its recruitment of germ cell-less to the periphery [12] the silencing during neutrophil differentiation could well be related to the increase in the NE surface area:DNA ratio. Neutrophil lobulation is blocked in the Pelger-Huet anomaly disorder associated with mutations in the INM protein LBR [118].

## 7. Summary

Whether through lineage-heritable gene positioning, sequestration of transcription factors, or recruitment of transcriptional repressors and histone modifying enzymes, the NE contributes its own version of epigenetics to the fine-tuning of differentiation, stem cell maintenance and gene expression. The complexity of interactions and mechanisms for silencing at the NE are likely to increase dramatically in the future as recent NE proteomic studies in both yeast and mammals have identified many novel uncharacterized proteins at the



## Nuclear Envelope Epigenetics

NE [79,138-140] and overexpression of several of these novel INM proteins alters chromatin organization (N. Zuleger, P. Malik, L. Florens and E. Schirmer, unpublished observations). Moreover indications of tissue-specific differences in NE composition [141,142] argue for differences in NE epigenetics in different cell types. It will be particularly interesting in the future to insert the LacO loci mentioned above into different cell types that have differences in the original distribution of peripheral heterochromatin to test how the pre-existing repressive environment of the periphery varies among different cell types.

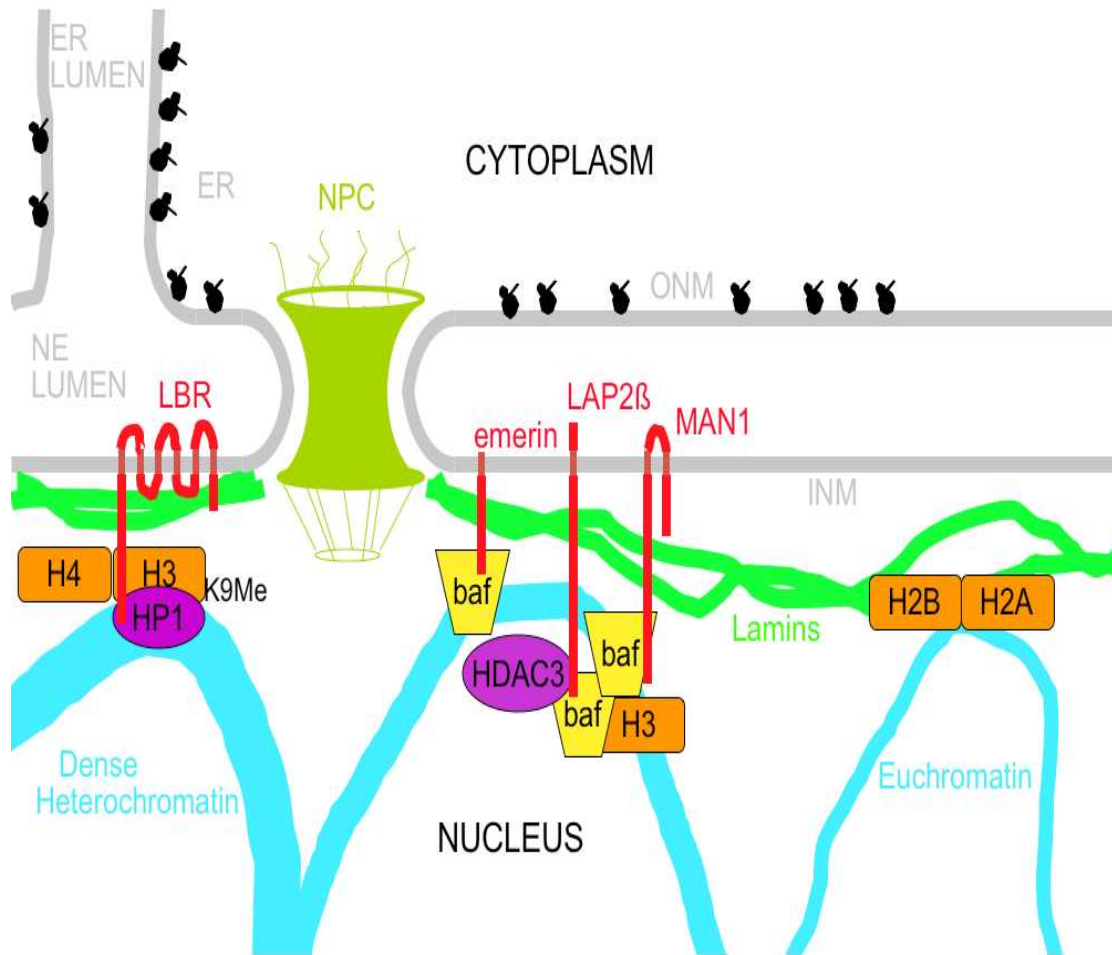
A particularly intriguing observation in analyzing the NE proteome is that the unique INM proteins indicated to be the most abundant are almost without exception lacking in enzymatic functions, yet they seem to have an incredibly large number of binding partners [143]. Moreover these binding partners appear to literally coat the surface of the INM proteins in the cell [142]. Thus it is reasonable to assume that the effects of NE proteins in epigenetic regulation derive from a combination of their variable expression in different cell types and their ability to recruit specific chromatin modifying proteins to the NE. The colossal scale of NPCs, with over 30 core proteins and many additional peripherally associated proteins forming >50 MDa complexes, could allow parts of the NPC to recruit factors that propagate silenced chromatin while others activate genes. The finding moreover that some of these proteins have boundary/ insulator activity allows for active and repressed states to occur within a short stretch of chromatin and thus increases the complexity of active/ inactive genes in the proximity of the NPCs. If NPCs have even a fraction of the tissue variation indicated at the NE, the range of possible combinations for varied regulation is enormous.

## **Acknowledgements**

I thank colleagues Maria Vogelauer and Irina Stancheva for critical reading of the manuscript and the Wellcome Trust for funding.

**Legends to Figures and Tables**

Fig. 1.

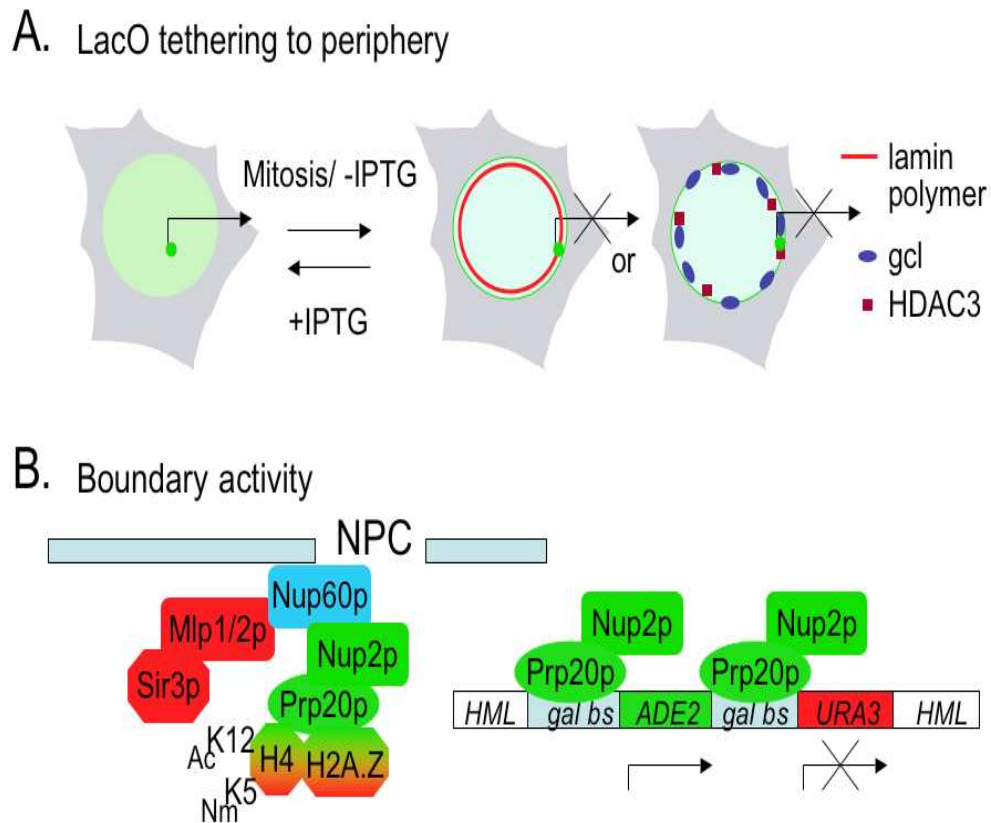


Schematic of nuclear envelope organization. The nuclear envelope (NE) is a double membrane system continuous with the endoplasmic reticulum (ER). In addition to sharing proteins with the proximal ER, the outer nuclear membrane (ONM) has a few characterized unique NE proteins. The inner nuclear membrane (INM) contains many more unique integral proteins, which commonly are associated with the intermediate filament lamin polymer and chromatin. The membrane is perforated by nuclear pore complexes (NPCs), large macromolecular assemblies upwards of 50 MDa that direct transport of large molecules in and out of the nucleus. Differences in the interactions between INM proteins and their

## Nuclear Envelope Epigenetics

chromatin and chromatin-modifying interaction partners could result in different types of chromatin accumulating at the periphery. For example, lamins bind core histones (H2A:H2B:H3:H4), LBR binds to epigenetically marked histones and HP1, LAP2 $\beta$  binds to the histone deacetylase HDAC3, and several INM proteins bind the BAF DNA crosslinker.

Fig. 2.



Systems for assembling specific chromatin at the NE. A. In the lac operator system a gene locus is active when at the nuclear interior (left panel), but becomes repressed at the periphery (right panels). Movement to the periphery requires going through mitosis and the locus can be released from the periphery with IPTG treatment. Repression could occur through steric constraints (*e.g.* association with the lamin polymer) or by recruitment of transcriptional repressors (germ cell-less [gcl])/ histone modifying enzymes (HDAC3). B. Boundary activity at the NPCs yields characteristics of both silent and active chromatin. The boundary assay (bottom) places the *URA3* and *ADE2* genes within a partially derepressed HML (mating type) locus with *ADE2* flanked by Gal4p binding sequences (gal bs). If a protein fused to the Gal4p DNA binding domain allows *ADE2* expression while *URA3* remains shut off, then it is

## Nuclear Envelope Epigenetics

said to have boundary activity. If the cells are grown in the absence of adenine they need expression of this *ADE2* gene to survive, but in the presence of the drug 5-fluoroorotic acid (5-FOA) expression from the *URA3* gene becomes toxic. Thus the ability to grow in the combined absence of adenine and presence of 5-FOA when a particular NPC protein is fused to the Gal4p DNA binding domain indicates its role in boundary activity. Results using this assay suggest that the Nup60p and Mlp1/2p proteins that have previously been shown to be important for telomere tethering to the periphery are also involved in boundary activity, but in association with Nup2p and the Ran-GTP exchange factor Prp20p. Prp20p mediates the interaction with chromatin through binding “poised” histones with opposing epigenetic marks (*e.g.* acetylated [Ac] K12 and unmodified [Nm] K5) and the H2A.Z variant that is sometimes associated with silenced chromatin.

## Nuclear Envelope Epigenetics

Table 1. Changes in histone modifications between peripheral and central localization for the Mash1 gene.

Gene Bias	Mash1 periphery	Mash1 interior
Silent		
H3K9me3	+/-	+/-
H3K27me3	+++	+
Active		
H3K9Ac	+	+++
H4Ac	+/-	++

[49]

Table 2. Diseases caused by nuclear envelope protein mutations

NE protein	disease	Primary tissue affects	reference
Lamins			
Lamin A	Emery-Dreifuss muscular dystrophy (EDMD) type 2 (AD)	muscle	[95]
	Emery-Dreifuss muscular dystrophy (EDMD) type 3 (AR)	muscle	[96]
	Limb-girdle muscular dystrophy type 1B (LGMD-1B)	muscle	[97]
	Charcot-Marie-Tooth disorder type 2B1 (CMT-2B1)	nerve	[101]
	Mandibuloacral dysplasia (MAD) type A/B	multiple	[144]
	Autosomal dominant lipodystrophy with diabetes, hepatic steatosis, hypertrophic cardiomyopathy and leukomelanodermic papules	multiple	[145]
	Dunnigan-type familial partial lipodystrophy (FPLD2)	fat	[98,100]

## Nuclear Envelope Epigenetics

	Seip syndrome (BSCL2)	fat	[146]
	Dilated cardiomyopathy with conduction defect (CMD1A)	heart	[103]
	Restrictive dermopathy (RD)	skin	[104]
	Hutchison-Gilford Progeria syndrome (HGPS)	aging	[105,106]
	Atypical Werner Syndrome (AWS)	aging	[147]
Lamin B1	Adult-onset autosomal dominant leukodystrophy	nerve	[102]
Lamin B2	Barraquer-Simons syndrome	fat	[99]
Transmembrane Proteins			
Emerin	Emery-Dreifuss muscular dystrophy (EDMD) type 1 (X)	muscle	[107]
Lamin B-receptor	Pelger-Huet anomaly (PHA)	neutrophils	[118]
	Greenburg/HEM skeletal dysplasia (GSD/HEM)	bone	[112]
MAN1	Buschke-Ollendorff syndrome (BOS)	bone	[111]
	Melorheostosis	bone	[111]
Nesprin	Emery-Dreifuss muscular dystrophy (EDMD)	muscle	[109]
	Cerebellar ataxia (AR)	nerve	[113]
NE-associated			
TorsinA	Torsion dystonia (DYT1)	nerve	[115,116]
FACE-1	Restrictive dermopathy (RD)	skin	[104]
LAP2 $\alpha$	cardiomyopathy	heart	[108]
Aladin	Triple A syndrome	multiple	[110]
Nup60	Infantile bilateral striatal necrosis	brain	[114]

(AD), autosomal dominant; (AR), autosomal recessive; (X), X-linked

## References

- [1] H.G. Callan and S.G. Tomlin. Experimental studies on amphibian oocyte nuclei. I. Investigation of the structure of the nuclear membrane by means of the electron microscope. *Proc R Soc of Lond [Biol]* 137 (1950) 367-378.
- [2] M. Suntharalingam and S.R. Went. Peering through the pore: nuclear pore complex structure, assembly, and function. *Dev Cell* 4 (2003) 775-789.
- [3] E.C. Schirmer and R. Foisner. Proteins that associate with lamins: many faces, many functions. *Exp Cell Res* 313 (2007) 2167-2179.
- [4] T. Dechat, K. Pflughaar, K. Sengupta, T. Shimi, D.K. Shumaker, L. Solimando and R.D. Goldman. Nuclear lamins: major factors in the structural organization and function of the nucleus and chromatin. *Genes Dev* 22 (2008) 832-853.
- [5] J. Lammerding, P. Schulze, T. Takahashi, S. Kozlov, T. Sullivan, R. Kamm, C. Stewart and R. Lee. Lamin A/C deficiency causes defective nuclear mechanics and mechanotransduction. *J Clin Invest* 113 (2004) 370-378.
- [6] J. Liu, T. Ben-Shahar, D. Riemer, M. Treinin, P. Spann, K. Weber, A. Fire and Y. Gruenbaum. Essential roles for *Caenorhabditis elegans* lamin gene in nuclear organization, cell cycle progression, and spatial organization of nuclear pore complexes. *Mol Biol Cell* 11 (2000) 3937-3947.
- [7] E.C. Schirmer and L. Gerace. The stability of the nuclear lamina polymer changes with the composition of lamin subtypes according to their individual binding strengths. *J Biol Chem* 279 (2004) 42811-42817.
- [8] E.C. Schirmer, T. Guan and L. Gerace. Involvement of the lamin rod domain in heterotypic lamin interactions important for nuclear organization. *J Cell Biol* 153 (2001) 479-489.



- [9] **D.J. Ellis, H. Jenkins, W.G. Whitfield and C.J. Hutchison. GST-lamin fusion proteins act as dominant negative mutants in *Xenopus* egg extract and reveal the function of the lamina in DNA replication. *J Cell Sci* 110 (1997) 2507-2518.**
- [10] **R. Moir, T. Spann, H. Herrmann and R. Goldman. Disruption of nuclear lamin organization blocks the elongation phase of DNA replication. *J Cell Biol* 149 (2000) 1179-1192.**
- [11] **T.P. Spann, R.D. Moir, A.E. Goldman, R. Stick and R.D. Goldman. Disruption of nuclear lamin organization alters the distribution of replication factors and inhibits DNA synthesis. *J Cell Biol* 136 (1997) 1201-1212.**
- [12] **E. Nili, G.S. Cojocaru, Y. Kalma, D. Ginsberg, N.G. Copeland, D.J. Gilbert, N.A. Jenkins, R. Berger, S. Shaklai, N. Amariglio, F. Brok-Simoni, A.J. Simon and G. Rechavi. Nuclear membrane protein LAP2beta mediates transcriptional repression alone and together with its binding partner GCL (germ-cell-less). *J Cell Sci* 114 (2001) 3297-3307.**
- [13] **R. Somech, S. Shaklai, O. Geller, N. Amariglio, A.J. Simon, G. Rechavi and E.N. Gal-Yam. The nuclear-envelope protein and transcriptional repressor LAP2beta interacts with HDAC3 at the nuclear periphery, and induces histone H4 deacetylation. *J Cell Sci* 118 (2005) 4017-4025.**
- [14] **R.I. Kumaran, B. Muralikrishna and V.K. Parnaik. Lamin A/C speckles mediate spatial organization of splicing factor compartments and RNA polymerase II transcription. *J Cell Biol* 159 (2002) 783-793.**
- [15] **B.R. Johnson, R.T. Nitta, R.L. Frock, L. Mounkes, D.A. Barbie, C.L. Stewart, E. Harlow and B.K. Kennedy. A-type lamins regulate retinoblastoma protein function by promoting subnuclear localization and preventing proteasomal degradation. *Proc Natl Acad Sci U S A* 101 (2004) 9677-9682.**
- [16] **E. Markiewicz, K. Tilgner, N. Barker, M. van de Wetering, H. Clevers, M. Dorobek, I. Hausmanowa-Petrusewicz, F.C. Ramaekers, J.L. Broers, W.M. Blankesteyn, G. Salpingidou, R.G. Wilson, J.A. Ellis and C.J. Hutchison. The**

- inner nuclear membrane protein emerin regulates beta-catenin activity by restricting its accumulation in the nucleus. *EMBO J* 25 (2006) 3275-3285.**
- [17] **S. Osada, S.Y. Ohmori and M. Taira. XMAN1, an inner nuclear membrane protein, antagonizes BMP signaling by interacting with Smad1 in *Xenopus* embryos. *Development* 130 (2003) 1783-1794.**
- [18] **T. Ozaki, M. Saijo, K. Murakami, H. Enomoto, Y. Taya and S. Sakiyama. Complex formation between lamin A and the retinoblastoma gene product: identification of the domain on lamin A required for its interaction. *Oncogene* 9 (1994) 2649-2653.**
- [19] **A.E. Mirsky and V. Allfrey. Biochemical activities of the cell nucleus. *Dis Nerv Syst* 21(2)Suppl (1960) 23-28.**
- [20] **R. Hirschhorn, M.I. Decsy and W. Troll. The effect of PHA stimulation of human peripheral blood lymphocytes upon cellular content of euchromatin and heterochromatin. *Cell Immunol* 2 (1971) 696-701.**
- [21] **A. Bird. DNA methylation patterns and epigenetic memory. *Genes Dev* 16 (2002) 6-21.**
- [22] **T. Jenuwein and C.D. Allis. Translating the histone code. *Science* 293 (2001) 1074-1080.**
- [23] **M.J. Hendzel and D.P. Bazett-Jones. Probing nuclear ultrastructure by electron spectroscopic imaging. *J Microsc* 182 (1996) 1-14.**
- [24] **H. Pickersgill, B. Kalverda, E. de Wit, W. Talhout, M. Fornerod and B. van Steensel. Characterization of the *Drosophila melanogaster* genome at the nuclear lamina. *Nat Genet* 38 (2006) 1005-1014.**
- [25] **D. Zink, H. Bornfleth, A. Visser, C. Cremer and T. Cremer. Organization of early and late replicating DNA in human chromosome territories. *Exp Cell Res* 247 (1999) 176-188.**
- [26] **A.V. Pindyurin, C. Moorman, E. de Wit, S.N. Belyakin, E.S. Belyaeva, G.K. Christophides, F.C. Kafatos, B. van Steensel and I.F. Zhimulev. SUUR joins**

- separate subsets of PcG, HP1 and B-type lamin targets in *Drosophila*. *J Cell Sci* **120** (2007) 2344-2351.
- [27] C.R. Brown, C.J. Kennedy, V.A. Delmar, D.J. Forbes and P.A. Silver. Global histone acetylation induces functional genomic reorganization at mammalian nuclear pore complexes. *Genes Dev* **22** (2008) 627-639.
- [28] D. Makatsori, N. Kourmouli, H. Polioudaki, L.D. Shultz, K. McLean, P.A. Theodoropoulos, P.B. Singh and S.D. Georgatos. The inner nuclear membrane protein lamin B receptor forms distinct microdomains and links epigenetically marked chromatin to the nuclear envelope. *J Biol Chem* **279** (2004) 25567-25573.
- [29] M. Gotta and S.M. Gasser. Nuclear organization and transcriptional silencing in yeast. *Experientia* **52** (1996) 1136-1147.
- [30] L. Maillet, C. Boscheron, M. Gotta, S. Marcand, E. Gilson and S.M. Gasser. Evidence for silencing compartments within the yeast nucleus: a role for telomere proximity and Sir protein concentration in silencer-mediated repression. *Genes Dev* **10** (1996) 1796-1811.
- [31] O.M. Aparicio, B.L. Billington and D.E. Gottschling. Modifiers of position effect are shared between telomeric and silent mating-type loci in *S. cerevisiae*. *Cell* **66** (1991) 1279-1287.
- [32] D.E. Gottschling, O.M. Aparicio, B.L. Billington and V.A. Zakian. Position effect at *S. cerevisiae* telomeres: reversible repression of Pol II transcription. *Cell* **63** (1990) 751-762.
- [33] E.D. Andrulis, A.M. Neiman, D.C. Zappulla and R. Sternglanz. Perinuclear localization of chromatin facilitates transcriptional silencing. *Nature* **394** (1998) 592-595.
- [34] T. Laroche, S.G. Martin, M. Gotta, H.C. Gorham, F.E. Pryde, E.J. Louis and S.M. Gasser. Mutation of yeast Ku genes disrupts the subnuclear organization of telomeres. *Curr Biol* **8** (1998) 653-656.

- [35] V. Galy, J.C. Olivo-Marin, H. Scherthan, V. Doye, N. Rascalou and U. Nehrass. Nuclear pore complexes in the organization of silent telomeric chromatin. *Nature* 403 (2000) 108-112.
- [36] H. Scherthan, M. Jerratsch, B. Li, S. Smith, M. Hulten, T. Lock and T. de Lange. Mammalian meiotic telomeres: protein composition and redistribution in relation to nuclear pores. *Mol Biol Cell* 11 (2000) 4189-4203.
- [37] L. Maillet, F. Gaden, V. Brevet, G. Fourel, S.G. Martin, K. Dubrana, S.M. Gasser and E. Gilson. Ku-deficient yeast strains exhibit alternative states of silencing competence. *EMBO Rep* 2 (2001) 203-210.
- [38] F. Feuerbach, V. Galy, E. Trelles-Sticken, M. Fromont-Racine, A. Jacquier, E. Gilson, J.C. Olivo-Marin, H. Scherthan and U. Nehrass. Nuclear architecture and spatial positioning help establish transcriptional states of telomeres in yeast. *Nat Cell Biol* 4 (2002) 214-221.
- [39] E.D. Andrulis, D.C. Zappulla, A. Ansari, S. Perrod, C.V. Laiosa, M.R. Gartenberg and R. Sternglanz. Esc1, a nuclear periphery protein required for Sir4-based plasmid anchoring and partitioning. *Mol Cell Biol* 22 (2002) 8292-8301.
- [40] M.R. Gartenberg, F.R. Neumann, T. Laroche, M. Blaszczyk and S.M. Gasser. Sir-mediated repression can occur independently of chromosomal and subnuclear contexts. *Cell* 119 (2004) 955-967.
- [41] W.F. Marshall, A.F. Dernburg, B. Harmon, D.A. Agard and J.W. Sedat. Specific interactions of chromatin with the nuclear envelope: positional determination within the nucleus in *Drosophila melanogaster*. *Mol Biol Cell* 7 (1996) 825-842.
- [42] T.I. Gerasimova, K. Byrd and V.G. Corces. A chromatin insulator determines the nuclear localization of DNA. *Mol Cell* 6 (2000) 1025-1035.
- [43] J.A. Wallace and G. Felsenfeld. We gather together: insulators and genome organization. *Curr Opin Genet Dev* 17 (2007) 400-407.

- [44] **J.A. Croft, J.M. Bridger, S. Boyle, P. Perry, P. Teague and W.A. Bickmore.**  
**Differences in the localization and morphology of chromosomes in the human nucleus. *J Cell Biol* 145 (1999) 1119-1131.**
- [45] **J.A. Sanchez and L.J. Wangh.** **New insights into the mechanisms of nuclear segmentation in human neutrophils. *J Cell Biochem* 73 (1999) 1-10.**
- [46] **X. Ding, R. Xu, J. Yu, T. Xu, Y. Zhuang and M. Han.** **SUN1 is required for telomere attachment to nuclear envelope and gametogenesis in mice. *Dev Cell* 12 (2007) 863-872.**
- [47] **J. Schmitt, R. Benavente, D. Hodzic, C. Hoog, C.L. Stewart and M. Alsheimer.**  
**Transmembrane protein Sun2 is involved in tethering mammalian meiotic telomeres to the nuclear envelope. *Proc Natl Acad Sci U S A* 104 (2007) 7426-7431.**
- [48] **S.T. Kosak, J.A. Skok, K.L. Medina, R. Riblet, M.M. Le Beau, A.G. Fisher and H. Singh.** **Subnuclear compartmentalization of immunoglobulin loci during lymphocyte development. *Science* 296 (2002) 158-162.**
- [49] **R.R. Williams, V. Azuara, P. Perry, S. Sauer, M. Dvorkina, H. Jorgensen, J. Roix, P. McQueen, T. Misteli, M. Merkenschlager and A.G. Fisher.** **Neural induction promotes large-scale chromatin reorganisation of the *Mash1* locus. *J Cell Sci* 119 (2006) 132-140.**
- [50] **S.L. Hewitt, F.A. High, S.L. Reiner, A.G. Fisher and M. Merkenschlager.**  
**Nuclear repositioning marks the selective exclusion of lineage-inappropriate transcription factor loci during T helper cell differentiation. *Eur J Immunol* 34 (2004) 3604-3613.**
- [51] **D. Zink, M.D. Amaral, A. Englmann, S. Lang, L.A. Clarke, C. Rudolph, F. Alt, K. Luther, C. Braz, N. Sadoni, J. Rosenecker and D. Schindelbauer.**  
**Transcription-dependent spatial arrangements of CFTR and adjacent genes in human cell nuclei. *J Cell Biol* 166 (2004) 815-825.**

- [52] **J.R. Chubb, S. Boyle, P. Perry and W.A. Bickmore. Chromatin motion is constrained by association with nuclear compartments in human cells. *Curr Biol* 12 (2002) 439-445.**
- [53] **D. Grunwald, R.M. Martin, V. Buschmann, D.P. Bazett-Jones, H. Leonhardt, U. Kubitscheck and M.C. Cardoso. Probing intranuclear environments at the single-molecule level. *Biophys J* 94 (2008) 2847-2858.**
- [54] **M.R. Paddy, A.S. Belmont, H. Saumweber, D.A. Agard and J.W. Sedat. Interphase nuclear envelope lamins form a discontinuous network that interacts with only a fraction of the chromatin in the nuclear periphery. *Cell* 62 (1990) 89-106.**
- [55] **A.S. Belmont, Y. Zhai and A. Thilenius. Lamin B distribution and association with peripheral chromatin revealed by optical sectioning and electron microscopy tomography. *J Cell Biol* 123 (1993) 1671-1685.**
- [56] **D. Bouvier, J. Hubert, A.P. Seve and M. Bouteille. Characterization of lamina-bound chromatin in the nuclear shell isolated from HeLa cells. *Exp Cell Res* 156 (1985) 500-512.**
- [57] **A. Malhas, C.F. Lee, R. Sanders, N.J. Saunders and D.J. Vaux. Defects in lamin B1 expression or processing affect interphase chromosome position and gene expression. *J Cell Biol* 176 (2007) 593-603.**
- [58] **L.E. Finlan, D. Sproul, I. Thomson, S. Boyle, E. Kerr, P. Perry, B. Ylstra, J.R. Chubb and W.A. Bickmore. Recruitment to the nuclear periphery can alter expression of genes in human cells. *PLoS Genet.* 4 (2008) e1000039.**
- [59] **R.I. Kumaran and D.L. Spector. A genetic locus targeted to the nuclear periphery in living cells maintains its transcriptional competence. *J Cell Biol* 180 (2008) 51-65.**
- [60] **K.L. Reddy, J.M. Zullo, E. Bertolino and H. Singh. Transcriptional repression mediated by repositioning of genes to the nuclear lamina. *Nature* 452 (2008) 243-247.**

- [61] J.M. Holaska, K. Lee, A.K. Kowalski and K.L. Wilson. Transcriptional repressor germ cell-less (GCL) and barrier to autointegration factor (BAF) compete for binding to emerin in vitro. *J Biol Chem* 278 (2003) 6969-6975.
- [62] T. Haraguchi, J.M. Holaska, M. Yamane, T. Koujin, N. Hashiguchi, C. Mori, K.L. Wilson and Y. Hiraoka. Emerin binding to Btf, a death-promoting transcriptional repressor, is disrupted by a missense mutation that causes Emery-Dreifuss muscular dystrophy. *Eur J Biochem* 271 (2004) 1035-1045.
- [63] J.M. Holaska, S. Rais-Bahrami and K.L. Wilson. Lmo7 is an emerin-binding protein that regulates the transcription of emerin and many other muscle-relevant genes. *Hum Mol Genet* 15 (2006) 3459-3472.
- [64] K. Bodoor, S. Shaikh, D. Salina, W.H. Raharjo, R. Bastos, M. Lohka and B. Burke. Sequential recruitment of NPC proteins to the nuclear periphery at the end of mitosis. *J Cell Sci* 112 (1999) 2253-2264.
- [65] T. Haraguchi, T. Koujin, T. Hayakawa, T. Kaneda, C. Tsutsumi, N. Imamoto, C. Akazawa, J. Sukegawa, Y. Yoneda and Y. Hiraoka. Live fluorescence imaging reveals early recruitment of emerin, LBR, RanBP2, and Nup153 to reforming functional nuclear envelopes. *J Cell Sci* 113 (2000) 779-794.
- [66] A. Mattout-Drubezki and Y. Gruenbaum. Dynamic interactions of nuclear lamina proteins with chromatin and transcriptional machinery. *Cell Mol Life Sci* 60 (2003) 2053-2063.
- [67] M. Goldberg, A. Harel, M. Brandeis, T. Rechsteiner, T.J. Richmond, A.M. Weiss and Y. Gruenbaum. The tail domain of lamin Dm0 binds histones H2A and H2B. *Proc Natl Acad Sci U S A* 96 (1999) 2852-2857.
- [68] H. Polioudaki, N. Kourmouli, V. Drosou, A. Bakou, P.A. Theodoropoulos, P.B. Singh, T. Giannakouros and S.D. Georgatos. Histones H3/H4 form a tight complex with the inner nuclear membrane protein LBR and heterochromatin protein 1. *EMBO Rep* 2 (2001) 920-925.

- [69] Q. Ye and H.J. Worman. Interaction between an integral protein of the nuclear envelope inner membrane and human chromodomain proteins homologous to *Drosophila* HP1. *J Biol Chem* 271 (1996) 14653-14656.
- [70] N. Kourmouli, P.A. Theodoropoulos, G. Dialynas, A. Bakou, A.S. Politou, I.G. Cowell, P.B. Singh and S.D. Georgatos. Dynamic associations of heterochromatin protein 1 with the nuclear envelope. *EMBO J* 19 (2000) 6558-6568.
- [71] K. Furukawa. LAP2 binding protein 1 (L2BP1/BAF) is a candidate mediator of LAP2- chromatin interaction. *J Cell Sci* 112 (1999) 2485-2492.
- [72] K. Lee, T. Haraguchi, R. Lee, T. Koujin, Y. Hiraoka and K. Wilson. Distinct functional domains in emerin bind lamin A and DNA-bridging protein BAF. *J Cell Sci* 114 (2001) 4567-4573.
- [73] R. Montes de Oca, K.K. Lee and K.L. Wilson. Binding of barrier to autointegration factor (BAF) to histone H3 and selected linker histones including H1.1. *J Biol Chem* 280 (2005) 42252-42262.
- [74] Y. Suzuki, H. Yang and R. Craigie. LAP2alpha and BAF collaborate to organize the Moloney murine leukemia virus preintegration complex. *EMBO J* 23 (2004) 4670-4678.
- [75] R. Zheng, R. Ghirlando, M.S. Lee, K. Mizuuchi, M. Krause and R. Craigie. Barrier-to-autointegration factor (BAF) bridges DNA in a discrete, higher-order nucleoprotein complex. *Proc Natl Acad Sci U S A* 97 (2000) 8997-9002.
- [76] N. Dhillon and R.T. Kamakaka. A histone variant, Htz1p, and a Sir1p-like protein, Esc2p, mediate silencing at HMR. *Mol Cell* 6 (2000) 769-780.
- [77] D.G. Brickner, I. Cajigas, Y. Fondufe-Mittendorf, S. Ahmed, P.C. Lee, J. Widom and J.H. Brickner. H2A.Z-mediated localization of genes at the nuclear periphery confers epigenetic memory of previous transcriptional state. *PLoS Biol* 5 (2007) e81.



- [78] **J.H. Brickner and P. Walter. Gene recruitment of the activated INO1 locus to the nuclear membrane. PLoS Biol 2 (2004) e342.**
- [79] **E.C. Schirmer, L. Florens, T. Guan, J.R.r. Yates and L. Gerace. Nuclear membrane proteins with potential disease links found by subtractive proteomics. Science 301 (2003) 1380-1382.**
- [80] **J.A. Nielsen, L.D. Hudson and R.C. Armstrong. Nuclear organization in differentiating oligodendrocytes. J Cell Sci 115 (2002) 4071-4079.**
- [81] **C. Johnson, D. Primorac, M. McKinstry, J. McNeil, D. Rowe and J.B. Lawrence. Tracking COL1A1 RNA in osteogenesis imperfecta. splice-defective transcripts initiate transport from the gene but are retained within the SC35 domain. J Cell Biol 150 (2000) 417-432.**
- [82] **P.C. Park and U. De Boni. A specific conformation of the territory of chromosome 17 locates ERBB-2 sequences to a DNase-hypersensitive domain at the nuclear periphery. Chromosoma 107 (1998) 87-95.**
- [83] **M. Schmid, G. Arib, C. Laemmli, J. Nishikawa, T. Durussel and U.K. Laemmli. Nup-PI: the nucleopore-promoter interaction of genes in yeast. Mol Cell 21 (2006) 379-391.**
- [84] **A. Taddei, G. Van Houwe, F. Hediger, V. Kalck, F. Cubizolles, H. Schober and S.M. Gasser. Nuclear pore association confers optimal expression levels for an inducible yeast gene. Nature 441 (2006) 774-778.**
- [85] **K. Ishii, G. Arib, C. Lin, G. Van Houwe and U.K. Laemmli. Chromatin boundaries in budding yeast: the nuclear pore connection. Cell 109 (2002) 551-562.**
- [86] **D.J. Dilworth, A.J. Tackett, R.S. Rogers, E.C. Yi, R.H. Christmas, J.J. Smith, A.F. Siegel, B.T. Chait, R.W. Wozniak and J.D. Aitchison. The mobile nucleoporin Nup2p and chromatin-bound Prp20p function in endogenous NPC-mediated transcriptional control. J Cell Biol 171 (2005) 955-965.**

- [87] S.K. Kurdistani, S. Tavazoie and M. Grunstein. Mapping global histone acetylation patterns to gene expression. *Cell* 117 (2004) 721-733.
- [88] J.M. Casolari, C.R. Brown, S. Komili, J. West, H. Hieronymus and P.A. Silver. Genome-wide localization of the nuclear transport machinery couples transcriptional status and nuclear organization. *Cell* 117 (2004) 427-439.
- [89] Y.H. Chi, K. Haller, J.M. Peloponese, Jr. and K.T. Jeang. Histone acetyltransferase hALP and nuclear membrane protein hsSUN1 function in decondensation of mitotic chromosomes. *J Biol Chem* 282 (2007) 27447-27458.
- [90] B.C. Capell and F.S. Collins. Human laminopathies: nuclei gone genetically awry. *Nat Rev Genet* 7 (2006) 940-952.
- [91] J.M. Cronshaw and M.J. Matunis. The nuclear pore complex: disease associations and functional correlations. *Trends Endocrinol Metab* 15 (2004) 34-39.
- [92] R. Foisner, U. Aebi, G. Bonne, Y. Gruenbaum and G. Novelli. 141st ENMC International Workshop inaugural meeting of the EURO-Laminopathies project "Nuclear Envelope-linked Rare Human Diseases: From Molecular Pathophysiology towards Clinical Applications", 10-12 March 2006, Naarden, The Netherlands. *Neuromuscul Disord* 17 (2007) 655-660.
- [93] A. Mattout, T. Dechat, S.A. Adam, R.D. Goldman and Y. Gruenbaum. Nuclear lamins, diseases and aging. *Curr Opin Cell Biol* 18 (2006) 335-341.
- [94] H.J. Worman and G. Bonne. "Laminopathies": a wide spectrum of human diseases. *Exp Cell Res* 313 (2007) 2121-2133.
- [95] G. Bonne, M.R. Di Barletta, S. Varnous, H.M. Becane, E.H. Hammouda, L. Merlini, F. Muntoni, C.R. Greenberg, F. Gary, J.A. Urtizbera, D. Duboc, M. Fardeau, D. Toniolo and K. Schwartz. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery- Dreifuss muscular dystrophy. *Nat Genet* 21 (1999) 285-288.

- [96] M. Raffaele Di Barletta, E. Ricci, G. Galluzzi, P. Tonali, M. Mora, L. Morandi, A. Romorini, T. Voit, K.H. Orstavik, L. Merlini, C. Trevisan, V. Biancalana, I. Housmanowa-Petrusewicz, S. Bione, R. Ricotti, K. Schwartz, G. Bonne and D. Toniolo. Different Mutations in the LMNA Gene Cause Autosomal Dominant and Autosomal Recessive Emery-Dreifuss Muscular Dystrophy. *Am J Hum Genet* 66 (2000) 1407-1412.
- [97] A. Muchir, G. Bonne, A.J. van der Kooi, M. van Meegen, F. Baas, P.A. Bolhuis, M. de Visser and K. Schwartz. Identification of mutations in the gene encoding lamins A/C in autosomal dominant limb girdle muscular dystrophy with atrioventricular conduction disturbances (LGMD1B). *Hum Mol Genet* 9 (2000) 1453-1459.
- [98] H. Cao and R.A. Hegele. Nuclear lamin A/C R482Q mutation in Canadian kindreds with Dunnigan- type familial partial lipodystrophy. *Hum Mol Genet* 9 (2000) 109-112.
- [99] R.A. Hegele, H. Cao, D.M. Liu, G.A. Costain, V. Charlton-Menys, N.W. Rodger and P.N. Durrington. Sequencing of the reannotated LMNB2 gene reveals novel mutations in patients with acquired partial lipodystrophy. *Am J Hum Genet* 79 (2006) 383-389.
- [100] S. Shackleton, D.J. Lloyd, S.N. Jackson, R. Evans, M.F. Niermeijer, B.M. Singh, H. Schmidt, G. Brabant, S. Kumar, P.N. Durrington, S. Gregory, S. O'Rahilly and R.C. Trembath. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. *Nat Genet* 24 (2000) 153-156.
- [101] A. De Sandre-Giovannoli, M. Chaouch, S. Kozlov, J. Vallat, M. Tazir, N. Kassouri, P. Szepietowski, T. Hammadouche, A. Vandenberghe, C. Stewart, D. Grid and N. Levy. Homozygous defects in LMNA, encoding lamin A/C nuclear-envelope proteins, cause autosomal recessive axonal neuropathy in human (Charcot-Marie-Tooth disorder type 2) and mouse. *Am J Hum Genet* 70 (2002) 726-736.

- [102] Q.S. Padiath, K. Saigoh, R. Schiffmann, H. Asahara, T. Yamada, A. Koeppen, K. Hogan, L.J. Ptacek and Y.H. Fu. Lamin B1 duplications cause autosomal dominant leukodystrophy. *Nat Genet* 38 (2006) 1114-1123.
- [103] D. Fatkin, C. MacRae, T. Sasaki, M.R. Wolff, M. Porcu, M. Frenneaux, J. Atherton, H.J. Vidaillet, Jr., S. Spudich, U. De Girolami, J.G. Seidman, C. Seidman, F. Muntoni, G. Muehle, W. Johnson and B. McDonough. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 341 (1999) 1715-1724.
- [104] C.L. Navarro, A. De Sandre-Giovannoli, R. Bernard, I. Boccaccio, A. Boyer, D. Genevieve, S. Hadj-Rabia, C. Gaudy-Marqueste, H.S. Smitt, P. Vabres, L. Faivre, A. Verloes, T. Van Essen, E. Flori, R. Hennekam, F.A. Beemer, N. Laurent, M. Le Merrer, P. Cau and N. Levy. Lamin A and ZMPSTE24 (FACE-1) defects cause nuclear disorganization and identify restrictive dermopathy as a lethal neonatal laminopathy. *Hum Mol Genet* 13 (2004) 2493-2503.
- [105] M. Eriksson, W.T. Brown, L.B. Gordon, M.W. Glynn, J. Singer, L. Scott, M.R. Erdos, C.M. Robbins, T.Y. Moses, P. Berglund, A. Dutra, E. Pak, S. Durkin, A.B. Csoka, M. Boehnke, T.W. Glover and F.S. Collins. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature* 423 (2003) 293-298.
- [106] A. De Sandre-Giovannoli, R. Bernard, P. Cau, C. Navarro, J. Amiel, I. Boccaccio, S. Lyonnet, C. Stewart, A. Munnich, M. Le Merrer and N. Levy. Lamin A Truncation in Hutchinson-Gilford Progeria. *Science* (2003).
- [107] S. Bione, E. Maestrini, S. Rivella, M. Mancini, S. Regis, G. Romeo and D. Toniolo. Identification of a novel X-linked gene responsible for Emery-Dreifuss muscular dystrophy. *Nat Genet* 8 (1994) 323-327.
- [108] M.R. Taylor, D. Slavov, A. Gajewski, S. Vlcek, L. Ku, P.R. Fain, E. Carniel, A. Di Lenarda, G. Sinagra, M.M. Boucek, J. Cavanaugh, S.L. Graw, P. Ruegg, J.

- Feiger, X. Zhu, D.A. Ferguson, M.R. Bristow, J. Gotzmann, R. Foisner and L. Mestroni. Thymopoietin (lamina-associated polypeptide 2) gene mutation associated with dilated cardiomyopathy. Hum Mutat 26 (2005) 566-574.**
- [109] **Q. Zhang, C. Bethmann, N.F. Worth, J.D. Davies, C. Wasner, A. Feuer, C.D. Ragnauth, Q. Yi, J.A. Mellad, D.T. Warren, M.A. Wheeler, J.A. Ellis, J.N. Skepper, M. Vorgerd, B. Schlotter-Weigel, P.L. Weissberg, R.G. Roberts, M. Wehnert and C.M. Shanahan. Nesprin-1 and -2 are involved in the pathogenesis of Emery-Dreifuss Muscular Dystrophy and are critical for nuclear envelope integrity. Hum Mol Genet 16 (2007) 2816-2833.**
- [110] **J.M. Cronshaw and M.J. Matunis. The nuclear pore complex protein ALADIN is mislocalized in triple A syndrome. Proc Natl Acad Sci U S A 100 (2003) 5823-5827.**
- [111] **J. Hellemans, O. Preobrazhenska, A. Willaert, P. Debeer, P.C. Verdonk, T. Costa, K. Janssens, B. Menten, N. Van Roy, S.J. Vermeulen, R. Savarirayan, W. Van Hul, F. Vanhoenacker, D. Huylebroeck, A. De Paepe, J.M. Naeyaert, J. Vandesompele, F. Speleman, K. Verschueren, P.J. Coucke and G.R. Mortier. Loss-of-function mutations in LEMD3 result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis. Nat Genet 36 (2004) 1213-1218.**
- [112] **H. Waterham, J. Koster, P. Mooyer, G.G. Noort, R. Kelley, W. Wilcox, R. Wanders, R. Hennekam and J. Oosterwijk. Autosomal Recessive HEM/Greenberg Skeletal Dysplasia Is Caused by 3beta-Hydroxysterol Delta14-Reductase Deficiency Due to Mutations in the Lamin B Receptor Gene. Am J Hum Genet 72 (2003) 1013-1017.**
- [113] **F. Gros-Louis, N. Dupre, P. Dion, M.A. Fox, S. Laurent, S. Verreault, J.R. Sanes, J.P. Bouchard and G.A. Rouleau. Mutations in SYNE1 lead to a newly discovered form of autosomal recessive cerebellar ataxia. Nat Genet 39 (2007) 80-85.**

- [114] L. Basel-Vanagaite, L. Muncher, R. Straussberg, M. Pasmanik-Chor, M. Yahav, L. Rainshtein, C.A. Walsh, N. Magal, E. Taub, V. Drasinover, H. Shalev, R. Attia, G. Rechavi, A.J. Simon and M. Shohat. Mutated nup62 causes autosomal recessive infantile bilateral striatal necrosis. *Ann Neurol* 60 (2006) 214-222.
- [115] P. Gonzalez-Alegre and H.L. Paulson. Aberrant cellular behavior of mutant torsinA implicates nuclear envelope dysfunction in DYT1 dystonia. *J Neurosci* 24 (2004) 2593-2601.
- [116] T.V. Naismith, J.E. Heuser, X.O. Breakefield and P.I. Hanson. TorsinA in the nuclear envelope. *Proc Natl Acad Sci U S A* 101 (2004) 7612-7617.
- [117] R.E. Goodchild and W.T. Dauer. Mislocalization to the nuclear envelope: an effect of the dystonia-causing torsinA mutation. *Proc Natl Acad Sci U S A* 101 (2004) 847-852.
- [118] K. Hoffmann, C. Dreger, A. Olins, D. Olins, L. Shultz, B. Lucke, H. Karl, R. Kaps, D. Muller, A. Vaya, J. Aznar, R. Ware, N. Sotelo Cruz, T. Lindner, H. Herrmann, A. Reis and S. K. Mutations in the gene encoding the lamin B receptor produce an altered nuclear morphology in granulocytes (Pelger-Huet anomaly). *Nat Genet* 31 (2002) 410-414.
- [119] F. Muntoni, G. Bonne, L.G. Goldfarb, E. Mercuri, R.J. Piercy, M. Burke, R.B. Yaou, P. Richard, D. Recan, A. Shatunov, C.A. Sewry and S.C. Brown. Disease severity in dominant Emery Dreifuss is increased by mutations in both emerin and desmin proteins. *Brain* 129 (2006) 1260-1268.
- [120] M. Bakay, Z. Wang, G. Melcon, L. Schiltz, J. Xuan, P. Zhao, V. Sartorelli, J. Seo, E. Pegoraro, C. Angelini, B. Shneiderman, D. Escolar, Y.W. Chen, S.T. Winokur, L.M. Pachman, C. Fan, R. Mandler, Y. Nevo, E. Gordon, Y. Zhu, Y. Dong, Y. Wang and E.P. Hoffman. Nuclear envelope dystrophies show a transcriptional fingerprint suggesting disruption of Rb-MyoD pathways in muscle regeneration. *Brain* 129 (2006) 996-1013.

- [121] G. Melcon, S. Kozlov, D.A. Cutler, T. Sullivan, L. Hernandez, P. Zhao, S. Mitchell, G. Nader, M. Bakay, J.N. Rottman, E.P. Hoffman and C.L. Stewart. **Loss of emerin at the nuclear envelope disrupts the Rb1/E2F and MyoD pathways during muscle regeneration.** *Hum Mol Genet* 15 (2006) 637-651.
- [122] C.A. Sewry, S.C. Brown, E. Mercuri, G. Bonne, L. Feng, G. Camici, G.E. Morris and F. Muntoni. **Skeletal muscle pathology in autosomal dominant Emery-Dreifuss muscular dystrophy with lamin A/C mutations.** *Neuropathol Appl Neurobiol* 27 (2001) 281-290.
- [123] L. Verga, M. Concardi, A. Pilotto, O. Bellini, M. Pasotti, A. Repetto, L. Tavazzi and E. Arbustini. **Loss of lamin A/C expression revealed by immuno-electron microscopy in dilated cardiomyopathy with atrioventricular block caused by LMNA gene defects.** *Virchows Arch* 443 (2003) 664-671.
- [124] R.D. Goldman, D.K. Shumaker, M.R. Erdos, M. Eriksson, A.E. Goldman, L.B. Gordon, Y. Gruenbaum, S. Khuon, M. Mendez, R. Varga and F.S. Collins. **Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome.** *Proc Natl Acad Sci U S A* 101 (2004) 8963-8968.
- [125] A. Fidzianska, D. Toniolo and I. Hausmanowa-Petrusewicz. **Ultrastructural abnormality of sarcolemmal nuclei in Emery-Dreifuss muscular dystrophy (EDMD).** *J Neurol Sci* 159 (1998) 88-93.
- [126] N.M. Maraldi, S. Squarzoni, P. Sabatelli, G. Lattanzi, A. Ognibene and F.A. Manzoli. **Emery-Dreifuss muscular dystrophy, nuclear cell signaling and chromatin remodeling.** *Adv Enzyme Regul* 42 (2002) 1-18.
- [127] A. Ognibene, P. Sabatelli, S. Petrini, S. Squarzoni, M. Riccio, S. Santi, M. Villanova, S. Palmeri, L. Merlini and N.M. Maraldi. **Nuclear changes in a case of X-linked Emery-Dreifuss muscular dystrophy.** *Muscle Nerve* 22 (1999) 864-869.
- [128] T. Sullivan, D. Escalante-Alcalde, H. Bhatt, M. Anver, N. Bhat, K. Nagashima, C.L. Stewart and B. Burke. **Loss of A-type lamin expression compromises**

- nuclear envelope integrity leading to muscular dystrophy. *J Cell Biol* 147 (1999) 913-920.
- [129] Y. Wang, A.J. Herron and H.J. Worman. Pathology and nuclear abnormalities in hearts of transgenic mice expressing M371K lamin A encoded by an LMNA mutation causing Emery-Dreifuss muscular dystrophy. *Hum Mol Genet* 15 (2006) 2479-2489.
- [130] D.K. Shumaker, T. Dechat, A. Kohlmaier, S.A. Adam, M.R. Bozovsky, M.R. Erdos, M. Eriksson, A.E. Goldman, S. Khuon, F.S. Collins, T. Jenuwein and R.D. Goldman. Mutant nuclear lamin A leads to progressive alterations of epigenetic control in premature aging. *Proc Natl Acad Sci U S A* 103 (2006) 8703-8708.
- [131] G. Lattanzi, M. Columbaro, E. Mattioli, V. Cenni, D. Camozzi, M. Wehnert, S. Santi, M. Riccio, R. Del Coco, N.M. Maraldi, S. Squarzoni, R. Foisner and C. Capanni. Pre-Lamin A processing is linked to heterochromatin organization. *J Cell Biochem* 102 (2007) 1149-1159.
- [132] P. Scaffidi and T. Misteli. Lamin A-dependent nuclear defects in human aging. *Science* 312 (2006) 1059-1063.
- [133] M. Columbaro, C. Capanni, E. Mattioli, G. Novelli, V.K. Parnaik, S. Squarzoni, N.M. Maraldi and G. Lattanzi. Rescue of heterochromatin organization in Hutchinson-Gilford progeria by drug treatment. *Cell Mol Life Sci* 62 (2005) 2669-2678.
- [134] A.L. Olins, B. Buendia, H. Herrmann, P. Lichter and D.E. Olins. Retinoic acid induction of nuclear envelope-limited chromatin sheets in HL-60. *Exp Cell Res* 245 (1998) 91-104.
- [135] A.D. Friedman. Transcriptional regulation of granulocyte and monocyte development. *Oncogene* 21 (2002) 3377-3390.



- [136] S.T. Kosak, D. Scalzo, S.V. Alworth, F. Li, S. Palmer, T. Enver, J.S. Lee and M. Groudine. Coordinate gene regulation during hematopoiesis is related to genomic organization. *PLoS Biol* 5 (2007) e309.
- [137] K. Theilgaard-Monch, L.C. Jacobsen, R. Borup, T. Rasmussen, M.D. Bjerregaard, F.C. Nielsen, J.B. Cowland and N. Borregaard. The transcriptional program of terminal granulocytic differentiation. *Blood* 105 (2005) 1785-1796.
- [138] J. Cronshaw, A. Krutchinsky, W. Zhang, B. Chait and M. Matunis. Proteomic analysis of the mammalian nuclear pore complex. *J Cell Biol* 158 (2002) 915-927.
- [139] M. Dreger, L. Bengtsson, T. Schoneberg, H. Otto and F. Hucho. Nuclear envelope proteomics: novel integral membrane proteins of the inner nuclear membrane. *Proc Natl Acad Sci U S A* 98 (2001) 11943-11948.
- [140] M.P. Rout, J.D. Aitchison, A. Suprapto, K. Hjertaas, Y. Zhao and B.T. Chait. The yeast nuclear pore complex: composition, architecture, and transport mechanism. *J Cell Biol* 148 (2000) 635-651.
- [141] E.C. Schirmer and L. Gerace. The nuclear membrane proteome: extending the envelope. *Trends Biochem Sci* 30 (2005) 551-558.
- [142] D. Tunnah, C.A. Sewry, D. Vaux, E.C. Schirmer and G.E. Morris. The apparent absence of lamin B1 and emerin in many tissue nuclei is due to epitope masking. *J Mol Histol* 36 (2005) 337-344.
- [143] L. Bengtsson and K.L. Wilson. Multiple and surprising new functions for emerin, a nuclear membrane protein. *Curr Opin Cell Biol* 16 (2004) 73-79.
- [144] G. Novelli, A. Muchir, F. Sangiuolo, A. Helbling-Leclerc, M. D'Apice, C. Massart, F. Capon, P. Sbraccia, M. Federici, R. Lauro, C. Tudisco, R. Pallotta, G. Scarano, B. Dallapiccola, L. Merlini and G. Bonne. Mandibuloacral dysplasia is caused by a mutation in LMNA-encoding lamin A/C. *Am J Hum Genet* 71 (2002) 426-431.
- [145] F. Caux, E. Dubosclard, O. Lascols, B. Buendia, O. Chazouilleres, A. Cohen, J. Courvalin, L. Laroche, J. Capeau, C. Vigouroux and S. Christin-Maitre. A new

**clinical condition linked to a novel mutation in lamins A and C with generalized lipoatrophy, insulin-resistant diabetes, disseminated leukomelanodermic papules, liver steatosis, and cardiomyopathy. J Clin Endocrinol Metab 88 (2003) 1006-1013.**

**[146] A.B. Csoka, H. Cao, P.J. Sammak, D. Constantinescu, G.P. Schatten and R.A. Hegele. Novel lamin A/C gene (LMNA) mutations in atypical progeroid syndromes. J Med Genet 41 (2004) 304-308.**

**[147] L. Chen, L. Lee, B.A. Kudlow, H.G. Dos Santos, O. Sletvold, Y. Shafeghati, E.G. Botha, A. Garg, N.B. Hanson, G.M. Martin, I.S. Mian, B.K. Kennedy and J. Oshima. LMNA mutations in atypical Werner's syndrome. Lancet 362 (2003) 440-445.**