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Role of the Nuclear Lamina in Genome Organization and Gene Expression

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The nuclear lamina is a major structural component of metazoan nuclei that has long been thought to provide an anchoring site for interphase chromosomes and have a role in gene regulation. Recent genome-wide mapping studies and functional experimental data strongly support these roles of the nuclear lamina. Here, we discuss new insights into various aspects of genome–nuclear lamina interactions, with emphasis on the links with gene regulation and with dynamics during cellular differentiation.

The nucleoplasmic surface of the nuclear envelope (NE) in metazoans is coated by a filamentous network of proteins, termed the nuclear lamina (NL) (Dechat et al. 2008; Prokocimer et al. 2009). The major components of the mammalian NL are A-type lamins A and C, which are variants derived from the single *LMNA* gene, and B-type lamins, expressed from separate *LMNB1* and *LMNB2* genes. B-type lamins are expressed throughout development in all cell types, whereas lamins A and C become expressed only after embryonic day 9 (E9) in mouse embryos (Rober et al. 1989) and are undetectable in both human or mouse cultured embryonic stem cells (ESCs) (Stewart and Burke 1987; Constantinescu et al. 2006). Nematodes only have one, ubiquitously expressed, lamin gene (Liu et al. 2000), whereas *Drosophila* have a single A-type and a single B-type lamin gene that show a similar developmental expression pattern as that of mammalian A- and B-type lamins (Riemer et al. 1995).

The NL is tightly associated with the inner nuclear membrane (INM). This association is mediated by transmembrane proteins such as lamin B receptor (LBR) emerin and lamin-associated protein 2 β (LAP2β), both of which are inserted into the INM and interact specifically with lamins (Wilson and Foisner 2010). The NE is interspersed with nuclear pore complexes (NPCs) that span across the nuclear membrane and form the transport channels between the nuclear interior and the cytoplasm (Hetzer and Wente 2009; Xylourgidis and Fornerod 2009). NPCs tend to be located at gaps in the NL, indicating that they should not be considered part of the NL (Schermelleh et al. 2008). The NE contains many other, often still poorly characterized, proteins (Schirmer et al. 2003; Batrakou et al. 2009) that may be involved in NL functions.

One function of the NL is to provide sturdiness to the nucleus, which may be of particular importance in tissues such as muscle and skin that are under frequent physical strain. Indeed, depletion of lamins affects nuclear shape and reduces resistance to external forces (Lammerding et al. 2006; Shimi et al. 2008). Yet the remarkably broad range of phenotypes that result from loss or mutation of lamins and lamin-interacting proteins indicates that each of these proteins has not only a structural function but also important regulatory roles. For example, lamin B1 and B2$^{-/-}$ mice die immediately after birth as a result of lung and bone cerebral defects, respectively (Vergnes et al. 2004; Coffinier et al. 2010), whereas deletion of lamin A causes severe muscular dystrophy (Sullivan et al. 1999), defects in B- and T-cell development (Hale et al. 2010), and loss of differentiation potential in muscle cells (Frock et al. 2006). In *Drosophila*, loss of the single B-type lamin causes defects in locomotion, tracheal development, and nuclear positioning in the oocyte and eye (Lenz-Bohme et al. 1997; Guillemin et al. 2001; Patterson et al. 2004), whereas deletion of the sole A-type lamin causes lethality (Schulze et al. 2005). In humans, a perplexing spectrum of disorders has been linked to mutations in lamins and other NL proteins, including premature ageing, muscular distrophies, lipodistrophies, and insulin resistance (for review, see Worman et al. 2010). The etiology of these disorders is not understood but it is becoming increasingly clear that the NL has major roles in the organization of chromatin and regulation of gene expression. Here, we focus on recent findings regarding these basic functions of the NL.

MICROSCOPY OF CHROMATIN AT THE NL

Over the years, microscopy studies have extensively characterized chromatin at the nuclear periphery. Early microscopy already suggested a difference in the nature of chromatin between the nuclear interior and its periphery (Moses 1956, and references therein). General staining of chromatin showed that a denser form of chromatin accumulates at the periphery. Later, it was found that peripheral chromatin tends to replicate later in S phase (O'Keefe et al. 1992) than internal chromatin, exhibits low transcriptional activity (Jackson et al. 1993), and tends to lack histone modifications that mark active genes (Sadoni et al. 1999; Bartova et al. 2005). These and other results have led to a picture of a compact and inactive type of chromatin at the nuclear periphery.

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Fluorescence in situ hybridization (FISH) has identified several genes and loci that show nonrandom positioning at the periphery. In mammals, genes that are located at the periphery are often, but not always, inactive (Takizawa et al. 2008). In addition, entire chromosomes can exhibit preferred positions relative to the NE (Croft et al. 1999; Bolzer et al. 2005). These observations are crucial to our understanding of nuclear organization. But FISH microscopy has two drawbacks. First, its resolution is not high enough to discriminate positioning near the NL from molecular contact with the NL. Second, only a few loci can be visualized simultaneously, making it difficult to build a comprehensive picture of chromosome organization relative to the NL.

MOLECULAR MAPPING OF GENOME–NL INTERACTIONS BY DamID

Some of the limitations of microscopy approaches have now been overcome by DamID, a genome-wide molecular mapping approach that readily identifies genome–NL contacts as they occur in vivo (outlined in Fig. 1A). This technique uses DNA adenine methyltransferase (Dam), an enzyme from *Escherichia coli* that methylates adenines in the sequence motif GATC of double-stranded DNA. When Dam is fused to a NL protein such as a lamin and expressed in living cells, it will be targeted to the NL. Any DNA in molecular proximity of this fusion protein will become methylated by Dam. Because adenine methylation is not endogenously present in most eukaryotes, this results in a unique and stable "footprint" on the DNA in contact with the NL. After a period of time (typically 24–48 h), the genomic DNA is isolated, and by using restriction endonucleases that specifically recognize adenine-methylated GATC sequences, it is possible to purify or selectively amplify all adenine-methylated DNA fragments (Greil et al. 2006; Vogel et al. 2007). These are subsequently labeled and hybridized to a genomic tiling microarray. By comparing the methylation pattern obtained with the Dam-fusion protein to that of unfused Dam (that can freely diffuse throughout the nucleus), genomic regions that specifically interact with the NL can be identified (Fig. 1B).

LAMINA-ASSOCIATED DOMAINS

A striking feature of NL interaction maps is their block-like pattern: Large genomic domains with strong NL interactions alternate with similarly long stretches of low interaction levels (Figs. 1A,B and 2A). DamID maps in human and mouse cells show that lamina-associated domains (LADs) range from 50 kb to 10 Mb in size, with a median of ~0.5 Mb. Both human and mouse genomes have ~1100–1400 LADs that are distributed over all chro-

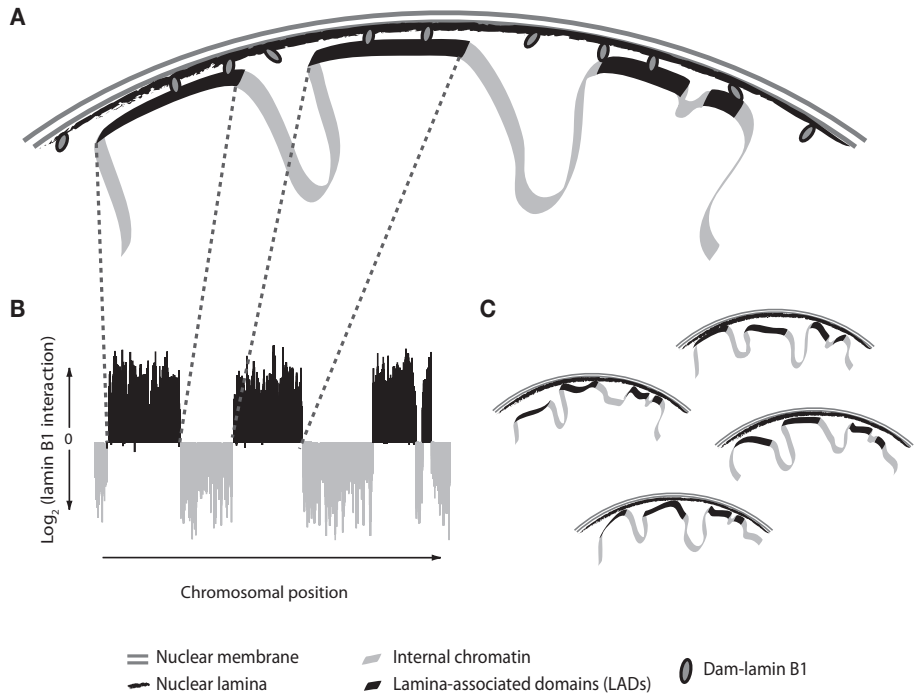

Figure 1. (*A*) Illustration of chromosomal organization in an interphase nucleus, with chromosomes organized into lamina-associated domain (LADs) (black) and inter-LADs (light gray). During DamID, a Dam-lamin B1 fusion protein (black rimed ovals) is incorporated in the NL. This fusion protein then methylates any chromatin that comes into contact with the NL. (*B*) A simulated lamin B1-binding profile as expected, based on *A*. A positive $\log_2$ (Dam-lamin B1:Dam) ratio on the *y* axis represents lamina interaction (black), whereas negative ratios represent inter-LADs (light gray). Interactions are measured, on average, every 1 kb (according to the resolution of the microarray used) and plotted along the *x* axis to generate a chromosomal map. (*C*) Potential stochastic interactions of the genome and the NL in a population of cells showing many different possible genome–NL interactions. The DamID profile of a population of such mixed conformations would look like *B*.

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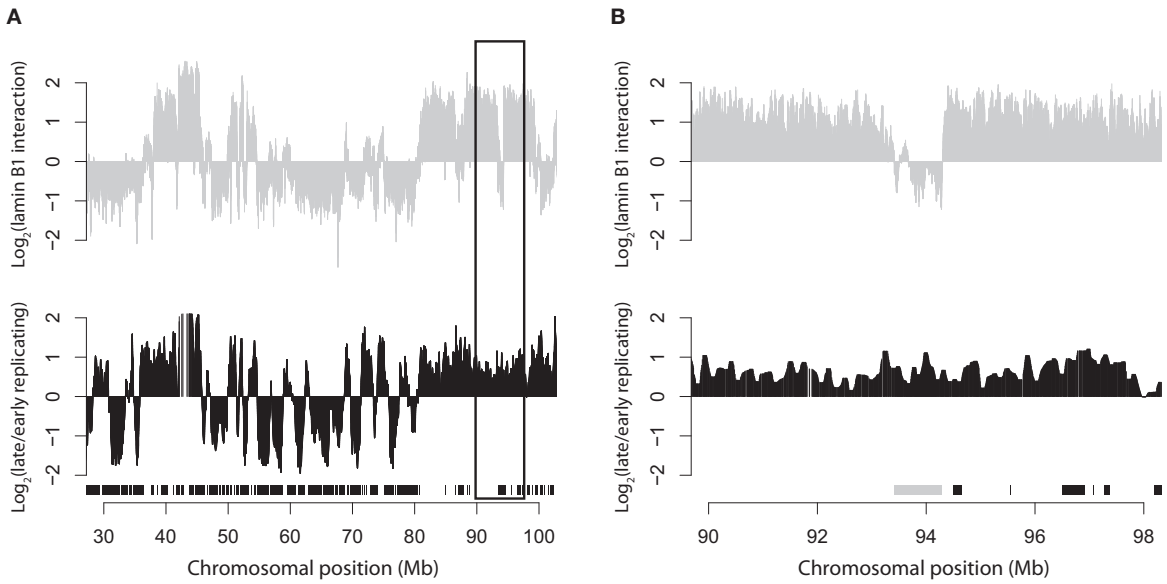

Figure 2. Relationship between genome-NL interactions and replication timing. (*A*) Partial map of mouse chromosome 14 comparing lamin B1 interactions (light gray) (Peric-Hupkes et al. 2010) to replication timing (dark gray) (Hiratani et al. 2008) in neural precursor (NP) cells. (*B*) Close-up of boxed region in *A* that contains *Pcdh9* (light gray box), a gene that becomes activated in NP cells. Black boxes represent genes.

mosomes. Some chromosomes (such as human chromosome 19) have a lower LAD density, which correlates with their more interior radial position inside the nucleus (Guelen et al. 2008; Peric-Hupkes et al. 2010). A similar discrete LAD pattern is observed in *Drosophila* cells (Pickersgill et al. 2006; van Bemmel et al. 2010). Thus, this remarkable domain organization appears to be conserved over millions of years of metazoan evolution.

Overall, gene density in LADs is ~1.5-fold to 2-fold lower inside LADs compared to inter-LAD regions. Nevertheless, LADs all together harbor thousands of genes. Remarkably, the vast majority of these genes are transcriptionally silent: their mRNA expression levels are very low, and the promoters of LAD genes lack RNA polymerase II and histone modifications that are typical of active transcription (Pickersgill et al. 2006; Guelen et al. 2008; Peric-Hupkes et al. 2010). Thus, LADs represent a strongly repressive chromatin type (see below).

In mammals, LADs have sharp borders and are often demarcated by specific features, such as binding of CTCF, promoters directed outward from the LAD, and CpG islands. These elements occur preferentially just outside the LADs (within a few kilobase of the LAD borders), suggesting that they may block expansion of the LAD. The presence of such sequence elements suggests that LAD organization is at least, in part, "hard coded" in the genome. However, many LAD borders lack these three features, suggesting that additional unknown sequence elements might demarcate LAD borders. The binding of CTCF at LAD borders is especially intriguing because this protein is thought to be involved in higher-order folding of chromatin (Zlatanova and Caiafa 2009; Ohlsson et al. 2010) and could thus provide an additional link between LADs and chromosomal organization.

LADs AND REPRESSIVE EPIGENETIC MODIFICATIONS

Several marks of repressive chromatin are linked to LADs, but the relationships may be somewhat complex. Histone H3 lysine 9 dimethylation (H3K9me2), a modification that is bound by heterochromatin protein 1 (HP1), is enriched in mammalian LADs (Guelen et al. 2008; Wen et al. 2009). In contrast, in *Drosophila*, the genomic interaction patterns of HP1 and lamin are nonoverlapping (Pickersgill et al. 2006; Filion et al. 2010), indirectly indicating that H3K9me2 heterochromatin in fruit flies is distinct from LADs. The hallmark of Polycomb-mediated repression, H3K27me3, is only modestly enriched in LADs in both *Drosophila* and mammals (Pickersgill et al. 2006; Guelen et al. 2008). That the overlap of LADs and other repressive chromatin types is incomplete suggests that LADs may, in part, constitute a still uncharacterized type of repressive chromatin.

The timing of DNA replication during S phase varies along the genome in a block-like pattern (Schubeler et al. 2002; MacAlpine et al. 2004; Farkash-Amar et al. 2008; Hiratani et al. 2008; Schwaiger et al. 2009). Interestingly, late-replicating domains generally overlap with LADs (Pickersgill et al. 2006; Peric-Hupkes et al. 2010; Yaffe et al. 2010), which is consistent with cytological observations that mid- to late-replicating DNA tends to be located near the nuclear periphery (O'Keefe et al. 1992). However, a more detailed inspection reveals that this correlation between late replication and NL interactions may not be perfect: It tends to break down at borders of LADs and at individual transcription units (Fig. 2A,B) (see also Peric-Hupkes et al. 2010). Thus, late-replicating regions and LADs are related but not always identical.

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STOCHASTIC NATURE OF NL INTERACTIONS

Approximately 35%–40% of the mammalian genome consists of LADs (Guelen et al. 2008; Peric-Hupkes et al. 2010). How can such a large portion of the genome be in contact with the NL? Comparison to microscopy data provides an important clue. Whereas FISH of individual genomic loci clearly shows that LADs are preferentially located at the nuclear periphery compared to inter-LADs, this is not true in every single cell of a population (Pickersgill et al. 2006; Guelen et al. 2008; Peric-Hupkes et al. 2010). Instead, contacts between LADs and the NL appear to be stochastic. Within a population of cells, the chromosomes can adopt many different conformations in individual cells (Fig. 1C), with a given locus only represented at the NL in a subpopulation of cells. When viewed over a population of cells, this results in a distinct pattern of LADs and inter-LADs (Fig. 1B). Due to the limited resolution of FISH (and possible disruptive effects of the harsh denaturing conditions) it is difficult to determine exactly how frequently a particular LAD is in molecular contact with the NL; however, rough estimates suggest a frequency range of 10%–50% in a population of unsynchronized cells (Pickersgill et al. 2006).

This stochastic behavior may be an intrinsic property of the chromatin fiber. First, live cell imaging has shown that most chromosomal loci exhibit constrained Brownian motion of <0.5 µm (Marshall et al. 1997; Heun et al. 2001; Chubb et al. 2002). In addition, movements over longer distances have been observed, particularly early in G_1 phase (Vazquez et al. 2001; Thomson et al. 2004). Second, after mitosis, the positioning of entire chromosomes inside the newly formed nucleus shows a substantial random component (Bolzer et al. 2005). As a consequence, in each nucleus, some chromosomes may be randomly "trapped" in the nuclear interior, and thus the LADs on these chromosomes may not contact the NL.

LADs AND THE FINE DISTRIBUTION OF LAMINS

A detailed light microscopy study in differentiated mammalian cells has suggested that the NL is not homogeneous: There appear to be patches of NL where both A- and B-type lamins are present, intermingled with patches composed exclusively of A- or B-type lamins (Shimi et al. 2008). Depletion of lamin B1 enhances the separation of lamin B2 and A/C regions, where gene-rich euchromatin preferentially associates with A/C-type lamin patches. These results raise the possibility that also under normal conditions, distinct genomic regions interact with each lamin type. In addition, it may be of importance that lamins (particularly A type) are present at relatively low but detectable concentrations in the nuclear interior (Broers et al. 1999; Moir et al. 2000). Perhaps these internal lamins also interact with specific loci in the genome. Comparative genome-wide mapping the interaction patterns of all A- and B-type lamins should provide insight into these issues.

NL–GENOME INTERACTION DYNAMICS DURING DEVELOPMENT

Detailed studies of selected genes using FISH have shown that changes in transcription during differentiation of ESCs correlate with changes in nuclear localization (Williams et al. 2006; Hepperger et al. 2008; Hiratani et al. 2008). During nematode development, tissue-specific promoters driving reporter genes showed basically the same behavior. The reporter gene arrays localized to the periphery when inactive and moved toward the interior following tissue-specific activation (Meister et al. 2010). Thus, silent loci tend to move toward the nuclear interior upon activation.

We recently used DamID to visualize changes in molecular NL contacts of the entire genome during the differentiation of mouse ESCs via neural precursor (NP) cells into astrocytes (ACs). This well-established in vitro differentiation system provides an excellent model to reveal the dynamics of chromatin folding during lineage commitment and terminal differentiation. The DamID results yielded several interesting insights (Peric-Hupkes et al. 2010).

First, as in differentiated cells, the genome of ESCs shows a clear LAD organization (Fig. 3); the number and size distribution of LADs is similar to those in differentiated cells. It has been proposed that chromatin is more plastic in mammalian ESCs compared to chromatin in differentiated cells (Meshorer and Misteli 2006), and in nematodes the positioning of tissue-specific genes appears mostly random in nuclei of early embryonic cells, whereas the positioning is linked to gene activity in differentiated cells (Meister et al. 2010). Nevertheless, the genome-wide DamID data indicate that a clear NL–genome interaction structure is present in mouse ESCs.

Second, this basal structure as found in ESCs is progressively modified during subsequent steps of differentiation (Fig. 3). In each step, ~10% of all genes show increased or decreased interactions with the NL. Most genes that change position from ESCs to NP cells keep their new position in the next differentiation step from NP cells to ACs; in other words, refolding of the genome is cumulative in sequential differentiation steps. Single genes as well as clusters of neighboring genes are found to relocate. For single genes, the changes in NL interactions are typically limited to the transcription unit, suggesting that contacts with the NL can be regulated locally.

Third, loss of NL interaction often correlates with increased transcription and vice versa. However, a subset of silent genes that dissociate from the NL following the ESC→NP cell transition are not activated right away but rather have a higher propensity to become expressed at later stages of differentiation. Conversely, silent genes that move toward the NL in the first differentiation step are less likely to be activated later. This suggests that the NL helps to stably repress genes, and detachment from the NL can "unlock" a gene for activation at a later stage in development (Fig. 3).

Taken together, these genome-wide maps of NL interactions indicate that chromosomes are extensively reshaped during differentiation and suggest that mechanisms exist to specifically relocate defined loci toward and from the NL.

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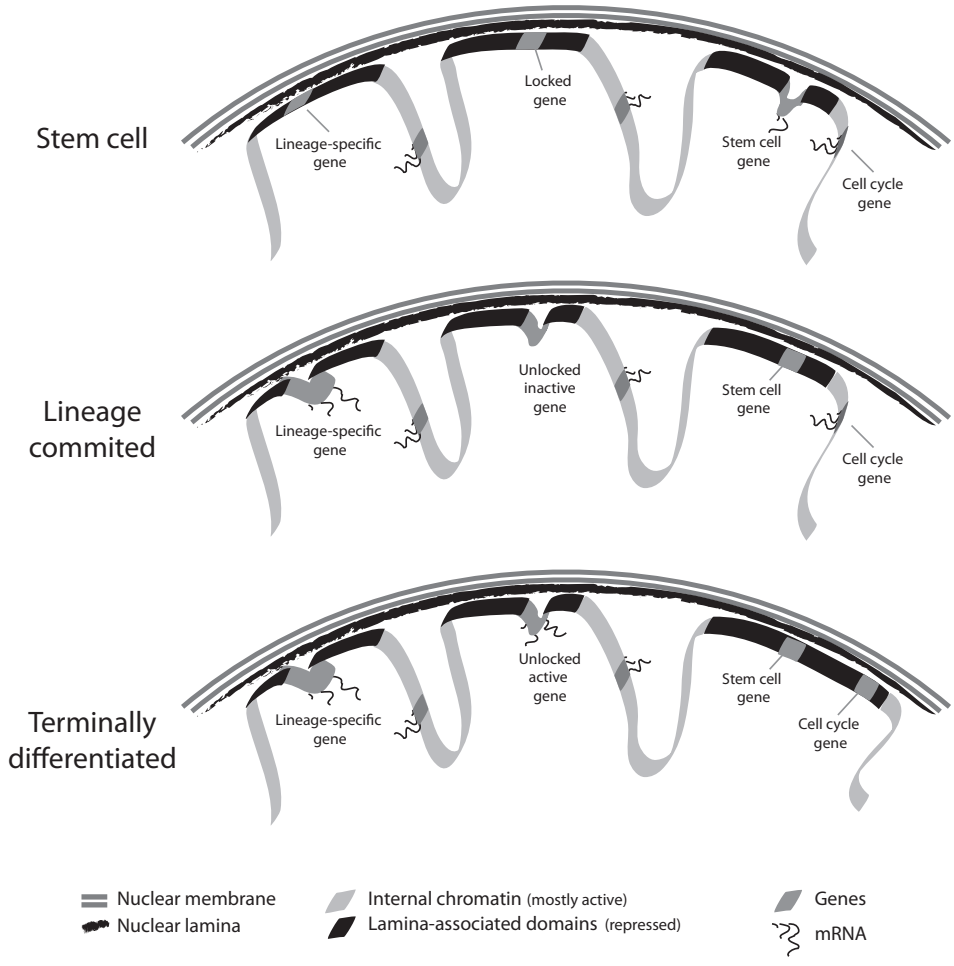

Figure 3. Model of dynamic reshaping of NL-genome interactions during the stem cell→lineage-committed and subsequent lineage-committed→terminal differentiaton steps (Peric-Hupkes et al. 2010). Active genes are generally in the nuclear interior and genes at the NL are mostly inactive. Following activation, genes tend to relocate to the nuclear interior (see lineage-specific gene) and certain groups of silenced genes increase their interaction with the NL (see stem cell and cell cycle genes). A subclass of genes (locked genes) becomes activated in a two-step manner: First, they move away from the NL without activation (unlocked inactive gene) and subsequently become activated (unlocked activated gene) during the next step of differentiation.

THE NL AND GENE SILENCING: CAUSE AND EFFECT

Additional evidence indicates that the NL directly contributes to gene repression. Studies in mammalian cells and in *Drosophila* used the physical interaction between the LacO-binding sequence and fusion proteins of LacI and various NL components to target selected genomic loci to the NL. This demonstrated that the expression levels of reporter genes and endogenous genes can be reduced when these genes are forced to interact with the NL (Finlan et al. 2008; Reddy et al. 2008). The magnitude of the repressive effect is highly variable, ranging from virtually no detectable effect (Kumaran and Spector 2008) to a >90% reduction in gene activity. Interestingly, the response to NL tethering depends on the promoter that drives the reporter gene and on the genomic integration site of the reporter construct (Dialynas et al. 2010). Such position- or promoter-dependent effects may underlie our observation that some endogenous genes can be active despite being located inside a LAD (Guelen et al. 2008). The molecular basis of this differential sensitivity to NL-mediated silencing remains to be resolved.

The second line of evidence comes from knockdown of various NL components. In *Drosophila*, depletion of B-type lamin led to activation of genes that were previously in contact with the NL (Shevelyov et al. 2009), arguing for a direct repressive effect of the NL. Knockdown and knockout experiments of lamins in mouse and human, however, show mixed results. Mutations in lamin A/C affect gene expression in several ways, in part depending on the mutation (Andrés 2009). Knockdown of B-type lamins can give rise to apoptosis (Harborth et al. 2001), lead to an increase in active transcription marks but not in transcription (Shimi et al. 2008), influence the expression of a wide array of genes (Malhas et al. 2007), and even cause loss of transcription (Tang et al. 2008). At present, it is difficult to combine these results from mammalian cells

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into a simple model. It is likely that the roles of NL components in gene regulation are diverse and cell-type specific. To what extent the observed effects on gene activity are direct or indirect consequences also remains to be resolved.

Although the NL tethering experiments in mammalian cells and the lamin B knockout effects on gene expression in *Drosophila* clearly indicate that the NL has an active role in gene repression, this does not rule out that the inverse is also true: Genes may relocate as a consequence of changes in their transcriptional activity. The latter model is supported by the observation that an inactive transgene array located near the NL can move to the nuclear interior as the result of the targeting of a transcriptional activator to the array (Chuang et al. 2006). We therefore suggest that causality between nuclear location and gene activity may work both ways: Following repression, some genes may relocate to the NL, where their inactive state is "locked" by the additional repressive effects of the NL. Conversely, activation of a gene may cause it to move to the nuclear interior, where it is no longer under the repressive influence of the NL and thus remains stably active. This dual positive-feedback system may contribute to the establishment of robust gene-expression programs during cellular differentiation.

INTERACTIONS OF THE GENOME WITH NPCs

It has now become clear that proteins of the NPCs also interact with specific sites of the genome (Brown et al. 2008; Capelson et al. 2010; Kalverda et al. 2010; Vaquerizas et al. 2010). Some of these interactions involve NPC proteins that are freely diffusing throughout the nucleoplasm, but the NPCs themselves can also bind hundreds of genes. Unlike NL-associated genes, NPC-associated genes are typically active. Thus, the NPC and the NL are functionally distinct compartments of the NE, which is consistent with their spatial separation (Schermelleh et al. 2008). Interestingly, NPC composition varies during differentiation and has an active role in neuronal differentiation (Lupu et al. 2008).

SUMMARY AND OUTLOOK

In summary, recent research has yielded important new insights into the role of the NL in gene regulation. The genomes of flies and mammals interact with the NL through hundreds of large, discrete LADs. These interactions appear to be, in part, stochastic. Most genes in LADs are repressed, and NL interactions directly contribute to this repression. Finally, during differentiation, hundreds of genes can relocate relative to the NL, and changes in NL interactions may contribute to the regulation of these genes. Despite these exciting advances, many questions remain, particularly with regard to the molecular mechanisms that underlie genome–NL interactions and the effects on gene expression.

One major question is the extent to which NL interactions of the genome are driven by primary sequence. For example, are there specific sequence elements in LADs that mediate NL interactions? A combination of bioinformatics and extensive experimental testing will be needed to identify any DNA sequences that control NL interactions. Such sequences are likely to be different for constitutive (cell-type invariant) and facultative (cell-type dependent) NL interactions.

It is also likely that chromatin has a key role in genome–NL interactions. Lamins have been reported to interact with nucleosomes (Goldberg et al. 1999), and it is conceivable that certain posttranslational modifications of histones modulate such interactions. Various other chromatin components, e.g., heterochromatin proteins, can interact with NL components, but how these interactions contribute to genome–NL interactions is still largely unclear.

Similarly, the NL itself harbors numerous proteins that could be involved in genome interactions. Many NL proteins have been found to interact with DNA-binding and chromatin proteins (Taddei et al. 2004; Wilson and Foisner 2010). Yet many other proteins in the NL and INM have remained uncharacterized thus far (Schirmer and Gerace 2005). Given that 35%–40% of the genome interacts with the NL, it is likely that a wide range of proteins have evolved to contribute to and regulate these interactions.

Finally, it will be crucial to gain better understanding of the dynamics of genome–NL interactions. New microscopy techniques with subdiffraction resolution may provide detailed views of the stochastic nature of these interactions and the underlying mechanisms. Perhaps it will be possible to scale DamID mapping down to single cells. All in all, there are many more exciting questions regarding the dynamics of genome–NL interactions to answer in the future.

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