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Nuclear Lamins and Chromatin: When Structure Meets Function

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Introduction

The nucleus of eukaryotic cells can be sub-divided into three main compartments: chromatin, intranuclear non-membrane bound complexes (which more or less act like cytoplasmic “organelles”), and the nuclear envelope (NE) (Schneider and Grosschedl, 2007; Spector, 2006; Verstraeten *et al.*, 2007). The NE is composed of the outer and inner nuclear membrane (INM), nuclear pore complexes (NPCs) and the nuclear lamina. The latter is a proteinaceous meshwork underlying the INM and is connected to NPCs (Aaronson and Blobel, 1975). There is also evidence for a structural meshwork inside the nucleus (Barboro *et al.*, 2002; Hozak *et al.*, 1995; Vlcek *et al.*, 2001). This internal nucleoskeleton together with the peripheral lamina forms a scaffold which is involved in chromatin organization and the correct spatial and temporal progression of nuclear processes such as DNA replication and transcription (Bridger *et al.*, 2007; Dechat *et al.*, 2008; Dorner *et al.*, 2007). Major components of this scaffold are the nuclear lamins (Shumaker *et al.*, 2003). In this review we discuss recent findings supporting the role of lamins in the organization and regulation of chromatin.

An Overview of the Nuclear Lamins

Nuclear lamins, type V intermediate filament proteins, are divided into A- and B-types based on their sequence homologies (Broers *et al.*, 2006; Goldman *et al.*, 2002; Shumaker *et al.*, 2003). All A-type lamins are encoded by a single gene (*LMNA*). Their major isoforms are lamins A and C, which are derived by alternative splicing. The two major mammalian B-type lamins, lamins B1 and B2, are encoded by different genes (*LMNB1* and *LMNB2*). At least one lamin isoform is present in every nucleated metazoan cell (Melcer *et al.*, 2007). In mammals, expression of the A- and B-type lamins is developmentally regulated, resulting in cell type-specific complements of lamins (Broers *et al.*, 2006; Dechat *et al.*, 2008; Verstraeten *et al.*, 2007). The B-type lamins are expressed in undifferentiated human and mouse embryonic stem cells and throughout the early stages of mouse development, while A-type lamins are not expressed until day 10 in mouse development (Constantinescu *et al.*, 2006; Rober *et al.*, 1989; Stewart and Burke, 1987).

Lamin monomer structure consists of an α-helical central rod domain with globular N-terminal head and C-terminal tail domains [Figure 1; (Herrmann and Foisner, 2003; Stuurman *et al.*, 1998)]. The central rod domain forms parallel coiled-coil lamin dimers that

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subsequently assemble into higher order structures. In vitro, these structures tend to take the form of paracrystals rather than typical 10 nm intermediate filaments (Herrmann and Aebi, 2004; Melcer *et al.*, 2007). However, the actual structure of A- and B- type lamin polymers in a living cell remains unknown. Lamins contain a nuclear localization sequence (NLS) within their tail domain close to the C-terminal end of the central rod [Figure 1; (Loewinger and McKeon, 1988)]. Immediately following the NLS, a segment of the tail is folded into a structural motif similar to a type S immunoglobulin fold (Ig-fold) [Figure 1; (Dhe-Paganon *et al.*, 2002; Krimm *et al.*, 2002)]. All lamins, except for lamin C, terminate with a CAAX-box that is involved in numerous post-translational modifications including the farnesylation of the cysteine, removal of the –AAX and carboxymethylation of the cysteine (Rusinol and Sinensky, 2006; Young *et al.*, 2005). These modifications are thought to be important for the efficient targeting of the lamins to the INM (Dechat *et al.*, 2007; Krohne *et al.*, 1989; Rusinol and Sinensky, 2006). While B-type lamins remain farnesylated and carboxymethylated, lamin A is further processed by the zinc metalloproteinase, Zmpste24/FACE1, to remove an additional 15 residues from its C-terminus including the farnesylated and carboxymethylated cysteine (Corrigan *et al.*, 2005).

Lamins provide the nucleus with mechanical stability and nuclear shape and are involved in establishing connections between the nucleoskeleton and the cytoskeleton (Crisp and Burke, 2008; Dahl *et al.*, 2008; Houben *et al.*, 2007; Rowat *et al.*, 2008). Connections between these structural systems are thought to be important for signal transduction (Parnaik, 2008; Stewart *et al.*, 2007). At the onset of mitosis, lamins are disassembled in a phosphorylation dependent manner and subsequently dispersed in the cell (Fields and Thompson, 1995). During the anaphase/telophase transition they start to reassemble around segregating chromosomes (Moir *et al.*, 2000b). Recently, B-type lamins have been shown to be involved in the formation of a matrix-like network essential for the assembly of the mitotic spindle (Tsai *et al.*, 2006). In addition to their structural functions, lamins are involved in several nuclear processes such as DNA replication, transcription, DNA repair and the epigenetic organization of chromatin (Dechat *et al.*, 2008). Over the past 9 years, a large number of mutations in the human *LMNA* gene have been associated with numerous diseases including autosomal dominant Emery-Dreyfuss muscular dystrophy (AD-EDMD), familial partial lipodystrophy (FPLD), dilated cardiomyopathy, and the progeroid syndromes Hutchinson-Gilford progeria syndrome (HGPS), atypical Werner syndrome, restricted dermopathy, and mandibuloacral dysplasia type A (MADA) (Broers *et al.*, 2006; Capell and Collins, 2006; Worman and Bonne, 2007). These diseases are now collectively termed “laminopathies”.

Nuclear Lamins and Their Association with Chromatin

The organization of interphase chromosomes into specific compartments and territories within the nucleus of eukaryotic cells is essential for proper chromatin function (Dillon, 2008; Fraser and Bickmore, 2007; Kalverda *et al.*, 2008; Lanctot *et al.*, 2007; Misteli, 2007; Trinkle-Mulcahy and Lamond, 2008). There is increasing evidence that nuclear lamins play an important role in this organization. This evidence comes mainly from three experimental approaches: biochemical analyses of the interaction of lamins with chromatin/histones; microscopy; and alteration of chromatin organization and functions due to expression of mutant lamins or lamin deficiencies.

Biochemical Analyses

Lamins A/C have been shown to bind to mitotic chromosomes in vitro in a lamin B and membrane independent fashion (Burke, 1990; Glass and Gerace, 1990). In addition, A-type lamins, but not B-type lamins bind to polynucleosomal particles isolated from avian erythrocytes (Yuan *et al.*, 1991). There is evidence that the α-helical central rod domain of lamins alone is responsible for the association of human lamin A/C with mitotic

chromosomes (Glass *et al.*, 1993). This association seems to be dependent on the assembly state of the truncated lamin used, as the association is mainly observed under conditions which favor the assembly of the rod domain into higher order structures (Glass *et al.*, 1993). In addition, the C-terminal tail domains of human lamins A, C, B1 and B2 (which do not assemble into higher order structures) also bind to chromatin in vitro (Taniura *et al.*, 1995). For lamin C, the chromatin binding region maps to a 35 amino acid segment between the rod domain and the Ig-fold, suggesting that the NLS and nearby sequences are involved (Taniura *et al.*, 1995). Taken together, these results suggest that there are at least two different chromatin binding sites present in lamin A/C: one in the rod domain, which requires a higher order lamin structure, and one located in the C-terminal tail domain, which is independent of lamin polymerization and requires the NLS. The interaction of lamin A/C with chromatin is most likely mediated by chromosome-associated proteins since trypsinization of chromosomes inhibits their interactions with the rod domain of lamin C (Glass *et al.*, 1993). In further support of this, the lamin C tail binds to a core histone fraction isolated from rat liver, but not to DNA extracted from rat liver chromatin fragments (Taniura *et al.*, 1995).

The C-terminal tail domains of the B-type lamins in *Drosophila* (lamin Dm0) and *C. elegans* (LMN-1) also bind to chromosomes (Goldberg *et al.*, 1999; Mattout *et al.*, 2007). The binding of lamin Dm0 to chromosomes is independent of its polymerization state, but requires the NLS and the short region between the NLS and the rod domain. This binding can be displaced with histones H2A and/or H2B, but not with histones H1, H3 or H4 (Goldberg *et al.*, 1999). In agreement with these latter results, lamin Dm0 binds directly to histone H2A (Mattout *et al.*, 2007). This interaction requires the NLS of lamin Dm0 and the N- and C-terminal histone tails. An NLS-dependent interaction with chromosomes and histone H2A is also found for LMN-1 (Mattout *et al.*, 2007).

Besides binding to chromatin via histones, full length lamins may also bind directly to DNA (Rzepecki *et al.*, 1998; Shoeman and Traub, 1990; Stierle *et al.*, 2003). Interestingly, the interaction of lamin A/C with plasmid DNA seems to involve several residues within the Ig-fold and also the NLS (Stierle *et al.*, 2003). Cross-linking experiments using *Drosophila* K_C cells suggest that interphase but not mitotic lamin Dm0 binds to both DNA and RNA (Rzepecki *et al.*, 1998). The DNA regions thought to be associated with lamins are the scaffold/matrix attachment regions (S/MARs) (Baricheva *et al.*, 1996; Luderus *et al.*, 1992; Luderus *et al.*, 1994; Zhao *et al.*, 1996). These regions are involved in the regulation of transcription, replication and the condensation of chromosomes. They are also thought to play a role in the overall organization of chromatin within the nucleus (Gluch *et al.*, 2008). The binding of lamins to S/MARs appears to require the polymerization of the protein (Zhao *et al.*, 1996).

Microscopy

A close association of chromosome ends with the nuclear surface has been recognized since 1887 (Boveri, 1887). Early transmission electron microscopy initially describing the nuclear lamina also reveals its close association with peripheral heterochromatin (Fawcett, 1966; Patrizi and Poger, 1967). Optical sectioning studies of *Drosophila* salivary gland nuclei show that heterochromatic regions frequently localize at the NE and that the chromocenter is always apposed to the NE (Hochstrasser *et al.*, 1986). A close association of nuclear lamins with peripheral heterochromatin is also evident in combined light and electron microscopy (Belmont *et al.*, 1993; Paddy *et al.*, 1990). In addition, the heterochromatic chromocenter of polytene chromosomes co-localizes with lamin Dm0 at the nuclear periphery of *Drosophila* salivary gland cells (Baricheva *et al.*, 1996). Confocal immunofluorescence microscopy clearly demonstrates that peripheral nuclear lamins are closely associated with heterochromatin as visualized either by Hoechst staining or by antibodies directed against

methylated histones [Figure 2; (Shumaker *et al.*, 2006)]. With respect to the latter, a main fraction of histone H3 trimethylated at lysine 9 (H3K9me3), which is mainly associated with constitutive heterochromatin (Martin and Zhang, 2005; Sarma and Reinberg, 2005), localizes in close association with the inner surface of the nuclear lamina (Figure 2). Furthermore, the inactive X chromosome (Xi), a heterochromatic mass containing histone H3 trimethylated at lysine 27 (H3K27me3) (Plath *et al.*, 2003), is often closely associated with peripheral lamins [Figure 2; (Shumaker *et al.*, 2006)].

The Effects of Mutant Lamins and Altered Lamin Expression on Chromatin Structure and Function

Although all of the studies described above demonstrate that chromatin and lamins are closely associated, at least at the nuclear periphery, they do not provide evidence for a direct involvement of lamins in the organization and function of chromatin. An actual role for lamins in chromatin organization has been revealed by the study of cells derived from *LMNA* null mice. In *LMNA*$^{-/-}$ mouse embryonic fibroblasts (MEFs) and cardiomyocytes, a partial loss of peripheral heterochromatin can be observed by electron microscopy (Galiova *et al.*, 2008; Nikolova *et al.*, 2004; Sullivan *et al.*, 1999). This loss is accompanied by the condensation of chromosome territories and by the rearrangement of centromeric heterochromatin (Galiova *et al.*, 2008). Evidence for the role of lamins in chromatin organization has also been derived from studies of Herpes simplex virus infected cells. During lytic infection the cell attempts to silence the viral genome by assembling viral DNA into heterochromatin (Cereghini and Yaniv, 1984). In *LMNA*$^{-/-}$ MEFs, the viral DNA becomes even more heterochromatic compared to wild type MEFs, leading to reduced viral gene expression, DNA replication, and growth (Silva *et al.*, 2008).

Alterations in peripheral heterochromatin caused by a mutation in a nuclear lamina protein were first observed in muscle and cultured skin cells from a patient suffering from X-linked EDMD (Ognibene *et al.*, 1999). This disease is caused by a mutation in the gene encoding the lamin A binding protein, emerin (Holaska and Wilson, 2006). A detachment or loss of heterochromatin from the nuclear periphery and/or a general loss of heterochromatin is also seen in cells derived from patients suffering from diseases caused by mutations in *LMNA*. These diseases include AD-EDMD (Sabatelli *et al.*, 2001), FPLD (Capanni *et al.*, 2003), MADA (Filesi *et al.*, 2005; Lombardi *et al.*, 2007), and HGPS (Columbaro *et al.*, 2005; Goldman *et al.*, 2004). In HGPS fibroblasts the loss of heterochromatin is accompanied by changes in various epigenetic patterns; specifically, by an overall decrease in both H3K9me3 and H3K27me3, as well as an increase in tri-methylation of histone H4 at lysine 20 (H4K20me3) (Columbaro *et al.*, 2005; Scaffidi and Misteli, 2005; Shumaker *et al.*, 2006). In addition, the association of the Xi with H3K27me3 is lost and co-localization of HP1α with H3K9me3 is dramatically reduced (Shumaker *et al.*, 2006). C2C12 myoblasts expressing a lamin A protein carrying an AD-EDMD mutation A also show a loss of H3K27me3 from the Xi and a dissociation of H3K9me3 from pericentric heterochromatin (Hakelien *et al.*, 2008). These myoblasts fail to hypertrimethylate H3K4 on the myogenin gene promoter leading to impaired differentiation into myotubes. Interestingly, hypertrimethylation of H3K4, which normally leads to gene activation, is also decreased upon over-expression of wild type lamin A in C2C12 myoblasts (Hakelien *et al.*, 2008). Taken together these findings suggest that not only expression of mutant lamins, but also changes in the expression levels of wild type lamins, have an impact on chromatin organization and that defects in the epigenetic regulation of chromatin are a common feature of different types of laminopathies. Interestingly, a decrease in H3K9me3 is also observed in cells derived from healthy elderly individuals (Scaffidi and Misteli, 2006) and these cells express low levels of a mutant lamin A normally associated with HGPS (Cao *et al.*, 2007;

McClintock *et al.*, 2007; Scaffidi and Misteli, 2006) suggesting a role for lamins in the normal aging process.

Besides their roles in anchoring heterochromatin to the nuclear periphery and the epigenetic regulation of chromatin, lamins also seem to be involved in chromosome positioning. Evidence for this comes from the finding that chromosome 18 is displaced from the nuclear periphery towards the nuclear interior in cells derived from patients suffering from some types of laminopathy (Charcot-Marie-Tooth type 2 B1, limb girdle muscular dystrophy, MADA, AD-EDMD, and HGPS) (Meaburn *et al.*, 2007) and in MEFs deficient in lamin B1 (Malhas *et al.*, 2007). The change in the localization of chromosomes from the nuclear interior to the nuclear periphery and vice versa might have an impact on the transcriptional regulation of genes located on those chromosomes (see below) and thus contribute to the disease phenotypes.

The Role of Lamins in Gene Regulation

The role of the nuclear lamina and of nuclear lamins in gene expression is highlighted in several recent reviews [see (Bridger *et al.*, 2007; Dechat *et al.*, 2008; Dorner *et al.*, 2007; Heessen and Fornerod, 2007; Shaklai *et al.*, 2007; Verstraeten *et al.*, 2007)]. Therefore we will focus on the most recent studies. In general the nuclear lamina is considered as a transcriptionally inactive region. Initial evidence for the involvement of lamins in transcription comes from a dominant negative lamin mutant which specifically impairs RNA polymerase II (pol II) mediated transcription (Spann *et al.*, 2002). Furthermore, overexpression of lamins A/C in HeLa cells causes a significant decrease in pol II transcription (Kumaran *et al.*, 2002). The downregulation of lamin B1 in HeLa cells by RNAi can also lead to an inhibition of pol II transcription and subsequently also of pol I transcription (Tang *et al.*, 2008). This transcriptional inhibition is accompanied by global nuclear and chromatin changes including alterations in the structural properties of nucleoli and nuclear speckles, the translocation of chromosome territories toward the nuclear periphery, and a loss of general chromosome loop organization in nucleoids. Prolonged downregulation of lamin B1 leads to cell death. However, downregulation of lamin A/C has none of the above described effects on the structural organization of the nucleus or of chromatin (Tang *et al.*, 2008). Defects in the regulation of transcription reflected by changes in gene expression patterns are also seen in lamin B1 deficient MEFs (Malhas *et al.*, 2007) and in various laminopathies (Dechat *et al.*, 2008). Lamin A/C has also been linked to retinoblastoma regulated transcription of E2F target genes (Dechat *et al.*, 2008; Dorner *et al.*, 2007).

The interaction of lamins with DNA in living cells can be mapped by DamID labeling of DNA directly associated with specific lamins (Guelen *et al.*, 2008; Pickersgill *et al.*, 2006). In this approach, the lamin protein fused to the *E. coli* enzyme DNA adenine methyl transferase (Dam) is expressed and methylated DNA fragments are sequenced to identify DNA sequences bound by the lamin. When applied to lamin Dm0 in *Drosophila* Kc cells, DNA sequences characterized as transcriptionally inactive and lacking active histone marks are identified (Pickersgill *et al.*, 2006). These DNA sequences are enriched in large intergenic regions that replicate in mid-to late S-phase. In human lung fibroblasts, the lamin B1-associated domains (LADs) of chromosomes are identified by ectopically expressing lamin B1 fused to Dam and hybridizing amplified adenine-methylated DNA to a high-density microarray (Guelen *et al.*, 2008). These LADs are about 1 mega base in size or larger and are interspersed in a distinct pattern with regions of chromosomes associated with very low levels of lamin B1. In general the LADs display a low gene density, an enrichment in heterochromatin as reflected by the presence of pericentromeric regions, H3K27me3 and H3K9me2, and low levels of pol II and H3K4me2 (Guelen *et al.*, 2008). In addition, about

three quarters of all gene deserts (exceptionally large gene-free regions) present within the human genome are associated with LADs and genes located within LADs are 5–10 fold less active than genes outside LADs. Taken together these studies suggest that the B-type lamins are associated with a repressive environment with respect to gene expression, even though actively transcribed genes are found within LADs (Guelen *et al.*, 2008).

To investigate the role of the nuclear lamina in gene regulation in more detail three independent studies take advantage of the LacO/LacI system. Briefly the transcriptional activity of either a reporter gene stably integrated into the genome (Kumaran and Spector, 2008; Reddy *et al.*, 2008) or of whole chromosomes (Finlan *et al.*, 2008) is monitored after their relocation from the nuclear interior to the periphery. Tethering to the nuclear lamina is achieved by fusing the LacI to either lamin B1 (Kumaran and Spector, 2008), emerin (Reddy *et al.*, 2008), or the lamina-associated polypeptide (LAP) 2β (Finlan *et al.*, 2008). Data from one of these studies show that the majority of reporter genes can be expressed in the nuclear lamina region when tethered by lamin B1 (Kumaran and Spector, 2008). In support of the idea that these reporter genes are actively transcribed, recruitment of pol II, as well as of the mRNA splicing factor SF2/ASF is observed. These results suggest that the nuclear lamina does not necessarily define a transcriptionally repressive environment.

Different results are obtained in the study using emerin to tether a reporter gene to the NE (Reddy *et al.*, 2008). These analyses show that most of the tethered reporters display no or reduced transcriptional activity at the nuclear lamina. When a mutant emerin that can not tether the reporter to the NE is used, no transcriptional repression is observed (Reddy *et al.*, 2008). These results indicate that transcriptional repression of the reporter gene requires its localization at the NE at least in this system. The seemingly contradictory results from these two studies may be related to the use of different promoters and reporter genes, different tethering proteins or different cell lines. Nevertheless, they indicate that the nuclear lamina contains not only transcriptionally repressive regions, but also regions that permit gene expression. In agreement with this possibility, tethering of whole chromosomes to the nuclear lamina by LAP2β-lacI can lead to the repression of some genes, whereas other genes are unaffected (Finlan *et al.*, 2008).

Lamins in DNA Replication

Lamin B is present at sites of BrdU incorporation and at replication foci containing the proliferating cell nuclear antigen (PCNA) in late S-phase of cultured cells suggesting a role for nuclear lamins in DNA replication (Moir *et al.*, 1994). The functional significance of this finding is supported by additional experiments using the *Xenopus* egg interphase extract nuclear assembly system. For example, nuclei assembled in a lamin-depleted extract are unable to replicate their DNA (Meier *et al.*, 1991; Newport *et al.*, 1990). In such extracts PCNA is also more extractable, indicating that its association with the nucleoskeleton/chromatin is dependent on lamins (Jenkins *et al.*, 1993). Subsequent studies further show that lamins are involved in the chain elongation phase of replication. When dominant negative lamin mutants are added to interphase extracts containing *Xenopus* nuclei, they cause the redistribution of endogenous lamins into intranuclear foci and the inhibition of replication (Ellis *et al.*, 1997; Moir *et al.*, 2000a; Spann *et al.*, 1997). The lamin foci formed in this manner also contain the DNA replication elongation factors PCNA and replication factor C (RFC) (Moir *et al.*, 2000a; Spann *et al.*, 1997). However, the distribution of the DNA initiation factors, DNA polymerase α, minichromosome maintenance protein 3 (MCM3) and the origin recognition complex (ORC) protein Orc2 appear unaltered (Moir *et al.*, 2000a). Transferring these lamin-disrupted nuclei to fresh extract leads to a normal lamin distribution and to the reinitiation of the chain elongation phase of replication (Moir *et al.*, 2000a).

Recent data show that in nuclei assembled in *Xenopus* egg interphase extracts for 5 to 120 minutes, *Xenopus* lamin B3 is closely associated with chromatin and PCNA [Figure 3; (Shumaker *et al.*, 2008)]. Furthermore it has been shown that the C-terminal tail domain of lamins can interact directly with PCNA, and that the interaction site is located in the Ig-fold. Both the tail domain and the Ig-fold of *Xenopus* lamin B3 prevent lamin polymerization as well as the assembly of nuclei in *Xenopus* egg interphase extracts (Lopez-Soler *et al.*, 2001; Shumaker *et al.*, 2005). When added to the assembly system, the *Xenopus* lamin B3 tail is closely associated with chromatin and leads to significant decreases in PCNA incorporation into nuclei and in DNA replication (Shumaker *et al.*, 2008). Interestingly, a mutation in the Ig-fold of Xenopus lamin B3, which mimics an *LMNA* mutation associated with EDMD [R453W; (Bonne *et al.*, 1999)], decreases its binding to PCNA and inhibits DNA replication (Shumaker *et al.*, 2008). These findings suggest that defects in DNA replication caused by the expression of disease causing lamin mutants may contribute to the altered nuclear functions responsible for some types of laminopathies.

Summary

In our model we propose that lamins are major components of a nuclear scaffold which is essential for various nuclear processes such as transcription, DNA replication, chromatin organization and DNA repair (Dechat *et al.*, 2008; Goldman *et al.*, 2002). We further speculate that this lamin based scaffold provides a docking site and organizing center for chromatin and the multicomponent complexes involved in chromatin regulation. Alterations in such a scaffold caused either by changes in lamin expression patterns or by the expression of disease causing mutant lamins can result in the misregulation of nuclear functions leading, for example, to defects in cell cycle progression and differentiation (Dechat *et al.*, 2008). In support of this two recent studies show that adult stem cell differentiation is impaired in HGPS and in premature-aging mice (Espada *et al.*, 2008; Scaffidi and Misteli, 2008).

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Figure 1.
Structure of nuclear lamins. Schematic drawing of a lamin polypeptide chain depicting the α-helical central rod domain, the N-terminal globular head domain and the C-terminal globular tail domain. In addition the nuclear localization signal (NLS) and the Ig-fold are indicated.

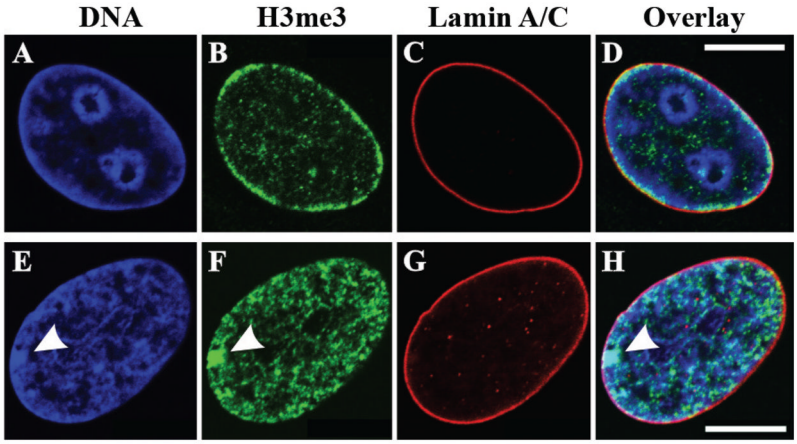

Figure 2.

Close association of heterochromatin with the nuclear lamina. Localization of lamins A/C (C, G), histone H3 trimethylated (H3me3) on lysine 9 (H3K9me3) (B), or on lysine 27 (H3K27me3) (F) in human foreskin fibroblasts (A–D) and human dermal fibroblasts from a female donor (E–H). DNA is stained with Hoechst dye (blue; A, E). Note that long stretches of heterochromatin, as revealed by Hoechst staining and by staining for H3K9me3, a histone modification associated mainly with constitutive pericentric heterochromatin, are in close proximity to and partially overlapping with peripheral lamins A/C in human foreskin fibroblasts (A–D). In addition, the Xi, which represents a large heterochromatic mass that can be visualized by staining with Hoechst and H3K27me3 (see arrowheads), is often found associated with lamins at the nuclear lamina (E–H). Scale bars, 10 μM.

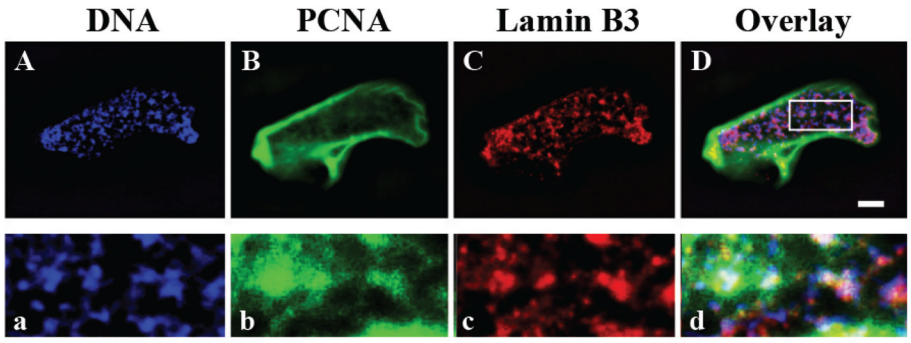

Figure 3.

Lamin B3 is closely associated with PCNA and chromatin in in vitro assembled nuclei. Localization of *Xenopus* lamin B3 (B, b; green) and PCNA (C, c; red) in a nucleus assembled in a *Xenopus* egg interphase extract for 130 min (A–D). DNA is stained with Hoechst dye (A, a; blue). The area in the box in D is enlarged (3.5×) to show the partial overlap between DNA, lamin B3 and PCNA (a–d). Brightness and contrast are enhanced in b compared to B for better visualization of the internal lamin B3 structures. Scale bar, 5 μM.