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Genome–nuclear lamina interactions: from cell populations to single cells

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Lamina-associated domains (LADs) are large genomic regions that interact with the nuclear lamina (NL) and help to guide the spatial folding of chromosomes in the interphase nucleus. LADs have been linked to gene repression and other functions. Recent studies have begun to uncover some of the molecular players that drive LAD–NL interactions. A picture emerges in which DNA sequence, chromatin components and nuclear lamina proteins play an important role. Complementary to this, imaging and single-cell genomics approaches have revealed that some LAD–NL interactions are variable from cell to cell, while others are very stable. Understanding LADs can provide a unique perspective into the general process of genome organization.

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Introduction: lamina associated domains

The spatial organization of chromosomes within the interphase nucleus has been linked to important biological processes such as gene regulation, DNA replication and DNA repair [1]. One key aspect of this spatial organization is the positioning of genomic loci relative to the nuclear lamina (NL). By means of the DamID (DNA adenine methyltransferase identification) [2,3] and ChIP (chromatin immunoprecipitation) [4] methods the genomic regions that interact with the nuclear lamina have been mapped in detail. These regions are generally referred to as lamina associated domains (LADs; Figure 1) [2–5].

There are >1000 LADs distributed throughout the mammalian genome. Their median size is in the range of 0.5 Mb, and they comprise ~35% of the genome [3]. LADs are relatively gene-poor, and most of the genes located in LADs have very low expression levels. LADs are thus mostly transcriptionally silent. Studies of nuclear lamina interactions during differentiation have revealed two different types of LADs [5–7]. Constitutive LADs (cLADs) are shared among all tested cell types, while facultative LADs (fLADs) are only associated with the NL in some cell types but not in others (Figure 1). cLADs contain even fewer genes than fLADs and their positions throughout the genome are highly conserved between mouse and human [6]. These features suggest that cLADs may be stable NL anchoring points that form a structural backbone of interphase chromosomes [6,8••].

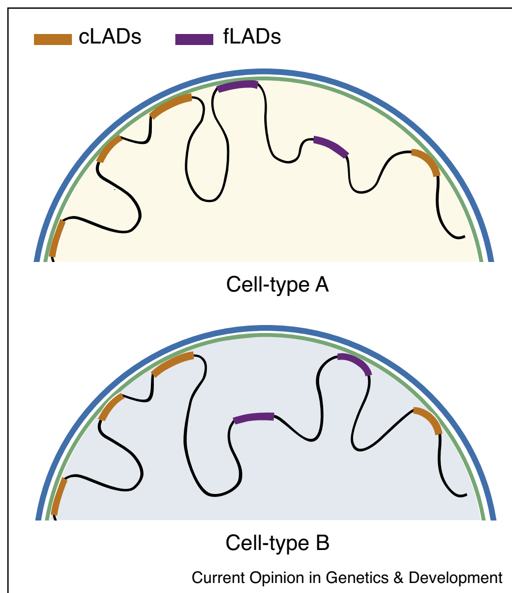
Here, we review new insights into the relationship between LADs, and gene regulation and other functions; the single-cell dynamics and cell-to-cell variability of LAD–NL interactions; and the molecular mechanisms that govern these interactions.

NL interactions, gene regulation and other nuclear functions

LADs have low levels of histone marks associated with gene activity, and are enriched in repressive histone marks such as H3K9me2 and H3K9me3 [3,5,8••,9,10] and in certain cell types also H3K27me2 [3]. During differentiation of mouse cells, several hundreds of genes (located in fLADs) move away or towards the NL, and this generally correlates with their activation or inactivation, respectively [2,5,11]. These data suggest that the nuclear periphery is a repressive compartment. Indeed, artificial tethering of an integrated reporter gene to the NL can result in the transcriptional down-regulation of the reporter gene and of some neighboring genes [12–15]. Conversely, forced activation of a gene located inside a LAD can induce relocation towards the nuclear interior, and this new position was observed to be maintained even after the transcriptional activator was lost [16•].

One possible interpretation of these data is that inactive genes are somehow preferentially positioned at the NL, and that the peripheral environment helps to reinforce their repressed state. Thus, once an inactive gene is located at the NL, it may be more difficult to activate it. A strong activator or chromatin remodelling factor may be able to overcome this repressive feedback loop and

Figure 1



Scheme showing the interaction between the nuclear lamina (NL) and two major classes of LADs: constitutive LADs (cLADs; orange), and facultative LADs (fLADs; purple) in two hypothetical distinct cell types.

cause relocation of the gene to the active chromatin compartment in the nuclear interior. There, the active environment of the nuclear interior might reinforce its active state.

However, observations in *Caenorhabditis elegans* that mutations in components of heterochromatin resulted in the loss of transcriptional repression of certain genes while still having perinuclear localization, or in the loss of perinuclear localization while still being repressed (see below), shows that transcription and localization can be uncoupled [17,18••]. Detachment of silent genes from the NL without their activation has also been observed in differentiating mouse embryonic stem cells [5]. Interactions with the NL may therefore not be essential for repression, but rather could add robustness to the repressed state of genes. In support of this, recent experiments have shown that mutations in genes required for sequestration at the NL hampered differentiation [18••,19].

In addition to reciprocal links with gene repression, evidence is accumulating that NL interactions are also linked to other nuclear functions. For example, the choice of DNA double-strand break repair pathway can be altered by relocalization of a locus to the NL [20]. Furthermore, LADs are known to overlap with domains that replicate late during S-phase [3,5]. The protein Rif-1 marks and controls the replication timing of these domains, as well as their spatial organization [21].

Single-cell dynamics of LAD–NL interactions

In vivo tagging and tracking of genomic regions that contact the NL in human cells revealed that the interactions are dynamic in interphase nuclei, because NL-interacting loci could be observed to move as much as ~1 μm from the NL within several hours [22]. However, this mobility is constrained because NL-contacting loci were never seen to move all the way to the nuclear interior, which is in agreement with earlier single-locus tagging results [23,24]. After mitosis the picture is very different: a substantial fraction of loci that contact the NL in the mother cell are relocated to the nuclear interior (often near nucleoli) in the daughter cells [22] (Figure 2a). This result has two implications: (i) some LADs associate with the NL in only a subset of cells in an otherwise homogeneous population – hence, not all of the ~35% of the genome classified as LADs interacts with the NL in each individual cell; (ii) after every mitosis LAD–NL interactions are reshuffled.

Recent genome-wide DamID mapping of NL contacts in single human cells [8••] underscored these findings. Analysis of hundreds of single-cell maps showed that each LAD has its own characteristic NL contact frequency (Figure 2b). The most consistent interactions involved the gene-poor cLADs, further supporting the notion that these may have a structural role. fLADs exhibit more cell-to-cell variation of their NL interactions, and the contact frequency correlates with the levels of H3K9me3 and inversely correlates with gene expression across the population of cells.

Interestingly, contacts of individual LADs in single cells typically involved long stretches of DNA, suggesting a zipper-like model of multivalent interactions (Figure 2c). At a bigger scale, LAD-dense chromosomes exhibited tighter contacts with the NL than LAD-poor chromosomes. Additionally, LADs on the same chromosome often showed coordinated interactions. Together, these results indicate that neighboring LADs interact with the NL in a cooperative manner [8••]. Single-cell maps thus reveal principles of NL interactions that cannot be easily inferred from population-averaged maps.

Sequence determinants of NL interactions

It is likely that the ability of a LAD to interact with the NL is at least in part encoded in the DNA sequence [7,25,26], but how is still unclear. One possible hint is the observation that cLADs have a relatively high AT content [6]. A wide range of proteins may exist that bind to AT-rich DNA without much additional sequence specificity [27], and it will be interesting to test their role in cLAD–NL interactions. Additionally, borders of LADs are often bound by the insulator protein CTCF [3]. Interestingly, CTCF seems to have an important role in defining NL interactions, as knockdown of CTCF affects the recruitment of specific loci to the nuclear periphery [28]. CTCF has been

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