



HAL
open science

Dissecting Gene Repression: Not Just Location, Location, Location

Tom Sexton

► **To cite this version:**

Tom Sexton. Dissecting Gene Repression: Not Just Location, Location, Location. Trends in Cell Biology, 2019, 29, pp.605 - 607. 10.1016/j.tcb.2019.06.001 . hal-03487957

HAL Id: hal-03487957

<https://hal.science/hal-03487957>

Submitted on 20 Dec 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **Dissecting gene repression: not just location, location, location**

2

3 Tom Sexton¹⁻⁴

4 ¹ Institute of Genetics and Molecular and Cellular Biology (IGBMC), Illkirch, France

5 ² CNRS UMR7104, Illkirch, France

6 ³ INSERM U1258, Illkirch, France

7 ⁴ University of Strasbourg, Illkirch, France

8 Correspondence: sexton@igbmc.fr (T.Sexton)

9

10 Keywords: lamina-associated domain, promoter transplantation, gene repression

11

12 Large heterochromatic domains are found tethered to the lamina. But is this nuclear
13 environment repressive *per se*, or just the “ground state” of inactive chromatin? Elegant
14 studies from the van Steensel group recently demonstrated that the lamina is indeed
15 repressive, but that intrinsic promoter properties also dictate gene activity.

16

17 Much of the transcriptionally inactive portion of the mammalian genome is located within
18 condensed heterochromatin, predominantly at the nuclear periphery. Around one third of
19 the genome forms kilobase-to-megabase-sized domains that are tethered to the nuclear
20 lamina (LADs, lamina-associated domains). These domains are enriched in heterochromatic
21 histone modifications and comprising gene-poor regions of low expression [1]. A long-
22 standing question is whether the nuclear lamina is in itself a repressive nuclear environment
23 or is merely the passive “stopping point” for inert chromatin. Artificially tethering specific
24 genomic loci to the lamina caused heterogeneous repression of the target genes and their
25 neighbors [2, 3], and around one tenth of genes within LADs are expressed [1], pointing to a
26 complex interplay of lamin association and gene expression regulation. High-throughput
27 experiments providing functional decoupling of nuclear localization and transcriptional
28 output are thus required to dissect active and passive repressive roles of LADs. A new study
29 from the van Steensel group has achieved just that, formally demonstrating that the lamina
30 does indeed form a repressive compartment, but that promoter and local chromatin context
31 determine the extent to which transcription can be modulated [4]. Their study combines two
32 promoter transplantation strategies, SuRE (survey of regulatory elements [5]) and TRIP
33 (thousands of reporters integrated in parallel [6]) to ask two complementary questions
34 (Figure 1):

35 *1. Are LAD promoters active when removed from the lamina?*

36 SuRE uses a barcoding system and RNA-seq to quantitatively measure the autonomous
37 promoter activity of millions of random genomic fragments inserted into episome libraries
38 [5]. In other words, the propensity of all promoters to activate transcription when removed
39 from their endogenous chromatin context can be assessed. By comparing SuRE results to

40 those from methods measuring (nascent) transcription from the endogenous promoter, the
41 extent to which the local chromatin affects gene expression can be gauged. In this manner,
42 promoters found in LADs are on average ten-fold less expressed than those outside of LADs
43 that have similar autonomous activity (SuRE signal), supporting an active repression role of
44 the lamina. However not all LAD promoters behave identically. Whereas around a third of
45 LAD promoters display more transcriptional activity when moved to episomes, implying that
46 they are repressed by their chromatin environment within LADs, another half are actually
47 silent in both SuRE and nascent transcript measures. These genes thus do not need to be
48 actively repressed, and are more likely to lack other factors required for their activation,
49 such as binding by specific transcription factors or engagement with enhancers. In
50 agreement, these “inactive” genes tend to be tissue-specific, suggesting that they are not
51 readily induced by ubiquitous transcription factors. Another portion of LAD promoters are
52 active whether within LADs or episomes, reminiscent of the previously reported “escaper”
53 LAD genes [1]. In contrast to the inactive gene class, escapers tend to be more ubiquitously
54 expressed across tissues.

55 *2. How is promoter activity altered when transplanted to different LAD regions?*

56 Conversely, TRIP inserts the same reporter construct into many different genomic locations;
57 high-throughput sequencing approaches allow the transcriptional output from each inserted
58 location to be measured simultaneously [6]. Three LAD “escaper” promoters, three LAD-
59 repressed promoters and one housekeeping gene promoter not found within a LAD were
60 compared in this manner [4]. Two major conclusions could be drawn. Firstly, when
61 comparing expression after insertion into LAD or inter-LAD locations, escaper promoters
62 were much less sensitive to repression by LAD environments, suggesting that the “escaper”

63 or “repressed” property of LAD response is indeed promoter-intrinsic. Notably, the
64 housekeeping reporter appeared completely insensitive to LAD localization, implying that
65 strong enough intrinsic promoter properties can completely override any lamin-mediated
66 repressive mechanisms. Secondly, the variability of reporter expression was very high
67 between LAD inserts, particularly for the repressed promoters, suggesting that the extent of
68 LAD-mediated repression is very heterogeneous according to the local chromatin context.
69 Modeling generally correlated the most repressive parts of LADs as those with the highest
70 enrichment in lamin binding, implying tightest attachment to the lamina. As may be
71 expected, the most transcriptionally permissive regions of LADs are generally enriched for
72 active histone modifications.

73 In combination, this study confirms and quantifies what has been previously proposed:
74 that LADs are genuine repressive, but heterogeneous, nuclear environments, and that the
75 interplay of promoter-intrinsic properties (e.g. bound transcription factors) and local
76 chromatin context determines final transcriptional output. However, some fundamental
77 questions remain. Firstly, how do LADs mediate gene repression? At the local scale, tighter
78 lamin binding correlates with greater repression, but it is unclear if this is more a
79 consequence of transcription displacing lamins than the lamina directly inhibiting
80 expression. This study found evidence that LADs impair transcriptional elongation of escaper
81 genes, rather than initiation, but mechanisms are still unclear. A growing body of
82 biochemical evidence suggests that inner nuclear membrane proteins interact with
83 transcriptional repressors and may even activate histone-modifying enzymes [e.g. 7], but
84 such mechanisms have yet to be observed *in vivo*. Secondly, what distinguishes “escaper”
85 promoters from LAD-repressed ones? With the exception of the completely insensitive
86 housekeeping gene promoter, LAD resistance cannot be simply explained by promoter

87 strength, since the escaper promoters tested by TRIP were not inherently stronger than the
88 LAD-repressed ones. It is intriguing that acetylation of lysine-122 of histone 3, a globular
89 domain modification that has been found to distinguish a specific subset of enhancers in
90 mouse embryonic stem cells [8], correlates with higher activity of escaper promoters but
91 repression of LAD-repressed ones. It remains to be seen if this finding still holds when TRIP is
92 extended to more promoters. Further, extension of the SuRE analysis to compare
93 transcriptional activity of enhancers found within or outside of LADs found a moderate
94 enrichment for binding of pioneer transcription factors. Carefully controlled perturbation
95 studies will be required to see if such correlations translate into mechanisms of LAD escape.
96 Since LADs themselves can vary in different tissues [9], it will also be very interesting to
97 extend the promoter transplantation assays to multiple cell types. In this manner, we can
98 see if “escaper” or “LAD-repressed” properties are completely intrinsic to DNA sequence, or
99 are modulated by the repertoire of available transcription factors. Combined with
100 mechanistic studies, these assays promise to be a Sure TRIP on the path to understanding
101 gene repression via nuclear localization.

- 102 1. Guelen L. et al. **Domain organization of human chromosomes revealed by mapping of**
103 **nuclear lamina interactions.** *Nature.* 2008;**453**:948-951.
- 104 2. Finlan L. E. et al. **Recruitment to the nuclear periphery can alter expression of genes in**
105 **human cells.** *PLoS genetics.* 2008;**4**:e1000039.
- 106 3. Reddy K. L. et al. **Transcriptional repression mediated by repositioning of genes to the**
107 **nuclear lamina.** *Nature.* 2008;**452**:243-247.
- 108 4. Leemans C. et al. **Promoter-Intrinsic and Local Chromatin Features Determine Gene**
109 **Repression in LADs.** *Cell.* 2019;**177**:852-864 e814.
- 110 5. van Arensbergen J. et al. **Genome-wide mapping of autonomous promoter activity in**
111 **human cells.** *Nature biotechnology.* 2017;**35**:145-153.
- 112 6. Akhtar W. et al. **Chromatin position effects assayed by thousands of reporters integrated in**
113 **parallel.** *Cell.* 2013;**154**:914-927.
- 114 7. Demmerle J. et al. **The nuclear envelope protein emerin binds directly to histone**
115 **deacetylase 3 (HDAC3) and activates HDAC3 activity.** *The Journal of biological chemistry.*
116 2012;**287**:22080-22088.
- 117 8. Pradeepa M. M. et al. **Histone H3 globular domain acetylation identifies a new class of**
118 **enhancers.** *Nature genetics.* 2016;**48**:681-686.

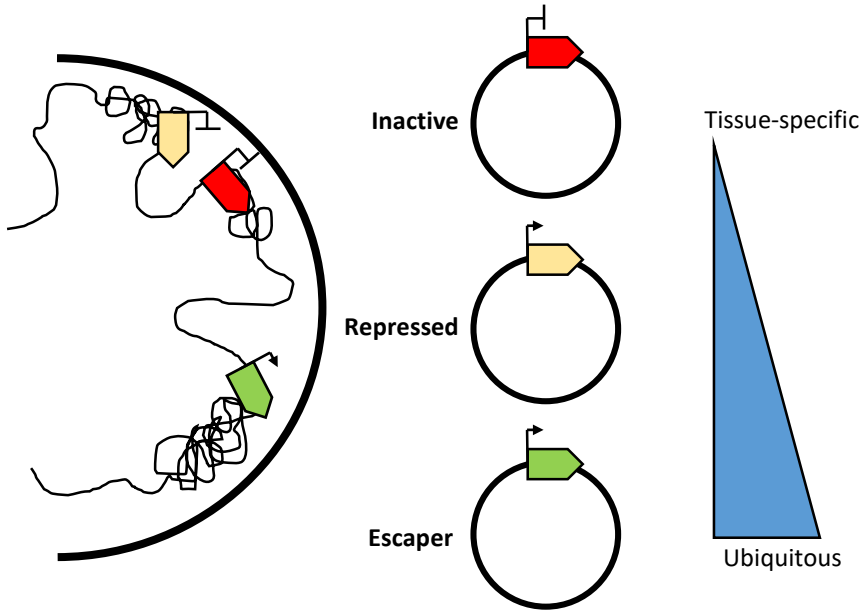
119 9. Peric-Hupkes D. et al. **Molecular maps of the reorganization of genome-nuclear lamina**
120 **interactions during differentiation.** *Molecular cell.* 2010;**38**:603-613.

121

122

123 **Figure 1. Promoter transplantation assays to understand LAD repression.** (a) SuRE assay
124 identifies three classes of LAD promoters: inactive (red), repressed (yellow) and escaper
125 (green). Inactive and repressed genes are transcriptionally shut down at the lamina in their
126 endogenous context, whereas escaper genes are expressed (left). When inserted into
127 episomal reporter constructs (right), inactive genes remain silent and escaper genes remain
128 active, but repressed genes, free from the LAD environment, are activated. Inactive genes
129 tend to be tissue-specific, whereas escaper genes are more ubiquitously expressed. (b) TRIP
130 assay assesses the heterogeneity of lamina-mediated repression. Promoters from the
131 repressed (yellow) or escaper (green) class are randomly integrated into the genome, and
132 the reporter expression from LAD insertions are assessed. Escaper promoters are less
133 affected by LAD insertion than repressed promoters. The most effective lamina-mediated
134 repression occurs where there is tightest lamin binding, and is weakest where there are
135 active histone marks; the histone modification H3K122ac appears to mark silencing and
136 activation, respectively, at repressed and escaper promoters. Figure adapted from [4]

(a)



(b)

