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EXTRA VIEW

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The connection between BRG1, CTCF and topoisomerases at TAD boundaries

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ABSTRACT

The eukaryotic genome is partitioned into topologically associating domains (TADs). Despite recent advances characterizing TADs and TAD boundaries, the organization of these structures is an important dimension of genome architecture and function that is not well understood. Recently, we demonstrated that knockdown of BRG1, an ATPase driving the chromatin remodeling activity of mammalian SWI/SNF enzymes, globally alters long-range genomic interactions and results in a reduction of TAD boundary strength. We provided evidence suggesting that this effect may be due to BRG1 affecting nucleosome occupancy around CTCF sites present at TAD boundaries. In this review, we elaborate on our findings and speculate that BRG1 may contribute to the regulation of the structural and functional properties of chromatin at TAD boundaries by affecting the function or the recruitment of CTCF and DNA topoisomerase complexes.

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Introduction

Recent advances in molecular biology and microscopy technologies have enhanced our understanding about the higher-order folding of the genome in an unprecedented manner.[1-5] It is now widely accepted that the dynamic folding of the chromatin is fundamental in regulating gene expression and DNA replication. The genome is folded in a hierarchical manner into chromosome territories, genomic compartments, and topologically associating domains (TADs), in which specific long-range looping interactions occur.[6] Each of these structures can be dynamically regulated during development, and perturbations in these folding units are associated with multiple diseases and cancer.[7-9]

One interesting feature that was revealed upon fine mapping of the folding of the genome is the TAD structures, which range from 100kb up to 1Mb in size.[7,10-13] TADs are units of chromosomes that exhibit higher frequency of physical contacts between genes and their cognate regulatory regions. The TADs have been shown to be stable across different species, cell types, and cellular conditions.[12] The replication timing, the presence of different histone modifications and the expression of the genes inside a TAD are highly correlated.[12,14,15] However, the underlying features that generate invariant TAD boundaries remain unknown. In human cells, TAD boundaries have been associated with the enrichment of CTCF, cohesin, DNase I hypersensitivity, certain histone marks and the timing of replication domains.[7,13,14] Furthermore, in *Drosophila*, the combinatorial binding of different types of insulators (also referred to as architectural proteins), such as BEAF32 and TFIIIC, is associated with the strength of the TAD boundary.[16,17] The boundaries serve as barriers to long- and short-range interactions between DNA sequences, thus the most likely interaction partner for a genomic region is another region within the same TAD. A strong TAD boundary limits interactions between the two adjacent TAD domains, whereas a weak TAD boundary allows a higher frequency of inter-TAD interactions.[17-19] Although a relationship between TAD boundaries and the binding of insulators has been demonstrated, the effects of enzymes that modify or remodel chromatin are largely unknown.

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The major ATPase subunit of the SWI/SNF chromatin remodeling complex, BRG1 (also known as SMARCA4), is required for proper nucleosome occupancy and positioning at target regions[20] as well as for establishing numerous long-range chromatin interactions.[21-26] BRG1 plays dual roles both as a transcriptional activator and repressor.[10] In this review, we highlight our recent finding that BRG1 contributes to TAD boundary strength and discuss the implications of BRG1 loss on nucleosome occupancy and higher order chromatin organization.[27]

BRG1 is associated with TAD boundaries

To delineate the role of BRG1 in genome architecture, we performed RNA-seq and Hi-C in control and BRG1 knockdown mammary epithelial MCF-10A cells.[27] Moreover, to probe BRG1 localization, we performed ChIP-seq in wild type parental MCF-10A cells. We reported that BRG1 regulates the expression of genes related to extracellular matrix and lipid synthesis. In addition, BRG1 knockdown resulted in the differential expression of many long non-coding RNAs, which are thought to be involved in genome organization.[28] ChIP-seq analysis of BRG1 demonstrated binding primarily (~60%) at genic regions.[27] Intergenic BRG1 peaks included super-enhancers, which are defined as clusters of regulatory regions with unusual enrichment of factor binding sites and/or histone modifications that are in close proximity,[29] though this classification has recently been challenged.[30] Taken together, our findings showed that BRG1 binding was widespread throughout the genome.

Comparison of the control and BRG1 knockdown Hi-C data sets revealed that the majority of the TAD boundaries were largely overlapping between control and BRG1 knockdown cells,[27] consistent with prior results.[31-33] However, more than 10% of the TAD boundaries were unique to either the control or the BRG1 knockdown cells, providing evidence that BRG1 may contribute to the integrity of TAD boundaries. In support of this concept, we observed an enrichment of BRG1 binding at TAD boundaries. This result may be expected since TAD boundaries have been shown to be enriched for both housekeeping and developmentally regulated genes.[13] Surprisingly, the strength of the TAD boundaries, as assessed using the insulation method,[34] was significantly reduced in BRG1 knockdown human mammary epithelial MCF-10A cells. In other words, upon BRG1 knockdown, there was a higher frequency of inter-TAD genomic interactions. We further validated this result by intersecting TAD boundaries with BRG1 ChIP-seq data and categorizing the boundaries as either BRG1 bound or not bound. The strength of TAD boundaries that were bound by BRG1 was stronger than the boundaries that lacked BRG1 localization.[27]

An explanation for the effect of BRG1 knockdown is that BRG1 loss may disrupt chromatin accessibility and preclude the binding of transcription factors and/or chromatin modifiers at TAD boundaries. To examine this possibility, we analyzed a publicly available MNase-seq data set from wildtype and BRG1 knockdown mouse embryonic fibroblast (MEF) cells.[20] By intersecting the nucleosome occupancy data with the ENCODE MEF CTCF ChIP-seq data set, we showed that there was decreased nucleosome occupancy at CTCF-bound regions in BRG1 knockdown cells when compared to control cells.[27] Thus, our results suggested that BRG1 plays a role at TAD boundaries by regulating nucleosome occupancy and possibly CTCF localization.

The CTCF connection

Dixon et al. recently hypothesized that the orderly positioning and occupancy of nucleosomes at TAD boundaries renders the local chromatin at the boundary "less flexible," and thus prevents long-range interactions surpassing the boundary.[35] The orderly positioning and occupancy of nucleosomes at TAD boundaries may be achieved by enriched CTCF binding, which positions ~20 nucleosomes around its binding sites.[36] Our observation of the relationship between BRG1 knockdown and the reduction of nucleosome occupancy around the CTCF sites supports such a mechanism.[27] It was recently shown that the directionality of CTCF binding is very strongly associated the formation of TADs,[37-41] though the relationship between BRG1 binding and CTCF binding site orientation remains to be determined. We propose that loss or knockdown of BRG1 results in the reduction of nucleosome occupancy at CTCF sites either through loss of its ATP-dependent chromatin remodeling activity or by negatively impacting CTCF binding (Fig. 1). Such an effect of BRG1 may also occur at regions where other chromatin organizers (e.g. cohesin) are bound.

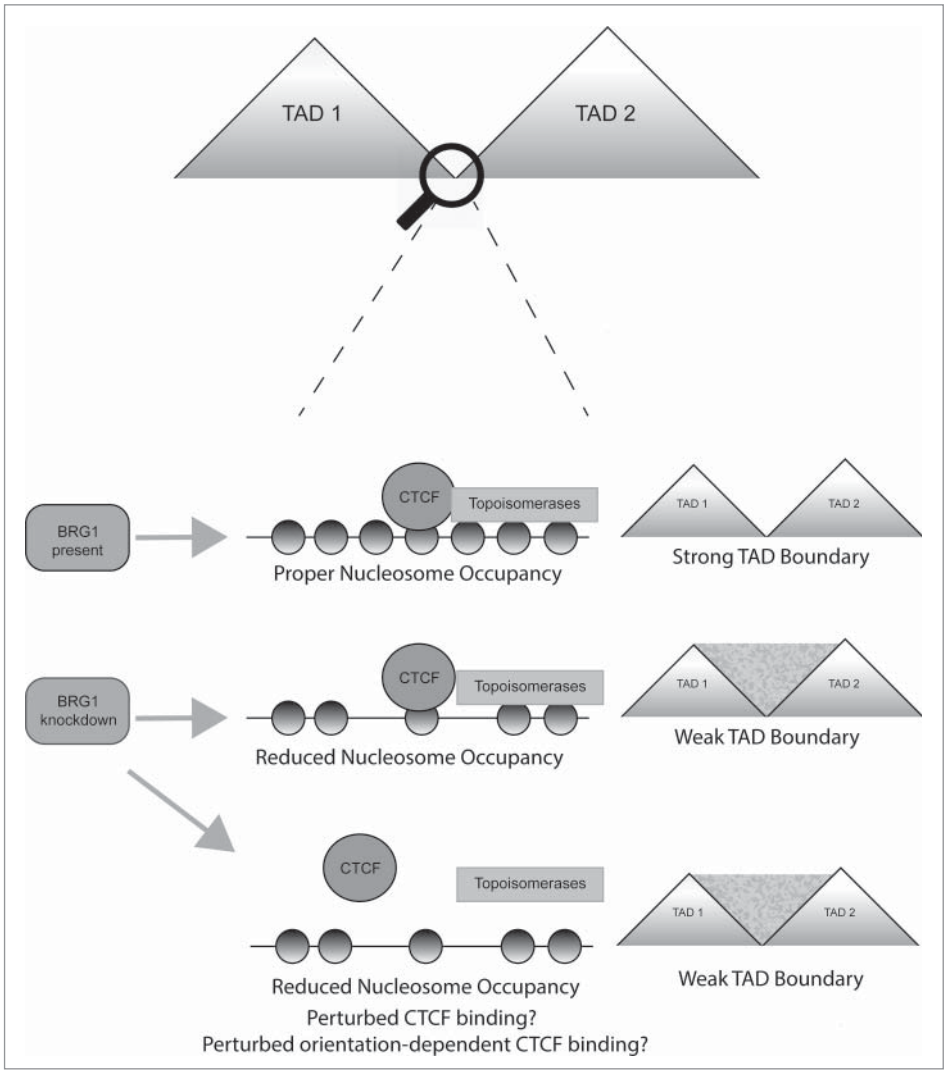

Figure 1. A schematic figure depicting the possible connection between BRG1, CTCF and topoisomerases. In the presence of BRG1 (top panel), CTCF and topoisomerases can efficiently bind to TAD boundaries and promote proper nucleosome occupancy and uncoiling of the DNA, resulting in a strong TAD boundary. We previously reported that nucleosome occupancy around CTCF sites was reduced upon BRG1 knockdown.[27] Therefore, we propose that upon BRG1 knockdown, CTCF and topoisomerases may interact with TAD boundary sequences, but the lack of ATP-dependent remodeling activity may alter nucleosome occupancy and affect boundary strength (middle panel). Alternatively, the binding of CTCF and topoisomerases may be perturbed, resulting in altered nucleosome occupancy and reduced boundary strength (bottom panel).

The TOP connection

The model proposed by Dixon et al.,[35] is reinforced by accumulating evidence that highlights the role of the topoisomerase complex as a regulator of TAD boundaries.[42] Recent results demonstrate that topoisomerase II beta (TOP2B) binding overlaps with almost half of CTCF/cohesin binding sites, and that TOP2B may facilitate supercoiling at CTCF sites in a transcription-dependent manner.[43] Direct links between topoisomerases and BRG1 are provided by a proteomic profiling using mass spectrometry that identified a significant interaction between BRG1 and TOP2B.[44] Consistent with this finding, BRG1 also binds to topoisomerase II alpha (TOP2A).[45] Furthermore, BRG1 is required for the recruitment of topoisomerase I (TOP1) to chromatin, and in the case of both TOP2A and TOP1, the ATPase activity of BRG1 has been shown to be essential for the recruitment of the topoisomerase proteins.[45,46] These findings suggest an interplay and functional cooperativity between CTCF, BRG1 and topoisomerases in the organization of TADs via the active regulation of TAD boundary regions.

Additional evidence for engagement of topoisomerases in genome organization is provided by studies from bacteria and yeast. A Hi-C study in prokaryotes

examined the biology of chromosomal interaction domains (CIDs), which are prokaryotic chromatin folding structures that are analogous to the eukaryotic TADs. Treatment of the prokaryotic cells with novobiocin, a drug that inhibits DNA gyrase (a homolog of topoisomerase II) and thus supercoiling, perturbed the sharpness and the positions of CID boundaries.[47] In yeast, fine resolution nucleosome mapping determined that self-associating domains similar to but smaller than TADs exist and that their boundaries were bound by the RSC chromatin remodeling enzyme.[48] The RSC ATPase is structurally related to BRG1, and the genetic analyses performed confirmed a role for RSC in yeast genome organization.[48] Moreover, Hrp1, an ATP-dependent chromatin remodeling protein from the CHD subfamily, was shown to collaborate with Top1 to maintain open chromatin at active gene regions in yeast.[49] Taken together, these findings suggest a strong link between chromatin remodeling enzymes, including the mammalian SWI/SNF complex, architectural proteins, and topoisomerases in genome organization.

Conclusions and future perspectives

We propose that the association between BRG1 knockdown and reduction in TAD boundary strength may be due to perturbations in the recruitment of CTCF and topoisomerases, and may therefore affect integrity of the chromatin structure and the "stiffness" of the chromatin at TAD boundaries (Fig. 1). In further support of the chromatin "stiffness" hypothesis, a recent study showed that a small deletion of a TAD boundary was not sufficient to disrupt the TAD domain, as it remained stable.[50] This result suggests that the boundary is not defined by the exact boundary sequence or length, but instead depends either on the supercoiling or the overall composition of the factors present at the boundary. Our recent data indicating that BRG1, and hence the mammalian SWI/SNF chromatin remodeling enzyme, binds to TAD boundaries and promotes boundary strength adds a novel biochemical activity, ATP-dependent chromatin remodeling, to the complex structure that regulates TAD formation and function. Other chromatin remodeling complexes may play similar roles, as these enzymes can function in a redundant manner.[51] Continued examination of the factors found at TAD boundaries will yield important insights into the biophysical properties of TADs and their boundaries, as well as into chromatin folding and overall genome organization that supports biological control.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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