Cohesin-dependent chromatin structures at a close view

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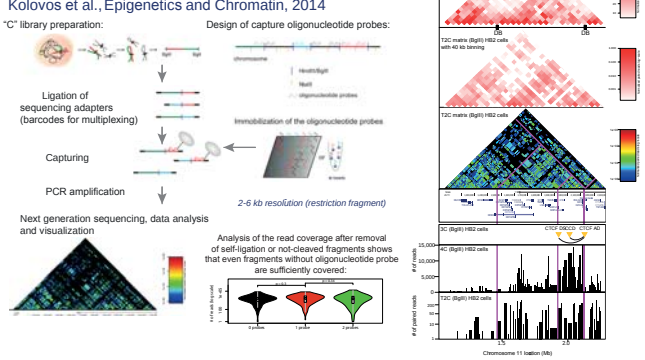
Background and summary:

The cohesin complex is an important factor for the three-dimensional organization of chromatin. Hi-C studies have shown that chromatin loops cluster together into topological domains [1]. Recently, we and others have used Hi-C to show how topological domains and subdomains change when the cohesin complex is depleted. Our study showed that topological domains are altered after cohesin depletion but not disrupted [2].
However, the current resolution of Hi-C (40kb) is not sufficient to yield information about the inside of TADs, for instance which long range contacts are affected in particular and which regions remain unaffected, are only interactions involving cohesin sites affected and how does the chromatin fibre rearrange without cohesin.
To address these question we have studied a 2.1 Mb region on the human chromosome 11 using the T2C technique [3]. This novel technique allows to generate Hi-C-type data at restriction fragment resolution (2-6 kb). Our selected region contains two topological domains and two imprinted gene clusters, H19/IGF2 and KCNQ1/KCNQ1OT1.

1. Dixon, J.R. et al. Nature, 2012. 485(7398): p. 376-80.
2. Zuin, J., Dixon J. R. et al., Proc Natl Acad Sci U S A, 2014. 111(3): p. 996-1001.
3. Kolovos, P. et al.,Epigenetics & Chromatin, 2014 Jun 16; 7:10. doi: 10.1186/1756-8935-7-10.

Chromatin Conformation Capturing – T2C

Kolovos et al., Epigenetics and Chromatin, 2014



Cohesin cleavage or CTCF depletion alter topological domains in different ways

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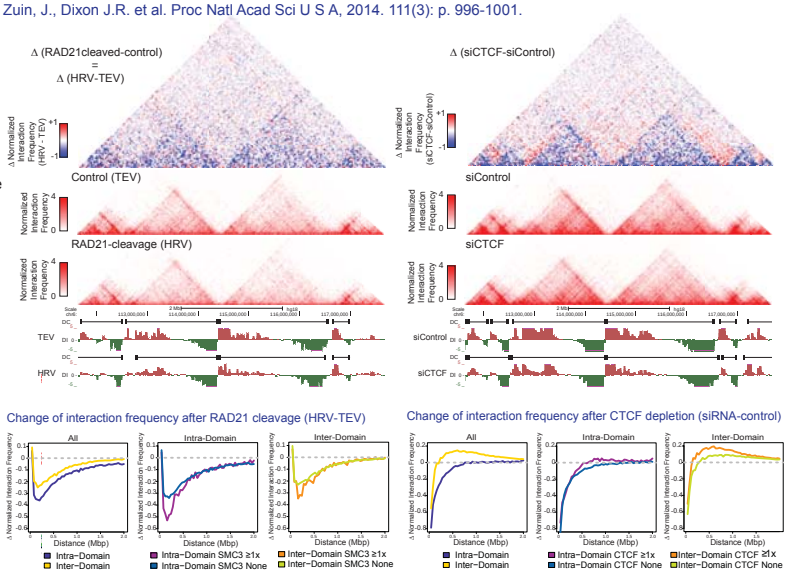


Change of interaction frequency after RAD21 cleavage (HRV-TEV)

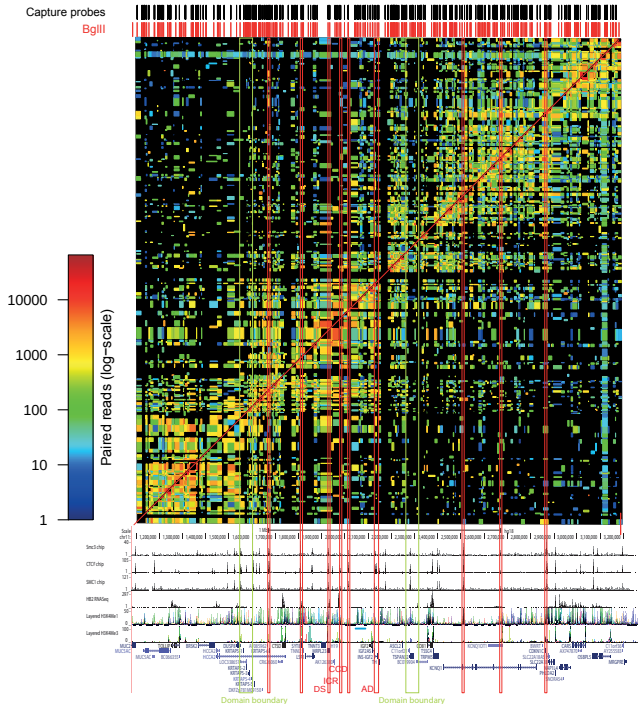
- Cohesin cleavage leads to a general loss of interaction mainly occurring between interacting regions less than 2Mb apart with a maximum loss in between 100-200Kb.
- Overall topological domain numbers do not change and domain boundaries might remain intact.

Change of interaction frequency after CTCF depletion (siRNA-control)

- CTCF depletion leads to reduced intra-domain interactions, mainly at interacting regions less than 100Kb apart
- We observe a gain of inter-domain interactions, indicating that the domain boundaries are weakened and the entire chromatin becomes more dynamic.

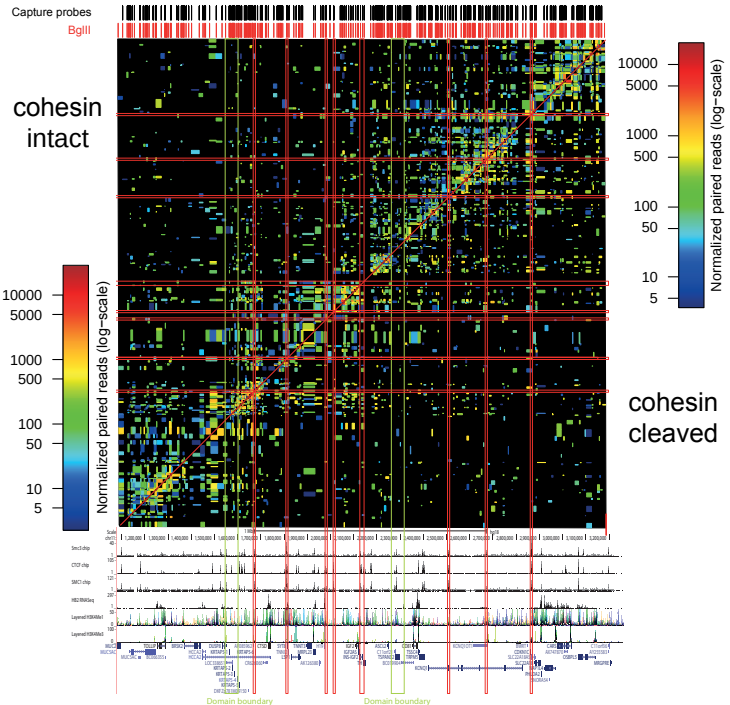
T2C interaction matrix from breast endothelial cells (HB2) (array normalization)

An HB2 cell 4C libray was enriched for ligation products of a region on the human chromosome 11 using one capture array and sequenced by paired-end sequencing obtaining 52 Mio raw reads and finally 2 Mio uniquely mapped read pairs in the region of interest (excluding self-ligation and non-digestion).



Composite T2C interaction matrix from HEK293T cells with intact cohesin and cleaved cohesin (library normalization)

4C libraries were prepared from control cells and cells with the RAD21 subunit of the cohesin complexed cleaved by protease (as above). After ligating the sequencing adapter with barcode the samples were mixed treated with one capture array. The enriched ligation products were sequenced by paired-end sequencing obtaining 19 Mio paired raw reads per sample.



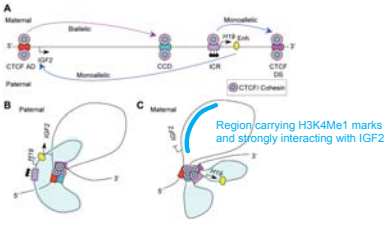
General observations:

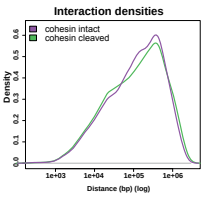
Cohesin/CTCF sites are often interacting, but not always and not necessarily with each other.

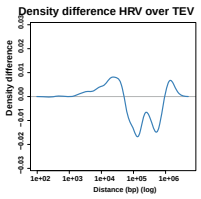
The two imprinted gene regions are separated by a domain boundary.

Novel interactions between the KCNQ1 gene and other imprinted genes in the locus (CDKN1C, SLC22A18, PHLDA2).

Previous model for the interactions around H19 and IGF2 (3C based, Nativio et al., 2009)







Cohesin-Dependent Chromatin Structure at a Close View

Zuin, J., van den Werken, H. J. G., Kolovos, P., Brouwer, R. W. W., Kockx, C. E. M., van IJcken, W. F. J., Grosveld, F. G., **Knoch, T. A.** & Wendt, K. S.

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Abstract

The cohesin complex is an important factor for the three-dimensional organization of chromatin. Hi-C studies have shown that chromatin loops cluster together into topological domains. Recently, we and others have used Hi-C to show how topological domains and subdomains change when the cohesin complex is depleted. Our study showed that topological domains are altered after cohesin depletion but not disrupted. However, the current resolution of Hi-C (40kb) is not sufficient to yield information about the inside of TADs, for instance which long range contacts are affected in particular and which regions remain unaffected, are only interactions involving cohesin sites affected and how does the chromatin fibre rearrange without cohesin. To address these question we have studied a 2.1 Mb region on the human chromosome 11 using our novel T2C technique which allows to generate a Hi-C type dataset at restriction fragment resolution (2-6 kb). Our selected region contains two topological domains and two imprinted gene clusters, H19/IGF2 and KCNQ1/KCNQ1OT1. We have generated T2C maps for two different cell types, a breast endothelial cell line and HEK293T cells, and also for cells where the cohesin complex was destroyed in interphase by proteolytic cleavage of its RAD21 subunit. We will present our results addressing the aforementioned questions. Further we have also reinvestigated previously published data concerning the interactions and potential co-regulation between the imprinted gene clusters and their imprinted control regions.

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Keywords:

Genome, genomics, genome organization, genome architecture, structural sequencing, architectural sequencing, systems genomics, coevolution, holistic genetics, genome mechanics, genome statistical mechanics, genomic uncertainty principle, multilism genotype-phenotype, genome function, genetics, gene regulation, replication, transcription, repair, homologous recombination, simultaneous co-transfection, cell division, mitosis, metaphase, interphase, cell nucleus, nuclear structure, nuclear organization, chromatin density distribution, nuclear morphology, chromosome territories, subchromosomal domains, chromatin loop aggregates, chromatin rosettes, chromatin loops, chromatin quasi fibre, chromatin density, persistence length, spatial distance measurement, histones, H1.0, H2A, H2B, H3, H4, mH2A1.2, DNA sequence, complete sequenced genomes, molecular transport, obstructed diffusion, anomalous diffusion, percolation, long-range correlations, fractal analysis, scaling analysis, exact yard-stick dimension, box-counting dimension, lacunarity dimension, local nuclear dimension, nuclear diffuseness, parallel super computing, grid computing, volunteer computing, polymer model, analytic mathematical model, Brownian Dynamics, Monte Carlo, fluorescence *in situ* hybridization (FISH), targeted chromatin capture (T2C) confocal laser scanning microscopy, fluorescence correlation spectroscopy, spatial precision distance microscopy, super-resolution microscopy, two dimensional fluorescence correlations spectroscopy (2D-FCS) auto-fluorescent proteins, CFP, GFP, YFP, DsRed, fusion protein, *in vivo* labelling,

information browser, visual data base access, holistic viewing system, integrative data management, extreme visualization, three-dimensional virtual environment, virtual paper tool.

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