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## 3D genome organization: setting the stage and introducing its players

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1 Editorial

2

3 **3D genome organization: setting the stage and introducing its players**

4 The introduction of Chromosome Conformation Capture (3C) by Job Dekker and colleagues in 2002,  
5 followed by derivatives that incorporate high-throughput sequencing—most notably Hi-C—have  
6 transformed the study of eukaryotic 3D genome organization [1, 2]. Whereas prior imaging-based  
7 studies mostly focused on the positioning of genomic regions within the cell nucleus or relative to  
8 other structures, 3C-based approaches directly revealed higher-order chromatin structure. Their  
9 widespread use has identified, in mammalian cells, a multi-level organization that incorporates multi-  
10 megabase chromatin compartments, which are linked to overall transcriptional output, sub-megabase  
11 Topologically Associating Domains (TADs), which are demarcated by insulator proteins like CTCF,  
12 and at the smallest scales ensembles of chromatin loops, which link regulatory elements, and contact  
13 domains, which correspond to clustered regions that carry the same histone modifications (see e.g. [2-  
14 7]).

15 In this special issue of *Briefings in Functional Genomics* on 3D genome organization, and two  
16 preceding publications, a generation of scientists whose careers paralleled this still young field take  
17 the stage to comment on the most important past and future developments. Their reviews cover a  
18 broad spectrum of topics related to 3D genome structure, ranging from available technologies and  
19 their applications, via structuration and dynamics in different eukaryotic models and cell types, the  
20 advances in polymer physics-inspired computational simulations to explain this structuration, to its  
21 importance for human disease. Combined, this collection provides a comprehensive overview how far  
22 this dynamic field has advanced in less than two decades, and where the future may bring us.

23 Übelmesser and Papantonis, in a review that precedes this special issue, provide a detailed  
24 introduction of the technologies to study 3D genome organization, with a particular emphasis on Hi-C.  
25 Moreover, they discuss how new developments, both based on genomics and imaging, are helping to  
26 improve the resolution, to reduce experimental biases, to provide new insights into the cell-to-cell  
27 variation and to identify the different factors and nuclear substructures that shape 3D genome  
28 organization [8].

29 In four reviews, either in this special issue or recently published, the overall concepts of 3D  
30 genome organization are introduced, related to what is known about their structure, function and  
31 dynamics in different eukaryotic systems [9-12]. Pachano and colleagues discuss chromatin  
32 architecture in mammalian embryonic stem cells, with a particular focus on the repressive Polycomb  
33 group (PcG) proteins and associated histone modifications. Within stem cells, PcG proteins acts as a  
34 major multi-scale organizer of the genome that incorporates both local and distant interactions among  
35 repressed regions within an otherwise active nuclear environment. Such an organization may be

36 particularly beneficial for these pluripotent cells, as it provides both an efficient means of repression  
37 while maintaining a flexible differentiation potential [9]. In a similar vein, Van Schoonhoven and  
38 colleagues review how the dynamic nature of 3D genome organization in mammalian lymphocytes (B  
39 and T cells) is linked to transcriptional regulation and cellular identity. Moreover, they highlight the  
40 importance of the multi-scale organization and how transcription factors can drive changes in this  
41 organization during cellular differentiation and lymphocyte activation. Finally, they discuss how 3D  
42 genome organization is actively involved in the rearrangement of antigen-receptor loci, which is a  
43 unique feature of lymphocytes [10]. Both these reviews thus emphasize the shared importance of a  
44 dynamic and multi-scale 3D genome organization in mammalian cells.

45 The reviews by Grob and by Moretti and colleagues provide overviews of 3D genome  
46 organization in two other well-characterized eukaryotic models; flowering plants and *Drosophila*  
47 *melanogaster*. In both plants and insects, the genome adopts a dynamic multi-scale organization that  
48 incorporates compartments, TAD-like structures and chromatin loops, confirming the universal nature  
49 of multi-level organization in higher eukaryotes. Nonetheless, interesting differences are discussed as  
50 well, including differences in size scales, in factors that structure the genome (e.g. the expanded  
51 repertoire of insulator proteins in *Drosophila*) and in the function of 3D structures themselves (e.g. the  
52 KNOT, which safeguards plant genomes against invasive DNA elements) [11, 12].

53 Moving on to a more structural focus, Canat, Veillet and colleagues discuss how genomics-  
54 based assays have revealed how the eukaryotic genome is positioned within the cell nucleus.  
55 Particularly, they discuss how the interactions of genomic regions with nuclear landmarks like the  
56 nucleolus, nuclear lamina, nuclear pores and pericentromeric heterochromatin act as major drivers for  
57 the separation of active and inactive regions in the genome. Moreover, they discuss the dynamic  
58 interplay between these interactions with nuclear landmark, the changes in transcriptional regulation  
59 and the self-organizing properties of the genome within the nuclear space [13]. This latter aspect of  
60 self-organization is further discussed in following reviews about polymer-based modeling [14, 15].  
61 First, Brackley and Marenduzzo introduce how polymer physics-inspired computer simulations have  
62 revealed how bridging-induced microphase separation can explain the self-self aggregation that is  
63 commonly observed in 3D genome organization. Moreover, they discuss how such simulations can be  
64 used to make predictions about the active nature of biological processes, based on the dynamics  
65 observed in imaging experiments [14]. Next, Ghosh and Jost discuss how biophysical modeling has  
66 revealed “loop extrusion” as a second mechanism that has a major effect on 3D genome organization.  
67 Simulations of dynamic loop extrusion, incorporating proteins from the Structural Maintenance of  
68 Chromosome family (SMC; e.g. the Cohesin complex) and stabilization by insulator proteins (e.g.  
69 CTCF), were able to explain the emergence of TAD structure within Hi-C maps, thus providing  
70 important guidance for experimental investigations [15].

71           The last two contributions in this special issue focus on practical consequences of 3D genome  
72 organization, although from a very different angle. Anania and Lupiáñez summarize current insights  
73 into how 3D genome organization is implicated in human disease and developmental defects. Whereas  
74 nearly all currently known examples are ultimately caused by rewiring of chromatin loops, in many  
75 cases the causative event can be traced back to either a disruption of structuring factors, usually  
76 resulting in a more global reorganization of genome architecture, or mutations in the DNA sequence,  
77 with usually more local effects [16]. Finally, Xu and Dixon discuss how the unique nature of Hi-C  
78 data can be exploited to extract information about genomes that is difficult to assess by conventional  
79 sequencing approaches. In 3C-based assays, including Hi-C, distal genomic fragments are linked  
80 based on close spatial proximity within the same cell and, particularly in mammals, on the same copy  
81 of a chromosome. This review therefore details how the use of Hi-C can be extended to facilitate  
82 genome-assembly, the identification of structural variants, the phasing of haplotypes in di- or  
83 polyploid organisms and isolation of individual genome sequences from complex populations of cells  
84 [17].

85           In conclusion, this special issue provides a comprehensive overview of the field of 3D genome  
86 organization, as provided by a new generation of scientists. The reviews touch on a wide range of  
87 topics, covering technology, computational approaches, structural aspects, biological systems and  
88 human disease. This collection can thus serve as an excellent introduction to this young, dynamic and  
89 exciting field, both by providing an overview of the current state of affairs and by providing hints of  
90 future directions.

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95

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