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Review

Chromosome domain architecture and dynamic organization of the fission yeast genome

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ABSTRACT

Advanced techniques including the chromosome conformation capture (3C) methodology and its derivatives are complementing microscopy approaches to study genome organization, and are revealing new details of three-dimensional (3D) genome architecture at increasing resolution. The fission yeast *Schizosaccharomyces pombe* (*S. pombe*) comprises a small genome featuring organizational elements of more complex eukaryotic systems, including conserved heterochromatin assembly machinery. Here we review key insights into genome organization revealed in this model system through a variety of techniques. We discuss the predominant role of Rabl-like configuration for interphase chromosome organization and the dynamic changes that occur during mitosis and meiosis. High resolution Hi-C studies have also revealed the presence of locally crumpled chromatin regions called "globules" along chromosome arms, and implicated a critical role for pericentromeric heterochromatin in imposing fundamental constraints on the genome to maintain chromosome territoriality and stability. These findings have shed new light on the connections between genome organization and function. It is likely that insights gained from the *S. pombe* system will also broadly apply to higher eukaryotes.

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1. Introduction

Determining how chromosomes, which contain the genetic information specifying proper developmental and gene expression programs, are organized within the nuclear space has remained a major driving force in the nuclear architecture field [1–3]. The physical compaction of chromosomes and the spatial organization of the genome are critical for maintaining genome stability and for the proper regulation of many nuclear functions, including transcription, replication, recombination, and repair [4–7]. Several layers of organization are imposed on the chromatin fiber, ranging from nucleosomal packaging to intricate levels of higher-order folding. Factors involved in chromatin assembly, including heterochromatin machinery that targets specific genomic sites and architectural proteins such as condensin and cohesin, play important roles in genome organization. Exactly how these factors contribute to the organization of genome function and how they facilitate dynamic changes in chromosome architecture during the cell cycle are just beginning to be revealed.

The advent of several advanced techniques has allowed packaging, folding, and genomic interactions to be studied in increasingly fine detail. Molecular based approaches, including 3C and its derivatives, have been used to study specific loci of interest as well as genome-wide interactions to gain insight into the physical organization and spatial configuration of chromosomes [8–13]. Short and long-range interactions both within and between chromosomes have been determined from global interaction contact maps obtained by these methods. These studies have yielded important conceptual advances, including the compartmentalization of the human genome into open and closed states, chromosome territoriality, and the fractal globule nature of the chromatin fiber [13]. Evidence of megabase-sized topologically associating domains (TADs) has been discovered in various systems [14–16]. In parallel, advanced microscopy studies at increasing resolution are

Abbreviations: 3C, chromosome conformation capture; *mat*, mating-type locus; SPB, spindle pole body; *rDNA*, ribosomal DNA; NE, nuclear envelope; LEM, LAP2 emerin MAN1; LAP, lamina-associated peptide; *cnt*, centromere central core; *IR*, inverted repeat; cen, centromere; Pol III, RNA polymerase III; COC, chromosome organizing clamps; TE, transposable element; *LTR*, long terminal repeat; *WTF*, with TF LTRs; MAR/SAR, matrix/scaffold attachment region; ELP, enrichment of ligation products; GCC, genome conformation capture; KEE, knot engaged element; IHI, interactive heterochromatic islands; NMS, Ndc80–Mis12–Spc7; LINC, linker of nucleoskeleton and cytoskeleton; TAD, topologically associating domain

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complementing molecular studies, providing visual clues to genome organization at single cell resolution [17,18].

Among the various model organisms, the fission yeast *Schizosaccharomyces pombe* has emerged as a useful system to study 3D genome organization. *S. pombe* comprises a small genome with hallmarks of more complex eukaryotes. The 13.8 Mb *S. pombe* genome is comprised of three relatively large chromosomes. Centromeres ranging in size from ~35 to 110 kb are organized into two distinct domains: the unique central core bound by CENP-A and kinetochore proteins, and the surrounding pericentromeric repeats [19,20] (Fig. 1A). Extended heterochromatin domains coat pericentromeric repeats and subtelomeric regions as well as the silent mating-type (*mat*) interval (Fig. 1A) [21]. Studies of heterochromatin assembly pathways involving conserved proteins, such as Clr4/Suv39h and Swi6/HP1 that are present in *S. pombe*, have provided insights into the critical functions of this specialized chromatin [20,22,23]. In particular, work that focused on the *mat* locus has yielded many groundbreaking discoveries over the years, including the epigenetic inheritance of differential chromatin states and the mechanisms by which boundary DNA elements prevent spreading of heterochromatin into neighboring gene-rich euchromatin regions [24–27].

In this review we summarize the findings from the fission yeast model system that have advanced our understanding of 3D genome architecture. Some reflect similar findings in higher organisms, indicating universal and fundamental genome organization principles, while others have revealed new insights and uncovered important key concepts underlying genome architecture that are also likely to universally apply.

2. Global organization of the *S. pombe* interphase genome

Eukaryotic chromosomes are specifically organized during interphase. *S. pombe* chromosomes display a polarized arrangement, in which centromeres of all three chromosomes are clustered adjacent to the spindle pole body (SPB), which is the centrosome equivalent in yeast, while telomeres are also associated with each other at the opposing hemisphere near the nuclear periphery [28] (Fig. 1B). Ribosomal DNA (*rDNA*) repeats at the ends of chromosome III are compartmentalized within the nucleolus [29]. This polarized array is known as the Rabl configuration, which was first described in salamander larvae cells in 1885 [30]. When first observed, this configuration was thought to be a passive continuation of the chromosome configuration from the prior anaphase, in which chromosomes are pulled into the daughter cells with centromeres leading and telomeres trailing behind. However, Rabl-like configuration can be established de novo (i.e. without a prior anaphase) in both budding and fission yeast [31,32], suggesting that the polarized array of yeast chromosomes is likely not just a relic of anaphase.

Indeed, the Rabl configuration may be important for proper functioning of the genome during interphase. Sustained by both chromosome–chromosome (clustering of centromeres and telomeres) and chromosome-nuclear envelope interactions, the constraints generated by these interactions ensure that specific chromosomal regions (and genes) are confined to distinct molecular environments within the nuclear space. The positional guidance provided by the Rabl configuration may promote genome compartmentalization, which may impact the transcription of genes and the establishment of chromosome territoriality (see below). Moreover, recent evidence suggests that the interphase clustering of centromeres could provide an organizational framework to allow efficient kinetochore capture during mitosis [33]. Indeed, centromere de-clustering has been shown to correlate with defects in chromosome segregation [33]. In mammals, chromosomes surround the spindle in a ring in mitosis and meiosis, which might efficiently expose all of the kinetochores to the spindle and facilitate their capture [34,35]. Thus, leveraging the 3D organization

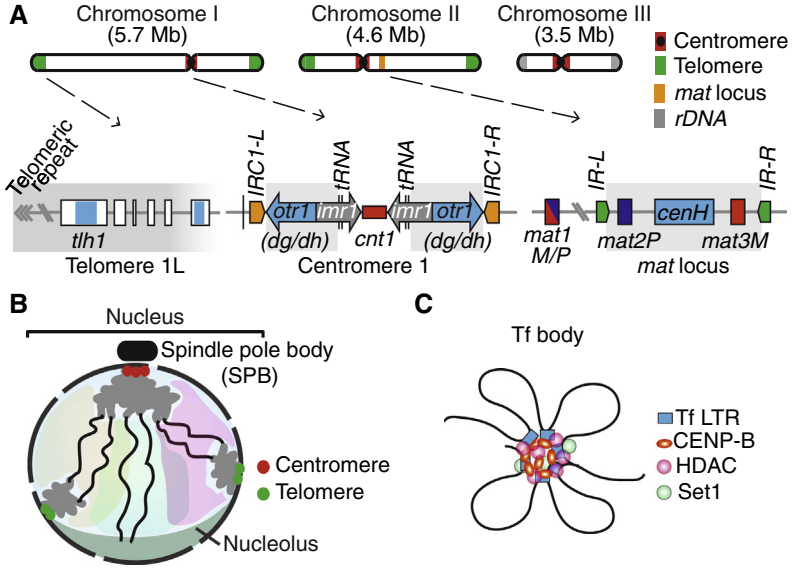

Fig. 1. Constitutive heterochromatin domains and the 3D organization of the *S. pombe* genome. (A) The three *S. pombe* chromosomes contain large blocks of heterochromatin that coats centromeres, telomeres and the silent mating-type (*mat*) interval. At centromeres, outer (*otr*) and innermost (*imr*) repeats surround the central core (*cnt*) domain, which is the site of kinetochore formation. The *otr* regions contain *dg* and *dh* repeats that are targets of heterochromatin formation by RNAi. *tRNAs* or *IRC* inverted repeats serve as heterochromatin boundary elements. A broad distribution of heterochromatin is also observed at the subtelomeric regions containing *tlh1* and its paralogs, which contain a *dh*-like element within the coding region. The heterochromatin domain at the *mat* region contains silent *mat2* and *mat3* loci, which serve as donors of genetic information for the active *mat1* locus. The *cenH* element with homology to *dg* and *dh* repeats nucleates heterochromatin, which in turn spreads across the domain surrounded by *IR-L* and *IR-R* inverted repeat boundary elements. Heterochromatin domains are highlighted in gray. (B) During interphase, chromosomes are arranged in a Rabl configuration. Interphase chromatin is subjected to various constraints and is confined to a limited sub-nuclear space (a degree of chromosome territory). (C) *Tf2* retrotransposons dispersed across the genome are organized into discrete nuclear foci, called Tf bodies. CENP-B proteins collaborate with histone modifying activities such as HDACs and Set1 to form 2–3 Tf bodies in the nucleus.

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