Function of Junk: Pericentromeric Satellite DNA in Chromosome Maintenance

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Satellite DNAs are simple tandem repeats that exist at centromeric and pericentromeric regions on eukaryotic chromosomes. Unlike the centromeric satellite DNA that comprises the vast majority of natural centromeres, function(s) for the much more abundant pericentromeric satellite repeats are poorly understood. In fact, the lack of coding potential allied with rapid divergence of repeat sequences across eukaryotes has led to their dismissal as "junk DNA" or "selfish parasites." Although implicated in various biological processes, a conserved function for pericentromeric satellite DNA remains unidentified. We have addressed the role of satellite DNA through studying chromocenters, a cytological aggregation of pericentromeric satellite DNA from multiple chromosomes into DNA-dense nuclear foci. We have shown that multivalent satellite DNA-binding proteins cross-link pericentromeric satellite DNA on chromosomes into chromocenters. Disruption of chromocenters results in the formation of micronuclei, which arise by budding off the nucleus during interphase. We propose a model that satellite DNAs are critical chromosome elements that are recognized by satellite DNA-binding proteins and incorporated into chromocenters. We suggest that chromocenters function to preserve the entire chromosomal complement in a single nucleus, a fundamental and unquestioned feature of eukaryotic genomes. We speculate that the rapid divergence of satellite DNA sequences between closely related species results in discordant chromocenter function and may underlie speciation and hybrid incompatibility.

HISTORY OF SATELLITE DNA RESEARCH

The term "heterochromatin" was first introduced by Emil Heitz (Heitz 1928) to describe regions of the genome that remained condensed even during interphase. A major constituent of heterochromatin is "satellite DNA," AT-rich tandem repeats, which are found in centromeric and pericentromeric regions of most of eukaryotic chromosomes. They were identified in early cesium chloride density centrifugation experiments as "satellite" bands that sedimented at different densities compared to the rest of genomic DNA because of skewed AT/GC contents (Kit 1961; Sueoka 1961; Sybalski 1968).

Despite the fact that the majority of eukaryotic centromeres are comprised of satellite DNA (Wong and Rattner 1988; Joseph et al. 1989; Willard 1990; Sun et al. 1997, 2003; Schueler et al. 2001), the lack of conservation in centromere repeat sequences, the "centromere paradox" (Henikoff et al. 2001), allied with the identification of neocentromeres lacking repeat sequences (Voullaire et al. 1993; du Sart et al. 1997; Barry et al. 1999) has led to the prevailing model that centromeres are defined in an epigenetic manner (Karpen and Allshire 1997; Allshire and Karpen 2008; Fukagawa and Earnshaw 2014). Nonetheless, satellite repeats underlying centromeres are speculated to have certain functionality to support centromeric function (Rosin and Mellone 2017).

Pericentromeric satellite DNA far surpasses centromeric satellite DNA in abundance, constituting up to 50% of genomes in certain cases (Garrido-Ramos 2017). Despite its abundance, the function of pericentromeric satellite DNA remains poorly understood. Unlike centromeric satellite DNA, whose role in chromosome segregation is indicated in kinetochore function, pericentromeric satellite DNA has been often dismissed as "junk DNA" (Ohno 1972), "selfish parasitic DNA" (Orgel and Crick 1980), or "fossils of centromeric evolution" (Malik 2009). However, many species contain substantial amounts of pericentromeric satellite DNA in their genome, whose maintenance poses a significant burden on the cell's resources. This has led researchers to speculate that pericentromeric satellite DNA may serve critical, yet unidentified roles that justify their large burden on the cell.

Cytologically, pericentromeric satellite DNA is organized into chromocenters within eukaryotic nuclei (Mayer et al. 2005). Initially, chromocenters were identified in plant cells as strongly stained foci when treated with nucleic acid dyes (Baccarini 1908). The composition of these foci remained unknown until the invention of in situ hybridization, which showed that chromocenters are dense aggregations of pericentromeric satellite DNA from multiple heterologous chromosomes (Jones 1970; Pardue and Gall 1970). Chromocenters show DNA methylation and histone methylation on H3K9/H4K20, epigenetic modifications associated with chromatin compaction and tran-

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scriptional repression (Saksouk et al. 2015; Nishibuchi and Déjardin 2017). Much like pericentromeric satellite DNA, the role of chromocenters as a cytological structure has also remained obscure.

PERICENTROMERIC HETEROCHROMATIN/ SATELLITE DNA: EXIST TO BE REPRESSED?

Both centromeric and pericentromeric satellite DNA are heterochromatinized via similar mechanisms involving epigenetic modifications, RNAi machinery, and heterochromatin-associated proteins (Allshire and Madhani 2017; Nishibuchi and Déjardin 2017 and references therein). In brief, heterochromatin is characterized by DNA methylation and histone modifications associated with transcriptional silencing such as histone H3K9 methylation. H3K9 trimethylation, which is catalyzed by a histone methyl transferase (Su(var)3-9 in *Drosophila*, Suv39 and SETDB1 in mammals), is recognized by heterochromatin protein 1 (HP1), a hallmark of constitutive heterochromatin. Recruitment of heterochromatin proteins to the underlying satellite DNA requires transcription via a few mechanisms (Hall et al. 2012; Biscotti et al. 2015; Saksouk et al. 2015). First, transcription of satellite DNA leads to Dicer-dependent siRNA production, which is required for the establishment and maintenance of heterochromatin state (Bühler and Moazed 2007; Moazed 2011). Second, recent studies showed that noncoding satellite DNA transcripts recruit Suv39 enzymes to centromeric and pericentromeric sequences, leading to heterochromatinization (Johnson et al. 2017; Shirai et al. 2017; Velazquez Camacho et al. 2017). Interestingly, satellite DNA transcription has also been implicated in the formation of chromocenters in early mouse embryos (Probst et al. 2010).

Whereas heterochromatinization of centromeres has clear functional implications in chromosome segregation (Allshire and Karpen 2008; Fukagawa and Earnshaw 2014), it remains unclear why pericentromeric satellite DNA must be silenced. Its derepression has been shown to cause a plethora of problems, such as DNA damage through the accumulation of RNA:DNA hybrids (Zeller et al. 2016), chromosome missegregation, and meiotic hyper recombination (Peters et al. 2001; Bouzinba-Segard et al. 2006; Hahn et al. 2013; Tasselli et al. 2016), although it is often unclear whether these defects are caused by perturbation of centromeric or pericentromeric heterochromatin. Transcriptional derepression of satellite DNA is also associated with human pathologies such as cancer (Eymery et al. 2009; Ting et al. 2011; Zhu et al. 2011; Bersani et al. 2015), aging (Shumaker et al. 2006; De Cecco et al. 2013a, 2013b), senescence (Enukashvily et al. 2007), and cardiomyopathy (Gaubatz and Cutler 1990; Haider et al. 2012). Accordingly, most studies thus far have investigated the mechanisms of heterochromatin transcriptional silencing, based on the reasoning that its derepression is problematic. However, if pericentromeric heterochromatin serves no function, the easiest solution would be the removal of these sequences, rather than silencing through heterochromatinization. Thus, why satellite DNA/constitutive heterochromatin exists in the first place, and whether pericentromeric satellite DNA serves any fundamental function, is poorly understood.

PROPOSED ROLES OF PERICENTROMERIC SATELLITE DNA

Based on the reasoning that such a large component of the genome cannot be nonfunctional, many researchers have speculated roles of satellite DNAs—for example, playing structural roles or mediating meiotic homologous pairing (Yunis and Yasmineh 1971; Walker 1971; John and Miklos 1979; Kuhn et al. 2011).

One prevailing model of satellite DNA function is their involvement in meiotic homologous chromosome pairing. Cytologically, satellite DNA show strong pairing in meiotic prophase in a broad range of species (Yunis and Yasmineh 1971; Hawley et al. 1992; Dernburg et al. 1996), leading to a popular idea that satellite DNA may regulate meiotic chromosome pairing. However, earlier studies using various chromosomal deficiencies that delete most of satellite DNA (for review, see John and Miklos 1979; Miklos and John 1979) concluded that satellite DNA/heterochromatin is not required for chromosome pairing. It is possible that satellite DNA-mediated pairing may function redundantly in parallel with other mechanisms that facilitate chromosomal pairing.

Another example of putative satellite DNA function is found in the *Drosophila* Y chromosome. Although *Drosophila* Y chromosomes are highly heterochromatic, they contain several embedded genes that are required for male fertility. These genes contain megabase-sized introns consisting of satellite DNA that are transcribed in spermatocytes, forming a lamp brush–like structure termed Y-loops (John and Miklos 1979; Bonaccorsi et al. 1988, 1990; Pisano et al. 1993). It has been proposed that these large intronic transcripts may fulfill a protein-binding function and sequester proteins required for later meiotic stages (Bonaccorsi et al. 1988, 1990; Pisano et al. 1993). Alternatively, intronic heterochromatin may serve to repress expression of these fertility factors in nonspermatocyte cells. However, it should be noted that it has not been possible to delete intronic satellite DNA to determine effects on the expression of fertility genes. Interestingly, a recent study suggested that intronic satellite DNA is a phenomenon specific to genes on the Y chromosome. By comparing the Y chromosomes of *Drosophila melanogaster* and *Drosophila pseudoobscura*, it was found that orthologous genes translocated from the *D. melanogaster* Y to a *D. pseudoobscura* autosome have reduced intron sizes (Chang and Larracuente 2017). Yet *D. pseudoobscura* spermatocytes show cytologically recognizable Y-loops, indicating that a distinct set of genes on the *D. pseudoobscura* Y chromosome have acquired mega intron(s). This implies that satellite DNA may play a role in gene expression specifically for Y chromosome genes, which are always maintained in a heterochromatic environment, except for once in their lifetime during spermatocyte development.

Additional studies have indicated a role for satellite DNA transcription in response to cellular stress, most prominently during the heat shock response (Jolly et al. 2004; Rizzi et al. 2004; Valgardsdottir et al. 2008; Pezer and Ugarkovic 2012). In human cells, heat shock induces the expression of the HSF1 protein, which accumulates on nuclear stress bodies and up-regulates the transcription of the pericentromeric SatIII satellite DNA (Jolly et al. 2004; Rizzi et al. 2004). It has been proposed that the massive activation of SatIII transcription might sequester many factors required for global transcription and splicing, thus leading to down-regulation of transcription under stress (Biamonti and Vourc'h 2010). Likewise, human SatII, whose transcription is up-regulated in cancer cells, has been shown to sequester the MeCP2 (methyl CpG binding) protein, demonstrating the ability of satellite DNA transcripts to regulate the epigenetic state (Hall et al. 2017). In yet another example, satellite DNA transcripts from the *Drosophila* X chromosome are processed into small RNAs, promoting X chromosome recognition for dosage compensation in somatic cells (Menon et al. 2014; Joshi and Meller 2017).

These studies have highlighted the importance of satellite DNA in various biological processes. However, most of these examples of satellite DNA function pertain to species-specific phenomenon, and a unifying theme underlying satellite DNA function across eukaryotes is still lacking.

CHROMOCENTER BUNDLING PROTEINS

Studying the function of satellite DNA is challenging for obvious reasons. Foremost is the inability to remove these repetitive sequences, which can span megabases on chromosomes. Therefore, we initiated our study on the function of satellite DNA by focusing on satellite DNA-binding proteins, specifically, D1 in *Drosophila* and HMGA1 in mouse. Both proteins contain multiple AT-hook motifs, which bind the minor groove of AT-rich DNA (Reeves and Nissen 1990; Huth et al. 1997). D1 was identified as a nonhistone chromosomal protein (Rodriguez Alfageme et al. 1980), which was subsequently shown to have affinity for the 1.672 g/cm^3 satellite DNA ($\{AATAT\}_n$) from *Drosophila* (Rodriguez Alfageme et al. 1980; Levinger and Varshavsky 1982a, 1982b). The $\{AATAT\}_n$ satellite comprises a substantial fraction of *Drosophila* genome at nearly ~8% of the genome (Lohe et al. 1993). A role for D1 in constitutive heterochromatin has been suggested based on its effects on position effect variegation (Aulner et al. 2002).

HMGA1 (HMG-1/Y) was also identified as a mammalian nonhistone chromosomal protein (Goodwin et al. 1973; Lund et al. 1983). Further studies revealed its ability to bind satellite DNAs (Strauss and Varshavsky 1984), primarily the abundant pericentromeric satellite DNA called "major satellite" in mouse (Vissel and Choo 1989; Radic et al. 1992), which comprises nearly 6% of the genome (Lyon and Searle 1989). Consistent with the notion of pericentromeric heterochromatin forming chromocenter (Jones 1970; Pardue and Gall 1970; Guenatri et al. 2004), HMGA1 localizes to mouse chromocenters (Brocher et al. 2010).

We have found that both D1 and HMGA1 are required for clustering of chromocenter, suggesting a role of these satellite DNA-binding proteins in chromocenter formation (Fig. 1). In vitro experiments showed that HMGA1 could cross-link DNA molecules through its multiple AT-hooks (Vogel et al. 2011), suggesting HMGA1's biochemical capacity to cross-link multiple DNA strands. In an in vivo experiment, it was shown that exogenous expression of D1 in *Drosophila* salivary glands resulted in the ectopic fusion of heterologous chromosomes, likely at sites of intercalary heterochromatin (Smith and Weiler 2010). These published results and the fact that D1/HMGA1 are required for chromocenter formation led us to propose a model that D1 and HMGA1 are multivalent DNA-binding proteins capable of bundling multiple DNA strands, allowing clustering of pericentromeric satellite DNA from multiple chromosomes into chromocenters (Fig. 1). We found that exogenous expression of D1 protein, which can bind to mouse major satellite DNA, was sufficient to enhance the clustering of chromocenter in mouse cells, demonstrating the ability of D1 to facilitate the association/cross-linking of satellite DNA.

More direct evidence for D1 cross-linking its target DNA came from a protein fusion of D1 and LacI, which was sufficient to recruit euchromatic LacO repeat sequences into chromocenters. Finally, we observed chromatin threads, which are positive for D1/HMGA1 proteins, as well as their target satellite DNA sequences, connecting multiple chromosomes in early prophase cells, when individual chromosomes start condensing in preparation for mitosis. We speculate that these threads connecting prophase chromosomes are remnants of interchromosomal connections during interphase, which bundles chromosomes together into chromocenters. These threads are reminiscent of earlier observations of threads connecting mitotic chromosomes (Takayama 1975; Burdick 1976) that have later been shown to contain satellite DNA (Kuznetsova 2007).

Taken together, we propose that these satellite DNA-binding proteins (and perhaps other uncharacterized proteins that are known to bind to satellite DNA) participate in chromocenter formation by cross-linking their target DNA on multiple chromosomes.

FUNCTION OF CHROMOCENTER IN ENCAPSULATING THE FULL COMPLEMENT OF GENOME INTO A SINGLE NUCLEUS

The disruption of chromocenter formation in D1 mutant flies and HMGA1 knockdown cells provided a unique opportunity to interrogate the function of chromocenter/satellite DNA. We found that disruption of chromocenter upon D1/HMGA1 depletion resulted in a dramatic increase in micronuclei formation. Time-lapse live imaging revealed that the micronuclei formed during interphase, where micronuclei bud off from the rest of the nucleus. These results indicate that cross-linking of pericentro-

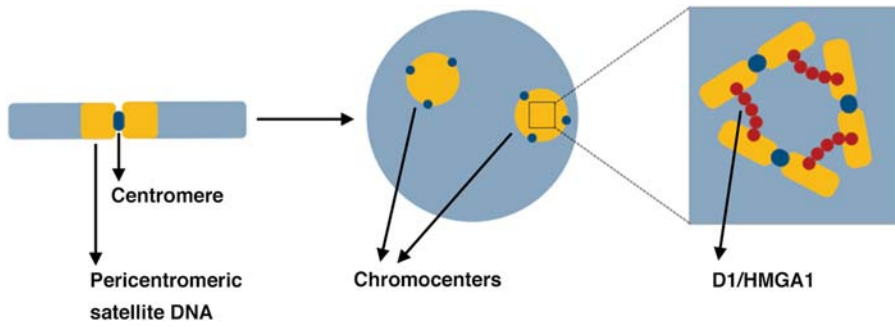

Figure 1. Model of chromocenter formation. Pericentromeric satellite DNA (yellow) is bound by satellite DNA-binding proteins (D1/HMGA1), which cross-link satellite DNA from multiple chromosomes, leading to chromocenter formation.

meric heterochromatin is important to form a physical network of chromosomes such that individual chromosomes do not float away from each other, leading to micronuclei formation (Fig. 2).

Packaging of the full complement of the genome into a single nucleus is a fundamental requirement for eukaryotic cells, whose genetic material is split into multiple chromosomes. Packaging of the genome in a single compartment must be a prerequisite for concerted gene function, for example, to allow a transcription factor to find its target genes. The importance of maintaining a single nucleus (i.e., prevention of micronuclei formation) has been shown by series of studies that demonstrated that (1) micronuclei exhibit defective DNA replication/DNA repair and increased DNA damage (Crasta et al. 2012), (2) micronuclei exhibit defective nuclear envelope integrity (Hatch et al. 2013), and (3) chromosomes within micronuclei are susceptible to chromosome shattering and rearrangements, termed chromothripsis (Hatch and Hetzer 2015; Zhang et al. 2015), which has been suggested to be a driver of oncogenesis. Similar to these micronuclei-associated defects, D1 mutation/HMGA1 knockdown resulted in accumulation of DNA damage and chromosomal breaks, leading to cell death. These results indicate that chromocenter formation, mediated by D1 and HMGA1, plays a critical role in encapsulating the full genome into a single nucleus, a failure of which leads to micronuclei formation and the resulting cellular defects.

Interestingly, even major nuclei showed defective integrity of the nuclear envelope in D1 mutant/HMGA1 knockdown cells. This suggested that chromocenter formation might be required not only for encapsulating all chromosomes into single nucleus, but also for maintaining nuclear envelope integrity. Early cytological studies showed that constitutive heterochromatin was juxtaposed to the nuclear envelope and around nucleoli (Rae and Franke 1972). Because of the enrichment of heterochromatin at the nuclear envelope, it is thought to function as a gene repressive compartment. Global analysis of gene expression at the nuclear envelope has shown that genes within lamin-associated domains (LADs) generally show decreased expression compared to genes outside of lamin-associated domains (Guelen et al. 2008). How do changes in constitutive heterochromatin clustering affect the integrity of the nuclear envelope? Interestingly, constitutively localized LADs are enriched for H3K9 methylation, are AT-rich and have been suggested to function as a structural backbone for the organization of interphase chromosomes (Meuleman et al. 2013). In addition, recent studies have shown that impairing heterochromatin using either RNAi of Prdm3/16 (Pinheiro et al. 2012) or chemical inhibitors of histone methyltransferases (Stephens et al. 2018) results in defects of the nuclear envelope. Because the majority of chromocenters are localized to the nuclear periphery (Mayer et al. 2005), chromocenter-forming proteins such as D1/HMGA1 may perhaps function by linking constitutive heterochromatin to nuclear envelope, or by facilitating nuclear envelope formation around the constitutive heterochromatin.

IS CHROMOCENTER FUNCTION UNIVERSAL?

We have presented the hypothesis that pericentromeric satellite DNA mediates chromocenter formation, which

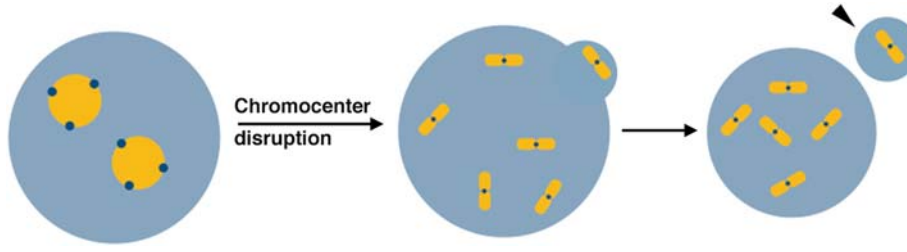

Figure 2. Chromocenter disruption leads to micronuclei formation. Loss of satellite DNA-binding proteins, D1/HMGA1, leads to micronuclei formation. Based on this result, we propose that bundling of multiple chromosomes via formation of chromocenter is critical to maintain the full complement of the genome into a single nucleus.

functions to encapsulate the full set of chromosomes into a single nucleus. Given the ubiquity of satellite DNA, we postulate that chromocenter formation and function may be a universal mechanism conserved across many species.

This hypothesis leads to a few speculations that may provide further insights into the biology of chromocenter. First, in certain cases, eukaryotic chromosomes appear to be completely lacking satellite DNA (e.g., horse chromosome 11, orangutan chromosome 12) (Wade et al. 2009; Piras et al. 2010; Locke et al. 2011) raising the question of if/how these chromosomes may be incorporated into chromocenters. Interestingly, a recent report has shown that transposable element (TE)-derived tandem repeats are a component of mouse chromocenters (Kuznetsova et al. 2016). TE-derived sequences are abundant, heterochromatinized and typically interspersed throughout eukaryotic chromosomes (Saksouk et al. 2015; Nishibuchi and Déjardin 2017), including pericentromeric heterochromatin, where they are present in complex islands within large satellite DNA tracts (Sun et al. 1997, 2003). In addition, satellite DNA is derived from transposable elements in certain cases (Heikkinen et al. 1995; Kapitonov et al. 1998; Kidwell 2002). Recognition of TE-derived repeats or their heterochromatic nature may help chromocenter formation, possibly mediating incorporation of satellite DNA-free chromosomes into chromocenters. Thus, chromosomes lacking typical satellite DNA might still participate in chromocenter formation via their resident TEs. Also, if TE-derived sequences indeed function to mediate chromocenter formation, it may force us to reconsider the biological status of TEs: instead of pure parasites, they may be symbionts of eukaryotic genomes.

The hypothesis that pericentromeric satellite DNA may be a critical component of chromosomes to ensure its maintenance leads to another interesting consideration. Generally, repetitive sequences are thought to be inherently unstable because of sporadic loss of copy number caused by intrachromatid recombination (Charlesworth et al. 1994; Stephan and Cho 1994). If satellite DNA were a critical structural component of the chromosome, it would have to be actively maintained. This is consistent with the fact that satellite DNA shows little within-species variation in the genomes of *Drosophila* species despite its potential instability (Bosco et al. 2007). Strikingly, it has been shown that satellite DNA can expand in cancer cells (Bersani et al. 2015). Although it was regarded as an "abnormality" of cancer cells, it might reflect the acquired immortality of cancer cells. Similar to the telomere maintenance mechanism, which is confined to immortal cells (germ cells, some somatic stem cells, and cancer cells), maintenance (expansion) of satellite DNA may be a privileged process that can only occur in immortal cells.

SPECULATION: SATELLITE DNA AND SPECIATION

It is widely appreciated that satellite DNA sequences are highly divergent even among closely related species (Ugarković and Plohl 2002). Rapid changes in the spectrum of satellite DNAs (dramatic expansion and shrinkage of a particular repeat sequence, leading to a vastly distinct landscape of satellite DNA composition in closely related species) has been attributed to processes such as intrachromatid recombination, unequal sister chromatid exchange, replication slippage, rolling circle amplification and reinsertion, and gene conversion (Charlesworth et al. 1994). The "library" hypothesis complements this idea, by postulating that each species does not entirely lose or acquire certain satellite repeat sequences but instead the related species share a common library of satellite sequences that merely fluctuate in copy number (Salser et al. 1976; Fry and Salser 1977).

Irrespective of the mechanisms that explain birth and death of satellite DNA repeat sequences, the highly divergent sequences of satellite DNA reinforced the idea that they are junk (Ohno 1972; Orgel and Crick 1980). On the other hand, the very same fact led to a speculation that rapid changes in satellite DNA sequences may underlie speciation, making two species incompatible with each other (Walker 1971; Yunis and Yasmineh 1971; John and Miklos 1979). Our hypothesis that satellite DNA is required for chromocenter formation can potentially offer an answer to this paradox. If satellite DNA functions as a platform for proteins that have the capacity to cross-link multiple DNA strands, the repeat sequence per se might not matter as much as its ability to be bound by cross-linking proteins (i.e., chromocenter proteins). If this is the case, evolutionary pressure will select for recognition of satellite DNA by binding proteins with less stringency for the exact sequence, which may rapidly change because of the inherent instability of repetitive DNA.

Now we are presented with a striking possibility: The rapid change in satellite DNA sequences over the course of evolution might quickly separate two populations within a species, because rapid changes in satellite DNA sequences must be matched by rapid changes in satellite DNA-binding proteins. Two populations may therefore be reproductively isolated because their satellite DNA and chromocenter-forming proteins become incompatible. If this is the case, hybrid incompatibility may arise from the incompatibility of chromocenter-forming factors (satellite DNA-binding proteins and their cognate repeat sequences) (Fig. 3). This is certainly a testable prediction, and encouragingly, the majority of speciation genes identified thus far bind constitutive heterochromatin (Sawamura 2012). For example, two hybrid incompatibility genes in *Drosophila*, *Hmr* and *Lhr* (Watanabe 1979; Hutter and Ashburner 1987; Barbash et al. 2003; Brideau et al. 2006), are known to localize to the chromocenters of polytene chromosomes (Satyaki et al. 2014) and pericentromeric heterochromatin of diploid nuclei (Blum et al. 2017), indicating that they may participate in chromocenter formation or its regulation. It would be of particular interest in the future to examine cell biological aspects of hybrid incompatibility to see whether they might present phenotypes that are consistent with these ideas (e.g., chromocenter disruption). It will also be of interest to examine the relationship between Hmr/Lhr and D1.

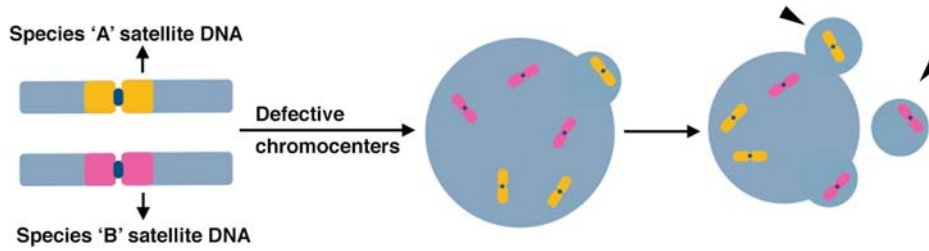

Figure 3. Hypothetical model of incompatibility between chromosomes from distinct species in forming chromocenter. The well-known fact that satellite DNA sequences are highly divergent between closely related species, combined with our finding that satellite DNA is critical for chromocenter formation and thus chromosome maintenance, leads to the question of whether chromosomes from different species can form chromocenters. We speculate that the incompatibility in chromocenter formation may underlie hybrid incompatibility.

CONCLUSION

As described above, here we present our hypothesis that chromocenter formation mediated by bundling of pericentromeric satellite DNA is a universal mechanism of eukaryotic cells to encapsulate the full complement of the genome into a single nucleus. Although satellite DNA function has remained enigmatic for a long time, our model offers explanations to many aspects of satellite DNA: lack of DNA sequence conservation, yet persistent presence in a broad range of eukaryotes, and cytological behavior of satellite DNA (chromocenter formation). Our model also provides several testable predictions, which need to be addressed in future studies. In summary, we propose that satellite DNA plays a fundamental role in the maintenance of the eukaryotic genome.

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