Karyotype Evolution in Holocentric Organisms

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Article Contents

- Introduction
- Holocentry across the Eukaryotic Tree of Life
- Mitosis and Meiosis in Holocentric Chromosomes
- Chromosome Number Evolution
- Holokinetic Drive
- General Evolutionary Patterns in Organisms with Holocentric Chromosomes

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Holocentric chromosomes are characterised by the presence of kinetochoric activity along the chromosome length. This atypical chromosomal architecture has evolved independently in a wide array of lineages across the tree of life. Different mechanisms have been developed to overcome meiotic problems posed by holocentry, such as inverted meiosis and restricted kinetochore activity. Although holocentric karyotypes present potential advantages through the fission and fusion events that characterise chromosome evolution in several holocentric lineages, there is no consistent evidence of increased diversification rates in holocentric lineages relative to monocentric lineages. The extended kinetochore in holocentric chromosomes has been hypothesised to enable a unique type of meiotic drive, 'holocentric drive', analogous to the meiotic drive of monocentric chromosomes. However, much research remains to understand holocentrism, especially elucidating the mechanism and evolutionary implications of meiosis in unrelated holocentric lineages.

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Introduction

Chromosomes in ca. 80% of eukaryote species present a primary constriction during metaphase at cell division, usually constituted by a heterochromatic region composed of specific, highly repetitive deoxyribonucleic acid (DNA) sequences. These regions, the centromeres, are the locus of kinetochores assembly (Cheerambathur and Desai, 2014; Neumann *et al.,* 2012). Microtubule spindle fibres attach to the outer plate poleward surface of the kinetochore and separate homologous chromosomes at anaphase (reductional division).

By contrast, up to 20% of eukaryote species present chromosomes without this clear primary constriction (Márquez-Corro *et al.,* 2018). In these organisms, centromeres are not localised, but rather occur continuously or repeatedly along chromosomes, and the kinetochoric activity is extended almost up to the telomeric regions. These are termed holocentric, holokinetic or polycentric chromosomes, as opposed to the monocentric chromosomes that dominate the tree of life. The more general 'polycentric' may be used to describe any chromosome with more than one centromere (Bureš *et al.,* 2013; Melters *et al.,* 2012; Mola and Papeschi, 2006).

Holocentric behaviour was first reported by Heilborn (1924) in *Carex*, and holocentric chromosomes were clearly described by Schrader (1935) in the spermatocyte division of the hemipteran (true bug) *Protenor belfragei*. Since then, holocentric chromosomes have been described in several lineages. Escudero *et al*. (2016) presented a phylogenetic comparative analysis, suggesting that (1) monocentry is ancestral in eukaryotes and (2) reversions to monocentric chromosomes have been inferred as more frequent than transitions to holocentry from monocentric ancestors. Various mechanisms of chromosome segregation have evolved in different holocentric lineages, suggesting multiple independent origins of holocentry from a monocentric ancestor rather than repeated losses from a holocentric ancestor (see section titled 'Mitosis and meiosis on holocentric

chromosomes'). An additional, rarer type of chromosome has recently been reported, the so-called meta-polycentric chromosomes, in which centromeres cluster together to form a lengthened primary constriction (*Pisum* and *Lathyrus* plant genera; Neumann *et al*., 2012, 2015).

Holocentry across the Eukaryotic Tree of Life

Whether chromosomes are holocentric or not has been largely overlooked in most karyotype studies, which have focused primarily on chromosome number and/or ploidy level. Monocentry has been assumed almost universally in the absence of clear evidence for holocentry, despite the fact that the restriction of kinetochoric activity to a localised area during meiosis is not diagnostic of monocentry (Melters *et al.,* 2012). In some cases precisely the opposite assumption has been made, and it can take several studies to correct a false attribution of holocentry to a monocentric organism, as in the cases of the moss *Pleurozium schreberi*, the angiosperm order Zingiberales and the arachnid order Palpigradi (Dawe and Hiatt, 2004; Král *et al.,* 2008; Mahanty, 1970). Our knowledge of the extent of holocentry and frequency of evolutionary transitions between monocentry and holocentry is therefore limited.

Our current understanding is that holocentry has arisen independently at least in three of the six eukaryotic superclades (Bureš *et al.,* 2013; Escudero *et al.,* 2016; Hipp *et al.,* 2013; Márquez-Corro *et al.,* 2018; Melters *et al.,* 2012; Mola and Papeschi, 2006). Rhizaria is the least studied eukaryotic superclade that presents holocentric lineages. Little research on centromere disposition or kinetochore activity has been conducted in the clade since holocentry was reported for *Aulacantha scolymantha* (Grell and Ruthmann, 1964; Lécher, 1973) and suggested by Hughes-Schrader and Ris (1941) for the plasmodiophorid genus *Spongospora* (based on Horne's (1930) description of chromosome segregation during mitosis). Archaeoplastida and Opisthokonta are the most widely studied taxa in terms of karyotype structure that present holocentric chromosomes, since these lineages include plants and animals, respectively.

The Archaeoplastida superclade includes holocentric lineages in both eudicots and monocots: *Myristica* (Magnoliales), Droseraceae (Caryophyllales), *Cuscuta* (Solanales), Melanthiaceae (Liliales) and Cyperaceae and Juncaceae (Poales). Recently, holocentry has been proposed for two additional lineages: the early divergent *Trithuria submersa* (Nymphaeales, Kynast *et al.,* 2014) and a species from the sister family of the Cyperaceae plus Juncaceae clade, *Prionium serratum* (Thurniaceae, Zedek *et al.,* 2016). However, there are uncertainties about the distribution of holocentry in *Cuscuta*, *Drosera*, Melanthiaceae and Myrisicaceae (Kolodin *et al.,* 2018; Márquez-Corro *et al.,* 2018). Besides angiosperms, holocentric chromosomes have not been detected in any other Archaeoplastida lineage, with the exception of the green algae family Zygnematophyceae (Brook, 1981; King, 1960).

In the Opisthokonta clade, holocentric chromosomes have never been reported from the early-diverging lineages, such as Fungi, through to the late-diverging groups that are related to the nephrozoans (i.e. xenacoelomorphs). Holocentry is, however, reported for several orders of Nematoda (Ascaridida, Rhabditida and Tylenchida), Arthropoda and velvet worms *Euperipatus* (Euonychophora). The arthropods are extremely diverse and particularly well studied, and holocentric chromosomes are known from a number of lineages: Chelicerata families Dysderidae and Segestriidae (Araneae), superfamily Buthoidea (Scorpiones), some species of Acariformes and *Rhipicephalus* (Ixodidae, Parasitiformes); Myriapoda orders Lithobiomorpha and Scutigeromorpha and Hexapoda orders Dermaptera, Hemiptera, Lepidoptera, Odonata, Phthiraptera, Psocoptera, Thysanoptera, Trichoptera and Zoraptera (see revision in Márquez-Corro *et al.,* 2018).

The distribution of holocentry across the eukaryote phylogeny has recently been proposed to be an adaptation to terrestriality (Zedek and Bureš, 2018). Holocentric chromosomes are particularly tolerant of fragmentation, because fragments formed in fission events can be inherited in holocentric organisms, whereas they will usually be lost in monocentric organisms due to the lack of centromere (Bureš *et al.,* 2013; Melters *et al.,* 2012; Mola and Papeschi, 2006). This could have yielded an advantage in the early conquest of terrestrial environments, where higher UV radiation posed higher mutation risks, especially for the early lineages of arthropods and nematodes (Zedek and Bureš, 2018).

Mitosis and Meiosis in Holocentric Chromosomes

Chromosome formation is mediated by conserved protein complexes (condensin I and condensin II) that are responsible for the general condensation of the chromatin and the strengthening of the whole chromosome structure (Hirano, 2016). Studies to date suggest that most eukaryotic centromeres are condensin II enriched, thus highly compacted. Although condensin I typically affects more of the chromosome than the centromere-restricted activity of condensin II, the holocentric *Caenorhabditis elegans* shows condensin II activity along the length of the chromosome (Hirano, 2016). The higher condensation of holocentric chromosomes has been proposed to solve merotelic attachments of kinetochores to microtubules – attachment of a kinetochore to both spindle poles – and thus contributes to chromosome segregation (Stear and Roth, 2002). Interestingly, some organisms such as Fungi (e.g. *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*) and Ciliophora (ciliates, i.e. *Tetrahymena thermophila*) have lost at least some of the genes coding for condensin II proteins (Hirano, 2016). This may explain why holocentry is unknown in those lineages, as less-condensed chromosomes may lead to merotelic attachments and, thus, failed segregation. No study we are aware of has investigated this question.

The kinetochore plate is attached to the centromeric chromatin following chromosome condensation and before the nuclear envelope disappears (Maiato *et al.,* 2004). Kinetochoric inner and outer plates are electron dense, whereas the middle layer presents low electron density and forms a trilaminar structure (McEwen and Dong, 2010). This structure is formed of the centromeric

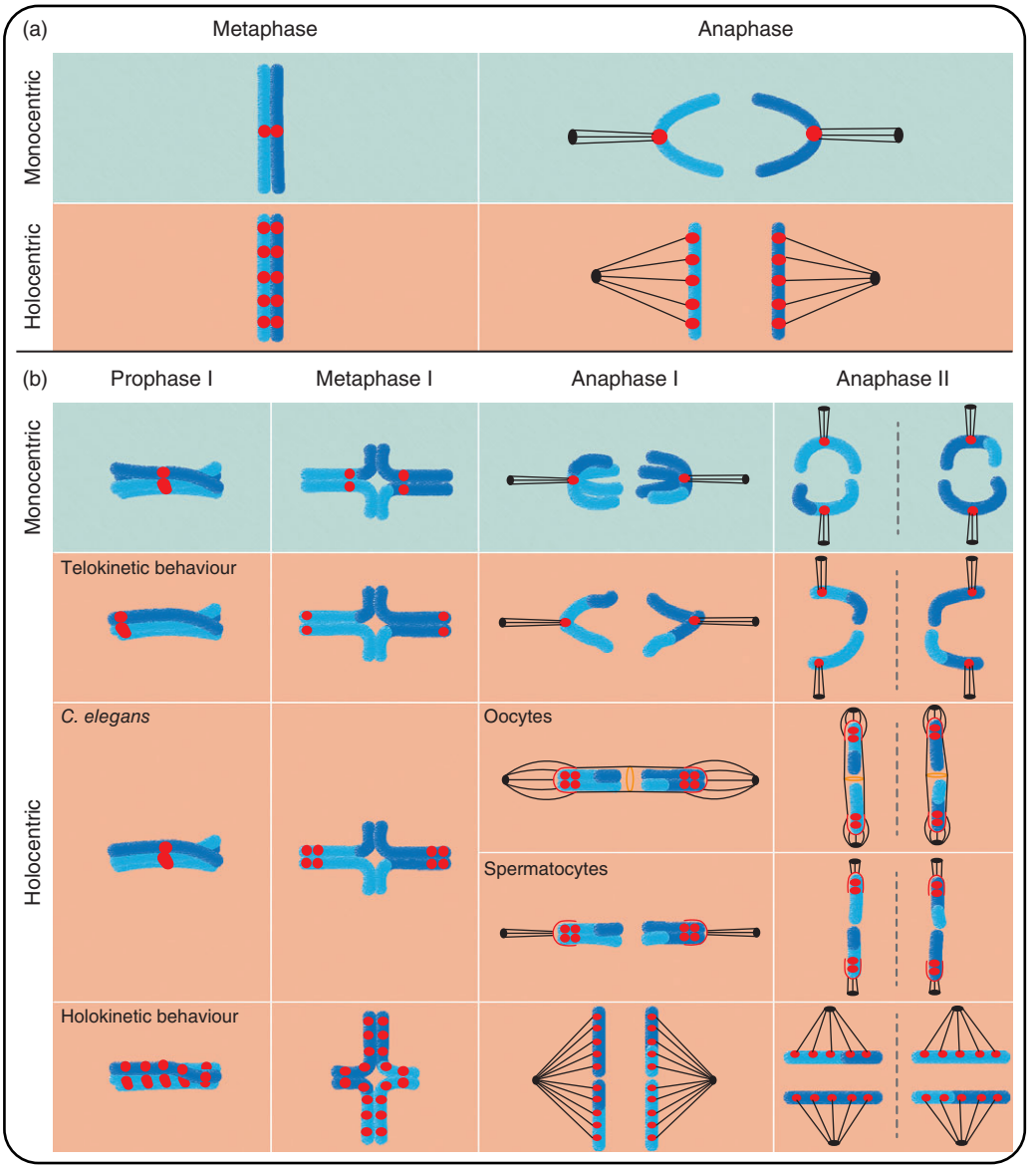

Figure 1 Mitosis (a) and meiosis (b) in monocentric and holocentric organisms. (a) During segregation, holocentric chromosomes migrate parallel to one another; monocentric chromosomes adopt a V shape as they migrate to the poles, dragged along by their centromeres. (b) In monocentric and holocentric chromosomes that present restricted kinetochoric activity (i.e. telokinetic and *C. elegans* chromosomes), chromosomes segregate during meiosis I and chromatids in meiosis II. By contrast, in holocentric organisms with inverted meiosis (i.e. truly holokinetic chromosomes), the order is reversed, the chromatids segregate in meiosis I and chromosomes in meiosis II. Note how *C. elegans* kinetochore (red line) adopts a characteristic cup shape along the active centromeres. Also, in early anaphase, a ring of chromokinesin (yellow line) is formed in the equatorial plate of *C. elegans* oocytes, from which noncentromeric microtubules push the chromosomes to each pole.

protein CENH3 (also called CENP-A), a specialised H3 histone. CENH3 appears bounded to the centromeric nucleosomal DNA, interspersed with typical H3 histone (Maddox *et al.*, 2004). CENH3 allows further assembly of proteins such as CENP-C (Maiato *et al.*, 2004), which is responsible for setting up the outer plate (Earnshaw, 2015). The outer kinetochore is mostly composed of proteins that are involved in connecting with microtubules (e.g. CENP-E, Maiato *et al.*, 2004).

Every eukaryotic organism presents at least one specialised conserved protein in the inner kinetochore – the abovementioned CENH3 – but some CENH3 isoforms have been reported in several species (e.g. *Luzula nivea* and *C. elegans*, Monen *et al.*, 2005; Moraes *et al.*, 2011; Nagaki *et al.*, 2005). The conservatism of CENH3 and the trilaminar kinetochoric structure are shared between monocentric and holocentric organisms (Maddox *et al.*, 2004). Exceptionally, loss of CENH3 and CENP-C genes has

been associated with several transitions from monocentry to holocentry in insects (Drinnenberg *et al.,* 2014), although kinetochore structure has been largely unchanged.

During mitotic anaphase, holocentric chromosomes differ from monocentric chromosomes in appearance (**Figure 1a**). The extended kinetochoric activity in the former allows multiple microtubule attachments and parallel movement of the chromosomes towards the poles, in contrast to the typical V-shaped monocentric chromosomes (Bureš *et al.,* 2013; Melters *et al.,* 2012; Mola and Papeschi, 2006). At the same time, meiosis is often not as straightforward in holocentric organisms. Meiotic pairing in holocentric chromosomes has been shown to generate morphologically distinctive associations. For example, holocentric trivalent chains whose central chromosome is bigger than the lateral chromosomes (heteromorphic chainlike trivalent) may result from fusion or fission events, analogous to Robertsonian fusions and centric fission in monocentric chromosomes. 'Frying pan trivalents' at meiotic metaphase (Faulkner, 1972) may arise from chromosome duplications (Faulkner, 1972). However, the mechanism by which these frying pan trivalents form has been questioned, at least when the trivalent is heteromorphic (Cayouette and Morisset, 1986). By contrast with trivalents, tetravalents in holocentric and monocentric organisms form by similar processes, generally heterozygosis for reciprocal translocation or tetrasomy (Faulkner, 1972), by relict homologies in ancient polyploids (Cayouette and Morisset, 1986) and the existence of 'fragile points' in the chromosomes (Luceño, 1994).

Without particular meiotic adaptations, chiasmata would produce cruciform chromosome pairings with kinetochoric activity in every arm, which could produce random segregation of broken chromosomes or prevent segregation altogether (Melters *et al.,* 2012). Holocentric chromosomes have evolved various mechanisms to overcome this problem (reviewed in Marques and Pedrosa-Harand, 2016).

Among holocentric organisms, *C. elegans* has been perhaps most carefully studied (Maddox *et al.,* 2004). To avoid random segregation during meiosis I, homologous chromosomes are separated either by microtubules pulling from a restricted kinetochore located at the chromosomes ends, in spermatocytes, or by microtubules growing between the homologous chromosomes in oocytes. The same occurs in meiosis II, when chromatids segregate to opposite poles (**Figure 1b**; Dumont *et al.,* 2010; Shakes *et al.,* 2009). Similarly, localised kinetochoric activity has been reported in true bug (Heteroptera) spermatocytes, in which the active centromere end can switch to the opposite end of the chromosome at meiosis II (Pérez *et al.,* 1997). In such cases, chromosomes function as monocentric chromosomes during meiosis and are also referred as telokinetic, due to the terminal kinetochoric activity.

Many holocentric lineages present a second meiotic innovation, inverted meiosis (Wahl, 1940), in which the typical prereductional meiosis is replaced by postreductional meiosis (**Figure 1b**). In inverted meiosis, the kinetochore is active along the entire length of the chromosome, rendering the chromosome holokinetic. During meiotic metaphase I, chromosomes rotate 90° as sister chromatids segregate to opposite poles, reducing the risk of breakage. Thus, chromatids are separated in anaphase I and chromosomes in anaphase II, in contrast to the prereductional meiosis, with chromosomes and chromatids splitting during anaphase I and II, respectively (Wahl, 1940; Viera *et al.,* 2009). After anaphase I, homologous chromatids pair again either at the ends or along the entire length (Nordenskiöld, 1962; Strandhede, 1965). Lineages with inverted meiosis include some mite species (i.e. *Tetranychus*) and angiosperm genera *Cuscuta*, *Luzula*, *Carex* and *Rhynchospora* (Davies, 1956; Marques and Pedrosa-Harand, 2016). The mechanisms involved in this remarkable evolutionary innovation are unknown.

Finally, achiasmatic meiosis has been reported from some organisms. In most holocentric meiosis, there are a maximum of two chiasmata per chromosome (Nordenskiöld, 1962; Monen *et al.,* 2005). In a few lineages, including some species of scorpions, Lepidoptera and Trichoptera (see Marques and Pedrosa-Harand, 2016), no crossing-over is produced in order to ensure the proper division of reductional meiosis. Interestingly, inverted, achiasmatic meiosis has been found in *Rhynchospora tenuis* (Cyperaceae, Cabral *et al.,* 2014).

Chromosome Number Evolution

Chromosome numbers have been widely used as a proxy to karyotype evolution. The study by Escudero *et al*. (2014), including monocentric and holocentric lineages, sheds light into the poor contribution of dysploidy to diversification. Although this could lead to questioning whether the holocentric adaptability to fission and fusion cannot be further exploited by evolution, diversification of holocentric lineages seems to be context dependent and requires further study (Márquez-Corro *et al.,* 2018). For instance, Cyperaceae shows different patterns of chromosome number evolution (Márquez-Corro *et al.,* 2019), which could correlate with diversification, dysploidy being the main evolutionary mechanism within *Carex*, the largest sedges genus. Accordingly, chromosome number has been inferred to present a strong phylogenetic signal, evolving towards an optimum and partially explained by morphological and bioclimatic variables (Ornstein–Uhlenbeck process; Escudero *et al.,* 2012). On the other hand, studies showed that chromosome number evolution on *Agrodiaetus* butterfly genus could be explained by Brownian motion walk (Vershinina and Lukhtanov, 2017).

Holokinetic Drive

The hypothesis of holokinetic drive has recently been advanced to help explain how karyotypes diversify in number and size in holocentric lineages (Bureš and Zedek, 2014). The hypothesised mechanism is analogous to centromeric drive in monocentric organisms (Henikoff *et al.,* 2001; Malik and Henikoff, 2009), which is an outcome of selection for kinetochoric plate length favouring preferential migration of chromosomes affected by Robertsonian fusion or centromeres enlarged by DNA duplication (Burrack *et al.,* 2011). In holokinetic chromosomes, such selection would affect the entire chromosome body, as kinetochoric activity is widely distributed. Thus, meiosis could drive diversification of karyotypes by preferentially selecting for high or low chromosomes number (i.e. via fissions and fusions,

Bureš and Zedek, 2014). Holokinetic drive produces negative 2C/2n correlation, either by selecting for karyotypes with a small number of big chromosomes (fused chromosomes with more duplicated DNA material) or with a high number of small chromosomes (fissioned, or polyploid karyotypes with DNA removal).

Holokinetic drive could consequently explain several patterns common in holokinetic lineages: (1) wide variation in chromosome number within and among closely related species, (2) divergent chromosome sizes within genera and (3) a negative relationship between DNA content and diploid chromosome number. While neutral processes could explain some of these patterns, holokinetic drive is the only obvious explanation for the negative correlation between chromosome number and genome size in holokinetic lineages (Bureš and Zedek, 2014).

General Evolutionary Patterns in Organisms with Holocentric Chromosomes

Holocentry is likely to be a derived trait in several eukaryote lineages (Escudero *et al.,* 2016). Although holocentry might be adaptive and thus under convergent selection, the evidence for convergent selection is equivocal (Márquez-Corro *et al.,* 2018). Nevertheless, as argued above, holocentry may have played an important role in early colonisation of terrestrial ecosystems or habitats prone to high UV radiation, such as mountain summits (Zedek and Bureš, 2018). A few experiments have demonstrated the role of holocentry in the preserving of chromosome fragments through meiosis and potentially increasing the fitness of holocentric organisms (Zedek *et al.,* 2016; Zedek and Bureš, 2019). This role in buffering against the fitness costs of chromosome fusion and fission has apparently allowed holocentric karyotypes to differentiate particularly rapidly (reviewed in Bureš *et al.,* 2013; Melters *et al.,* 2012; Mola and Papeschi, 2006).

There is still much unknown regarding holocentric chromosomes and their origin over the course of eukaryote phylogeny. Meiosis has been well studied in some species, especially the roundworm *C. elegans* and a few species of sedges and bugs (reviewed in Bureš *et al.,* 2013; Marques and Pedrosa-Harand, 2016; Melters *et al.,* 2012). However, we know little about the formation of the kinetochores. Why, for example do insect lineages that have lost CENH3 and CENP-C genes, responsible for kinetochore assembly, still present kinetochoric activity? Understanding holocentry will require more detailed organismal and comparative study across the tree of life, more experimental study of adaptation to different environments and a genome-level understanding of the effects of holocentric rearrangements on gene expression and linkage.

Glossary

CENP-A/CENH3 Centromere-specific histone H3 variant, necessary for the recruitment of proteins that constitute the inner kinetochore.

CENP-C Centromere protein of the inner kinetochore plate. One of its function is maintaining a proper kinetochore size.

CENP-E Centromere protein of the outer kinetochore plate. It intervenes in kinetochore-microtubule attachment.

Merotelic attachment Attachment of microtubules from both spindles poles led by deformation of centromere structure during its formation.

Telokinetic behaviour During meiosis, microtubules are attached to the kinetochores in the telomere region of the chromosomes.

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