Maize Centromeres and Knobs (neocentromeres)

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Abstract In most species, the only chromosomal domains that interact with the cytoskeleton are the centromeres. However in maize there are two motile domains: the centromeres and knobs/neocentromeres. Intensive research has been conducted on both domains. The intent of this review is to provide a broad overall perspective on centromere and knob structure, to compare and contrast their behavior, and to summarize current interpretations of their evolutionary past.

1 Centromeres

1.1 Centromeric DNA

The spindle interacts primarily with kinetochores, which mark the centromeric DNA. Contrary to popular interpretations (Pennisi 2001) the DNA sequence of most centromeres has very little or no impact on kinetochore location. Current views suggest that kinetochores can 'move' under selection and that new kinetochores can attach in regions that have no sequence similarity to centromeres elsewhere in the genome. For instance, in humans, functional kinetochores have formed over apparently random gene-containing regions (Warburton 2004). Similarly, a barley centromere can move laterally to a new position that lacks any sequences found at other centromeres (Nasuda et al. 2005). Even on stable centromeres there is no obvious delineation in sequence between known centromeric DNA and flanking heterochromatic (pericentromeric) DNA (Nagaki et al. 2004).

Although particular sequence motifs are probably not required for centromere function, the overall repetitive structure of centromeric DNA may have a strong impact on centromere stability over evolutionary time (Dawe and Henikoff 2006). Most centromeres are characterized by some type of simple tandem repeat array.

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The most common repeat unit is 150–180 bp, which roughly correlates with the size of a nucleosome. Centromeres evolve very quickly and show astonishing variation even among the grasses. For instance the tandem repeats of maize and barley centromeres have no homology (Cheng and Murata 2003). However the same repeats tend to be found at each chromosome within a species, indicating that centromeres do not evolve independently. In maize, the major tandem repeat is a 156 bp sequence known as CentC (Ananiev et al. 1998c). We presume the arrays can extend continuously for many kilobases. Analysis of stretched DNA fibers suggests that the total length of CentC arrays varies among centromeres from as little as <100 kb to as much as several thousand kb (Jin et al. 2004).

Grass centromeres contain a novel class of retroelements known as Centromeric Retroelements (Jiang et al. 2003). The term 'CR element' is used to describe Centromeric Retroelements generally, and more specific notations are used to describe the elements in individual species. For instance maize CR elements are called CRM and rice CR elements are called CRR. CR elements were first discovered as conserved small centromere-specific sequences (Aragon-Alcaide et al. 1996; Jiang et al. 1996) and later shown to be portions of full length Ty3/Gypsy retroelements (Presting et al. 1998). CR elements are among the most conserved known retroelements, having overall identities as high as 85% across cereal species that diverged 60 million years ago (Zhong et al. 2002).

Within the centromere proper, defined by the presence of kinetochore proteins, CR elements are particularly abundant. However CR elements are also found in the pericentromeric regions – the heterochromatic domains that surround all centromeres [pericentromeres and centromeres are strikingly different at the cytological chromatin level, with centromeres staining weakly for DNA and pericentromeres staining very brightly]. The copy numbers of CR elements range in the thousands per genome and are found in virtually all grasses with the possible exception of *Oryza brachyantha* (Lee et al. 2005). CRM elements are active on an evolutionary time scale and are known to insert within CentC arrays and other CRM elements (Nagaki et al. 2003). The unique centromere-specific nature of CR elements, their broad conservation within a dynamic context, and the polymorphism they provide for sequence analysis (below) have made the grasses the preeminent models for plant centromere research.

1.2 Centromeric Chromatin

Given the epigenetic nature of centromere specification and their striking sequence polymorphism, how do we know that CentC and CRM are centromeric DNAs? Centromeres are defined by the presence of kinetochore proteins, and the most fundamental kinetochore protein is a histone variant known as CENH3. CENH3 is similar to H3 in the core domain that binds to other histones, but differs in the key N-terminal domain that interacts with the outside chromatin environment. As a rule the N-termini of CENH3s are entirely different from those of H3 (Henikoff et al. 2000) and appear to exclude most euchromatic and heterochromatic binding

proteins. In their place a third class of chromatin (centrochromatin) is formed that organizes kinetochores. The unique N-terminus is also useful in the laboratory since antibodies can be prepared that differentiate CENH3 from H3.

With specific antisera, chromatin immunoprecipitation (ChIP) can be employed to identify the DNAs that interact with the kinetochore. In this technique, antisera are incubated with fragmented chromatin, precipitated, and subjected to analysis. By this method both CentC and CRM were shown to interact with CENH3 (Zhong et al. 2002). It appears that only a fraction of the CentC and CRM are bound to CENH3 at any given time. This interpretation is supported by experiments where DNA and CENH3 were visualized simultaneously (Jin et al. 2004). Thus, CentC and CRM are not sufficient and probably not necessary to organize the overlying kinetochore.

Efforts to assay individual loci relative to their CENH3 association are still in their infancy. As yet only two sequenced CentC-containing BACs are published (Nagaki et al. 2003). Analysis of the sequence revealed no classical single-copy domains (as expected), but it was discovered that CRM insertion points are often unique (Luce et al. 2006). Using primers directed against such insertion points, single copy polymorphic markers were developed. This made it possible to map the BACs, as well as assay the markers in ChIP samples (Luce et al. 2006). One BAC mapped to a central position on chromosome 8 and was shown to interact with CENH3, providing the first precise mapping of a maize centromere. It should be possible to use similar methods to map all ten maize centromeres as new sequence data are released and annotated.

The available data suggest that CentC and CRM may be particularly effective centromeric DNA sequences: they are not required, but are 'better' than most sequences at recruiting the kinetochore. So far this is only a correlative argument. To prove this, we will need to transform centromeric BACs into maize and show that the introduced DNA can independently organize kinetochores. These experiments have yet to be completed for maize, but have been done in rice (Phan et al. 2007). Centromeric BACs were introduced by biolistic transformation and the resulting plants studied. The insertions appeared to be as large or larger than the true centromeres, however there was no evidence of secondary kinetochore activity associated with them. These data support the view that centromeres are defined epigenetically, and that even the most common centromere repeats are not sufficient to organize kinetochores.

2 Knobs and Neocentromeres

2.1 Knob Structure

Maize is known for the 'knobs' that McClintock and others used to identify and track chromosomes. Unlike centromeres, which appear as weakly stained constrictions on chromosomes, knobs appear as darkly staining, large, bulbous structures. Knobs are found at 23 known positions near the ends or in mid-arm (interstitial) positions

(Kato 1976). They are highly polymorphic, with some strains having no visible knobs and others with as many as 14 (Kato 1976). They also vary widely in size, with nearly invisible knobs in some strains and massive knobs in others (Kato 1976; Adawy et al. 2004).

One of the first cloned maize DNAs was the primary knob unit, now called the 180 bp repeat (Peacock et al. 1981). More recently a second knob repeat called TR1 was identified (Ananiev et al. 1998a) which is present on many knobs, though in minor proportion relative to the 180 bp repeat. Both repeats, like CentC, are arrayed in tandem for many kilobases/knob (Adawy et al. 2004). Knobs also contain a smattering of transposable elements, though the overall frequency/bp is much lower than in any other segment of the genome (Ananiev et al. 1998b; Mroczek and Dawe 2003). Simple selfish DNA scenarios do not adequately explain the existence and polymorphism of knobs – classic selfish elements should be more evenly distributed and generally located in low recombination regions (Charlesworth et al. 1994).

2.2 Abnormal Chromosome 10 and Meiotic Drive of Knobs

The largest knob in maize occurs on a rare chromosomal variant known as Abnormal chromosome 10 (Ab10) (Longley 1938). While observing meiosis in strains that contained Ab10, Marcus Rhoades made an important discovery. In strains that carry Ab10, all knobs (not just the Ab10 knob) move rapidly forward and arrive at spindle poles far in advance of the centromeres during anaphase I and II (Rhoades and Vilkomerson 1942). Rhoades referred to them as neocentromeres since they showed centromere-like behavior. Neocentromeres can be very dramatic – often stretching chromosome arms the entire length of the spindle (Fig. 1A). At the time Rhoades suspected that neocentromeres were knobs in a new role. Peacock et al. (1981) later demonstrated by in situ hybridization that knobs and neocentromeres were indeed the same.

In further studies, Rhoades discovered that Ab10 is preferentially segregated to progeny. Instead of the expected 50/50 ratio in testcrosses, Ab10 showed roughly 75/25 (Rhoades 1942). He ruled out all known and trivial explanations and concluded that Ab10 must be somehow promoting its own transmission (Rhoades 1942). Rhoades and others went on to show that at least three other knobs show the same levels of preferential segregation when Ab10 is present (Longley 1945; Rhoades and Dempsey 1985). These data suggest that all 23 knobs are preferentially segregated, but only when Ab10 is present.

The general phenomenon of preferential segregation is now referred to as meiotic drive (Sandler and Novitski 1957; Burt and Strivers 2006). In a classic model for meiotic drive in maize (Rhoades 1952), Rhoades proposed that Ab10 shows preferential segregation because of neocentromere activity (Fig. 2). Only plants that are heterozygous for a knob show drive, since those without knobs have no means to, and those homozygous for a knob show a standard 50/50 ratio (since they compete against themselves). Preferential segregation proceeds as follows:

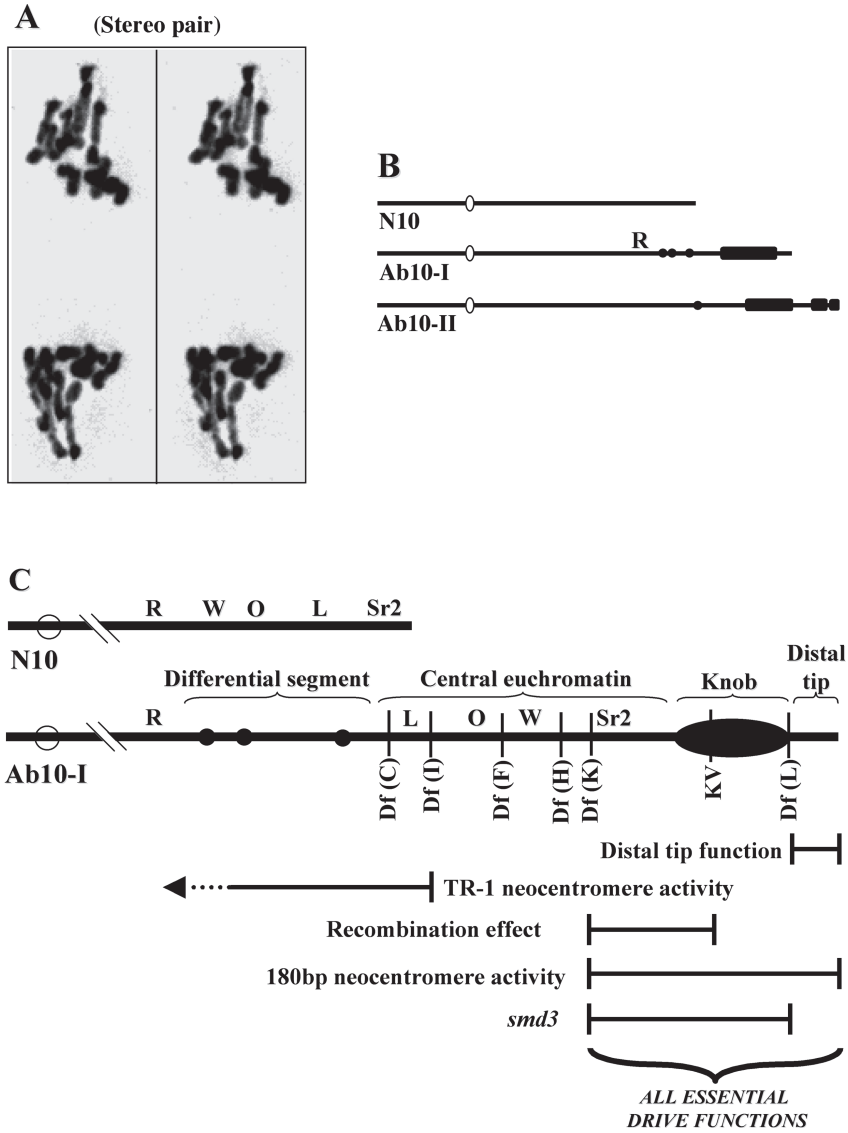

Fig. 1 Ab10 and neocentromeres. **A**) Neocentromeres. Anaphase II is shown as a stereo pair with knobs pulled towards poles. To see the image in pseudo-3D, cross your eyes or use a pair of appropriate viewing glasses. **B**) The major variants of chromosome 10. Ab10-I differs from Ab10-II by the number of TR1-rich chromomeres (small dots) and the presence of an additional knob on the tip of the long arm. **C**) The Ab10 haplotype. Only the non-recombining segment of Ab10 is shown (for point of reference note the R gene, which is also shown in 'B'). Rhoades discovered that W2, O7, and L13 were inverted on Ab10. This inversion, as well a second inversion, has been confirmed by RFLP mapping. Also shown are the locations of known meiotic functions. For additional detail see (Hiatt and Dawe 2003b; Mroczek et al. 2006)

1) Recombination occurs between the centromere and knob. This occurs frequently since all 23 knobs are far enough from centromeres to be genetically unlinked.
2) Once exchanged, the chromatids (known as heteromorphic dyads) orient with the knob towards the pole as neocentromere activity commences at meiosis I.
3) The knobs retain a polar position through meiotic interphase, and again line up with the knobs facing towards the outside of what will become the linear tetrad in meiosis II.
4) At the completion of meiosis, the upper three spores die naturally, leaving only the bottom cell (containing Ab10) to become the egg.

It is important to note that the Rhoades model was derived and tested in male meiocytes, when in fact male parents do not show drive because all four products of meiosis produce gametophytes. Unfortunately empirical tests on female meiocytes are exceedingly difficult. Only a few female meiocytes have been observed in Ab10 strains, just enough to show that neocentromeres are present (I. Golubovskaya, personal communication). The maximum possible drive by this mechanism is 83.3%, which is the maximum number of heteromorphic dyads that can be produced at a genetic distance >50 cM from the centromere (allowing for multiple crossovers among the four chromatids; see (Buckler et al. 1999).

2.3 Cell Biology of Neocentromeres

Several forms of data suggest that neocentromeres move on the spindle by a mechanism that is quite different from kinetochore-mediated chromosome movement. Perhaps the most straightforward evidence is that neocentromeres are known to lack three key kinetochore proteins: CENH3, CENP-C, and MAD2 (Dawe et al. 1999; Yu 2000; Dawe and Hiatt 2004). However, there are also other compelling arguments. Live-cell imaging revealed that neocentromeres move 50% faster than centromeres on the meiotic spindle, and that they begin poleward movement in prometaphase, which is earlier than the centromeres (Yu et al. 1997). Neocentromeres move along the sides of microtubules, whereas the kinetochores interact with microtubules in an end-on fashion (Yu et al. 1997). The ends of microtubules are known to regulate kinetochore movement. Thus, while centromeres/kinetochores are moving (relatively) slowly towards the poles in procession, neocentromeres rapidly slide along microtubule sidewalls by an unknown mechanism.

Other data show that the two major knob repeats differ in their neocentromere behavior. When TR1 arrays are present along with the 180 bp repeat in the same knob, they occupy separate domains. Both TR1 and 180 bp repeats are active in neocentromeres, but TR1 is much more effective. It appears to bind very tightly to microtubules, often spreading out along a fiber for a long distance. Further, TR1 arrays always precede 180 bp arrays on the spindle. The result is that TR1 appears as ‘beaks’ extending well ahead of the ball-shaped masses of 180 bp, with the entire complex of knob repeats moving faster than centromeres.

A frequently asked question is why neocentromeres never cause chromosome breakage. How does the neocentromere know to move in the same direction as the kinetochore? The answer probably lies in the fact that neocentromeres begin to move poleward as soon as there is a semblance of a spindle to move on, which is prior to the movement of the kinetochores towards the poles. The early movement could swing the attached kinetochores towards the same pole as the neocentromere. Under this view a neocentromere chooses a pole and the kinetochore follows (Yu et al. 1997).

2.4 Ab10 Structure and Trans-Acting Factors

Genetic analyses indicate that only the last third of the long arm of Ab10 is responsible for meiotic drive. The terminal segment is surprisingly large; probably close to 55 map units and containing up to 75 megabases of DNA (Hiatt and Dawe 2003a; Mroczek et al. 2006). The functional portion of Ab10 is referred to as the Ab10 haplotype. There are at least two major forms of the haplotype: Ab10-I, which occurs in maize and teosinte, and Ab10-II, which is only found in teosinte. The two chromosomes differ in external appearance but have many of the same genes and functions (Fig. 1B; (Rhoades and Dempsey 1988). In this review only a brief treatment of Ab10 structure is given. Further information can be found in (Hiatt and Dawe 2003b; Dawe and Hiatt 2004; Burt and Strivers 2006; Mroczek et al. 2006).

Ab10 can be subdivided into four major domains: the distal tip, the knob, the central euchromatin, and the differential segment. The large knob is composed almost entirely of the 180 bp knob repeats, while the differential segment contains three small knobs (called chromomeres) composed of TR1. Rhoades believed that the large knob itself was causing preferential segregation and referred to Ab10 as 'K10' (K being a general nomenclature for knobs). However, late in his life he showed that removal of the major Ab10 knob abolished drive but not neocentromere activity at other knobs (Rhoades and Dempsey 1986). These data indicate that neocentromere activity is not caused by the special structure of Ab10 but by its encoded trans-acting factors.

Building on prior studies, a mutant screen was developed to identify genes that controlled meiotic drive (Dawe and Cande 1996). Mutants and deletions derived from this screen, as well as a known set of terminal deficiencies, were used to construct a map of functions within the haplotype (Fig. 1C; (Hiatt and Dawe 2003a; Hiatt and Dawe 2003b). The map has also been integrated with an RFLP map of N10-derived genes (Mroczek et al. 2006). The combined data show that the central euchromatin contains a large inversion of N10-derived genes as well as a smaller inversion within it (the inversion of *L13 O7* and *W2* was first described by Rhoades; (Rhoades and Dempsey 1985)). The inverted regions appear to have little role in meiotic drive, but serve to block recombination with N10 and stabilize the haplotype.

On the proximal side of the central euchromatin is the differential segment that contains three TR1-rich chromomeres. Interestingly, the differential segment contains at least one gene that is specialized for TR1 neocentromere activity (Hiatt et al. 2002). The spatial separation of the TR1 region and its linkage to a sequence-specific

neocentromere-activating gene suggests that a TR1 'cassette' evolved independently of the primary 180-bp system. Supporting this interpretation is the fact that the Ab10-II variant has very little TR1 repeat and lacks the TR1-specific activating phenotype (Mroczek et al. 2006).

With the exception of the TR1 region, all known drive functions map distal to the last N10-homologous gene (*sr2*). Nothing is known of the single copy sequence there, and the available data suggest that it was obtained from another species several million years ago (Mroczek et al. 2006). Among the meiotic drive functions that lie distal to *sr2* are: 1) the 180 bp neocentromere-activating gene(s); 2) a gene that increases recombination in structural heterozygotes (presumably to ensure recombination between the Ab10 haplotype and centromere is >50 cM); 3) two unknown genes that are required for meiotic drive but have no role in neocentromere activity or the recombination effect. The unknown genes may be involved in stabilizing knob position between meiosis I and II (Fig. 2) (Hiatt and Dawe 2003b; Mroczek et al. 2006).

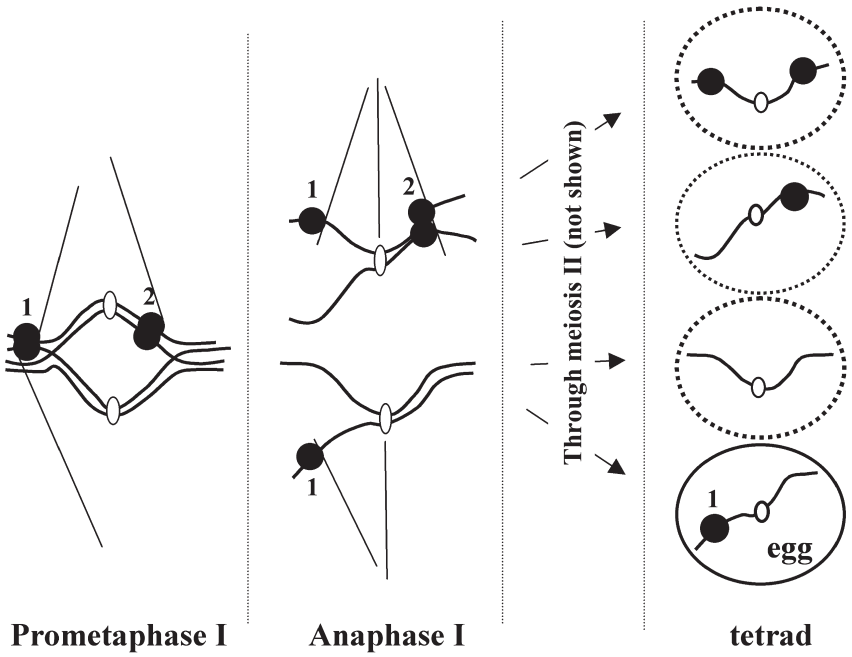

Fig. 2 The Rhoades model for meiotic drive. A chromosome that contains two knobs is used for the purposes of illustration (in fact it is rare for a chromosome to have two knobs). In the meiosis shown, recombination occurred proximal to knob 1, but distal to knob 2. Note that the crossover places knob 1 on both chromosomes, whereas without a crossover knob 2 remains on one chromosome. All knobs form neocentromeres at meiosis I and II. The orientation established in meiosis I is maintained through meiosis II by an unknown mechanism. The result is that knob 1 is segregated to the bottom, functional megaspore (egg). Given this recombination pattern, knob 1 is assured a position in the egg cell, but knob 2 can only segregate to the egg cell half the time

The presence of Ab10 explains one of the 23 knobs. The other 22 knobs appear to have evolved as a consequence of the presence of Ab10, by taking advantage of both the repeats and transacting factors provided by Ab10 (Buckler et al. 1999). The size and frequency of knobs in maize races correlates well with the presence of Ab10 (Buckler et al. 1999). Rare transposition events presumably brought samples of knob repeats to other chromosome arms at appropriate positions >50 cM from centromeres. Such arrays are expected to expand and contract by occasional unequal recombination (Smith 1976). This would in turn set the stage for rapid escalations in knob size, since large knobs are more effective neocentromeres (Yu et al. 1997) and preferentially segregated over small knobs (Kikudome 1959).

Given the mechanism it employs, it would appear that Ab10 (and knobs) have an overwhelming advantage and should rapidly go to fixation. However Ab10 remains a rare chromosomal variant. There are at least three reasons why this is the expected outcome. The first is that Ab10 only shows drive when it is heterozygous; once it is common enough to be frequently present as homozygous, it loses its edge. The second is that the Ab10 haplotype contains a long section of required maize genes in the central euchromatin. These do not readily exchange with N10 and as a result are expected to accumulate deleterious alleles at a high frequency. Homozygous Ab10 plants do appear to be 'sicker', but it is difficult to separate this effect from inbreeding. No systematic studies have been carried out to test whether Ab10 is a deleterious chromosome in the homozygous state. The third is that any successful meiotic drive system is inherently bad for a species since selfish components can control the organism's evolutionary path. The expectation, which has been demonstrated in Drosophila (see Ardlie 1998), is that host modifiers will evolve to suppress drive. We assume similar modifiers are present in maize and that these have helped limit the spread of Ab10.

3 Using Meiotic Drive Logic to Understand Centromere Evolution

An important aspect of meiotic drive is that it has the capacity to evolve without regard to host fitness (Ardlie 1998). This produces a 'genomic conflict' (Burt and Strivers 2006), where the selfish interests of the DNA are at odds with the interests of the organism. Any allele linked to a knob is constrained in evolutionary terms, since it is fated to increase in the population whether or not it is a fit allele. As the majority of the maize genome is linked to a knob, meiotic drive is presumed to have had a major impact on the makeup of maize (Buckler et al. 1999). At least eight other species have neocentromeres (Dawe and Hiatt 2004). It is possible that many of the interstitial heterochromatic blocks in eukaryotes have a similar history of meiotic drive.

If an occasional neocentromere can have a major affect on the genetic makeup of a species, then centromeres gone awry could have a debilitating impact (Henikoff et al. 2001). With even a small segregation advantage, selfish centromere repeats could rapidly sweep through a population. Given this potential, it is likely that there

is strong (selfish) selection for centromere repeats to increase their capacity to 'attract' the kinetochore (Henikoff et al. 2001; Dawe and Henikoff 2006). This probably occurs through mutation events that confer sequence-specific binding interactions between repeats and inner kinetochore proteins. Once a group of repeats have acquired sequence-specific roles, they could further increase their transmission by increasing the size of repeat arrays, the size of the kinetochore, and the likelihood they will interact with the spindle (Henikoff et al. 2001; Dawe and Henikoff 2006). A driven centromere would drag linked genes with it, almost certainly to the detriment of the organism.

In principle, centromere drive can be thwarted with epigenetics (Dawe and Henikoff 2006). If the DNA's grip on the kinetochore were loosened so that sequence has little or no consistent role, then the effect of meiotic drive would be lessened or eliminated. It has been proposed that the respective roles of genetics and epigenetics have cycled over time (Dawe and Henikoff 2006). When centromeric DNA acquires the capacity to bind tightly to inner kinetochores, the organism responds by changing the structure of the inner kinetochore proteins and restoring sequence independent (epigenetic) inheritance. Supporting this view is the fact that two fundamental DNA binding proteins of the kinetochore, CENH3 and CENP-C, show strong evidence of adaptive evolution (Talbert et al. 2004). A cycling pattern also explains the rapid evolution of centromeric DNA. Whenever the inner kinetochores change, the DNA sequences start anew, reinventing themselves to adapt to the new binding interface (Dawe and Henikoff 2006). In addition, a cycling pattern helps to explain why centromeres do not expand uncontrollably to encompass larger and larger regions.

It is noteworthy that the Ab10 meiotic drive system – the first discovered and most thoroughly understood meiotic drive system – provided the framework on which the centromere drive hypothesis was built. Thus, although maize neocentromere and centromeres have very different roles and mechanisms of movement, their modes of evolution may have much in common.

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