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Meiotic CENP-C is a shepherd: Bridging the space between the centromere and the kinetochore in time and space

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Abstract

While many of the proteins involved in the mitotic centromere and kinetochore are conserved in meiosis, they often gain a novel function due to the unique needs of homolog segregation during meiosis I. CENP-C is a critical component of the centromere for kinetochore assembly in mitosis. Recent work, however, has highlighted the unique features of meiotic CENP-C. Centromere establishment and stability require CENP-C loading at the centromere for CENP-A function. Pre-meiotic loading of proteins necessary for homolog recombination as well as cohesion also rely on CENP-C, as do the main scaffolding components of the kinetochore. Much of this work relies on new technologies that enable *in vivo* analysis of meiosis like never before. Here we strive to highlight the unique role of this highly conserved centromere protein that loads onto centromeres prior to M-phase onset, but continues to perform critical functions through chromosome segregation. CENP-C is not merely a structural link between the centromere and the kinetochore, but also a functional one joining the processes of early prophase homolog synapsis to late metaphase kinetochore assembly and signaling.

INTRODUCTION

The centromere is a lynchpin for inheritance of the genetic material. During M-phase (mitosis or meiosis) all associated DNA along the chromosome follows its centromere to the specified daughter cell without deviation. Errors in chromosome segregation result in cell aneuploidy which is a hallmark of cancer and a leading cause of development disorders and infertility. Understanding meiotic aneuploidy specifically is a complex task because there isn't a good *ex vivo* model (cell culture does not mimic meiosis), therefore much of the work is accomplished in organismal models. In meiosis, the centromere has two main functions: 1) to act during early prophase as a centromere clustering site and potentially a loading zone for homolog synapsis and cohesion 2) during prometaphase and metaphase to act as the attachment site for the transient microtubule-binding kinetochore apparatus.

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CENP-A is the histone 3 variant that epigenetically marks the centromere. It is a very stable component of the centromere that is a receptacle of post-translational modifications (from acetylation to methylation, ubiquitylation to phosphorylation) that signal to other centromere components for loading or unloading necessary for supporting the main functions of the centromere (1). CENP-C is a more dynamic centromere protein that is also found localized at the centromeres throughout the cell cycle in both mitosis and meiosis (Figure 1) (2–7).

In meiotic cells (specifically *Drosophila*, budding yeast, and vertebrates) it appears that the majority of centromere-localized proteins (including cohesins and synaptonemal complex components as well as CENP-A itself) load onto centromeres very early, namely in pre-meiotic S-phase or in zygotene of meiosis I (MI) (8–17). The kinetochore proteins, in contrast, do not do so until prometaphase of MI. The tight regulation of early loaded proteins (CENP-A and cohesins), especially in oocyte meiosis, is accompanied by a stable phenotype where prophase knockdown yields no meiotic phenotype because they are already loaded and stably incorporated (8). Unpublished work from our lab indicates that shRNA's to cohesin components expressed in late prophase after pachytene do not exhibit cohesion defects indicating the stably loaded complexes are unaffected. On the other hand, prophase knockdown of kinetochore components results in severe meiotic errors. CENP-C seems to bridge this gap. CENP-C has been shown to have a broad range of dynamic loading throughout the cell cycle from interphase through mitosis and meiosis in human cell culture (3), *Drosophila* cell culture (6, 18), *Drosophila* embryos (19), and *Drosophila* oocytes (Figure 1, Fellmeth and McKim unpublished data). It is present on centromeres prior to M-phase onset, but knockdown results in kinetochore and cell cycle failure. Here we focus on recent developments investigating the roles of CENP-C in either the early centromere functions such as centromere establishment and homolog synapsis as well as later tasks such as kinetochore assembly and signaling.

CENTROMERE INSTALLATION AND IDENTITY

During S-phase, the existing CENP-A is segregated equally to each new strand, leaving each chromosome with half the amount that they started with. The cell then uses the existing centromeres as an epigenetic template for re-establishment before the next round of division. CENP-A is typically deposited in a DNA-replication independent manner unlike canonical H3 (20–22). Therefore, during replication, the amount of CENP-A nucleosomes per chromosome is halved and the newly inserted nucleosomes contain H3 as a placeholder for later CENP-A incorporation (6, 23, 24). One would not expect vast differences in centromere establishment between mitotic and meiotic cells, because all of these steps occur outside of M-phase. However, there is significant variability in centromere formation across species and even cell types within the same organism. In mitotic cells, the centromere is a necessary loading dock for formation of the kinetochore which in turn is required for accurate chromosome segregation. Clarifying whether these functions remain in meiotic cells is pertinent where the unique needs of homolog synapsis and recombination occur.

The process of centromere renewal occurs in three main steps: *1) licensing, 2) deposition*, and *3) stabilization*. CENP-C is critical for all three steps and its early loss (prior to centromere re-establishment) results in failure to form functional centromeres while later

CENP-C loss (after CENP-A deposition) can lead centromeric instability and dissociation (Figure 2A) (25, 26).

1. *Licensing* The cell must actively "read" the nucleosomes present along a new chromosome, identify places rich in CENP-A nucleosomes as centromeric regions, and mark them in order to recruit the machinery for deposition of new CENP-A. Centromeric H3 tails contain post-translational modifications different than non-centromeric H3, which also acts as a marker for centromeric chromatin and this potentially acts to recruit the Mis18 complex which is a CENP-A licenser in most organisms with regional centromeres (as well as yeast with point centromeres) (1, 27). In these organisms, the Mis18 complex functions with the aid of CENP-C, RbAp46/48, and HJURP binds to centromeric regions, and recruits CENP-A loading machinery (27–34).

2. *Deposition* Once the sites for CENP-A placement have been identified, the cell must then replace H3 histones with CENP-A histones until they are at the desired, pre-replication concentration. The presence of the Mis18 complex at the centromeres then brings in CENP-A via its chaperone HJURP (or Scm3 in fission yeast and Cal1 in flies) (35–41). In *Drosophila*, CAL1 contains binding domains for both CID (CENP-A homolog) and CENP-C but there is no Mis18 homolog. Despite the differences in licensing, the mechanism relating CENP-A initial amount to CENP-A deposited amount may be consistent between *Drosophila* and humans (27). CAL1 has been proposed to act as the limiting factor in centromere establishment in mitotic cells as CENP-C potentially prevents the excessive release of CAL1 from the nucleolus (42, 43). *Drosophila* spermatocytes depleted of CAL1 show a dramatic reduction in CID (2, 44). CENP-C also plays a role in CENP-A loading in mitotic cells (2, 4, 6, 32, 45–47), and likewise in male meiotic cells depleted of CENP-C, there is a loss of centromeric CID though the reduction is not as significant as in the CAL1 knockdown (2). This difference in CID reduction indicates that the tripartite complex of CAL1, CID, and CENP-C is not a case of all or nothing loading but rather CAL1 and CID might localize together independent of CENP-C. A study analyzing *Cal1* and *Cenp-C* mutants, also in *Drosophila* sperm, observed similar results indicating that a loss of CAL1 or CENP-C leads to a reduction in CENP-A centromere localization (43). CENP-C has been shown to bind CENP-A, HJURP, and DNA at the centromeres in HeLa cells and *in vitro* (48, 49). This relationship appears to be reciprocal where loss of either CAL1 or CID causes a reduction in CENP-C localization as well (2, 4).

3. *Stabilization* Newly formed CENP-A nucleosomes are not stable on their own and can be rapidly degraded and replaced with H3 histones in an effort to prevent neocentromere formation unless they are marked for stability (43, 44, 50–55). The mechanism of this regulation is still largely unclear, though there is evidence that the CENP-A binding protein, CENP-N (part of the CCAN), acts as a clamp between the DNA and CENP-A further stabilizing its incorporation (56). This hypothesis was further supported by in vitro evidence that CENP-C and CENP-N act to promote CENP-A nucleosome stability (25, 26).

It is interesting to see that CENP-C plays a role in each step of centromere establishment in multiple systems: recruiting the Mis18 complex for licensing in vertebrates and fission yeast, regulating CAL1 release from the nucleolus in *Drosophila*, contributing to chaperone duties for deposition, and increasing stability of the formed CENP-A nucleosomes for maintenance. These critical functions likely contribute to the reason that CENP-C is one of very few components of the inner centromere that are conserved in all eukaryotes (57–60).

CENTROMERE CLUSTERING AND PAIRING

The clustering and then pairing of centromeres in early prophase I is critical for accurate homolog segregation. Clustering occurs when all centromeres bunch together into a single or relatively few foci, while pairing is only between two homologous centromeres. It is predicted that centromere clustering is important to facilitate homologous chromosome pairing (61–63). In addition, early pairing between non-homologous centromeres could be a protective measure against centromeric crossovers and these pairs ultimately swap to homologous as synapsis progresses. CENP-C plays a role in both the clustering and pairing of centromeres as is evidenced by the loss of pairing of homologous centromeres and a failure to maintain clustering in CENP-C mutants in *Drosophila* oocytes (Figure 2B) (55).

SYNAPTONEMAL COMPLEX AND COHESION AT THE CENTROMERE

Meiosis is accompanied with very specific requirements distinct from mitosis, chiefly the regulation necessary for segregating homologs while maintaining sister chromatid cohesion during meiosis I. The process of homolog segregation begins in pre-meiotic S-phase with homolog pairing and the establishment of centromeric cohesion. This is followed by creation of double-stranded breaks (DSB’s) some of which mature into crossovers during early prophase I. This process is facilitated by the formation of the synaptonemal complex (SC). Both of these processes are critical for homolog segregation as crossovers mature into chiasmata which are a key structure for homolog cohesion (64), and the cohesins themselves are necessary for SC formation (8). Both of these processes contribute to genomic stability and mutants in these genes result in high levels of aneuploidy associated with infertility (65, 66). A key feature of both of these complexes is that they load and perform their functions very early (primarily pre-meiotic S-phase).

The synaptonemal complex holds homologous chromosomes together and regulates genetic recombination during meiosis through interactions with the chromosome axis. The complex is composed of lateral elements that run parallel to the chromosomes and transverse elements that are perpendicular to the axis and hold together homologs. The transverse element is C(3)G (in *Drosophila*) or SYCP-3 (in mice) but the lateral elements (also known as axis proteins) are unknown (9, 67, 68).

The centromere is an initiating site for SC formation in yeast and *Drosophila* during early prophase, as well as the last site of localization after arm SC has dissolved later in prophase (69–72). Studies of CENP-C mutants have not revealed a SC loading impairment, however they do fail to retain centromeric SC later in pachytene (55). These same mutants exhibit a centromere clustering defect (mentioned in the previous section) which is in agreement with

other studies indicating that the SC itself also plays a role in centromere clustering (55, 71) though because of the late SC phenotype in CENP-C mutants, this relationship is not likely directly through CENP-C itself. It's also not entirely clear if this represents the true nature of CENP-C's relationship with SC loading because the mutants tested were not true null, only hypomorphs.

Cohesins serve multiple functions in meiosis including co-orientation of sister chromatids in MI (73, 74), repressing centromeric crossovers necessary for fidelity of homolog segregation (75, 76), and assembly of the synaptonemal complex (8). Meiotic cohesins are highly enriched in the pericentromeric regions (77–82). This enrichment relies on the Ctf19 complex (CCAN) in budding yeast (83–85) and recent work has identified that this is by recruitment of the Scc2/4 loaders (86) through phosphorylation by Dbf4-dependent kinase (DDK) (87). This discovery is exciting because it demonstrates a direct link from DDK and DNA replication to cohesion establishment, though the two functions are not dependent on each other (88). Specifically, DDK is recruited to centromeres by Ctf3 (the Mis6 CCAN component) and then phosphorylates Ctf19 (the CENP-P CCAN component), which then recruits Scc2/4 (NIPBL/Mau2 cohesin loader) if Scc1 is present (86, 87). While *Drosophila* are lacking the CCAN, they do have meiotic pericentromeric cohesion enrichment and this potentially requires CENP-C in place of the missing CCAN components.

Recent work in *Drosophila* oocytes indicates that there are two distinct subsets of meiotic cohesins, one required for synaptonemal complex formation between homologs early in prophase (C(2)M, Stromalin, and NippedB), and one that maintains sister chromatid cohesion until metaphase II (SUNN/SOLO/ORD) (8). The evidence from *Drosophila* oocytes indicates that, while loss of centromeric CENP-C leads to a destabilization of the SC, the meiotic cohesion complex responsible for SC assembly (C(2)M complex) is not the one primarily located at the centromere (SUNN/SOLO) (8, 55). Loss of the SUNN/SOLO/ORD complex does result in a centromere clustering defect similar to that observed in CENP-C and SC mutants (55, 71, 72, 89, 90). All of this data cumulatively indicates that while the precise relationship is not yet clear, the CENP-C functions of synapsis, cohesion, and centromere clustering involve the loading or maintenance of cohesins (SUNN/SOLO/ORD in *Drosophila*) and centromeric SC.

CENTROMERES AND RECOMBINATION

Recombination is a critical component of meiosis and necessary to promote genetic diversity and chromosome segregation. However, crossovers occurring at or near the centromere are associated with errors in segregation leading to aneuploidy (76, 91, 92). Potentially in response to this or other unidentified reasons, the cell has developed mechanisms to prevent recombination in pericentromeric regions, and recent work has identified components of the centromere as being critical for this function (72, 90–92).

Early work identified that the structure of the heterochromatin itself can repress DSB formation and subsequent recombination (93, 94), yet other regions of heterochromatin were not equally repressed indicating that this cannot be the only mechanism. Relocation of the centromere itself still yields the same level of repression in the new region, and

combined with the previous observations, it has lead to investigations into the role of centromere localized proteins in CO repression (95). The most important consideration in selecting potential proteins of interest is timing. DSB formation and repair occur during early prophase, long before the kinetochore has formed, when only the CCAN, CENP-C, and Mis12 are found at the centromere (96, 97). Work in budding yeast has identified the Ctf19 complex (CCAN) as being responsible for preventing centromere-proximal DSB's as well as preventing recombination in any DSBs that do occur (75). They also showed that this effect is in part due to enhanced cohesins near the centromere, potentially promoting double strand break repair from sister chromatid templates rather than homologs, and partly due to recruitment of the SC protein Zip1. Whether this effect is then performed by CENP-C in organisms lacking the CCAN (such as *Drosophila*) or another unidentified component is unknown. Though it is tempting to think that CENP-C may also play a role in this critical protective mechanism due to its localization and involvement in cohesion.

KINETOCHORE ASSEMBLY AND FUNCTION

The kinetochore is a transient multi-complex structure existing in M-phase that links the chromosome to the spindle microtubules in order to direct the accurate segregation of genetic information into daughter cells. Unlike centromere proteins which do not appear to vary between mitosis and meiosis, there are components of the kinetochore such as Meikin, and Aurora Kinase C that have meiosis specific functions (98, 99).

The kinetochore is made up of the KMN network which is in turn a series of three complexes: Knl1c, Mis12c, and Ndc80c. Due to its interphase localization, we have classified the Mis12 protein itself as a centromere protein here, but the other components of the complex (Dsn1, Nsl1, and Pmf1) load during M-phase and are part of the inner (or chromatin proximal) kinetochore by interacting with the CCAN via CENP-C (Figure 2C) (100–103). The Mis12c binds directly to CENP-C via its Nnf1 subunit (100) and is stably incorporated in mitotic centromeres similar to CENP-C (3). The Mis12c in turn recruits Knl1/SPC105 via its Nsl1 subunit. Knl1/SPC105 then forms a dimer with Zwint (absent in *Drosophila*) and is a hub for checkpoint signaling. This potentially cooperates with CENP-C to recruit the Ndc80c (made up of Ndc80, Nuf2, SPC24, and Spc25) that is the microtubule receptor of the kinetochore (104–109).

In most organisms, the CCAN and CENP-C act in parallel to recruit Mis12C and then the outer kinetochore during M-phase (100, 101, 110–112). However, *Drosophila* provides a unique opportunity to study CENP-C without redundant pathways because the CCAN is lacking in this system. For example, in HeLa cells, the N-terminus of CENP-C has been shown necessary for Mis12C recruitment as well as KNL1, but only partially responsible for recruitment of NDC80 indicating that this critical component is probably also recruited by CCAN components (102). In *Drosophila*, NDC80 binding is completely obliterated by loss of SPC105R but it is unclear whether CENP-C has NDC80 binding properties as well (100, 113–116).

The kinetochore is also a site for critical checkpoint signaling via the chromosome passenger complex (CPC) and the spindle assembly checkpoint (SAC). AURKB has been shown

to phosphorylate Dsn1 of the Mis12C which initiates kinetochore assembly and that this activity is regulated by CENP-C (117–121).

CONCLUSION

CENP-C has proven to be an integral component of the centromere from the beginning of meiosis to the end. It functions in the earliest stages of centromere identity by recruiting CENP-A and its chaperone, and then stabilizing newly formed CENP-A nucleosomes. It also supports centromere clustering and appears to have a role in cohesion establishment, homolog synapsis, and crossover distribution. CENP-C is also critical for kinetochore assembly and chromosome segregation. It appears to be the only centromere-localized protein, excluding the histone variant itself CENP-A, that is present and necessary early in prophase as well as present and necessary for kinetochore structure and function during prometaphase and metaphase. Being such a critical meiotic component, studying CENP-C can be difficult because early meiotic failures tend to mask later phenotypes. One approach to this problem, possible in systems like *Drosophila*, is to identify separation of function mutants and use available genetic tools to knock out CENP-C activities at specific times during meiosis.

The unique loading patterns and combination of functions attributed to CENP-C raise many questions. Labs currently investigating CENP-C are certainly focused on a broad range from structural analyses and binding with CENP-A nucleosomes, involvement in cohesion and synapsis, function in kinetochore assembly, and the relationship with SAC signaling molecules in metaphase. These studies may reveal why CENP-C is required early during meiotic pachytene, why it is loaded during prophase in the pause between pachytene and metaphase, and is this loading before nuclear envelope breakdown important for kinetochore function during the meiotic divisions.

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Summary Points

- CENP-C is a critical component of the centromere as loss of CENP-C results in loss of centromere identity, aneuploidy and cell death.
- CENP-C is known in mitotic cells to be necessary for centromere establishment as well as kinetochore assembly. While recent work in meiosis has confirmed this, there is new evidence that CENP-C is also necessary for meiotic prophase activity.
- New studies have explored the use of techniques that make it easier to observe the effects of CENP-C on *in vivo* meiosis.

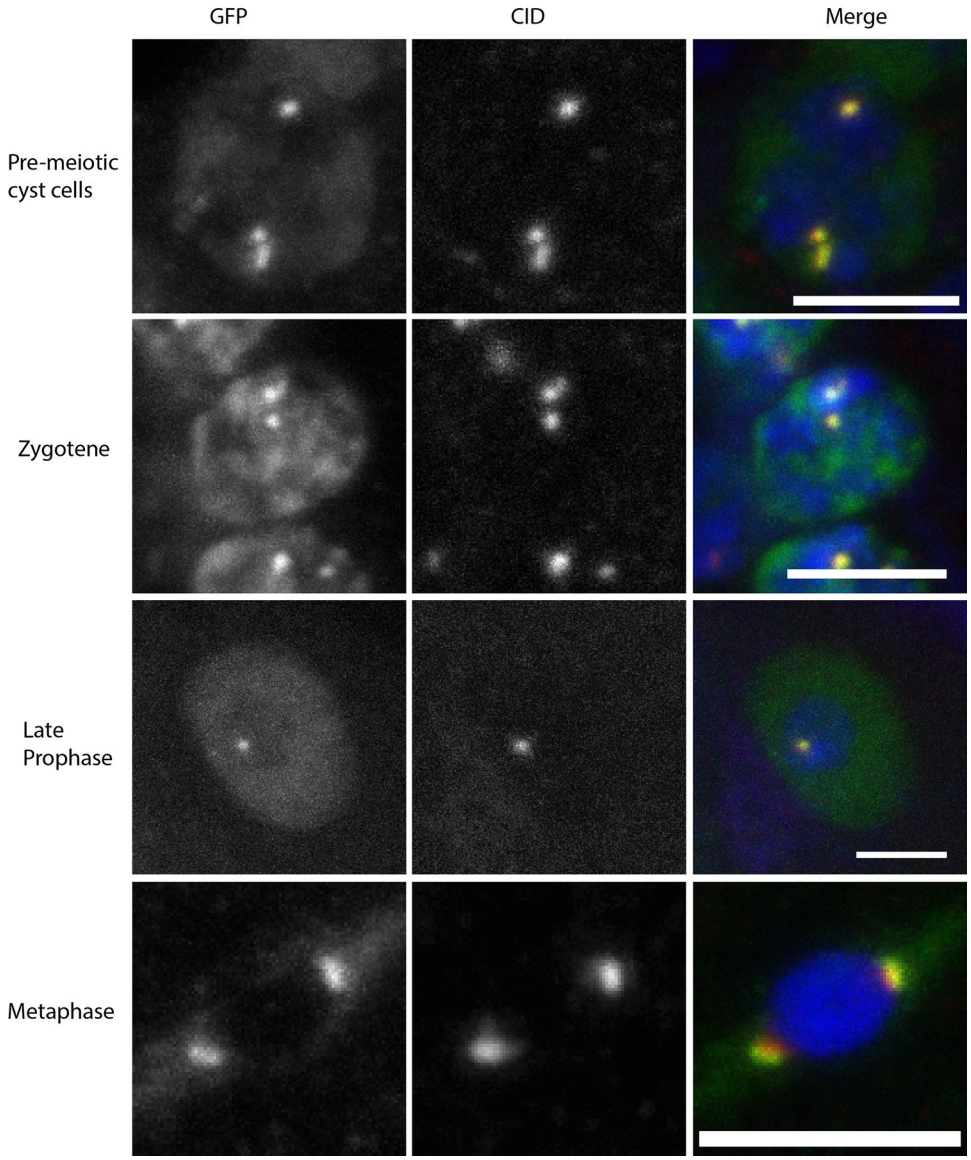

Figure 1- CENP-C localizes at centromeres in all stages of meiosis e in *Drosophila*.
EGFP-CENP-C (green) expressed in *Drosophila* oocytes co-localizes with CID antibody (Red, *Drosophila* CENP-A). Blue is DNA. Scale bars represent 5μm.

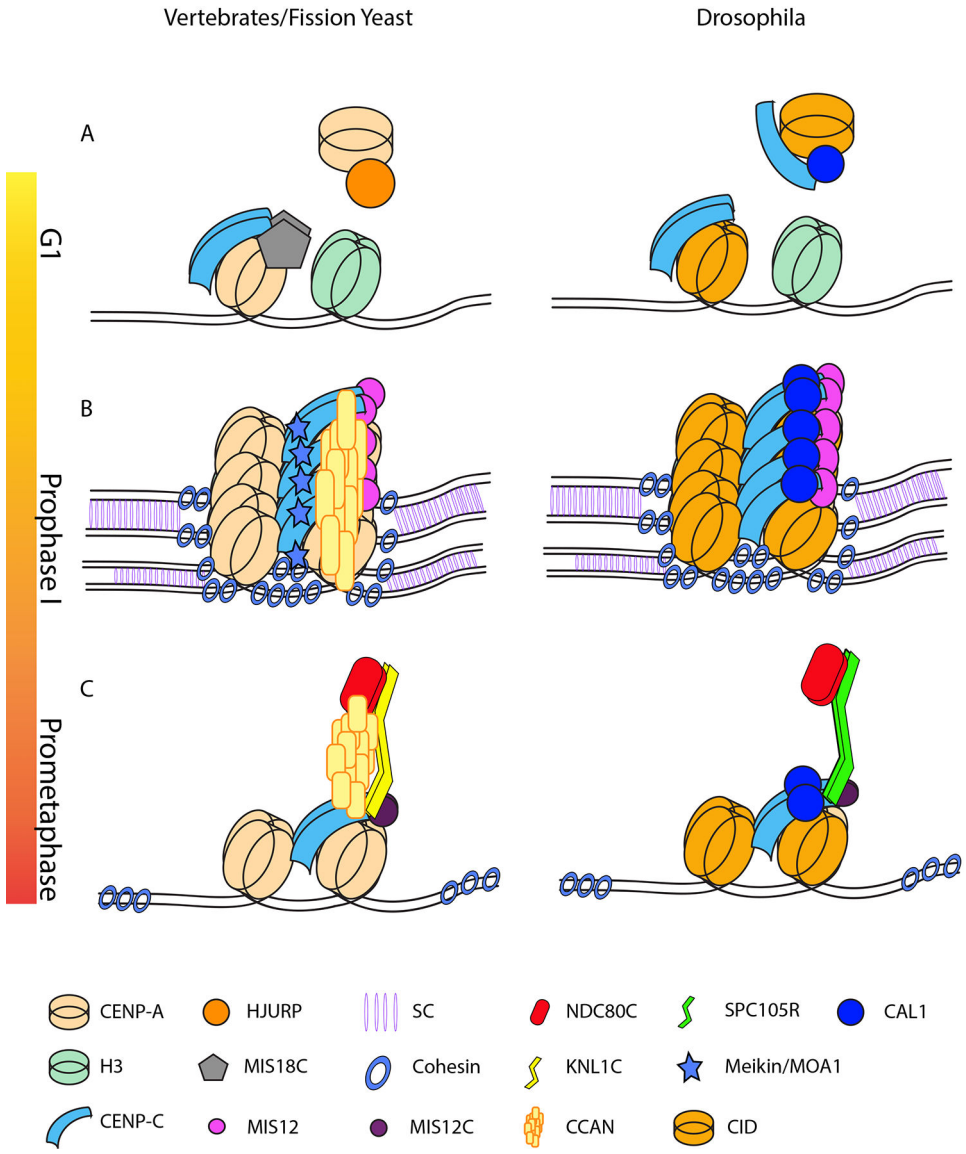

Figure 2- Model of CENP-C activity throughout meiosis.

While there is evidence of these proteins in meiotic tissue, the interactions in the vertebrate model depicted here are largely based on mitotic data. A) In vertebrates and fission yeast, CENP-C and MIS18C recruit CENP-A to the centromere via the HJURP/CENP-C/CENP-A complex. In *Drosophila*, Mis18 is absent and it appears that CAL1 takes over the role of Mis18 and HJURP combined to bring CID and CENP-C together. This meiotic interaction has been confirmed in *Drosophila* spermatocytes (2, 43, 44). B) CENP-C is important for SC and cohesion assembly which promotes centromere clustering (55). The presence of CENP-C and its interaction with Meikin have been shown in mice (98). C) The CCAN, CENP-C, and MIS12C recruit KNL1C/SPC105R and NDC80C to create a functional kinetochore (122).