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Review

Centromere regulation: New players, new rules, new questions

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ABSTRACT

Centromeres support the assembly of the kinetochore on every chromosome and are therefore essential for the proper segregation of sister chromatids during cell division. Centromere identity is regulated epigenetically through the presence of the histone H3 variant CENP-A. CENP-A regulation and incorporation specifically into centromeric nucleosomes are the matter of intensive studies in many different model organisms. Here we briefly review the current knowledge in centromere biology with a focus on *Drosophila melanogaster* and how these insights lead to new rules and challenges.

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Chromosome inheritance requires centromeres

Proper chromosome segregation is essential for maintaining normal chromosome number (euploidy) during mitosis and meiosis, and is therefore crucial for germ cell and zygote formation, differentiation and development of somatic tissues and organs. Aneuploidy – the loss or gain of chromosomes in a cell – is a hallmark of cancer (Thompson et al., 2010). Knowledge of the basic biology of inheritance is essential if we are to understand the complex relationship between aneuploidy and human disease.

The region on every linear chromosome that is required for accurate chromosome segregation is termed the centromere. Functionally, the centromere is the minimal chromatin element that is sufficient to promote normal formation of the kinetochore, the proteinacious structure that links microtubules to chromosomes (Welburn and Cheeseman, 2008). The kinetochore is also responsible for sensing errors in chromosome attachment to the spindle. The components of the Spindle Assembly Checkpoint (SAC) associate with the kinetochore and delay the metaphase to anaphase transition until all chromosomes have reached bipolar attachment to the spindle.

Centromeres are usually located at a stably inherited site on each chromosome and are embedded into pericentric heterochromatin. Centromeric DNA sequences are extremely variable between species and even between different chromosomes in the same cell. For example, centromeres in *Drosophila melanogaster* consist of several islands of complex DNA embedded in long regions of repetitive DNA, whereas human centromeric DNA contains long arrays of tandemly repeated alpha-satellite DNA that can stretch over mega bases (Allshire and Karpen, 2008). There is significant evidence that centromeric DNA and its surrounding pericentric heterochromatin are not necessary for the specification of centromere location (centromere identity). First, formation of fully functional neocentromeres has been reported on normally non-centromeric euchromatic regions suggesting that the DNA sequence is not necessary for centromere formation (Choo, 2001). Second, dicentric chromosomes exist in which a functional kinetochore forms only at one of the two centromeric regions, demonstrating that centromeric DNA is not sufficient for kinetochore formation (Agudo et al., 2000). Finally, chromosome rearrangements are a hallmark of evolution and speciation, and are accompanied by centromere gains, losses, and movements, independent of underlying DNA sequences (Henikoff and Furuyama, 2010).

Epigenetic mechanisms define centromere identity and inheritance

Centromere identity is regulated by epigenetic mechanisms in most eukaryotes, which means that the specification of centromere location is inherited from one cell and organismal generation to the next independently of the underlying DNA sequence (Allshire and Karpen, 2008). The composition of centromeric chromatin is rather unique: instead of the canonical octameric nucleosome formed by two copies of H2A, H2B, H3 and H4, centromeric nucleosomes contain the histone H3 variant CENP-A (CENtromeric Protein A; CID for Centromere Identifier in Drosophila) in place of H3 only at functional centromeres. CENP-A is thought to be a key factor that regulates centromere identity epigenetically. CENP-A homologues

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have been identified from yeasts to mammals, demonstrating an evolutionary link between the centromeres of these organisms. The importance of CENP-A for kinetochore function has been established by several gene depletion studies in different organisms. Elimination of mammalian CENP-A leads to failure to localize essential kinetochore proteins, chromosome segregation defects, and embryonic lethality (Howman et al., 2000). Similarly, Drosophila CID is also an essential protein, required for kinetochore formation and faithful chromosome segregation (Blower et al., 2006). Interestingly, not only the absence but also the overexpression of CENP-A can lead to a high degree of chromosome missegregation and lethality. Overexpression can cause mislocalization of CENP-A to ectopic sites, as shown experimentally in human cells and Drosophila (Heun et al., 2006; Jager et al., 2005; Van Hooser et al., 2001). Strong CID overexpression in Drosophila leads to the formation of functional, ectopic kinetochores at some sites of CID incorporation into chromatin and causes massive segregation defects (Heun et al., 2006, Fig. 1). Why only some of the ectopic sites form functional kinetochores that recruit and attach to microtubule fibers still needs to be investigated. A specific chromatin environment consisting of certain histone modification marks or the presence of repetitive elements in the vicinity may favor the functionality of certain sites. Importantly, CENP-A has also been shown to be massively upregulated in different tumors (Ma et al., 2003; Tomonaga et al., 2003). It is however unclear whether CENP-A overexpression in human cells is a cause or a consequence of tumorigenesis. The results from Drosophila indicate that CENP-A misregulation alone can cause chromosome segregation defects. While similar scenarios may occur during tumorigenesis, future studies will need to address this hypothesis.

Centromeric chromatin is different from euchromatin and heterochromatin

The importance of post-translational modifications of histones on gene regulation and chromatin integrity has become apparent in recent years, and new modifications as well as combinations of different modifications are constantly being identified (Campos and Reinberg, 2009). Centromeric chromatin in flies and humans contains interspersed blocks of CENP-A and H3 nucleosomes (Sullivan and Karpen, 2004). These domains may form a specialized three-dimensional structure during mitosis that serves as a unique platform for kinetochore formation. The histone H3-containing domains display a pattern of modifications that are distinct from both euchromatin and heterochromatin: histone acetylation and H3K9 methylation are mostly absent, whereas H3K4 dimethylation, H3K27 methylation and H3K36 methylation are present (Bergmann et al., 2010; Lam et al., 2006; Sullivan and Karpen, 2004). These distinct chromatin modifications at centromeres may be important for the correct assembly of the kinetochore, and may also contribute to centromere identity. For example, the distinct centromeric modification pattern could recruit a unique set of histone-binding proteins that influence the higher-order structure of the centromere in mitotic chromosomes. These proteins could also recruit newly synthesized CENP-A and specify centromere identity epigenetically. In accordance to this model, centromeric H3K4me2 has recently been shown to be required for long-term kinetochore maintenance as lack of H3K4me2 progressively leads to impaired loading of newly synthesized CENP-A (Bergmann et al., 2010). Even though all canonical histones are known to contain post-translational modifications (PTMs), little is known about PTMs of CENP-A and how PTMs may influence different aspects of centromere biology, from loading of CID and recruiting components of the kinetochore to the correct chromosome attachment and segregation.

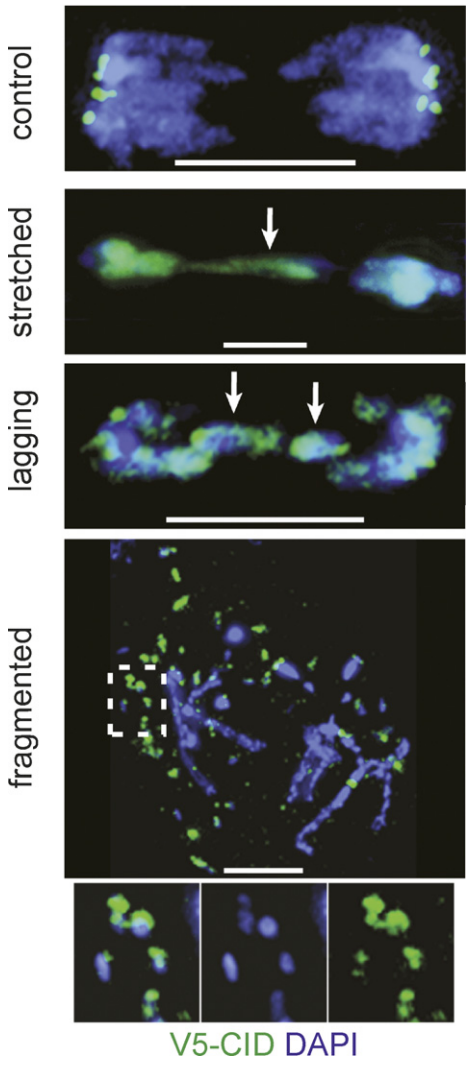

Fig. 1. CID overexpression produces mitotic defects in Drosophila. Chromosome behavior in CID-V5 misexpressing larval discs and brains (blue = DAPI, green = CID). Low CID overexpression is associated with CID incorporation only at endogenous centromeres and normal progression through mitosis ('control'). High CID overexpression leads to ectopic CID incorporation into chromosome arms, which produced stretched, lagging, and fragmented chromosomes at anaphase. The white arrows mark the corresponding chromosome phenotype. Chromosome fragments within the white box are shown at higher magnification below. The fragments contain CID, and are most commonly located close to the spindle poles, suggesting that they were produced by abnormal spindle attachments at more than one chromosomal site (Heun et al., 2006). Scale bars, 5 μm.

CID incorporation into the centromeres is replication-independent in higher eukaryotes

Canonical histones assemble with newly duplicated DNA as the replication fork progresses aided by several loading complexes. On the other hand, the timing of replenishment of CENP-A at centromeres varies between species: in yeast CENP-A incorporation into centromeric chromatin takes place before mitosis in S or G2 (Pearson et al., 2001; Takayama et al., 2008). In contrast, in higher eucaryotes although CENP-A is produced in G2, it is only deposited at centromeres at the end of the following mitosis, during late telophase-early G1 in the case of human CENP-A, during anaphase for CID in the Drosophila syncytial embryo, and during metaphase in Drosophila cultured cells (Jansen et al., 2007; Mellone et al., 2011; Schuh et al., 2007). Therefore, CID incorporation into centromeric nucleosomes is replication-independent,

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