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Foreword: the centromere and kinetochore in creatures great and small

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Abbreviations

CENP-A	centromeric modified histone H3 (CENH3, Cid, Cnp1, Cse4, HCP3)
CCAN	constitutive centromere-associated network
HJURP	Holiday junction recognition protein
KMN	KNL1, and the Mis12 and Ndc80 complexes
Scm3	non-histone centromere assembly protein (yeast)

This special issue of Chromosome Research is a collection of reviews that present current work in centromere and kinetochore biology. When the editors, Drs. Conly Rieder and Herbert Macgregor, asked us to develop this special issue, we eagerly embraced the opportunity to assemble a group of papers on our favorite topic. However, this task proved challenging as the field has advanced in dramatic ways since the term centromere was first coined in CD Darlington's description of the external mechanics of chromosomes. In fact, in the last year alone, there have been 762 papers cited in PubMed that are focused on some aspect of centromere structure, organization, and/or function. It was impossible to include papers from every facet of centromere biology, but this special issue cuts a broad swath through the diversity of centromere-based research that has been produced since the last Chromosome Research Special Issue on Centromeres was published in 2004.

The German zoologist Anton Schneider published the first description of mitotic chromosomes, what he had called "chromatic nuclear figures" (Schneider 1873). For over a century, the process by which genetic material segregates with each cell generation has fascinated biologists. The centromere is pivotal to cell division. Classic biology textbooks initially considered this part of the chromosome to be a silent, passive, and inert architectural feature of chromatin. However, the myriad technological advances in microscopy, genomics, and genetic engineering, coupled with the diversity of species studied over the last 20 years has reshaped this view; the centromere is now considered an active and dynamic feature of the genome. It is clear from over 130 years of study in chromosome biology that properly functioning centromeres are critical to achieving accurate cell division. A fundamental component of centromere function is a variant histone protein that defines active centromeres. Reflecting the diversity of model systems employed in this field, there is a corresponding range in names for this protein, CENP-A (vertebrates), CENH3 (plants and *fungi*), Cid (flies), Cnp1 (fission yeast), Cse4 (budding yeast), and HCP3 (worms). Each

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of these aliases is used throughout this special issue. One facet of this field we hope to see emerge is a consensus on this naming system as the diversity of models will no doubt expand.

Research on properties of CENP-A nucleosomes and dynamics of CENP-A protein has been particularly intense in the past 5 years; we have included three reviews in this special issue that discuss different aspects of this fascinating centromere-specific histone. Delphine Quénet and Yamini Dalal discuss the structure and topology of the CENP-A nucleosome and the dynamics of this specialized nucleosome during the cell cycle. Luis Valente, Mariana Silva, and Lars Jansen present exciting data on how CENP-A assembly is temporally regulated. They discuss the recent findings that have revealed the orchestration of chromatin environment and cell cycle regulators in controlling CENP-A assembly machinery and the constitutive centromere-associated network (CCAN). Finally, Ragini Phansalkar, Pascal Lapierre, and Barbara Mellone consider the similarities and differences in the features of the CENP-A assembly proteins, focusing on the *Drosophila* protein CAL1 and comparing its properties to closely related proteins Scm3 (yeasts) and HJURP (mammals). They present an intriguing hypothesis for the evolution of independent chaperones in divergent lineages, such as yeast, flies, and humans.

While the importance of CENP-A in centromere specification and maintenance is largely undisputed, recent studies have explored the ideal environment within which a centromere is assembled to ensure successful chromosome segregation. Centromere regions contain CENP-A nucleosomes interspersed with nucleosome containing canonical H3 that is modified by methylation at lysine 4 and lysine 36 (Sullivan and Karpen 2004; Bergmann et al. 2011). This euchromatic-like chromatin is surrounded by classical heterochromatin that is repressive for gene transcription but is necessary for building a proper kinetochore. Jan Bergmann, Bill Earnshaw, and colleagues describe studies using synthetic centromeres in the form of human artificial chromosomes to test the role of euchromatin and heterochromatin in centromere organization and function. They discuss how a balance between chromatin states is required for *de novo* mammalian centromere function and inheritance of centromere identity. Extending the importance of heterochromatin in centromere function and chromosome stability, Brandon Lowe, Benjamin Alper, and Janet Partridge discuss how the fission yeast *Schiozsaccharomyces pombe* has emerged as a leading model for dissecting the interplay between centromeric transcription, RNAi, and other processes, such as replication and RNA decay, in establishment of centromeric heterochromatin. Transcription within the centromere region is also necessary for establishing chromatin environment and ensuring proper centromere function in multicellular organisms. Laura Hall, Sarah Mitchell, and Rachel O'Neill explore pericentromeric vs. centromeric transcripts (PCTs vs. CTs) in various organisms and discuss how features of the transcripts (size, structure, location) could regulate heterochromatin formation and centromere assembly under normal, stressed, and/or disease conditions.

Once CENP-A chromatin is assembled, a cascade of proteins is recruited to the centromere to build the kinetochore and to ultimately establish contacts between the chromosome and the spindle microtubules. Tetsuya Hori and Tatsuo Fukagawa consider the molecular architecture of the kinetochore and the properties of the different protein complexes that are required to build a mature kinetochore. They discuss the intricacies of the CCAN (constitutive centromere-associated network) and KMN (KNL1, and the Mis12 and Ndc80 complexes) protein networks that interface between CENP-A chromatin and microtubules. Related to this, Antonio Pereira and Helder Maiato discuss the kinetics of microtubule flux and metaphase duration in maintaining mitotic fidelity. Much attention is paid to centromeric chromatin, and CENP-A in particular, but these reviews illustrate the overall complexity of building a functional mitotic kinetochore.

Centromeres are typically considered as point or regional loci on the chromosome and most studies have concentrated on understanding how these functional units are organized and behave. However, centromeres come in diverse varieties that are highlighted in three reviews in this special issue. Holocentric chromosomes, those on which the centromere is formed along the entire length of the chromosome, raise questions about how centromere identity is established within an environment that contains genes and active transcription. Daniël Melters, Leocadia Paliulus, Ian Korf, and Simon Chan discuss holocentric chromosomes in nematodes and other organisms, highlighting the challenges holocentrics face during segregation in meiosis versus mitosis. Kaitlin Stimpson, Justyne Matheny, and Beth Sullivan highlight dicentric chromosomes, those that have two regional centromeres, in the context of centromere

activity and chromosome stability. Although originally considered inherently unstable based on the pioneering studies of Barbara McClintock in maize (McClintock 1941), dicentrics in humans can be extremely stable, due to the poorly understood process of centromere inactivation. It is now appreciated that dicentrics in many organisms, including model organisms, such as fission yeast and plants, can be stable. The authors summarize recent findings that have deepened our understanding of dicentric behavior and fate after formation in both model organisms and humans. A third type of centromere is the neocentromere, a new centromere that forms on non-centromeric DNA and/or in a region that does not correspond to the exact location of the endogenous centromere. Laura Burrack and Judy Berman describe neocentromere formation in the pathogenic yeast *Candida albicans*, both in native and engineered forms, and discuss the utility of varied model systems for understanding different functional and structural components involved in de novo centromere emergence.

The development of a reference for the human genome has been heralded as one of the most important scientific innovations of the last decade. Since 1999, the number of "completely sequenced" genomes has grown rapidly from smaller, less complex genomes of bacterias and yeasts, to the large genomes of mammals. However, these efforts have proven inadequate for most in the centromere field. In fact, a single, completely assembled, human centromere has yet to be achieved. Large-scale genome projects and the development of massively parallel, high throughput sequencing techniques now afford the opportunity to examine the genomic landscape of large, complex centromeres. Two reviews in this issue explore the woefully under-represented, but sorely needed, field of centromere genomics. Karen Hayden describes genomics features of the human centromere, and of many complex eukaryotic centromeres. She highlights features of centromeres that have made reproducing a contiguous centromere sequence challenging, but that are also important indicators of regional functionality. Kristina Smith, Michael Freitag, and colleagues introduce genomic and epigenomic studies in filamentous fungi, emerging centromere model systems that include the species *Neurospora*, *Aspergillus*, and *Fusarium*. These models also offer unique opportunities to study centromere DNA and protein interactions and how such interactions affect the genomic landscape of the centromere.

This special issue covers many areas of centromere biology, ranging from the intensely studied CENP-A proteins to centromere/kinetochore architecture, and including atypical centromeres and the challenging but crucial area of centromere genomics. We believe that the reviews in this issue encapsulate some of the most exciting topics in our rapidly moving field. We are confident that after reading this Special Issue centromere biologists and nonspecialist readers alike will agree that the centromere is not a static chromosome feature, but instead is a dynamic entity involving complex protein networks and assembly cascades, a spectrum of epigenetic modifications, transcriptional activity, and evolutionary lability. Still, despite major scientific advances in the past 7 years, the centromere remains an enigmatic feature of the eukaryotic genome that continues to draw the attention of geneticists and cell biologists working in a diversity of organisms. As guest editors, we thank all of our colleagues who contributed such outstanding articles to this issue and were such a pleasure to work with from invitation to final production. We also acknowledge Conly Rieder and Herbert Macgregor, Editors in Chief of *Chromosome Research*, for their guidance during this endeavor and for establishing a high standard for completion of this issue. It is our hope that the variety of reviews presented here will deepen knowledge of our vast field while invigorating and inspiring those of us who work in this challenging yet fascinating area of biology.

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