Understanding the kinetochore's function and structure is crucial for comprehending how cells maintain chromosome stability during cell division. This multi-protein assembly ensures accurate chromosome segregation to daughter cells, preventing aneuploidy—a condition linked to diseases like cancer. This article explores the intricacies of the kinetochore, including its structural components, interactions with microtubules, and regulatory mechanisms. Structural Components The kinetochore is the main interface between chromosomes and spindle microtubules during cell division. It comprises over 100 proteins in distinct subcomplexes, categorized into inner and outer kinetochores, each with unique roles in chromosome segregation. The inner kinetochore, anchored to centromeric DNA, provides a stable foundation for the outer kinetochore, facilitated by CENP-A. CENP-A replaces conventional histone H3, creating a unique chromatin environment essential for kinetochore formation. The outer kinetochore interacts directly with spindle microtubules and includes the KMN network, crucial for microtubule attachment. The Ndc80 complex, a key player, forms a rod-like structure that extends from the kinetochore to bind microtubules, facilitating tension sensing and stabilizing attachments for accurate chromosome alignment and segregation. Additional protein complexes support the kinetochore's structural integrity and functionality. The CCAN (constitutive centromere-associated network) forms a scaffold around CENP-A nucleosomes, linking inner and outer components. This network is essential for recruiting the KMN network and maintaining structural cohesion. Kinases like Aurora B regulate the dynamic nature of the outer kinetochore through phosphorylation, modulating microtubule attachment and detachment for proper chromosome movement. Spindle Assembly Checkpoint The spindle assembly checkpoint (SAC) is crucial in maintaining genomic integrity during cell division, ensuring chromosomes are correctly attached to spindle microtubules before progressing from metaphase to anaphase. This checkpoint prevents aneuploidy, linked to cancers and genetic disorders. The SAC halts the cell cycle until all chromosomes are bi-oriented and under tension, safeguarding mitosis fidelity. Central to the SAC is its inhibition of the anaphase-promoting complex/cyclosome (APC/C), a large E3 ubiquitin ligase that targets specific proteins for degradation, triggering anaphase onset. Checkpoint proteins, including Mad1, Mad2, Bub1, Bub3, and BubR1, form a complex that interacts with the APC/C coactivator Cdc20, preventing ubiquitination of securin and cyclin B. This inhibition is maintained until correct attachment is achieved, ensuring synchronized chromosome segregation. The dynamic assembly and disassembly of checkpoint proteins at kinetochores are critical, highlighting the finely tuned balance of SAC activity. Recent studies reveal molecular intricacies of SAC signaling, such as Mad2's conformational change upon kinetochore recruitment, essential for its interaction with Cdc20. Mad1 facilitates this change, acting as a template for Mad2 activation. BubR1, in association with Bub3, not only contributes to Cdc20 inhibition but also stabilizes microtubule attachments, underscoring the complexity of SAC components. Microtubule Binding Interfaces Kinetochore-microtubule interactions are essential for accurate chromosome segregation. The Ndc80 complex, a primary player, forms an elongated structure that attaches to the microtubule lattice. This dynamic connection allows for tubulin subunit addition and removal, crucial for chromosome movement and alignment. The Dam1/DASH complex in yeast forms a ring around the microtubule, facilitating a robust connection that withstands forces during segregation. In higher eukaryotes, the Ska complex enhances the stability of kinetochore-microtubule attachments. These complexes are responsive to mechanical tension, undergoing conformational changes that stabilize attachment and ensure correct orientation of sister chromatids. Biochemical studies highlight phosphorylation's role in regulating these interfaces. Aurora B kinase, located at the inner centromere, phosphorylates components of the Ndc80 and Ska complexes, modulating their microtubule affinity. This reversible process allows fine-tuning of kinetochore-microtubule interactions in response to spindle apparatus feedback, critical for correcting misattachments and preventing erroneous segregation. Regulatory Complexes Regulatory complexes modulate kinetochore activity, ensuring precise chromosome segregation. Aurora B kinase, part of the Chromosomal Passenger Complex (CPC), is positioned at the inner centromere, sensing tension from spindle microtubules. It phosphorylates kinetochore substrates, including Ndc80 complex components, adjusting microtubule-binding affinity. This cycle is pivotal for correcting improper attachments and preventing missegregation. Mps1 kinase plays a prominent role in the spindle assembly checkpoint (SAC), recruited to unattached kinetochores to activate SAC components. This amplifies the checkpoint signal, delaying anaphase onset until accurate attachment. The interplay between Aurora B and Mps1 highlights a sophisticated regulatory network orchestrating kinetochore function. Visualization Techniques Advanced visualization techniques have been crucial in elucidating kinetochore structure and function. High-resolution imaging methods like cryo-electron microscopy (cryo-EM) provide insights into the molecular architecture of kinetochore complexes, revealing spatial organization and interactions with microtubules. Cryo-EM has been instrumental in visualizing the Ndc80 complex and its structural adaptations during segregation. Fluorescence microscopy, particularly super-resolution variants like STORM and PALM, enables dynamic observation of kinetochore components in living cells. These methods provide insights into real-time kinetochore behavior, such as SAC protein recruitment and dissociation. Time-lapse fluorescence microscopy captures the transient nature of kinetochore-microtubule interactions, highlighting rapid assembly and disassembly during cell division. Such imaging techniques are crucial in studying tension and mechanical forces on kinetochore stability, deepening understanding of dynamic regulation in chromosome segregation. Significance in Genome Stability The kinetochore is vital in maintaining genome stability, preventing aneuploidy and associated pathologies. Errors in kinetochore-microtubule attachments can lead to improper segregation, resulting in cells with abnormal chromosome numbers. Genomic instability is a hallmark of many cancers, underscoring the importance of precise kinetochore regulation. The SAC ensures cells do not proceed to anaphase until all chromosomes are correctly attached, acting as a fail-safe against chromosomal imbalances. Research shows defects in kinetochore components or regulatory pathways lead to genomic instability. Mutations in the Ndc80 complex or aberrations in Aurora B kinase activity are linked to increased chromosomal missegregation rates. This highlights the kinetochore's role in disease prevention. Understanding these mechanisms provides potential therapeutic targets; drugs modulating kinetochore function or regulatory pathways could combat cancers characterized by chromosomal instability. Ongoing study of kinetochores and their networks continues to illuminate their crucial role in cellular health and disease. Definition noun, plural: kinetochores A protein complex that assembles at the centromeric region of the chromosome during mitosis and meiosis Supplement The kinetochore is a protein structure. It forms at the centromere of every chromosome. Its main function is to bind microtubules of the spindle so that during metaphase the chromosomes would be able to properly align at the metaphase plate prior to anaphase, which is the pulling of chromosomes toward opposite poles of the cell. Thus, the kinetochore is important for the proper chromosome segregation. In most animal cells, the kinetochore is a disc-like complex forming on the side of every chromatid where spindle fibers would attach to. Thus, a human mitotic chromosome, being comprised of two sister chromatids linked together via a centromere, would have two kinetochores situated in opposite directions at the centromeric region. The kinetochore is comprised of an inner region (called inner kinetochore) and an outer region (called outer kinetochore). The inner kinetochore is tightly bound to the centromere DNA. The outer kinetochore is the one that interacts with the microtubules. Depending on the species, the number of microtubules attached to the kinetochore varies. In humans, there are about 15 microtubules attach to the kinetochore. Unlike the outer kinetochore that forms and becomes functional only during mitosis and meiosis, the inner kinetochore persists throughout the cell cycle. Word origin: Greek khôros ("space") See also: chromatid chromosome centromere mitosis meiosis spindle fiber Biology Online is the world's most comprehensive database of Biology terms and topics. Since 2001 it has been the resource of choice for professors, students, and professionals needing answers to Biology questions. Search over 75,000+ terms, news, insights, discoveries, and trends in Biology below: Share — copy and redistribute the material in any medium or format for any purpose, even commercially. Adapt — remix, transform, and build upon the material for any purpose, even commercially. The licensor cannot revoke these freedoms as long as you follow the license terms. Attribution — You must give appropriate credit , provide a link to the license, and indicate if changes were made . You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use. ShareAlike — If you remix, transform, or build upon the material, you must distribute your contributions under the same license as the original. No additional restrictions — You may not apply legal terms or technological measures that legally restrict others from doing anything the license permits. You do not have to comply with the license for elements of the material in the public domain or where your use is permitted by an applicable exception or limitation . No warranties are given. The license may not give you all of the permissions necessary for your intended use. For example, other rights such as publicity, privacy, or moral rights may limit how you use the material. There are 92 kinetochores in a human cell at mitosis. 01 Kinetochores are structures on chromatids where the spindle fibers attach during cell division to pull sister chromatids apart. Each chromatid has one kinetochore. 02 Human cells are diploid with 46 chromosomes, meaning they have 23 pairs of homologous chromosomes. 03 Before mitosis, during the S phase, each chromosome is replicated, leading to two sister chromatids per chromosome. Thus, there are 92 chromatids in a human cell during mitosis. 04 Since each chromatid has one kinetochore, the number of kinetochores is equal to the number of chromatids. 05 With 92 chromatids in a human cell during mitosis, there are 92 kinetochores. Unlock Step-by-Step Solutions & Ace Your Exams! Full Textbook Solutions Get detailed explanations and key concepts Unlimited Al creation Al flashcards, explanations, exams and more... Ads-free access To over 500 millions flashcards Money-back guarantee We refund you if you fail your exam. Over 30 million students worldwide already upgrade their learning with Vaia! These are the key concepts you need to understand to accurately answer the question. Kinetochores play a critical role in cell division, particularly during mitosis. These are the specialized protein structures located on the centromere of each chromatid. During mitosis, kinetochores are essential because they serve as the attachment sites for spindle fibers. Spindle fibers are responsible for segregating chromatids by pulling them apart towards opposite poles of the cell. Think of kinetochores as the "grip" or "handle" on the chromatids.This "grip" ensures that chromosome segregation is accurate, so that each new cell ends up with an identical set of chromosomes. Without properly functioning kinetochores, cells can end up with abnormal numbers of chromosomes, a condition known as aneuploidy. Chromatids are one of the two identical "sister" parts of a duplicated chromosome. Before a cell divides, during the S phase of the cell cycle, chromosomes replicate to form sister chromatids. These sister chromatids remain connected at the centromere and are eventually separated during mitosis. They are critical to ensure that each daughter cell receives an exact copy of the genome. Each chromosome thus transforms into two chromatids before cell division begins.Once separated, each chromatid becomes an independent chromosome in the daughter cells.This process ensures genetic continuity from one cell generation to the next, maintaining species characteristics. In humans, chromosomes are the carriers of genetic material. Humans are diploid organisms, meaning each cell contains two sets of chromosomes - one from each parent. This results in a total of 46 chromosomes arranged in 23 pairs in human cells. Of these pairs, 22 are autosomes and one pair consists of sex chromosomes (X and Y). To visually observe and count chromosomes, scientists often rely on karyotyping during the metaphase stage of cell division. Each chromosome pair is homologous, meaning they are similar in size, shape, and genetic content.This ensures that, during cell division, human cells accurately replicate and divide their genetic material.It's important for the normal functioning and development of human cells and tissues. Cell division is the process by which a parent cell divides to produce two or more daughter cells. It is vital for growth, reproduction, and repair in living organisms. In humans, mitosis and meiosis are the two primary types of cell division. Mitosis results in two genetically identical daughter cells, crucial for growth and tissue repair. Meanwhile, meiosis results in four genetically diverse daughter cells, which are essential for sexual reproduction. Mitosis consists of several stages: prophase, metaphase, anaphase, and telophase.The process is highly regulated to ensure accurate DNA replication and distribution.Throughout this process, the fidelity of chromosome segregation is essential for the health and functionality of the new cells formed. Proper chromosome segregation during cell division is critical to ensure that daughter cells inherit the correct number of chromosomes. Microtubules emanating from the spindle poles pull on sister chromatids to move one chromosome to each pole. The kinetochore, a protein complex on the chromosome, is key to regulating chromosome segregation. Kinetochores form attachments to microtubule ends (no easy feat since microtubules are constantly growing and shrinking), they sense tension to ensure that sister chromatids are connected to microtubules from opposite poles, and they signal the cell to stop cell division if attachment is not correct. Biggins gives an excellent overview of kinetochore structure and its critical functions in chromosome segregation. When Biggins began working on kinetochores, the experiments that she could do were limited by the lack of a method to purify intact kinetochores. In Part 2 of her talk, Biggins explains how her lab purified kinetochores from yeast (for the first time ever!). They showed that the purified protein complex functioned in the same manner in vitro as endogenous kinetochores. Using electron microscopy and other techniques, Biggins and her collaborators were able to visualize the structure of the kinetochore-microtubule attachment and demonstrate, surprisingly, that tension directly stabilizes the attachment. Dr. Sue Biggins studied biology as an undergraduate at Stanford University and initially thought she would apply to medical school after receiving her degree. However, after a summer working in a research lab, she changed her mind and decided to apply to graduate school. Biggins received her PhD in molecular biology from Princeton and was... Continue Reading A kinetochore is a protein patch on chromosomes that helps move them during cell division.Kinetochores connect to spindle fibers to ensure chromosomes are divided correctly between new cells.Kinetochores function in both mitosis and meiosis to help separate chromosomes into daughter cells. The place where two chromosomes (each known as a chromatid before the cell splits) are joined before they split into two is called the centromere. A kinetochore is the patch of protein found on the centromere of each chromatid. It is where the chromatids are tightly connected. When it's time, at the appropriate phase of cell division, the kinetochore's ultimate goal is move chromosomes during mitosis and meiosis. You can think of a kinetochore as the knot or central point in a game of tug-of-war. Each tugging side is a chromatid getting ready to break away and become part of a new cell. The word "kinetochore" tells you what it does. The prefix "kineto-" means "move," and the suffix "-chore" also means "move or spread." Each chromosome has two kinetochores. Microtubules that bind a chromosome are called kinetochore microtubules. Kinetochore fibers extend from the kinetochore region and attach chromosomes to microtubule spindle polar fibers. These fibers work together to separate chromosomes during cell division. Kinetochores form in the central region, or centromere, of a duplicated chromosome. A kinetochore consists of an inner region and an outer region. The inner region is bound to chromosomal DNA. The outer region connects to spindle fibers. Kinetochores also play an important role in the cell's spindle assembly checkpoint. During the cell cycle, checks are made at certain stages of the cycle in order to ensure that proper cell division takes place. One of the checks involves making sure that the spindle fibers are correctly attached to chromosomes at their kinetochores. The two kinetochores of each chromosome should be attached to microtubules from opposite spindle poles. If not, the dividing cell could end up with an incorrect number of chromosomes. When errors are detected, the cell cycle process is halted until corrections are made. If these errors or mutations cannot be corrected, the cell will self-destruct in a process called apoptosis. In cell division, there are several phases that involve the cell's structures working together to ensure a good split. In the metaphase of mitosis, kinetochores and spindle fibers help to position chromosomes along the central region of the cell called the metaphase plate. During anaphase, polar fibers push cell poles further apart and kinetochore fibers shorten in length, much like the children's toy, a Chinese finger trap. Kinetochores tightly grip polar fibers as they are pulled toward the cell poles. Then, the kinetochore proteins that are holding the sister chromatids together are broken down allowing them to separate. In the Chinese finger trap analogy, it would be as if someone took a scissor and cut the trap at the center releasing both sides. As a result, in cellular biology, sister chromatids are pulled toward opposite cell poles. At the end of mitosis, two daughter cells are formed with the full complement of chromosomes. In meiosis, a cell goes through the dividing process two times. In part one of the process, meiosis I, kinetochores are selectively attached to polar fibers extending from only one cell pole. This results in the separation of homologous chromosomes (chromosome pairs), but not sister chromatids during meiosis I. In the next part of the process, meiosis II, kinetochores are attached to polar fibers extending from both cell poles. At the end of meiosis II, sister chromatids are separated and chromosomes are distributed among four daughter cells. Three decades ago, Todd (1) postulated that wholesale fission of all "mediocentric" (metacentric, submetacentric, and subtelocentric) chromosomes in a complement plays a major role in chromosome evolution. According to Todd, karyotypic fission produces, as a consequence of a single mutational "event," dramatic differences in the diploid numbers of closely related species (2, 3). A diversity of karyotypes is generated through the random assortment of parent and fissioned homologous chromosomes. Immediate descendants of the fissioned parent would exhibit identical fundamental numbers of functional chromosomal arms but (potentially) very different diploid numbers. Todd saw karyotypic fission events, followed by the accumulation of pericentric inversions, as the driver for explosive speciation in adaptive radiations. He used the label "Karyotypic Fission Theory" to call attention to his implicit rejection of Darwinian gradualism in chromosomal evolution. Whole karyotypic fissioning can (at least theoretically) generate drastically different karyotypes in far fewer steps than are required according to competing explanations of chromosomal evolution, whether based on reciprocal or nonreciprocal chromosomal fission or fusion. Shortly after Todd's article was published, it was dismissed as preposterous by one of the leading theorists of chromosomal evolution, M. J. D. White (4). If chromosomal fissioning occurs only under unusual circumstances, how could an entire karyotype be expected to fission? A serious problem was the lack of a plausible cellular/molecular mechanism. Indeed, even single chromosomal fissioning appeared difficult to explain (refs. 5 and 6; see ref. 7 for review). Some researchers saw fissioning as requiring a ready supply of extra centromeres, perhaps in the form of vestigial chromosomes (Fig. 1a). But the existence of spare vestigial chromosomes had never been demonstrated. Todd (1) proposed another mechanism—centromeric mis-division and subsequent repair (Fig. 1b). White (4) doubted "whether simple breakage through the centromere of a metacentric can produce two fully functional and stable telocentric chromosomes, capable of persisting indefinitely." He added, "To suppose that all of the chromosomes of a karyotype would undergo this process simultaneously is equivalent to a belief in miracles, which has no place in science" (ref. 4, p. 401). With rare exceptions (8–11), Todd's theory has been ignored for more than a quarter of a century. Two previously posited mechanisms of metacentric chromosomal fissioning. Both are problematic (see text). (a) Spare vestigial chromosomes provide extra centromeres. (b) Centromeric misdivision is followed by repair. Centromeres are shown in red.In an article published in a recent issue of PNAS, Robin Kolnicki (12) offers a plausible mechanism (Kinetochore Reproduction Theory) for simultaneous chromosomal fissioning. Her argument is largely theoretical, but cellular/molecular evidence is provided for each of its components. Many of the ideas presented are not new; dicentric chromosomes have been known since the 1930s (13), but their linkage to Todd's Karyotypic Fission Theory is original with this paper. Kolnicki's Kinetochore Reproduction Theory has several components. During DNA replication just before meiotic synapsis and sister chromatid segregation, a mutational agent stimulates the production of extra kinetochores on all (or most) of the mediocentric chromosomes' newly synthesized sister strands. The newly synthesized strands now possess two functional kinetochores instead of one. These supernumerary kinetochores do not disrupt the distribution of chromosomes to daughter cells during meiosis because tension-sensitive mitotic checkpoints operate to prevent errors in chromosome segregation (as illustrated in Fig. 1A of ref. 12). Assuming none of the supernumerary kinetochores is later inactivated, descendants will inherit dicentric chromosomes with two functional kinetochores. When these chromosomes in turn replicate, each pair of sister chromatids will have four functional kinetochores (as illustrated in Fig. 1B of ref. 12). Again, the tension-sensitive checkpoints will prohibit errors in chromosome delivery during meiosis. But now fissioning and nonfissioning are equally probable, and for any pair of dicentric sister chromatids, the outcome will depend on whether spindle attachment is monopolar or bipolar. Under monopolar attachment, there will be no fissioning, and the dicentric chromosomes will be passed on, intact, to the next generation. Under bipolar attachment, chromosomal fissioning occurs. Because monopolar and bipolar attachment are equally probable, 50% of the pairs of dicentric sister strands can be expected to fission during any single meiosis. With such probabilities, it is easy to ascertain that in only 7 successive generations, 99% of the functionally dicentric chromosomes can be expected to have fissioned, and that in 10 generations, only 1 in 1,000 unfissioned dicentric chromosomes will remain. In the absence of strong selection pressure eliminating these variants, they may become fixed in small populations. Thus, we have what must be considered an evolutionarily instantaneous (or macromutational) "event"—"simultaneous" fissioning of all of the mutant mediocentric chromosomes in a complement. This theory is attractive for a number of reasons. First, none of the posited prefission steps (i.e., the production of supernumerary kinetochores, the retention and inheritance of chromosomes with two functional kinetochores) should have deleterious effects on cell division or phenotypes. In addition, unstable telocentric chromosomes produced by fissioning are likely to be repaired by the high amounts of telomerase in embryonic cells, so the fissioned chromosomes themselves should function normally. Fissioning should have no negative consequences for meiotic synapsis in succeeding generations, as the two fissioned autosomal acrocentrics pair easily with their homologous mediocentrics. Indeed, selection might favor the retention of fissioned acrocentrics over homologous mediocentrics, if smaller chromosomes are more likely than larger ones to segregate without error during cell division (14). The only chromosomes that would not be expected to synapse properly after fissioning are the sex chromosomes (1); strong selection pressure should promote the retention of unfissioned X-chromosomes. This might well help to explain the relative conservatism of X-chromosomes across a wide variety of organisms (15). Karyotypic Fission Theory embraces the well-substantiated general predictions of reciprocal ("Robertsonian") translocation theory (16–18). These predictions are that redistribution of DNA (with pairs of acrocentrics demonstrably homologous to single mediocentric chromosomes) should occur without changes in the amount of DNA, and that closely related taxa will share commonly the same fundamental number of chromosome arms but not the same diploid number (because their karyotypes differ only by reciprocal translocations). These sorts of differences should (and do) occur at an intraspecific level. (Other types of meiotic errors, such as pericentric inversions, alter the fundamental number without affecting the diploid number.) Specific predictions of karyotypic fission theory include the occurrence of very different diploid numbers in closely related species with the same fundamental number and of distributions among closely related species of karyotypes that might be generated through a single karyotype fission event. Finally, Karyotypic Fission Theory predicts that low diploid numbers will be primitive for clades. Whereas Kolnicki offers a plausible mechanism for simultaneous chromosomal fissioning, the jury is still out on the generality of this occurrence. Even if Todd and Kolnicki are correct about the feasibility of wholesale karyotypic fissioning, it would simply join a battery of known mechanisms of chromosomal evolution, the relative frequency of which has yet to be determined. That relative frequency must be assessed by using studies of chromosomal banding and painting as well as proper (cladistic outgroup) analysis of the probable ancestral karyotypes of particular phylogenetic groups. There are, of course, many examples of karyotypic differences among closely related species that simply cannot be explained via karyotypic fissioning. For example, the differences between the Indian (2n = 6 or 7) and Chinese (2n = 24) muntjac karyotypes cannot be explained in this manner (19). Nevertheless, Karyotypic Fission Theory owes its relative obscurity more to the lack of a plausible cellular/molecular mechanism than to perceived weaknesses in its explanatory power. Kolnicki offers such a mechanism, and her work should stimulate further research on the plausibility as well as the potential explanatory power of karyotypic fission events. Kolnicki's Kinetochore Reproduction Theory may even explain empirical observations that appear to contravene karyotypic fissioning in particular clades (e.g., refs. 9 and 11). For example, Finelli et al. (11) embrace fission as the primary vehicle for differences between the karyotypes of green monkeys and humans, but they dismiss Karyotypic Fission Theory because reciprocal chromosome painting suggests that most break points lie outside the centromere regions. If, as Kolnicki suggests, one of the possible mechanisms of kinetochore reproduction involves the epigenetic formation of neokinetochores in regions previously devoid of centromeric activity, and if such synthesis is followed by chromosome breakage between kinetochores, this objection may be moot. Kolnicki's attempt to link karyotype fissioning and speciation is weak and unnecessary. Although it is true that karyotypic rearrangements may become fixed by genetic drift in small populations during the course of speciation, assigning these rearrangements a causative role in the process flies in the face of the extensive literature that argues otherwise (20–24). Todd and Kolnicki have argued that difficulties in the meiotic pairing of fissioned and unfissioned homologous chromosomes can be expected to arise through the accumulation of pericentric inversions on fissioned chromosomes, thereby generating immediate reproductive isolation. However, for deleterious inversions to trigger speciation, they would need to spread through the population. Rearrangements appear first in populations as heterozygotes, and inviable or sterile heterozygotes will be eliminated by normalizing natural selection, regardless of how fit the corresponding homozygotes might be (20). The chances of fixing a deleterious rearrangement, the effects of which are strong enough to present a significant barrier to gene flow, are extremely low without the aid of a prolonged and severe population bottleneck (21, 23). It is nevertheless possible that karyotypic fissioning explains major evolutionary changes in karyotypes. Certainly it poses a welcome challenge to the hegemony that Robertsonian fusion has exercised over interpretations of chromosomal evolution during the past 50 years. In our view, it is unlikely that one process or the other can independently account for the wide range of karyotype structures that are observed, or that the derived or ancestral nature of a taxon can be inferred from its diploid and/or fundamental numbers. For example, few lemur specialists would embrace the suggestion that the 2n = 66 largely acrocentric karyotype shared by the dwarf lemur genera Microcebus, Mirza, and Cheirogaleus was evidence of a recent radiation of this group. But used in conjunction with other phylogenetic data, karyotypic fissioning may help to explain dramatic differences in diploid numbers between closely related species, which were previously inexplicable.

1.Todd N B. J Theor Biol. 1970;26:445–480. doi: 10.1016/0022-5193(70)90096-2. [DOI] [PubMed] [Google Scholar] 2.Todd N B. Paleobiology. 1975;1:175–188. [Google Scholar] 3.Todd N B. In: Environmental Evolution: Effects of the Origin and Evolution of Life on Planet Earth. Margulis L, Olendzenski L, editors. Cambridge, MA: MIT Press; 1992. pp. 275–292. [Google Scholar] 4.White M J D. Animal Cytology and Evolution. 3rd Ed. Cambridge, U.K.: Cambridge Univ. Press; 1973. [Google Scholar] 5.Egozcue J. Experientia. 1971;27:969–971. doi: 10.1007/BF02135779. [DOI] [PubMed] [Google Scholar] 6.Imai H T, Crozier R H. Am Nat. 1980;116:537–569. doi: 10.1086/283646. [DOI] [PubMed] [Google Scholar] 7.Martin R D. Primate Origins and Evolution: A Phylogenetic Reconstruction. Princeton: Princeton Univ. Press; 1990. [Google Scholar] 8.Giusto J P, Margulis L. BioSystems. 1981;13:267–302. doi: 10.1016/0303-2647(81)90007-1. [DOI] [PubMed] [Google Scholar] 9.Stanyon R. BioSystems. 1983;16:57–63. doi: 10.1016/0303-2647(83)90025-4. [DOI] [PubMed] [Google Scholar] 10.Kolnicki R L. Symbiosis. 1999;26:123–141. [Google Scholar] 11.Finelli P, Stanyon R, Plesker R, Ferguson-Smith M A, O'Brien P C, Wienberg J. Mamm Genome. 1999;10:713–718. doi: 10.1007/s003359901077. [DOI] [PubMed] [Google Scholar] 12.Kolnicki R L. Proc Natl Acad Sci USA. 2000;97:9493–9497. doi: 10.1073/pnas.97.17.9493. [DOI] [PMC free article] [PubMed] [Google Scholar] 13.Mather K, Stone L H A. J Genet. 1933;28:1–24. [Google Scholar] 14.Schubert I, Oud J L. Cell. 1997;88:515–520. doi: 10.1016/s0092-8674(00)81891-7. [DOI] [PubMed] [Google Scholar] 15.Ohno S, Becak W, Becak M L. Chromosoma. 1964;15:14–30. doi: 10.1007/BF00326912. [DOI] [PubMed] [Google Scholar] 16.Robertson W R B. J Morphol. 1916;27:129–331. [Google Scholar] 17.Matthey R. Experientia. 1945;1:50–56. , 78–86. [Google Scholar] 18.Matthey R. Les Chromosomes des Vertébrés. Lausanne, Switzerland: F. Rouge; 1949. [Google Scholar] 19.Liming S, Yingying Y, Xingsheng D. Cytogenet Cell Genet. 1980;26:22–27. doi: 10.1159/000131417. [DOI] [PubMed] [Google Scholar] 20.Dobzhansky T. Genetics and the Evolutionary Process. New York: Columbia Univ. Press; 1970. [Google Scholar] 21.Lande R. Evolution (Lawrence, KS) 1979;33:234–251. doi: 10.1111/j.1558-5646.1979.tb04678.x. [DOI] [PubMed] [Google Scholar] 22.Futuyma D J, Mayer G C. Syst Zool. 1980;29:254–271. [Google Scholar] 23.Barton N H, Hewitt G M. In: Evolution and Speciation: Essays in Honor of M. J. D. White. Atchley W R, Woodruff D S, editors. Cambridge, U.K.: Cambridge Univ. Press; 1981. pp. 109–145. [Google Scholar] 24.Paterson H E H. Evolution and the Recognition Concept of Species. Baltimore: Johns Hopkins Univ. Press; 1993. [Google Scholar]

In eukaryotes, cells of the body divide to make more cells in a process called _mitosis_. Reproductive organ cells undergo another sort of cell division called meiosis. In these processes, cells enter several phases to achieve division. Kinetochores play an important role in cell division, ensuring the proper distribution of DNA to daughter cells. Kinetochores and nonkinetochore microtubules are quite different in structure. They both work together to ensure the proper distribution of DNA to daughter cells in cell division. Eukaryotic cells undergo mitosis for new or growing tissues and for asexual reproduction. One cell divides into two new daughter cells, splitting the nucleus and chromosomes in order to do this. These new cells are identical. In order for this process to take place successfully, the chromosome number of cells must be maintained, meaning they must be copied for each new daughter cell. Humans have 23 pairs of chromosomes in each cell. Each chromosome stores DNA. The chromosome pairs are named sister chromatids, and the point at which they meet is called the centromere. Cell division's goal is to copy genetic material into new daughter cells in such a way that they are able to function properly. For this to happen, each unit of DNA must be recognized, so there must be a connection between it and other parts of the cell for distribution, and there must be a way to move the DNA to daughter cells. Between cell divisions, the cell is in a phase called interphase, which consists of the first gap or G1 phase, the S phase and the second gap or G2 phase. After interphase, mitosis begins with prophase. At this point chromatin in the nucleus is duplicated. The resulting sister chromatids are twisted compactly. The nucleolus goes away, and a structure called a spindle forms in the cytoplasm of the cell, made of spindle fibers. Prometaphase follows. In this step, there are nuclear envelope fragments in the cytoplasm. The spindle's microtubules, or long tubelike protein strands, advance upon the chromosomes to begin their work. At the adjoining centromere between the sister chromatids, a protein complex called a kinetochore appears. Microtubules attach to this new structure. In metaphase, centrosomes form at the opposing cell poles. The chromosomes arrange themselves in a line. Microtubules stretch toward the centrosomes, and a spindle is made. The microtubules perform the anaphase slide, moving the chromosomes until they are centralized on the cell's equator. During anaphase, the paired chromatids are separated. These form new chromosomes. Their centrosomes are pushed apart by nonkinetochore microtubules. The chromosomes are moved to the opposite ends of the cell. Telophase results in cellular elongation by the nonkinetochore microtubules. The former nuclear fragments help to create new nuclei for the daughter cells. Then the twisted chromosomes loosen. Finally, in cytokinesis, the actual cytoplasm of the cell is split to result in the new daughter cells. In 1880, anatomist Walther Flemming discovered the attachment site for mitotic spindles on chromosomes. This was the kinetochore. More recently, human kinetochores have been elucidated at a rapid pace. The kinetochore definition in biology is a protein complex that forms on chromosomes at their centers, in an area called the centromere. Kinetochores play the crucial role for properly distributing DNA to new daughter cells in mitosis. This protein complex is considered a macromolecule. While the DNA of different organisms varies widely, kinetochores are very similar across species, and are thus conserved. Kinetochores differ from nonkinetochore microtubules in numerous ways. Their structural difference is the first difference. Kinetochores are large structures made of many different proteins, assembled at the centromeres of chromosomes. Kinetochores serve as a bridge between the DNA of a chromosome and nonkinetochore microtubules. Nonkinetochore microtubules are polymers that work with kinetochores to align and separate chromosomes. Nonkinetochore microtubules can be long and spindly, and they serve different functions. These different structures must work together, however, to achieve control of chromosomes and their movement during mitosis. Kinetochores essentially work as tiny machines that interact with cellular structures to move chromosomes during cell division. This is a big responsibility for the kinetochore; if not moved properly, errors in the DNA could lead to deleterious genetic disorders or perhaps to cancer. A kinetochore needs a functional centromere so it can assemble on chromosomal DNA and get to work on its crucial role. The histone centromere protein A, or CENP-A, forms nucleosomes on centromeres. It serves as the site for kinetochores to form. CENP-A nucleosomes work with CENP-C, in the inner kinetochore, and this allows the kinetochore to be assembled so the chromatin to be copied. The kinetochore is used as a stable method of DNA recognition so mitosis can proceed. Once kinetochores are allowed to assemble on a chromosome, proteins gather and begin to build that aforementioned machine. In vertebrates, there can be over 100 proteins in one kinetochore. The inner kinetochore consists of proteins that interact with the chromatin's centromere. The outer kinetochores' proteins work to bind nonkinetochore microtubules. This is another difference between kinetochores and nonkinetochores. The assembly of the kinetochore is carefully conducted through the cell cycle so that once a cell enters mitosis, a dynamic assembly of the kinetochore can happen in minutes. Then the complex can disassemble as needed. The control of kinetochore assembly is assisted by phosphorylation. Kinetochores must work with many nonkinetochore microtubules directly. The complex called Ndc80 allows this interaction. It is a bit of a dance, as the microtubules are changing in length as they polymerize and depolymerize. The kinetochore must keep up. This "dance" generates force. During anaphase, the kinetochores get seized by nonkinetochore microtubules from the opposite poles and are pulled by those microtubules so the chromosomes can separate. The microtubule motors such as kinesin and dynein aid this. Additional force is generated when the microtubules depolymerize. The kinetochore acts as a controller of the microtubules' forces so it can line up chromosomes for segregation. The dynamic kinetochore is not just a tiny machine moving chromosomes apart. It also works as a check on quality control. Any mistakes made in the process could result in genetic errors. Kinetochores also work to stop faulty attachments with microtubules; this is aided by Aurora B kinase via phosphorylation. Near the core of centromeres, a protein complex called Pcs1/Mde4 works to prevent improper kinetochore attachments. For anaphase to happen properly, errors must be corrected, or else anaphase needs to be delayed. Proteins help to track down any of these errors; an error results in a signal at the kinetochore that results in the stopping of the cell cycle prior to anaphase. In sum, kinetochores differ from nonkinetochore microtubules in both structure and function. Both must work together to achieve successful cell division and conservation of DNA in new daughter cells. Hermance, Dianne. "The Differences Between Kinetochore & Nonkinetochore" sciencing.com, . 31 July 2019. APA Hermance, Dianne. (2019, July 31). The Differences Between Kinetochore & Nonkinetochore. sciencing.com. Retrieved from Chicago Hermance, Dianne. The Differences Between Kinetochore & Nonkinetochore last modified March 24, 2022. Share — copy and redistribute the material in any medium or format for any purpose, even commercially. Adapt — remix, transform, and build upon the material for any purpose, even commercially. The licensor cannot revoke these freedoms as long as you follow the license terms. Attribution — You must give appropriate credit , provide a link to the license, and indicate if changes were made . You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use. ShareAlike — If you remix, transform, or build upon the material, you must distribute your contributions under the same license as the original. No additional restrictions — You may not apply legal terms or technological measures that legally restrict others from doing anything the license permits. You do not have to comply with the license for elements of the material in the public domain or where your use is permitted by an applicable exception or limitation . No warranties are given. The license may not give you all of the permissions necessary for your intended use. For example, other rights such as publicity, privacy, or moral rights may limit how you use the material. In order to continue enjoying our site, we ask that you confirm your identity as a human. Thank you very much for your cooperation. Protein complex that allows microtubules to attach to chromosomes during cell division Image of kinetochores in pink A kinetochore (/kɪˈnɛtəkɔːr/, /-ˈniːtəkɔːr/) is a flared oblique-shaped protein structure associated with duplicated chromatids in eukaryotic cells where the spindle fibers, which can be thought of as the ropes pulling chromosomes apart, attach during cell division to pull sister chromatids apart.[1] The kinetochore assembles on the centromere and links the chromosome to microtubule polymers from the mitotic spindle during mitosis and meiosis. The term kinetochore was first used in a footnote in a 1934 Cytology book by Lester W. Sharp[2] and commonly accepted in 1936.[3] Sharp's footnote reads: "The convenient term kinetochore (= movement place) has been suggested to the author by J. A. Moore", likely referring to John Alexander Moore who had joined Columbia University as a freshman in 1932.[4] Monocentric organisms, including vertebrates, fungi, and most plants, have a single centromeric region on each chromosome which assembles a single, localized kinetochore. Holocentric organisms, such as nematodes and some plants, assemble a kinetochore along the entire length of a chromosome.[5] Kinetochores start, control, and supervise the striking movements of chromosomes during cell division. During mitosis, which occurs after the amount of DNA is doubled in each chromosome (while maintaining the same number of chromosomes) in S phase, two sister chromatids are held together by a centromere. Each chromatid has its own kinetochore, which face in opposite directions and attach to opposite poles of the mitotic spindle apparatus. Following the transition from metaphase to anaphase, the sister chromatids separate from each other, and the individual kinetochores on each chromatid drive their movement to the spindle poles that will define the two new daughter cells. The kinetochore is therefore essential for the chromosome segregation that is classically associated with mitosis and meiosis. The kinetochore contains two regions: an inner kinetochore, which is tightly associated with the centromere DNA and assembled in a specialized form of chromatin that persists throughout the cell cycle; an outer kinetochore, which interacts with microtubules; the outer kinetochore is a very dynamic structure with many identical components, which are assembled and functional only during cell division. Even the simplest kinetochores consist of more than 19 different proteins. Many of these proteins are conserved between eukaryotic species, including a specialized histone H3 variant (called CENP-A or CenH3) which helps the kinetochore associate with DNA. Other proteins in the kinetochore adhere it to the microtubules (MTs) of the mitotic spindle. There are also motor proteins, including both dynein and kinesin, which generate forces that move chromosomes during mitosis. Other proteins, such as Mad2, monitor the microtubule attachment as well as the tension between sister kinetochores and activate the spindle checkpoint to arrest the cell cycle when either of these is absent.[6] The actual set of genes essential for kinetochore function varies from one species to another.[7][8] Kinetochore functions include anchoring of chromosomes to MTs in the spindle, verification of anchoring, activation of the spindle checkpoint and participation in the generation of force to propel chromosome movement during cell division.[9] On the other hand, microtubules are metastable polymers made of α- and β-tubulin, alternating between growing and shrinking phases, a phenomenon known as dynamic instability.[10] MTs are highly dynamic structures, whose behavior is integrated with kinetochore function to control chromosome movement and segregation. It has also been reported that the kinetochore organization differs between mitosis and meiosis and the integrity of meiotic kinetochore is essential for meiosis specific events such as pairing of homologous chromosomes, sister kinetochore monoorientation, protection of centromeric cohesin and spindle-pole body cohesion and duplication.[11][12] The kinetochore is composed of several layers, observed initially by conventional fixation and staining methods of electron microscopy,[13][14] (reviewed by C. Rieder in 1982[15]) and more recently by rapid freezing and substitution.[16] Kinetochore structure and components in vertebrate cells. Based on Maiato et al. (2004).[9] The deepest layer in the kinetochore is the inner plate, which is organized on a chromatin structure containing nucleosomes presenting a specialized histone (named CENP-A, which substitutes histone H3 in this region), auxiliary proteins, and DNA. DNA organization in the centromere (satellite DNA) is one of the least understood aspects of vertebrate kinetochores. The inner plate appears like a discrete heterochromatin domain throughout the cell cycle. External to the inner plate is the outer plate, which is composed mostly of proteins. This structure is assembled on the surface of the chromosomes only after the nuclear envelope breaks down.[13] The outer plate in vertebrate kinetochores contains about 20 anchoring sites for MTs (+) ends (named kMTs, after kinetochore MTs), whereas a kinetochore's outer plate in yeast (Saccharomyces cerevisiae) contains only one anchoring site. The outermost domain in the kinetochore forms a fibrous corona, which can be visualized by conventional microscopy, yet only in the absence of MTs. This corona is formed by a dynamic network of resident and temporary proteins implicated in the spindle checkpoint, in microtubule anchoring, and in the regulation of chromosome behavior. During mitosis, each sister chromatid forming the complete chromosome has its own kinetochore. Distinct sister kinetochores can be observed at first at the end of G2 phase in cultured mammalian cells.[17] These early kinetochores show a mature laminar structure before the nuclear envelope breaks down.[18] The molecular pathway for kinetochore assembly in higher eukaryotes has been studied using gene knockouts in mice and in cultured chicken cells, as well as using RNA interference (RNAi) in C. elegans, Drosophila and human cells, yet no simple linear route can describe the data obtained so far.[citation needed] Fluorescence microscopy micrographs, showing the endogenous human protein Mad1 (one of the spindle checkpoint components) in green, along the different phases in mitosis; CENP-B, in red, is a centromeric marker, and DAPI (in blue) stains DNA The first protein to be assembled on the kinetochore is CENP-A (Cse4 in Saccharomyces cerevisiae). This protein is a specialized isoform of histone H3.[19] CENP-A is required for incorporation of the inner kinetochore proteins CENP-C, CENP-H and CENP-I/MIS6.[20][21][22][23][24] The relation of these proteins in the CENP-A-dependent pathway is not completely defined. For instance, CENP-C localization requires CENP-H in chicken cells, but it is independent of CENP-I/MIS6 in human cells. In C. elegans and metazoa, the incorporation of many proteins in the outer kinetochore depends ultimately on CENP-A. Kinetochore proteins can be grouped according to their concentration at kinetochores during mitosis: some proteins remain bound throughout cell division, whereas some others change in concentration. Furthermore, they can be recycled in their binding site on kinetochores either slowly (they are rather stable) or rapidly (dynamic). Proteins whose levels remain stable from prophase until late anaphase include constitutive components of the inner plate and the stable components of the outer kinetocore, such as the Ndc80 complex,[25][26] KNL/KBP proteins (kinetochore-null/KNL-binding protein),[27] MIS proteins[27] and CENP-F.[28][29] Together with the constitutive components, these proteins seem to organize the nuclear core of the inner and outer structures in the kinetochore. The dynamic components that vary in concentration on kinetochores during mitosis include the molecular motors CENP-E and dynein (as well as their target components ZW10 and ROD), and the spindle checkpoint proteins (such as Mad1, Mad2, BubR1 and Cdc20). These proteins assemble on the kinetochore in high concentrations in the absence of microtubules; however, the higher the number of MTs anchored to the kinetochore, the lower the concentrations of these proteins.[30] At metaphase, CENP-E, Bub3 and Bub1 levels diminish by a factor of about three to four as compared with free kinetochores, whereas dynein/dynactin, Mad1, Mad2 and BubR1 levels are reduced by a factor of more than 10 to 100.[30][31][32][33] Whereas the spindle checkpoint protein levels present in the outer plate diminish as MTs anchor,[33] other components such as EB1, APC and proteins in the Ran pathway (RanGap1 and RanBP2) associate to kinetochores only when MTs are anchored.[34][35][36][37] This may belong to a mechanism in the kinetochore to recognize the microtubules' plus-end (+), ensuring their proper anchoring and regulating their dynamic behavior as they remain anchored. A 2010 study used a complex method (termed "multiclassifier combinatorial proteomics" or MCCP) to analyze the proteomic composition of vertebrate chromosomes, including kinetochores.[38] Although this study does not include a biochemical enrichment for kinetochores, obtained data include all the centromeric subcomplexes, with peptides from all 125 known centromeric proteins. According to this study, there are still about one hundred unknown kinetochore proteins, doubling the known structure during mitosis, which confirms the kinetochore as one of the most complex cellular substructures. Consistently, a comprehensive literature survey indicated that there had been at least 196 human proteins already experimentally shown to be localized at kinetochores.[39] The number of microtubules attached to one kinetochore is variable: in Saccharomyces cerevisiae only one MT binds each kinetochore, whereas in mammals there can be 15–35 MTs bound to each kinetochore.[40] However, not all the MTs in the spindle attach to one kinetochore. There are MTs that extend from one centrosome to the other (and they are responsible for spindle length) and some shorter ones are interdigitated between the long MTs. Professor B. Nicklas (Duke University), showed that, if one breaks down the MT-kinetochore attachment using a laser beam, chromatids can no longer move, leading to an abnormal chromosome distribution.[41] These experiments also showed that kinetochores have polarity, and that kinetochore attachment to MTs emanating from one or the other centrosome will depend on its orientation. This specificity guarantees that only one chromatid will move to each spindle side, thus ensuring the correct distribution of the genetic material. Thus, one of the basic functions of the kinetochore is the MT attachment to the spindle, which is essential to correctly segregate sister chromatids. If anchoring is incorrect, errors may ensue, generating aneuploidy, with catastrophic consequences for the cell. To prevent this from happening, there are mechanisms of error detection and correction (as the spindle assembly checkpoint), whose components reside also on the kinetochores. The movement of one chromatid towards the centrosome is produced primarily by MT depolymerization in the binding site with the kinetochore. These movements require also force generation, involving molecular motors likewise located on the kinetochores. Chromosomes attach to the mitotic spindle through sister kinetochores, in a bipolar orientation During the synthesis phase (S phase) in the cell cycle, the centrosome starts to duplicate. Just at the beginning of mitosis, both centrioles in each centrosome reach their maximal length, centrosomes recruit additional material and their nucleation capacity for microtubules increases. As mitosis progresses, both centrosomes separate to establish the mitotic spindle.[42] In this way, the spindle in a mitotic cell has two poles emanating microtubules. Microtubules are long proteic filaments with asymmetric extremes, a "minus"(-) end relatively stable next to the centrosome, and a "plus"(+) end enduring alternate phases of growing-shrinking, exploring the center of the cell. During this searching process, a microtubule may encounter and capture a chromosome through the kinetochore.[43][44] Microtubules that find and attach a kinetochore become stabilized, whereas those microtubules remaining free are rapidly depolymerized.[45] As chromosomes have two kinetochores associated back-to-back (one on each sister chromatid), when one of them becomes attached to the microtubules generated by one of the cellular poles, the kinetochore on the sister chromatid becomes exposed to the opposed pole; for this reason, most of the times the second kinetochore becomes attached to the microtubules emanating from the opposing pole,[46] in such a way that chromosomes are now bi-oriented, one fundamental configuration (also termed amphitelic) to ensure the correct segregation of both chromatids when the cell will divide.[47][48] Scheme showing cell cycle progression between prometaphase and anaphase. (Chromosomes are in blue and kinetochores in light yellow). When just one microtubule is anchored to one kinetochore, it starts a rapid movement of the associated chromosome towards the pole generating that microtubule. This movement is probably mediated by the motor activity towards the "minus" (-) of the motor protein cytoplasmic dynein,[49][50] which is very concentrated in the kinetochores not anchored to MTs.[51] The movement towards the pole is slowed down as far as kinetochores acquire kMTs (MTs anchored to kinetochores) and the movement becomes directed by changes in kMTs length. Dynein is released from kinetochores as they acquire kMTs[30] and, in cultured mammalian cells, it is required for the spindle checkpoint inactivation, but not for chromosome congression in the spindle equator, kMTs acquisition or anaphase A during chromosome segregation.[52] In higher plants or in yeast there is no evidence of dynein, but other kinesins towards the (-) end might compensate for the lack of dynein. Metaphase cells with low CENP-E levels by RNAi, showing chromosomes unaligned at the metaphase plate (arrows). These chromosomes are labeled with antibodies against the mitotic checkpoint proteins Mad1/Mad2. Hec1 and CENP-B label the centromeric region (the kinetochore), and DAPI is a specific stain for DNA. Another motor protein implicated in the initial capture of MTs is CENP-E; this is a high molecular weight kinesin associated with the fibrous corona at mammalian kinetochores from prometaphase until anaphase.[53] In cells with low levels of CENP-E, chromosomes lack this protein at their kinetochores, which quite often are defective in their ability to congress at the metaphase plate. In this case, some chromosomes may remain chronically mono-oriented (anchored to only one pole), although most chromosomes may congress correctly at the metaphase plate.[54] It is widely accepted that the kMTs fiber (the bundle of microtubules bound to the kinetochore) is originated by the capture of MTs polymerized at the centrosomes and spindle poles in mammalian cultured cells.[43] However, MTs directly polymerized at kinetochores might also contribute significantly.[55] The manner in which the centromeric region or kinetochore initiates the formation of kMTs and the frequency at which this happens are important questions,[according to whom?] because this mechanism may contribute not only to the initial formation of kMTs, but also to the way in which kinetochores correct defective anchoring of MTs and regulate the movement along kMTs. MTs associated to kinetochores present special features: compared to free MTs, kMTs are much more resistant to cold-induced depolymerization, high hydrostatic pressures or calcium exposure.[56] Furthermore, kMTs are recycled much more slowly than astral MTs and spindle MTs with free (+) ends, and if kMTs are released from kinetochores using a laser beam, they rapidly depolymerize.[41] When it was clear that neither dynein nor CENP-E is essential for kMTs formation, other molecules should be responsible for kMTs stabilization. Pioneer genetic work in yeast revealed the relevance of the Ndc80 complex in kMTs anchoring.[25][57][58][59] In Saccharomyces cerevisiae, the Ndc80 complex has four components: Ndc80p, Nuf2p, Spc24p and Spc25p. Mutants lacking any of the components of this complex show loss of the kinetochore-microtubule connection, although kinetochore structure is not completely lost.[25][57] Yet mutants in which kinetochore structure is lost (for instance Ndc10 mutants in yeast[60]) are deficient both in the connection to microtubules and in the ability to activate the spindle checkpoint, probably because kinetochores work as a platform in which the components of the response are assembled. The Ndc80 complex is highly conserved and it has been identified in S. pombe, C. elegans, Xenopus, chicken and humans.[25][26][57][61][62][63][64] Studies on Hec1 (highly expressed in cancer cells 1), the human homolog of Ndc80p, show that it is important for correct chromosome congression and mitotic progression, and that it interacts with components of the cohesin and condensin complexes.[65] Different laboratories have shown that the Ndc80 complex is essential for stabilization of the kinetochore-microtubule anchoring, required to support the centromeric tension implicated in the establishment of the correct chromosome congression in high eukaryotes.[26][62][63][64] Cells with impaired function of Ndc80 (using RNAi, gene knockout, or antibody microinjection) have abnormally long spindles, lack of tension between sister kinetochores, chromosomes unable to congregate at the metaphase plate and few or any associated kMTs. There is a variety of strong support for the ability of the Ndc80 complex to directly associate with microtubules and form the core conserved component of the kinetochore-microtubule interface.[66] However, formation of robust kinetochore-microtubule interactions may also require the function of additional proteins. In yeast, this connection requires the presence of the complex Dam1-DASH-DDD. Some members of this complex bind directly to MTs, whereas some others bind to the Ndc80 complex.[58][59][67] This means that the complex Dam1-DASH-DDD might be an essential adapter between kinetochores and microtubules. However, in animals an equivalent complex has not been identified, and this question remains under intense investigation. During S-Phase, the cell duplicates all the genetic information stored in the chromosomes, in the process termed DNA replication. At the end of this process, each chromosome includes two sister chromatids, which are two complete and identical DNA molecules. Both chromatids remain associated by cohesin complexes until anaphase, when chromosome segregation occurs. If chromosome segregation happens correctly, each daughter cell receives a complete set of chromatids, and for this to happen each sister chromatid has to anchor (through the corresponding kinetochore) to MTs generated in opposed poles of the mitotic spindle. This configuration is termed amphitelic or bi-orientation. However, during the anchoring process some incorrect configurations may also appear:[68] Scheme showing different anchoring configurations between chromosomes and the mitotic spindle.[55] monotelic: only one of the chromatids is anchored to MTs, the second kinetochore is not anchored; in this situation, there is no centromeric tension, and the spindle checkpoint is activated, delaying entry in anaphase and allowing time for the cell to correct the error. If it is not corrected, the unanchored chromatid might randomly end in any of the two daughter cells, generating aneuploidy: one daughter cell would have chromosomes in excess and the other would lack some chromosomes. syntelic: both chromatids are anchored to MTs emanating from the same pole; this situation does not generate centromeric tension either, and the spindle checkpoint will be activated. If it is not corrected, both chromatids will end in the same daughter cell, generating aneuploidy. merotelic: at least one chromatid is anchored simultaneously to MTs emanating from both poles. This situation generates centromeric tension, and for this reason the spindle checkpoint is not activated. If it is not corrected, the chromatid bound to both poles will remain as a lagging chromosome at anaphase, and finally will be broken in two fragments, distributed between the daughter cells, generating aneuploidy. Both the monotelic and the syntelic configurations fail to generate centromeric tension and are detected by the spindle checkpoint. In contrast, the merotelic configuration is not detected by this control mechanism. However, most of these errors are detected and corrected before the cell enters in anaphase.[68] A key factor in the correction of these anchoring errors is the chromosomal passenger complex, which includes the kinase protein Aurora B, its target and activating subunit INCENP and two other subunits, Survivin and Borealin/Dasra B (reviewed by Adams and collaborators in 2001[69]). Cells in which the function of this complex has been abolished by dominant negative mutants, RNAi, antibody microinjection or using selective drugs, accumulate errors in chromosome anchoring. Many studies have shown that Aurora B is required to destabilize incorrect anchoring kinetochore-MT, favoring the generation of amphitelic connections. Aurora B homolog in yeast (Ipl1p) phosphorilates some kinetochore proteins, such as the constitutive protein Ndc10p and members of the Ndc80 and Dam1-DASH-DDD complexes.[70] Phosphorylation of Ndc80 complex components produces destabilization of kMTs anchoring. It has been proposed that Aurora B localization is important for its function: as it is located in the inner region of the kinetochore (in the centromeric heterochromatin), when the centromeric tension is established sister kinetochores separate, and Aurora B cannot reach its substrates, so that kMTs are stabilized. Aurora B is frequently overexpressed in several cancer types, and it is currently a target for the development of anticancer drugs.[71] Main article: Spindle checkpoint The spindle checkpoint, or SAC (for spindle assembly checkpoint), also known as the mitotic checkpoint, is a cellular mechanism responsible for detection of: correct assembly of the mitotic spindle; attachment of all chromosomes to the mitotic spindle in a bipolar manner; congression of all chromosomes at the metaphase plate. When just one chromosome (for any reason) remains lagging during congression, the spindle checkpoint machinery generates a delay in cell cycle progression: the cell is arrested, allowing time for repair mechanisms to solve the detected problem. After some time, if the problem has not been solved, the cell will be targeted for apoptosis (programmed cell death), a safety mechanism to avoid the generation of aneuploidy, a situation which generally has dramatic consequences for the organism. Whereas structural centromeric proteins (such as CENP-B), remain stably localized throughout mitosis (including during telophase), the spindle checkpoint components are assembled on the kinetochore in high concentrations in the absence of microtubules, and their concentrations decrease as the number of microtubules attached to the kinetochore increases.[30] At metaphase, CENP-E, Bub3 and Bub1 levels decreases 3 to 4 fold as compared to the levels at unattached kinetochores, whereas the levels of dynein/dynactin, Mad1, Mad2 and BubR1 decrease >10-100 fold.[30][31][32][33] Thus at metaphase, when all chromosomes are aligned at the metaphase plate, all checkpoint proteins are released from the kinetochore. The disappearance of the checkpoint proteins out of the kinetochores indicates the moment when the chromosome has reached the metaphase plate and is under bipolar tension. At this moment, the checkpoint proteins that bind to and inhibit Cdc20 (Mad1-Mad2 and BubR1), release Cdc20, which binds and activates APC/CCdc20, and this complex triggers sister chromatids separation and consequently anaphase entry. Several studies indicate that the Ndc80 complex participates in the regulation of the stable association of Mad1-Mad2 and dynein with kinetochores.[26][63][64] Yet the kinetochore associated proteins CENP-A, CENP-C, CENP-E, CENP-H and BubR1 are independent of Ndc80/Hec1. The prolonged arrest in prometaphase observed in cells with low levels of Ndc80/Hec1 depends on Mad2, although these cells show low levels of Mad1, Mad2 and dynein on kinetochores (