Science 26 May 2000:
Vol. 288. no. 5470, pp. 1379 - 1384
DOI: 10.1126/science.288.5470.1379

REVIEW

Splitting the Chromosome: Cutting the Ties That Bind Sister Chromatids

Kim Nasmyth, * Jan-Michael Peters, Frank Uhlmann

In eukaryotic cells, sister DNA molecules remain physically connected from their production at S phase until their separation during anaphase. This cohesion is essential for the separation of sister chromatids to opposite poles of the cell at mitosis. It also permits chromosome segregation to take place long after duplication has been completed. Recent work has identified a multisubunit complex called cohesin that is essential for connecting sisters. Proteolytic cleavage of one of cohesin's subunits may trigger sister separation at the onset of anaphase.

Research Institute of Molecular Pathology (IMP), Dr. Bohr-Gasse 7, A-1030 Vienna, Austria.
* To whom correspondence should be addressed. E-mail: nasmyth@nt.imp.univie.ac.at

BACK TO BASICS: CHROMOSOME MECHANICS

Instructions for the behavior of every cell in the bodies of worms, flies, and humans will soon reside in public databases for all to read. A complete set of such instructions, packaged as chromosomes, is inherited by most cells in our body. Because of this, many if not most somatic nuclei in mammals are totipotent; that is, they are capable of programming all of mammalian development when injected into enucleated eggs (1). The cloning of Dolly had dramatic practical consequences, but its feasibility was never improbable on theoretical grounds. How cells inherit two complete packages of the genome at each cell division is one of the most fundamental questions in biology (Fig. 1A).

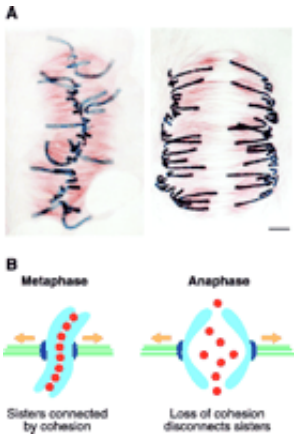

Fig. 1. The metaphase-to-anaphase transition. (**A**) Light micrographs of mitotic figures in endosperm of the African blood lily *Haemanthus katherinae* Bak. Microtubules are stained in red and chromosomes in blue. In metaphase (left), centromere regions are aligned on the spindle equator, whereas in anaphase (right), the arms of separated sister chromatids trail behind centromere regions, which move poleward. Bar, 10 μm. [Reprinted from (97) with permission] (**B**) A model depicting how cohesion structures (red dots) physically connect sister chromatids (light blue) during metaphase. Cohesion antagonizes the pulling forces exerted by spindle microtubules (green) on kinetochores (dark blue). During anaphase, loss of cohesion liberates sister chromatids for poleward movement. [View Larger Version of this Image (74K GIF file)]

Recent studies of the chromosome cycle have concentrated on control mechanisms, such as the crucial part played by cyclin-dependent protein kinases in triggering chromosome duplication and segregation (2) and surveillance mechanisms (checkpoints) that monitor the fidelity of these two processes (3). This focus on "control" is, however, a recent phenomenon. Earlier studies, largely cytological in nature, concentrated on the mechanics of chromosome segregation (4–7). What, for example, was "the nature of the initial act of doubling of the spireme thread (chromosome)" (5, p. 109), and how were the sister threads moved to opposite poles of the cell during mitosis?

The elucidation of DNA's structure largely answered the first of these questions (8), and work on cytoskeletal proteins like tubulin and the spindle fibers assembled from it has gone a long way toward solving the mystery of chromosome movement. In contrast, until recently the mechanisms by which sister chromatids are tied together after chromosome duplication and then separated at the metaphase-to-anaphase transition was largely neglected, despite being equally crucial for the mitotic process (9).

IMPORTANCE OF SISTER COHESION

The ability of eukaryotic cells to delay segregation of chromosomes until long after their duplication distinguishes their cell cycle from that of bacteria, in which chromosome segregation starts soon after the initiation of DNA replication (10). This temporal separation forms the basis for the cell cycle's partition into four phases--G_1, S, G_2, and M--and it has played a central role in the evolution of eukaryotic organisms. Meiosis, during which two rounds of chromosome segregation follow a single round of duplication, requires separable S and M phases. Furthermore, mitotic chromosome condensation, without which large genomes cannot be partitioned between daughter cells at cell division, would not be possible if chromosome segregation coincided with DNA replication. A gap between S and M phases therefore made possible the evolution of large genomes. It is sister chromatid cohesion that permits chromosome segregation to take place long after duplication. Cohesion provides a memory of a duplication process that may have occurred long ago (up to

50 years in the case of human oocytes)--a memory that defines which chromatids within a nucleus are to be parted from each other at cell division. Were chromatids to drift apart before building a mitotic spindle, there would be no way for cells to determine whether chromatids were sisters (to be segregated to opposite poles) as opposed to being merely homologous chromosomes, a distinction that is crucial for all diploid organisms.

The structures holding sister chromatids together are responsible for generating bilaterally symmetrical chromosomes during mitotic divisions. The bilateral symmetry of chromosomes underlies the symmetry of the spindle apparatus and hence forms the basis for the exact and symmetrical partition of chromosomes and the roughly equal partition of most other cell constituents at cell division. In addition, tying sister chromatids together generates a centromere geometry that favors the attachment of sister kinetochores to spindles that extend to opposite poles. Only those kinetochore-spindle connections that result in tension are stabilized, which enables the chromosome alignment process to be proofread (11). Despite its importance, the mechanism by which sister chromatids are tied together is still poorly understood.

CHROMATID SEPARATION INDEPENDENT OF THE SPINDLE APPARATUS

The chromatid separation process has also remained mysterious. It is an autonomous process that does not directly depend on the mitotic spindle (5, 7). This is most vividly seen in cells whose spindles have been destroyed by spindle poisons such as colchicine. In many organisms, in particular in plant cells, the cell cycle delay induced by colchicine is only transient, and chromatids eventually split apart in the complete absence of a mitotic spindle (12, 13) (Fig. 2). Mitosis in the presence of colchicine or colcemid (known as c-mitosis) leads to the production of daughter cells with twice the normal complement of chromosomes. This process is routinely used for manipulating plant genomes and may contribute to the therapeutic effects of Taxol in treating breast cancer.

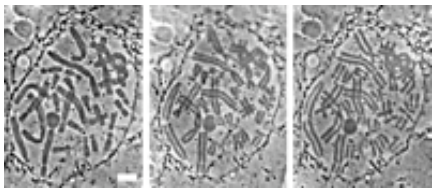

Fig. 2. Sister chromatid separation does not depend on the mitotic spindle. Light micrographs of mitosis in living flattened endosperm from *H. katherinae* Bak treated with colchicine (cmitosis). The micrographs were taken at 10-min intervals. Bar, 10 μm. [Reprinted from (12) with permission] [View Larger Version of this Image (103K GIF file)]

A TENSE PERIOD IN THE CELL CYCLE

Changes in the interaction between sister chromatids, as opposed to changes in the activity of spindle fibers, are thought to trigger the sudden movement of chromatids to the poles at the metaphase-to-anaphase transition. Destroying the spindle fiber that connects a chromosome to one pole by using ultraviolet (14) or laser microbeams (15) causes the entire chromosome (i.e., both chromatids) to move rapidly to the opposite pole. The implication is that sister chromatid pairs on the metaphase plate are under tension. Sisters are being pulled away from each other by spindles attached to oppositely oriented sister kinetochores. The apparatus that will move chromatids to

the poles during anaphase is therefore already engaged during metaphase. Metaphase is therefore viewed as a state of equilibrium in which traction exerted on kinetochores by spindle fibers is opposed by cohesion between sister chromatids (Fig. 1B) (7).

Loss of sister chromatid cohesion would therefore be sufficient for the sudden movement of chromatids to opposite poles at the metaphase-to-anaphase transition. According to this hypothesis, a specific apparatus binds chromatids together during replication, holds them in an orientation that facilitates the attachment of sister kinetochores to spindles extending to opposite poles, and resists the splitting force that results from this bipolar attachment to the spindle. Destruction of this specialized cohesive structure triggers movement of chromatids to opposite poles at the onset of anaphase.

In the absence of molecular details, this notion has remained a working hypothesis only. Indeed, until recently there has been little direct evidence that chromosome separation is due to the loss of cohesion as opposed to the onset of chromatid repulsion (7, 16). An affinity between sister chromatids might be sufficient to resist their tendency to be split by spindle forces up to and during metaphase. Anaphase could be triggered by a repulsive force that overcomes the sister's "natural" affinity. The notion that the midzone of anaphase spindles [or Belar's Stemmkörper (17)] might exert this repulsion is now discredited, but unknown repulsive forces may yet lurk in the crevices between sisters.

TIES THAT BIND CHROMATIDS TOGETHER

In many organisms, the regions around centromeres have a special role in holding sister chromatids together during metaphase. Flourescence in situ hybridization shows that most sister DNA sequences separate from each other (at least a short distance) soon after DNA replication (18). Nevertheless, sister chromatids usually do not acquire morphologically separate axes until prometaphase, well after the onset of chromosome condensation. Human chromosomes, for example, appear as undivided "sausages" during prophase even though they are already highly condensed (19) (Fig. 3A). When sister chromatid arms eventually emerge as separate entities during prometaphase, sister centromeric sequences still hug each other in a compact embrace known as the central constriction (Fig. 3, B and C). When late-mitotic events are inhibited by treatment with spindle poisons, separation of arm sequences continues while that of centromeres is blocked (20). The consequence is sister chromatid pairs connected only at centromeres, which though an artefact of drug treatment, is a classic image of mitotic chromosomes.

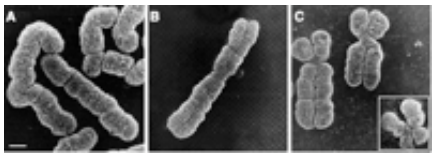

Fig. 3. Chromosome arms begin to separate in prometaphase. Scanning electron micrographs of human chromosomes isolated from cells in prophase (**A**), prometaphase (**B**), metaphase (**C**), and early anaphase [inset in (C)]. Bar, 1 μm. [Reprinted from (19) with permission] [View Larger Version of this Image (71K GIF file)]

The robust cohesion at centromeres may be due more to their heterochromatic nature than to their ability to form attachments to the mitotic spindle. Other heterochromatic chromosome domains, like the entire Y chromosome in flies, also remain tightly stuck together during mitotic arrest (21). A relation between heterochromatin and stickiness is also seen during normal mitoses. Human chromatid pairs move to the poles during anaphase with different kinetics, and the laggards are invariably chromosomes with the greatest amount of centromeric heterochromatin (22).

Despite the extra stickiness of centromeres, it is often this region which splits first at the onset of a normal anaphase. Traction exerted at centromeres peels sisters apart, with distal regions of chromosome arms being the last to separate (5, 20). In several organisms, including budding yeast (23, 24), diatoms (25), and the crustacean *Ulophysema öresundense* (26), sister centromeres are pulled most of the way to the poles even during metaphase, long before arm sequences separate. In these organisms, it appears that loss of cohesion along chromosome arms and not at centromeres is what triggers anaphase (20).

Despite these valuble insights, over a century of cytological observation has shed little light on the identity of the sister chromatid cohesion apparatus. In the absence of a biochemical approach, one way forward was inspired guesswork. Once it appeared likely that chromosomes contained one double-stranded DNA molecule, it was proposed that the central constriction might be due to the late replication of centromeric DNA. However, pulse-labeling experiments suggest that little or no DNA is replicated during mitosis (27). Another ingenious idea is that sister chromatids are held together by the intertwining (catenation) of sister DNA molecules that arises when two replication forks converge (28). According to this notion, increased topoisomerase II (Topo II) activity triggers the final decatenation of sister DNA molecules at the onset of anaphase. Though Topo II is clearly essential to disentangle chromatids (29), there is evidence for an independent cohesion apparatus. First, circular mini-chromosomes in yeast are held together in nocodazole-treated cells without any intertwining of sister molecules (30). Second, centromeres (though not entire chromosomes) disengage from each other and move to the poles in the absence of any detectable Topo II activity in fission yeast (31). Third, addition of Topo II inhibitors to mammalian cells in metaphase fails to block separation of sister centromeres at the onset of anaphase (32, 33).

COHESIN AND ITS FRIENDS

Genetics is the method of last resort when other approaches reach their limits. The identification of mutants such as desynaptic in maize (34) and MeiS332 in *Drosophila* (35, 36), in which sister chromatids dissociate prematurely during meiosis, provided the first inkling that sister chromatid cohesion might be mediated by special proteins (37). Despite its important role during meiosis, MeiS332 is dispensable for mitotic divisions and is therefore unlikely to be a universal component of the cohesion apparatus.

Genetic studies in yeast have meanwhile uncovered a multisubunit complex called cohesin that is essential for sister chromatid cohesion not only in yeast (38) but also

in vertebrates (39). An important breakthrough in the identification of cohesin was the discovery that proteolysis (40), mediated by a ubiquitin protein ligase responsible for destroying mitotic cyclins (41, 42), is needed for sister chromatid separation. This ligase, known as the anaphase-promoting complex (APC) or cyclosome (43), was initially thought to mediate proteolysis of cohesion proteins. Its role in sister chromatid separation turns out to be less direct; it in fact mediates destruction of an inhibitor of the sister-separating apparatus (44–47). Nevertheless, the premise that the APC destroyed cohesion proteins provided a new impetus to the search for proteinaceous bridges connecting sister chromatids. Screens for mutations that permitted separation of sister chromatids in cells lacking APC activity have now identified at least eight proteins essential for sister chromatid cohesion (38, 48–51). Remarkably, the function of all these proteins seem to be intimately connected (Fig. 4A).

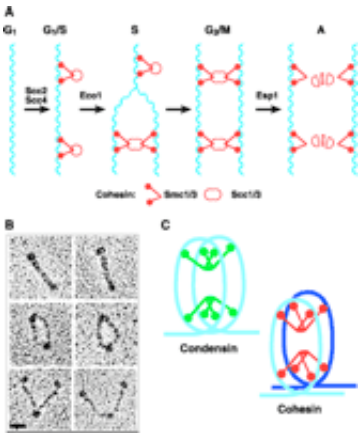

Fig. 4. Cohesin and friends. (**A**) A model illustrating how yeast proteins required for cohesion connect sister chromatids during DNA replication and maintain this association until the onset of anaphase. (**B**) Electron micrographs of homodimers of the *Bacillus subtilis* SMC protein. Three commonly observed conformations are shown. Bar, 20 nm. [Reprinted from (63) with permission] (**C**) A speculative model for how cohesin might join sister chromatids together, which is based on the premise that cohesin forms large supercoiled loops analogous to those proposed for condensin (shown alongside). [View Larger Version of this Image (55K GIF file)]

Four of these proteins, Smc1, Smc3, Scc1 (also called Mcd1 and Rad21), and Scc3, form a multisubunit complex called cohesin (38, 39). Indeed, Mcd1/Scc1 was independently isolated as a dosage suppressor of an Smc1 mutation (49). All four cohesin subunits are required both for establishing cohesion during S phase and (at least in yeast) for maintaining it until the onset of anaphase. Two other proteins, Scc2 (Mis4) and Scc4, form a separate complex that is required for the association of cohesin with chromosomes (52). Cohesin binds to specific chromosomal loci (including centromeres) for much of interphase (53–55), but it can only establish cohesion between sister chromatids during DNA replication, possibly when sister DNA molecules emerge from replication forks (56). Establishment of sister cohesion is therefore an integral part of S phase.

Another protein, Spo76, is required for orderly sister chromatid cohesion in *Sordaria* (57), a genus of fungi. Spo76 has homologs in many organisms, called Pds5 in budding yeast (58) and BimD in *Aspergillus nidulans* (59). It is not yet understood how Spo76/Pds5 cooperates with cohesin. In budding yeast a protein called Eco1 or Ctf7 is essential for establishing cohesion during S phase but not for maintaining it during G_2 or M phases (38, 51). Its fission yeast homolog Eso1 is also required for establishing

sister chromatid cohesion (60). Of all known cohesion proteins, the cohesin complex may lie at the heart of the cohesion process because cleavage of one of its subunits is essential for the separation of sister chromatids, at least in yeast (61). *Xenopus* cohesin is also needed for proper sister chromatid cohesion (39). Nevertheless, it is still uncertain how, or indeed whether, cohesin holds sisters together during metaphase in animal cells, as most of it dissociates from chromosomes by prometaphase (39). It is therefore possible that other important players remain to be identified.

Two cohesin subunits, Smc1 and Smc3, are members of a large family of related proteins whose evolution predates the split between eukaryotes and bacteria (62). All Smc proteins have related globular domains at their NH_2- and COOH-termini, joined by two long stretches of α-helical coiled-coil, which are linked by a central flexible hinge. Bacterial Smc proteins form antiparallel homodimers whose terminal globular domains are proposed to form an active adenosine triphosphatase (ATPase). The flexibility of the hinge region allows the Smc homodimer to adopt either a V or a linear shape (Fig. 4B) (63). It remains to be seen whether cohesin contains an Smc1/Smc3 heterodimer or Smc1 and Smc3 homodimers.

Little is known about the properties of cohesin in vitro, except that fragments from the COOH-terminal domain of Smc3 and its coiled-coil region can bind DNA (64). Smc1 and Smc3 belong to a subfamily of eukaryotic Smc proteins, which includes Smc2 and Smc4. The latter two proteins are components of the condensin complex, which is necessary for mitotic chromosome condensation (65–67). Condensin possesses ATPase activity and is capable of forming large supercoiled loops by introducing a global positive writhe (68). These positive supercoils might be the driving force for mitotic chromosome condensation. The presence of a pair of Smc proteins in both condensin and cohesin suggests that these two complexes might have similar although not identical activities. Cohesin might, for example, introduce large constrained supercoils, like those produced by condensin, at equivalent positions on each sister chromatid. The Scc1 subunit of cohesin might help link together equivalent coils from each sister (Fig. 4C). An ability to coil chromosomes would explain how cohesin contributes to chromosome compaction (49).

In animal cells, condensin binds to chromosomes at about the same time that most cohesin dissociates from them (39), between prophase and prometaphase. It is possible that condensin's ability to condense chromosomes as cells enter mitosis depends on the prior dissociation of most cohesin. The connections between sister DNA molecules might otherwise interfere with the locally processive coiling of each chromatid on itself. Cohesin could also contribute to chromosome compaction during interphase and early stages of mitosis by providing longitudinal links along chromatids as well as horizontal ones between sisters (49).

SECURIN: A PROTEIN WHOSE DESTRUCTION BY THE APC CONTROLS SISTER CHROMATID SEPARATION

Destruction of mitotic cyclins occurs at or shortly before sister chromatid separation but is not required for this process (40, 69). The discovery that the ubiquitin protein

ligase responsible for destroying cyclins was also required for separating sister chromatids (41) led to a hunt for other APC targets whose destruction might be necessary for sister separation. Two candidates soon emerged: Pds1 from budding yeast and Cut2 from fission yeast. Destruction of Pds1 and Cut2 proteins at the onset of anaphase depends on APC and is essential for sister chromatid separation (44–46). Although these two proteins have rather dissimilar primary sequences, it appears that they are members of a class of anaphase-inhibitory proteins existing in all eukaryotes and now called securins because of their role in controlling the onset of sister separation (Fig. 5).

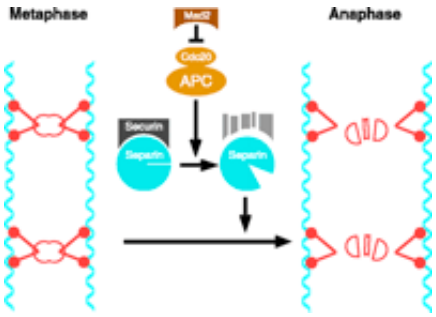

Fig. 5. The APC–separin pathway. A model illustrating how APC^{Cdc20} initiates anaphase through the activation of separin and subsequent cleavage of a cohesin subunit. [View Larger Version of this Image (19K GIF file)]

The human securin protein (70) is overproduced in many tumor cells (71) and is thought to be an oncogene (72). Increased securin levels might cause missegregation of chromosomes and thereby facilitate genome instability. A possible candidate for the securin homolog in *Drosophila* is the pimples protein, which like yeast and vertebrate securins is destroyed at the metaphase-to-anaphase transition (73). In budding yeast, Pds1 is only essential for proliferation at high temperatures (74), and its elimination permits sister separation in the absence of APC activity (44, 47). So, destruction of securin might be the APC's sole role in the triggering of sister separation, at least in yeast.

SEPARIN: AN ENDOPEPTIDASE NECESSARY FOR SEPARATING CHROMATIDS?

The budding yeast securin has what appears to be a single stable partner, a 180-kD protein called Esp1 (47). In fission yeast, Cut2 had previously been found to be associated with Cut1, an Esp1 homolog (75). Vertebrate securins are likewise associated with an Esp1 homolog (70). Esp1/Cut1–like proteins, now known as separins, are found in most if not all eukaryotes. They are usually large proteins, with molecular sizes from 180 to 200 kD, containing a conserved COOH-terminal "separin" domain. In budding yeast (47, 76), fission yeast (75), and *Aspergillus* (77), separins are essential for sister chromatid separation. Despite failing to separate sister chromatids, separin mutants proceed with most if not all other aspects of the cell cycle. It has been proposed that separins are dedicated "sister-separating" proteins whose activity is held in check by their association with securins. According to this hypothesis, the APC mediates sister chromatid separation by liberating separin from its inhibitory embrace by securin (Fig. 5) (47).

A clue to the mechanism by which separin splits sister chromatids was the observation that in budding yeast (contrary to most other eukaryotic cells) most Scc1 remains

bound to chromosomes until the metaphase-to-anaphase transition (48). The dissociation of Scc1 from chromosomes at the onset of anaphase depends on separin (47) and is accompanied by the proteolytic cleavage of Scc1, both in vivo and in vitro (61). Separin induces Scc1 cleavage at two related sites, each with an arginine in the P1 position. Mutation of either arginine to aspartic acid abolishes cleavage at that site but is not lethal to the cell. However, simultaneous mutation of both sites is lethal and prevents both sister chromatid separation and Scc1's dissociation from chromosomes (61). Similar potential cleavage sites are found in Rad21, the fission yeast Scc1 homolog, and their simultaneous (but not single) mutation also blocks chromosome segregation (78). Cleavage of cohesin's Scc1 subunit might therefore be a conserved feature of sister chromatid separation, at least in fungi (Fig. 5).

With the recent addition of several other separins to the databases, the conserved amino acid residues within the separin domain have been identified. They include a universally conserved histidine and cysteine residue, which is a hallmark of cysteine endopeptidases (79). The sequences flanking these two residues are characteristic of cysteine endopeptidases of the CD subclass, which includes caspases, legumains, and two bacterial proteases, gingipain and clostripain, (80). Thus, separin might indeed be the protease that cleaves Scc1. Whether cohesin's Scc1 subunit is the sole target of separin is presently unclear but certainly possible, for the only other yeast protein to contain good matches to the Scc1/Rad21 consensus is Rec8, a related protein that replaces Scc1 in the cohesin complex during meiosis (81). It will be crucial to address whether cleavage of Scc1 alone is sufficient to trigger anaphase in yeast and whether sister separation in animal and plant cells also depends on cleavage of cohesion proteins.

The proposed COOH-terminal catalytic domain of separin depends (at least for in vivo activity) on a long NH_2-terminal domain, which is bound by its inhibitory securin chaperone (82). Securin must do more than just inhibit separin, because sister separation fails to occur in cut2 (75) and pimples (73) mutants and is inefficient in pds1 securin mutants (47). Securin might either target separin to its future sites of action in the cell or help separin adopt a potentially active conformation, which is only unleashed on the cell when securins are destroyed by the APC.

CUTTING THE GORDIAN KNOT

Could proteolytic cleavage of a cohesin subunit really be a universal trigger for sister separation? If so, how does one explain the dissociation of the bulk of cohesin from chromosomes during prometaphase in organisms other than yeast (39)? In vertebrates, this process clearly occurs in the absence of APC activity and is therefore presumably not due to separin activity (83). The implication is that two separate pathways must exist for removing cohesin from chromosomes: one, thus far detected only in yeast, involving Scc1 cleavage at the metaphase-to-anaphase transition; and a second, possibly absent in yeast, that removes cohesin from chromosomes during prometaphase in the absence of cleavage (Fig. 6). It is of course possible that Scc1 is simply not cleaved at all by separin in animal cells and that some as yet unidentified cohesion protein that does indeed persist on chromosomes until metaphase is

separin's true target. Given the conservation of cell cycle mechanisms, it seems more likely that eukaryotic cells in fact possess both the cleavage and noncleavage cohesin-removal pathways and that separin's target is a residual amount of Scc1 associated with metaphase chromosomes, in particular in centromeric regions. Consistent with this hypothesis, a small fraction of cohesin remains associated with metaphase chromosomes in human cells, and a similar fraction of Scc1 is cleaved around anaphase (84). Let us therefore explore this working hypothesis further, bearing in mind that what applies to cohesin could equally apply to other as yet unidentified cohesion proteins.

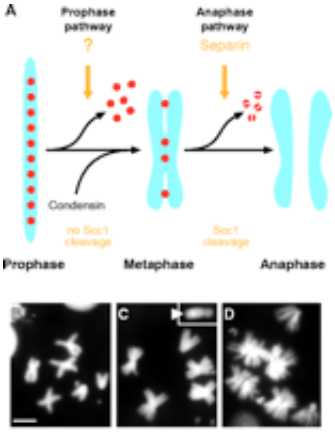

Fig. 6. (**A**) A two-step model for the sequential loss of sister chromatid cohesion in animal cells. The bulk of cohesion proteins may be removed from condensing chromosomes during prophase by a separin-independent pathway, which might involve mitotic kinases such as Cdk1, Polo, and Aurora. Activation of the separin pathway then initiates anaphase by cleaving residual cohesion proteins that remain on chromosomes, in particular at centromeres. (**B** to **D**) Mitotic chromosomes from wild-type *Drosophila* cells (B) and pimples mutant cells after one (C) and two (D) rounds of re-replication after possible failure of the separin pathway. [Reprinted from (73) with permission] Chromatids of autosomes are held together solely in pericentric heterochromatic regions but along the entire Y chromosome [inset in (C)]. Bar, 5 μm. [View Larger Version of this Image (47K GIF file)]

The noncleavage pathway would remove most cohesin during prophase/prometaphase by an as yet obscure mechanism. This pathway could involve phosphorylation of a cohesin subunit by mitotic protein kinases, because vertebrate cohesins rebind to chromatin in telophase when mitotic kinases are inactivated and chromosomes decondense (39). The dissociation of cohesin from chromatin during prophase coincides with, but does not depend on, the association of condensin with chromosomes. This first phase of cohesin removal may be crucial (possibly along with the arrival of condensin) for the initial splitting of chromosomes into two morphologically separable chromatids.

Although it commences during prophase, the noncleavage pathway possibly does not complete its task before separins are activated after congression of all chromatid pairs to the metaphase plate. This would explain why cohesion between chromosome arms is the last to be peeled away during undisturbed mitoses and why arm cohesion appears to be sufficient for orderly chromosome segregation when centromeric cohesion has been destroyed by a laser beam (20). Nevertheless, given sufficient time, the noncleavage pathway is capable of removing all cohesin from chromosome arms, which explains why sister chromatid arms fully separate whereas centromeres remain connected in cells treated with spindle poisons (13) or in *Drosophila* mutants lacking either the APC activator Fizzy/Cdc20 (21) or the putative securin pimples (Fig. 6B) (73).

According to our hypothesis, something prevents the full removal of cohesin from heterochromatic regions, including all centromeres, where the interface between sister chromatids during metaphase is far more extensive than along chromosome arms (85, 86). The final disentanglement of sister chromatids can only be achieved by cleavage of the "gordian knot" by separin. If as proposed by this hypothesis, cleavage of Scc1-like proteins is crucial for the final act of sister separation in all eukaryotic cells, this Achilles heal of the cohesion system deserves a nobler name ("gordin," for example) than the current ragbag of three-letter words inherited from different organisms. It is currently unclear what property of heterochromatin might protect cohesin (or other cohesion proteins for that matter) from the noncleavage dissociation pathway during metaphase. It is possible that the fairly widespread pathological phenomenon of premature centromere division (87), which is thought to cause aneuploidy and is found in patients with Roberts syndrome (88), might be caused by centromeric cohesion becoming susceptible to the noncleavage pathway.

CONTROLLED CUTTING

As Mazia noted in 1961, "metaphase strikes us as an interruption of the flow of events, during which the mitotic apparatus is waiting for something to happen" and that "chromosome splitting can be viewed as an event timed by a signal given by the cell and one that that does not depend on the mitotic apparatus" (7, p. 233). Mazia's "signal" is presumably the liberation of separin from its inhibition by securin. If so, what initiates this process? Time-lapse photography of mitosis supplied the answer: "Chromosomes that have already reached the equator wait for chromosomes delayed at one pole" (i.e., those that have not yet formed bipolar attachments to the spindle) "and only when the metaphase plate contains all the chromosomes does anaphase begin" (7, p. 268). This is a fairly clear description written over 40 years ago of the chromosome-alignment surveillance mechanism, which is also called the spindle assembly checkpoint (89). In most, but not all, eukaryotic cells, unaligned or lagging chromosomes transmit a signal by way of the protein Mad2, which inhibits the APC and its activator protein Cdc20 and thereby prevents the proteolysis of both B-type cyclins and securins. It is the block to securin destruction that prevents Scc1 cleavage and thereby sister chromatid separation (Fig. 5) (90).

The Mad2 pathway is thought to be essential for regulating mitosis in somatic cells of many organisms. In its absence, chromatin bridges, lagging chromosomes, and chromosome fragmentation are observed during anaphase (91). Most tumor cells are highly aneuploid and moreover have unstable karyotypes, which might be caused by defects in the Mad2 pathway (92). Nevertheless, destruction of securin by the APC is tightly regulated by mechanisms that are independent of Mad2. These involve the accumulation of Cdc20 protein only as cells enter mitosis (93, 94) and phosphorylation of APC by mitotic kinases, which enables the complex to respond to Cdc20 (95, 96). Strikingly, sister chromatid separation remains tightly regulated in budding yeast mutants lacking securin (90), suggesting that other mechanisms regulate cleavage of Scc1.

SUMMARY

The veil of mystery surrounding the sister separation process for over a century is finally lifting. There is now convincing evidence that the sudden movement of chromosomes to the poles at the onset of anaphase is triggered by cleavage of specific sister chromatid cohesion proteins. Future research must address the structural basis of cohesion and how it is established only at replication forks. It must also address the generality of mechanisms that dismantle cohesion at the metaphase-to-anaphase transition and how mistakes in this process contribute to human disease.

REFERENCES AND NOTES

1. I. Wilmut, A. E. Schnieke, J. McWhir, A. J. Kind, K. H. Campbell, *Nature* **385**, 810 (1997) [CrossRef] [ISI] [Medline] .
2. P. Nurse, *Nature* **344**, 503 (1990) [CrossRef] [ISI] [Medline] .
3. L. H. Hartwell and T. A. Weinert, *Science* **246**, 629 (1989) [Abstract/Free Full Text] .
4. W. Flemming, *Arch. Mikrosk. Ana.* **18**, 151 (1879) .
5. E. B. Wilson, *The Cell in Development and Heredity* (Macmillan, New York, ed. 3, 1925).
6. F. Schrader, *Mitosis* (Columbia Univ. Press, New York, 1944).
7. D. Mazia, *Mitosis and the Physiology of Cell Division*, J. Brachet and A. E. Mirsky, Eds. (Academic Press, New York, 1961), vol. 3.
8. J. D. Watson and F. H. C. Crick, *Nature* **171**, 964 (1953) [ISI] [Medline] .
9. M. P. Maguire, *Biochem. Cell Biol.* **68**, 1231 (1990) [ISI] [Medline] .
10. D. C. Lin and A. D. Grossman, *Cell* **92**, 675 (1998) [CrossRef] [ISI] [Medline] .
11. R. B. Nicklas and S. C. Ward, *J. Cell Biol.* **126**, 1241 (1994) [Abstract/Free Full Text] .
12. J. Mole-Bajer, *Chromosoma* **9**, 332 (1958) [ISI] [Medline] .
13. C. L. Rieder and R. E. Palazzo, *J. Cell Sci.* **102**, 387 (1992) [Free Full Text] .
14. K. Izutsu, *Mie Med. J.* **9**, 15 (1959) .
15. P. A. McNeill and M. W. Berns, *J. Cell Biol.* **88**, 543 (1981) [Abstract/Free Full Text] .
16. C. D. Darlington, *The Evolution of Genetic Systems* (Basic Books, New York, 1939).
17. K. Belar, *Wilhelm Roux Arch. Entwicklungsmech. Org.* **118**, 359 (1929) [CrossRef].
18. S. Selig, K. Okumura, D. C. Ward, H. Cedar, *EMBO J.* **11**, 1217 (1992) [ISI] [Medline] .
19. A. T. Sumner, *Chromosoma* **100**, 410 (1991) [CrossRef] [ISI] [Medline] .
20. C. L. Rieder and R. Cole, *J. Cell Sci.* **112**, 2607 (1999) [Abstract] .
21. S. Sigrist, H. Jacobs, R. Stratmann, C. F. Lehner, *EMBO J.* **14**, 4827 (1995) [ISI] [Medline] .
22. B. K. Vig, *Hum. Genet.* **57**, 247 (1981) [ISI] [Medline] .
23. T. Tanaka and K. Nasmyth, personal communication.
24. G. Goshima and M. Yanagida, *Cell* **100**, 619 (2000) [CrossRef] [ISI] [Medline] .
25. D. H. Tippet, J. D. Pickett-Heaps, R. L. Leslie, *J. Cell Biol.* **86**, 402 (1980) [Abstract/Free Full Text] .
26. Y. Melander, *Heriditas* **36**, 233 (1950) [ISI].
27. D. E. Comings, *Science* **154**, 1463 (1966) [Abstract/Free Full Text] .
28. A. W. Murray and J. W. Szostak, *Annu. Rev. Cell Biol.* **1**, 289 (1985) [CrossRef] [ISI] .
29. S. Dinardo, K. A. Voelkel, R. L. Sternglanz, *Proc. Natl. Acad. Sci. U.S.A.* **81**, 2616

(1984) [Abstract/Free Full Text] .
30. D. Koshland and L. Hartwell, *Science* **238**, 1713 (1987) [Abstract/Free Full Text] .
31. H. Funabiki, I. Hagan, S. Uzawa, M. Yanagida, *J. Cell Biol.* **121**, 961 (1993) [Abstract/Free Full Text] .
32. C. S. Downes, A. M. Mullinger, R. T. Johnson, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 8895 (1991) [Abstract/Free Full Text] .
33. G. J. Gorbsky, *Cancer Res.* **54**, 1042 (1994) [ISI] [Medline] .
34. M. P. Maguire, A. M. Paredes, R. W. Riess, *Genome* **34**, 879 (1991) [ISI] [Medline] .
35. B. K. Davis, *Mol. Gen. Genet.* **113**, 251 (1971) [CrossRef] [ISI] [Medline] .
36. L. S. B. Goldstein, *Chromosoma* **78**, 79 (1980) [CrossRef] [ISI] [Medline] .
37. A. W. Kerrebrock, D. P. Moore, J. S. Wu, T. L. Orr-Weaver, *Cell* **83**, 247 (1995) [CrossRef] [ISI] [Medline] .
38. A. Toth, *et al*., *Genes Dev.* **13**, 320 (1999) [Abstract/Free Full Text] .
39. A. Losada, M. Hirano, T. Hirano, *Genes Dev.* **12**, 1986 (1998) [Abstract/Free Full Text] .
40. S. L. Holloway, M. Glotzer, R. W. King, A. W. Murray, *Cell* **73**, 1393 (1993) [CrossRef] [ISI] [Medline] .
41. S. Irniger, S. Piatti, C. Michaelis, K. Nasmyth, *Cell* **81**, 269 (1995) [CrossRef] [ISI] [Medline] .
42. R. W. King, *et al*., *Cell* **81**, 279 (1995) [CrossRef] [ISI] [Medline] .
43. W. Zachariae and K. Nasmyth, *Genes Dev.* **13**, 2039 (1999) [Free Full Text] .
44. A. Yamamoto, V. Guacci, D. Koshland, *J. Cell Biol.* **133**, 99 (1996) [Abstract/Free Full Text] .
45. O. Cohen-Fix, J.-M. Peters, M. W. Kirschner, D. Koshland, *Genes Dev.* **10**, 3081 (1996) [Abstract] .
46. H. Funabiki, *et al*., *Nature* **381**, 438 (1996) [CrossRef] [ISI] [Medline] .
47. R. Ciosk, *et al*., *Cell* **93**, 1067 (1998) [CrossRef] [ISI] [Medline] .
48. C. Michaelis, R. Ciosk, K. Nasmyth, *Cell* **91**, 35 (1997) [CrossRef] [ISI] [Medline] .
49. V. Guacci, D. Koshland, A. Strunnikov, *Cell* **91**, 47 (1997) [CrossRef] [ISI] [Medline] .
50. K. Furuya, K. Takahashi, M. Yanagida, *Genes Dev.* **12**, 3408 (1998) [Abstract/Free Full Text] .
51. R. V. Skibbens, L. B. Corson, D. Koshland, P. Hieter, *Genes Dev.* **13**, 307 (2000) [Abstract/Free Full Text] .
52. R. Ciosk, *et al*., *Mol. Cell* **5**, 1 (2000) [CrossRef] [ISI] [Medline] .
53. T. Tanaka, M. P. Cosma, K. Wirth, K. Nasmyth, *Cell* **98**, 847 (1999) [CrossRef] [ISI] [Medline] .
54. Y. Blat and N. Kleckner, *Cell* **98**, 249 (1999) [CrossRef] [ISI] [Medline] .
55. P. C. Megee, C. Mistrot, V. Guacci, D. Koshland, *Mol. Cell* **4**, 445 (1999) [CrossRef] [ISI] [Medline] .
56. F. Uhlmann and K. Nasmyth, *Curr. Biol.* **8**, 1095 (1998) [CrossRef] [ISI] [Medline] .
57. D. van Heemst, H. James, S. Pöggeler, V. Berteaux-Lecellier, D. Zickler, *Cell* **98**, 261 (1999) [CrossRef] [ISI] [Medline] .
58. http://genome-www.stanford.edu/Saccharomyces/

59. S. H. Denison, E. Kafer, G. S. May, *Genetics* **134**, 1085 (1993) [Abstract] .
60. K. Tanaka, *et al*., *Mol. Cell. Biol.* **20**, 3459 (2000) [Abstract/Free Full Text] .
61. F. Uhlmann, F. Lottspeich, K. Nasmyth, *Nature* **400**, 37 (1999) [CrossRef] [ISI] [Medline] .
62. T. Hirano, *Genes Dev.* **13**, 11 (1999) [Free Full Text] .
63. T. E. Melby, C. N. Ciampaglio, G. Briscoe, H. P. Erickson, *J. Cell Biol.* **142**, 1595 (1998) [Abstract/Free Full Text] .
64. A. T. Akhmedov, B. Gross, R. Jessberger, *J. Biol. Chem.* **274**, 38216 (1999) [Abstract/Free Full Text] .
65. T. Hirano and T. J. Mitchison, *Cell* **79**, 449 (1994) [CrossRef] [ISI] [Medline] .
66. Y. Saka, *et al*., *EMBO J.* **13**, 4938 (1994) [ISI] [Medline] .
67. T. Hirano, R. Kobayashi, M. Hirano, *Cell* **89**, 511 (1997) [CrossRef] [ISI] [Medline] .
68. K. Kimura, V. V. Rybenkov, N. J. Crisona, T. Hirano, N. R. Cozzarelli, *Cell* **98**, 239 (1999) [CrossRef] [ISI] [Medline] .
69. U. Surana, *et al*., *EMBO J.* **12**, 1969 (1993) [ISI] [Medline] .
70. H. Zou, T. J. McGarry, T. Bernal, M. W. Kirschner, *Science* **285**, 418 (1999) [Abstract/Free Full Text] .
71. C. Saez, *et al*., *Oncogene* **18**, 5473 (1999) [CrossRef] [ISI] [Medline] .
72. L. Pei and S. Melmed, *Mol. Endocrinol.* **11**, 433 (1997) [Abstract/Free Full Text] .
73. R. Stratmann and C. F. Lehner, *Cell* **84**, 25 (1996) [CrossRef] [ISI] [Medline] .
74. A. Yamamoto, V. Guacci, D. Koshland, *J. Cell Biol.* **133**, 85 (1996) [Abstract/Free Full Text] .
75. H. Funabiki, K. Kumada, M. Yanagida, *EMBO J.* **15**, 6617 (1996) [ISI] [Medline] .
76. J. T. McGrew, L. Goetsch, B. Byers, P. Baum, *Mol. Biol. Cell* **3**, 1443 (1992) [Abstract] .
77. G. S. May, C. A. McGoldrick, C. L. Holt, S. H. Denison, *J. Biol. Chem.* **267**, 15737 (1992) [Abstract/Free Full Text] .
78. K. Nagao, F. Uhlmann, K. Nasmyth, M. Yanagida, unpublished results
79. A. J. Barrett, N. D. Rawlings, J. F. Woessner, Eds., *Handbook of Proteolytic Enzymes* (Academic Press, London, 1998).
80. J. M. Chen, N. D. Rawlings, R. A. Stevens, A. J. Barrett, *FEBS Lett.* **441**, 361 (1998) [CrossRef] [ISI] [Medline] .
81. F. Klein, *et al*., *Cell* **98**, 91 (1999) [CrossRef] [ISI] [Medline] .
82. K. Kumada, *et al*., *Curr. Biol.* **8**, 633 (1998) [CrossRef] [ISI] [Medline] .
83. I. Sumara and J.-M. Peters, personal communication.
84. I. Waizenegger, S. Hauf, J.-M. Peters, personal communication.
85. L. M. Lica, S. Narayanswami, B. A. Hamkalo, *J. Cell Biol.* **103**, 1145 (1986) [Abstract/Free Full Text] .
86. J. B. Rattner, *Bioessays* **13**, 51 (1991) [CrossRef] [ISI] [Medline] .
87. P. H. Fitzgerald, A. F. Pickering, J. M. Mercer, P. M. Miethke, *Ann. Hum. Genet.* **38**, 417 (1975) [ISI] [Medline] .
88. D. Tomkins, A. Hunter, M. Roberts, *Am. J. Med. Genet.* **4**, 17 (1979) [CrossRef] [ISI] [Medline] .
89. A. Amon, *Curr. Opin. Genet. Dev.* **9**, 69 (1999) [CrossRef] [ISI] [Medline] .
90. G. Alexandru, W. Zachariae, A. Schleiffer, K. Nasmyth, *EMBO J.* **18**, 2707 (1999) [CrossRef] [ISI] [Medline] .

31. J. Basu, *et al*., *J. Cell Biol.* **146**, 13 (1999) [Abstract/Free Full Text] .
32. D. P. Cahill, *et al*., *Nature* **392**, 300 (1998) [CrossRef] [ISI] [Medline] .
33. J. Weinstein, *J. Biol. Chem.* **272**, 28501 (1997) [Abstract/Free Full Text] .
34. M. Shirayama, W. Zachariae, R. Ciosk, K. Nasmyth, *EMBO J.* **17**, 1336 (1998) [CrossRef] [ISI] [Medline] .
35. M. Shteinberg, Y. Protopopov, T. Listovsky, M. Brandeis, A. Hershko, *Biochem. Biophys. Res. Commun.* **260**, 193 (1999) [CrossRef] [ISI] [Medline] .
36. E. R. Kramer, N. Scheuringer, A. V. Podtelejnikov, M. Mann, J.-M. Peters, *Mol. Biol. Cell* **11**, 1555 (2000) [Abstract/Free Full Text] .
37. A. Khodjakov, R. W. Cole, A. S. Bajer, C. L. Rieder, *J. Cell Biol.* **132**, 1093 (1996) [Abstract/Free Full Text] .

38. We thank E. Koonin for first pointing out the conserved His and Cys residues in the separin sequences. We also thank K. Nagao, I. Sumara, S. Hauf, I. Waizenegger, and M. Yanagida for communicating unpublished results; D. Schweizer and H. Tkadletz for help with the figures; A. Bajer, H. Erickson, C. Lehner, J. Mole-Bajer, C. Rieder, and A. Sumner for providing micrographs; S. Vrba for library support; and M. Glotzer, C. Lehner, A. Nasmyth, C. Rieder, D. Schweizer, and T. Skern for discussions and comments on the manuscript. Supported by grants from the Austrian Industrial Research Promotion Fund (FFF) and the Austrian Science Promotion Fund (FWF) to K.N. and J.-M.P.

J. Virol. **79**, 2597–2603
Abstract » Full Text » PDF »

Oligosyndactylism Mice Have an Inversion of Chromosome 8.
T. L. Wise and D. D. Pravtcheva (2004)
Genetics **168**, 2099–2112
Abstract » Full Text » PDF »

The Spindle Pole Body Assembly Component Mps3p/Nep98p Functions in Sister Chromatid Cohesion.
L. M. Antoniacci, M. A. Kenna, P. Uetz, S. Fields, and R. V. Skibbens (2004)
J. Biol. Chem. **279**, 49542–49550
Abstract » Full Text » PDF »

Meiotic and mitotic nondisjunction: lessons from preimplantation genetic diagnosis.
A. Kuliev and Y. Verlinsky (2004)
Hum. Reprod. Update **10**, 401–407
Abstract » Full Text » PDF »

Polo-like Kinase-1 Is Required for Bipolar Spindle Formation but Is Dispensable for Anaphase Promoting Complex/Cdc20 Activation and Initiation of Cytokinesis.
M. A. T. M. van Vugt, B. C. M. van de Weerdt, G. Vader, H. Janssen, J. Calafat, R. Klompmaker, R. M. F. Wolthuis, and R. H. Medema (2004)
J. Biol. Chem. **279**, 36841–36854
Abstract » Full Text » PDF »

Three Classes of Genes Mutated In Colorectal Cancers with Chromosomal Instability.
Z. Wang, J. M. Cummins, D. Shen, D. P. Cahill, P. V. Jallepalli, T.-L. Wang, D. W. Parsons, G. Traverso, M. Awad, N. Silliman, J. Ptak, S. Szabo, J. K. V. Willson, S. D. Markowitz, M. L. Goldberg, R. Karess, K. W. Kinzler, B. Vogelstein, V. E. Velculescu, and C. Lengauer (2004)
Cancer Res. **64**, 2998–3001
Abstract » Full Text » PDF »

Hrb27C, Sqd and Otu cooperatively regulate gurken RNA localization and mediate nurse cell chromosome dispersion in Drosophila oogenesis.
J. S. Goodrich, K. N. Clouse, and T. Schupbach (2004)
Development **131**, 1949–1958
Abstract » Full Text » PDF »

Identification of Two Novel Components of the Human NDC80 Kinetochore Complex.
R. Bharadwaj, W. Qi, and H. Yu (2004)
J. Biol. Chem. **279**, 13076–13085
Abstract » Full Text » PDF »

Chl1p, a DNA Helicase-Like Protein in Budding Yeast, Functions in Sister-Chromatid Cohesion.
R. V. Skibbens (2004)
Genetics **166**, 33–42
Abstract » Full Text » PDF »

Condensin-dependent localisation of topoisomerase II to an axial chromosomal

structure is required for sister chromatid resolution during mitosis.
P. A. Coelho, J. Queiroz-Machado, and C. E. Sunkel (2003)
J. Cell Sci. **116**, 4763-4776
Abstract » Full Text » PDF »

A role for Arf1 in mitotic Golgi disassembly, chromosome segregation, and cytokinesis.
N. Altan-Bonnet, R. D. Phair, R. S. Polishchuk, R. Weigert, and J. Lippincott-Schwartz (2003)
PNAS **100**, 13314-13319
Abstract » Full Text » PDF »

Two Distinct Pathways for Inhibiting Pds1 Ubiquitination in Response to DNA Damage.
R. Agarwal, Z. Tang, H. Yu, and O. Cohen-Fix (2003)
J. Biol. Chem. **278**, 45027-45033
Abstract » Full Text » PDF »

Human EFO1p exhibits acetyltransferase activity and is a unique combination of linker histone and Ctf7p/Eco1p chromatid cohesion establishment domains.
A. M. Bellows, M. A. Kenna, L. Cassimeris, and R. V. Skibbens (2003)
Nucleic Acids Res. **31**, 6334-6343
Abstract » Full Text » PDF »

Induction of C-Anaphase and Diplochromosome through Dysregulation of Spindle Assembly Checkpoint by Sodium Arsenite in Human Fibroblasts.
L.-H. Yih and T.-C. Lee (2003)
Cancer Res. **63**, 6680-6688
Abstract » Full Text » PDF »

The alternative Ctf18-Dcc1-Ctf8-replication factor C complex required for sister chromatid cohesion loads proliferating cell nuclear antigen onto DNA.
V. P. Bermudez, Y. Maniwa, I. Tappin, K. Ozato, K. Yokomori, and J. Hurwitz (2003)
PNAS **100**, 10237-10242
Abstract » Full Text » PDF »

Molecular Phenotype of Spontaneously Arising 4N (G2-Tetraploid) Intermediates of Neoplastic Progression in Barrett's Esophagus.
M. T. Barrett, D. Pritchard, C. Palanca-Wessels, J. Anderson, B. J. Reid, and P. S. Rabinovitch (2003)
Cancer Res. **63**, 4211-4217
Abstract » Full Text » PDF »

p53 deficiency and defective mitotic checkpoint in proliferating T lymphocytes increase chromosomal instability through aberrant exit from mitotic arrest.
K.-H. Baek, H.-J. Shin, J.-K. Yoo, J.-H. Cho, Y.-H. Choi, Y.-C. Sung, F. McKeon, and C.-W. Lee (2003)
J. Leukoc. Biol. **73**, 850-861
Abstract » Full Text » PDF »

Saccharomyces cerevisiae DNA Polymerase {varepsilon} and Polymerase {sigma} Interact Physically and Functionally, Suggesting a Role for Polymerase {varepsilon} in Sister Chromatid Cohesion.
S. Edwards, C. M. Li, D. L. Levy, J. Brown, P. M. Snow, and J. L. Campbell (2003)
Mol. Cell. Biol. **23**, 2733-2748

Abstract » Full Text » PDF »

Processing, localization, and requirement of human separase for normal anaphase progression.
A. Chestukhin, C. Pfeffer, S. Milligan, J. A. DeCaprio, and D. Pellman (2003)
PNAS **100**, 4574–4579
Abstract » Full Text » PDF »

The Unfolded Protein Response Is Required for Haploid Tolerance in Yeast.
K. Lee, L. Neigeborn, and R. J. Kaufman (2003)
J. Biol. Chem. **278**, 11818–11827
Abstract » Full Text » PDF »

Pituitary tumor transforming gene–null male mice exhibit impaired pancreatic beta cell proliferation and diabetes.
Z. Wang, E. Moro, K. Kovacs, R. Yu, and S. Melmed (2003)
PNAS **100**, 3428–3432
Abstract » Full Text » PDF »

Under arrest: cytostatic factor (CSF)–mediated metaphase arrest in vertebrate eggs.
B. J. Tunquist and J. L. Maller (2003)
Genes & Dev. **17**, 683–710
Full Text » PDF »

Selection on the Genes of Euplotes crassus Tec1 and Tec2 Transposons: Evolutionary Appearance of a Programmed Frameshift in a Tec2 Gene Encoding a Tyrosine Family Site-Specific Recombinase.
T. G. Doak, D. J. Witherspoon, C. L. Jahn, and G. Herrick (2003)
Eukaryot. Cell **2**, 95–102
Abstract » Full Text » PDF »

Endoproteolytic Activity of the Proteasome.
C.-W. Liu, M. J. Corboy, G. N. DeMartino, and P. J. Thomas (2003)
Science **299**, 408–411
Abstract » Full Text » PDF »

Linking Sister Chromatid Cohesion and Apoptosis: Role of Rad21.
D. Pati, N. Zhang, and S. E. Plon (2002)
Mol. Cell. Biol. **22**, 8267–8277
Abstract » Full Text » PDF »

Meiotic Cohesion Requires Accumulation of ORD on Chromosomes before Condensation.
E. M. Balicky, M. W. Endres, C. Lai, and S. E. Bickel (2002)
Mol. Biol. Cell **13**, 3890–3900
Abstract » Full Text » PDF »

Role of Hec1 in Spindle Checkpoint Signaling and Kinetochore Recruitment of Mad1/Mad2.
S. Martin-Lluesma, V. M. Stucke, and E. A. Nigg (2002)
Science **297**, 2267–2270

Abstract » Full Text » PDF »

Orchestrating the cell cycle in yeast: sequential localization of key mitotic regulators at the spindle pole and the bud neck.
V. J. Cid, J. Jimenez, M. Molina, M. Sanchez, C. Nombela, and J. W. Thorner (2002)
Microbiology **148**, 2647-2659
Full Text » PDF »

The anaphase-promoting complex: it's not just for mitosis any more.
J. W. Harper, J. L. Burton, and M. J. Solomon (2002)
Genes & Dev. **16**, 2179-2206
Full Text » PDF »

The anaphase promoting complex/cyclosome is required during development for modified cell cycles.
H. Kashevsky, J. A. Wallace, B. H. Reed, C. Lai, A. Hayashi-Hagihara, and T. L. Orr-Weaver (2002)
PNAS **99**, 11217-11222
Abstract » Full Text » PDF »

Spo13 regulates cohesin cleavage.
B. H. Lee, A. Amon, and S. Prinz (2002)
Genes & Dev. **16**, 1672-1681
Abstract » Full Text » PDF »

Human securin proteolysis is controlled by the spindle checkpoint and reveals when the APC/C switches from activation by Cdc20 to Cdh1.
A. Hagting, N. den Elzen, H. C. Vodermaier, I. C. Waizenegger, J.-M. Peters, and J. Pines (2002)
J. Cell Biol. **157**, 1125-1137
Abstract » Full Text » PDF »

Structural and Functional Analysis of the Human Mitotic-specific Ubiquitin-conjugating Enzyme, UbcH10.
Y. Lin, W. C. Hwang, and R. Basavappa (2002)
J. Biol. Chem. **277**, 21913-21921
Abstract » Full Text » PDF »

Phosphorylation of the mitotic regulator Pds1/securin by Cdc28 is required for efficient nuclear localization of Esp1/separase.
R. Agarwal and O. Cohen-Fix (2002)
Genes & Dev. **16**, 1371-1382
Abstract » Full Text » PDF »

Caspase Proteolysis of the Cohesin Component RAD21 Promotes Apoptosis.
F. Chen, M. Kamradt, M. Mulcahy, Y. Byun, H. Xu, M. J. McKay, and V. L. Cryns (2002)
J. Biol. Chem. **277**, 16775-16781
Abstract » Full Text » PDF »

Beyond the ABCs of CKC and SCC: Do centromeres orchestrate sister chromatid cohesion or vice versa?.

P. B Meluh and A. V Strunnikov (2002)
FEBS J. **269**, 2300–2314
Abstract » **Full Text »** **PDF »**

Control of localization of a spindle checkpoint protein, Mad2, in fission yeast.
A. E. Ikui, K. Furuya, M. Yanagida, and T. Matsumoto (2002)
J. Cell Sci. **115**, 1603–1610
Abstract » **Full Text »** **PDF »**

Inhibition of APC-mediated proteolysis by the meiosis-specific protein kinase Ime2.
M. Bolte, P. Steigemann, G. H. Braus, and S. Irniger (2002)
PNAS **99**, 4385–4390
Abstract » **Full Text »** **PDF »**

The Ubiquitin Ligase Component Siah1a Is Required for Completion of Meiosis I in Male Mice.
R. A. Dickins, I. J. Frew, C. M. House, M. K. O'Bryan, A. J. Holloway, I. Haviv, N. Traficante, D. M. de Kretser, and D. D. L. Bowtell (2002)
Mol. Cell. Biol. **22**, 2294–2303
Abstract » **Full Text »** **PDF »**

The S. pombe aurora-related kinase Ark1 associates with mitotic structures in a stage dependent manner and is required for chromosome segregation.
J. Petersen, J. Paris, M. Willer, M. Philippe, and I. M. Hagan (2002)
J. Cell Sci. **114**, 4371–4384
Abstract » **Full Text »** **PDF »**

Conserved Wat1/Pop3 WD-repeat protein of fission yeast secures genome stability through microtubule integrity and may be involved in mRNA maturation.
I. L. Ochotorena, D. Hirata, K.-i. Kominami, J. Potashkin, F. Sahin, K. Wentz-Hunter, K. L. Gould, K. Sato, Y. Yoshida, L. Vardy, and T. Toda (2002)
J. Cell Sci. **114**, 2911–2920
Abstract » **Full Text »** **PDF »**

In vivo dissection of the chromosome condensation machinery: reversibility of condensation distinguishes contributions of condensin and cohesin.
B. D. Lavoie, E. Hogan, and D. Koshland (2002)
J. Cell Biol. **156**, 805–815
Abstract » **Full Text »** **PDF »**

The ABCs of SMC proteins: two-armed ATPases for chromosome condensation, cohesion, and repair.
T. Hirano (2002)
Genes & Dev. **16**, 399–414
Full Text » **PDF »**

Condensin and cohesin display different arm conformations with characteristic hinge angles.
D. E. Anderson, A. Losada, H. P. Erickson, and T. Hirano (2002)
J. Cell Biol. **156**, 419–424
Abstract » **Full Text »** **PDF »**

Degradation or Maintenance: Actions of the Ubiquitin System on Eukaryotic Chromatin.
H. D. Ulrich (2002)
Eukaryot. Cell **1**, 1–10
Full Text » PDF »

Schizosaccharomyces pombe Bir1p, a Nuclear Protein That Localizes to Kinetochores and the Spindle Midzone, Is Essential for Chromosome Condensation and Spindle Elongation During Mitosis.
S. Rajagopalan and M. K. Balasubramanian (2002)
Genetics **160**, 445–456
Abstract » Full Text » PDF »

Kinesins klp5+ and klp6+ are required for normal chromosome movement in mitosis.
R. R. West, T. Malmstrom, and J. R. McIntosh (2002)
J. Cell Sci. **115**, 931–940
Abstract » Full Text » PDF »

Ctf3p, the Mis6 budding yeast homolog, interacts with Mcm22p and Mcm16p at the yeast outer kinetochore.
V. Measday, D. W. Hailey, I. Pot, S. A. Givan, K. M. Hyland, G. Cagney, S. Fields, T. N. Davis, and P. Hieter (2002)
Genes & Dev. **16**, 101–113
Abstract » Full Text » PDF »

Fission Yeast F-box Protein Pof3 Is Required for Genome Integrity and Telomere Function.
S. Katayama, K. Kitamura, A. Lehmann, O. Nikaido, and T. Toda (2002)
Mol. Biol. Cell **13**, 211–224
Abstract » Full Text » PDF »

Regulation of the Anaphase-promoting Complex by the Dual Specificity Phosphatase Human Cdc14a.
J. Bembenek and H. Yu (2001)
J. Biol. Chem. **276**, 48237–48242
Abstract » Full Text » PDF »

A Potential Role for Human Cohesin in Mitotic Spindle Aster Assembly.
H. C. Gregson, J. A. Schmiesing, J.-S. Kim, T. Kobayashi, S. Zhou, and K. Yokomori (2001)
J. Biol. Chem. **276**, 47575–47582
Abstract » Full Text » PDF »

APC2 Cullin Protein and APC11 RING Protein Comprise the Minimal Ubiquitin Ligase Module of the Anaphase-promoting Complex.
Z. Tang, B. Li, R. Bharadwaj, H. Zhu, E. Ozkan, K. Hakala, J. Deisenhofer, and H. Yu (2001)
Mol. Biol. Cell **12**, 3839–3851
Abstract » Full Text » PDF »

Mice Lacking Pituitary Tumor Transforming Gene Show Testicular and Splenic Hypoplasia, Thymic Hyperplasia, Thrombocytopenia, Aberrant Cell Cycle Progression, and Premature Centromere Division.
Z. Wang, R. Yu, and S. Melmed (2001)
Mol. Endocrinol. **15**, 1870–1879

Abstract » Full Text » PDF »

Novel Meiosis-Specific Isoform of Mammalian SMC1.
E. Revenkova, M. Eijpe, C. Heyting, B. Gross, and R. Jessberger (2001)
Mol. Cell. Biol. **21**, 6984-6998
Abstract » Full Text » PDF »

Genes Involved in Sister Chromatid Separation and Segregation in the Budding Yeast Saccharomyces cerevisiae.
S. Biggins, N. Bhalla, A. Chang, D. L. Smith, and A. W. Murray (2001)
Genetics **159**, 453-470
Abstract » Full Text » PDF »

Drosophila Separase is required for sister chromatid separation and binds to PIM and THR.
H. Jager, A. Herzig, C. F. Lehner, and S. Heidmann (2001)
Genes & Dev. **15**, 2572-2584
Abstract » Full Text » PDF »

Cohesin Cleavage by Separase Required for Anaphase and Cytokinesis in Human Cells.
S. Hauf, I. C. Waizenegger, and J.-M. Peters (2001)
Science **293**, 1320-1323
Abstract » Full Text » PDF »

A Meiotic Chromosomal Core Consisting of Cohesin Complex Proteins Recruits DNA Recombination Proteins and Promotes Synapsis in the Absence of an Axial Element in Mammalian Meiotic Cells.
J. Pelttari, M.-R. Hoja, L. Yuan, J.-G. Liu, E. Brundell, P. Moens, S. Santucci-Darmanin, R. Jessberger, J. L. Barbero, C. Heyting, and C. Hoog (2001)
Mol. Cell. Biol. **21**, 5667-5677
Abstract » Full Text » PDF »

Identification of an Overlapping Binding Domain on Cdc20 for Mad2 and Anaphase-Promoting Complex: Model for Spindle Checkpoint Regulation.
Y. Zhang and E. Lees (2001)
Mol. Cell. Biol. **21**, 5190-5199
Abstract » Full Text » PDF »

Conditional Mutations in {gamma}-Tubulin Reveal Its Involvement in Chromosome Segregation and Cytokinesis.
T. W. Hendrickson, J. Yao, S. Bhadury, A. H. Corbett, and H. C. Joshi (2001)
Mol. Biol. Cell **12**, 2469-2481
Abstract » Full Text » PDF »

The replication timing program of the Chinese hamster {beta}-globin locus is established coincident with its repositioning near peripheral heterochromatin in early G1 phase.
F. Li, J. Chen, M. Izumi, M. C. Butler, S. M. Keezer, and D. M. Gilbert (2001)
J. Cell Biol. **154**, 283-292
Abstract » Full Text » PDF »

Evidence that replication fork components catalyze establishment of cohesion between sister chromatids.
D. R. Carson and M. F. Christman (2001)
PNAS **98**, 8270–8275
Abstract » Full Text » PDF »

SWITCH1 (SWI1): a novel protein required for the establishment of sister chromatid cohesion and for bivalent formation at meiosis.
R. Mercier, D. Vezon, E. Bullier, J. C. Motamayor, A. Sellier, F. Lefevre, G. Pelletier, and C. Horlow (2001)
Genes & Dev. **15**, 1859–1871
Abstract » Full Text » PDF »

Functional Analysis of Kinetochore Assembly in Caenorhabditis elegans.
K. Oegema, A. Desai, S. Rybina, M. Kirkham, and A. A. Hyman (2001)
J. Cell Biol. **153**, 1209–1226
Abstract » Full Text » PDF »

A Caenorhabditis elegans cohesion protein with functions in meiotic chromosome pairing and disjunction.
P. Pasierbek, M. Jantsch, M. Melcher, A. Schleiffer, D. Schweizer, and J. Loidl (2001)
Genes & Dev. **15**, 1349–1360
Abstract » Full Text » PDF »

Characterization of a Novel Human SMC Heterodimer Homologous to the Schizosaccharomyces pombe Rad18/Spr18 Complex.
E. M. Taylor, J. S. Moghraby, J. H. Lees, B. Smit, P. B. Moens, and A. R. Lehmann (2001)
Mol. Biol. Cell **12**, 1583–1594
Abstract » Full Text » PDF »

Frequent fusion of the JAZF1 and JJAZ1 genes in endometrial stromal tumors.
J. I. Koontz, A. L. Soreng, M. Nucci, F. C. Kuo, P. Pauwels, H. van den Berghe, P. D. Cin, J. A. Fletcher, and J. Sklar (2001)
PNAS **98**, 6348–6353
Abstract » Full Text » PDF »

Metaphase Arrest with Centromere Separation in polo Mutants of Drosophila.
M. M. Donaldson, A. A.M. Tavares, H. Ohkura, P. Deak, and D. M. Glover (2001)
J. Cell Biol. **153**, 663–676
Abstract » Full Text » PDF »

Saccharomyces cerevisiae CTF18 and CTF4 Are Required for Sister Chromatid Cohesion.
J. S. Hanna, E. S. Kroll, V. Lundblad, and F. A. Spencer (2001)
Mol. Cell. Biol. **21**, 3144–3158
Abstract » Full Text »

DNA Replication Precedes Neuronal Cell Death in Alzheimer's Disease.
Y. Yang, D. S. Geldmacher, and K. Herrup (2001)
J. Neurosci. **21**, 2661–2668
Abstract » Full Text »

Asymmetrical segregation of chromosomes with a normal metaphase/anaphase checkpoint in polyploid megakaryocytes.
L. Roy, P. Coullin, N. Vitrat, R. Hellio, N. Debili, J. Weinstein, A. Bernheim, and W. Vainchenker (2001)
Blood **97**, 2238–2247
Abstract » Full Text » PDF »

Metaphase to Anaphase (mat) Transition-defective Mutants in Caenorhabditis elegans.
A. Golden, P. L. Sadler, M. R. Wallenfang, J. M. Schumacher, D. R. Hamill, G. Bates, B. Bowerman, G. Seydoux, and D. C. Shakes (2000)
J. Cell Biol. **151**, 1469–1482
Abstract » Full Text » PDF »

On the origin of metacentric, attached-X (A-X) chromosomes in Drosophila melanogaster males.
M. M. Green and R. Piergentili (2000)
PNAS
Abstract » Full Text »

Characterization of Vertebrate Cohesin Complexes and Their Regulation in Prophase.
I. Sumara, E. Vorlaufer, C. Gieffers, B. H. Peters, and J.-M. Peters (2000)
J. Cell Biol. **151**, 749–762
Abstract » Full Text » PDF »

Holding Your Own: Establishing Sister Chromatid Cohesion.
R. V. Skibbens (2000)
Genome Res. **10**, 1664–1671
Full Text »

Characterization of fission yeast cohesin: essential anaphase proteolysis of Rad21 phosphorylated in the S phase.
T. Tomonaga, K. Nagao, Y. Kawasaki, K. Furuya, A. Murakami, J. Morishita, T. Yuasa, T. Sutani, S. E. Kearsey, F. Uhlmann, K. Nasmyth, and M. Yanagida (2000)
Genes & Dev. **14**, 2757–2770
Abstract » Full Text »

A nonproteolytic function of the proteasome is required for the dissociation of Cdc2 and cyclin B at the end of M phase.
A. Nishiyama, K. Tachibana, Y. Igarashi, H. Yasuda, N. Tanahashi, K. Tanaka, K. Ohsumi, and T. Kishimoto (2000)
Genes & Dev. **14**, 2344–2357
Abstract » Full Text »

Degradation of Drosophila PIM regulates sister chromatid separation during mitosis.
O. Leismann, A. Herzig, S. Heidmann, and C. F. Lehner (2000)
Genes & Dev. **14**, 2192–2205
Abstract » Full Text »

Pol kappa : A DNA Polymerase Required for Sister Chromatid Cohesion.
Z. Wang, I. B. Castaño, A. De Las Peñas, C. Adams, and M. F. Christman (2000)
Science **289**, 774–779
Abstract » Full Text »

Human Chromatid Cohesin Component hRad21 Is Phosphorylated in M Phase and Associated with Metaphase Centromeres.
Md. T. Hoque and F. Ishikawa (2001)
J. Biol. Chem. **276**, 5059–5067
Abstract » Full Text » PDF »

Inhibition of APC-mediated proteolysis by the meiosis-specific protein kinase Ime2.
M. Bolte, P. Steigemann, G. H. Braus, and S. Irniger (2002)
PNAS **99**, 4385–4390
Abstract » Full Text » PDF »

On the origin of metacentric, attached-X (A-X) chromosomes in Drosophila melanogaster males.
M. M. Green and R. Piergentili (2000)
PNAS **97**, 14484–14487
Abstract » Full Text » PDF »

In vivo dissection of the chromosome condensation machinery: reversibility of condensation distinguishes contributions of condensin and cohesin.
B. D. Lavoie, E. Hogan, and D. Koshland (2002)
J. Cell Biol. **156**, 805–815
Abstract » Full Text » PDF »

Condensin and cohesin display different arm conformations with characteristic hinge angles.
D. E. Anderson, A. Losada, H. P. Erickson, and T. Hirano (2002)
J. Cell Biol. **156**, 419–424
Abstract » Full Text » PDF »

Mutation of YCS4, a Budding Yeast Condensin Subunit, Affects Mitotic and Nonmitotic Chromosome Behavior.
N. Bhalla, S. Biggins, and A. W. Murray (2002)
Mol. Biol. Cell **13**, 632–645
Abstract » Full Text » PDF »