ARTICLE

How Cells Get the Right Chromosomes

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When cells divide, the chromosomes must be delivered flawlessly to the daughter cells. Missing or extra chromosomes can result in birth defects and cancer. Chance events are the starting point for chromosome delivery, which makes the process prone to error. Errors are avoided by diverse uses of mechanical tension from mitotic forces. Tension stabilizes the proper chromosome configuration, controls a cell cycle checkpoint, and changes chromosome chemistry.

Every time a cell divides, the daughter cells must get the right chromosomes. For example, in humans, Down syndrome occurs when an error in meiosis results in a child with an extra copy of chromosome 21. Beyond the cost in human terms, Down syndrome has an estimated annual economic cost of $3.6 billion (*1*). Cells with missing or extra chromosomes can be equally ruinous in adults, by fueling the development of malignant cancer cells (*2*). Given the cost of errors, it is not surprising that cells take pains to avoid them.

Attachment and Chance Encounters

The mechanical attachment of a chromosome to the spindle determines its delivery to the daughter cells. The spindle of a dividing cell has two poles, and each duplicated chromosome has two attachment sites, kinetochores (Fig. 1). Attachment of the kinetochores to opposite poles results in the delivery of one copy of each chromosome to each daughter cell (Fig. 1). Long protein filaments, microtubules, link each kinetochore with a pole. The asymmetry of microtubules (*3*, *4*) leads to force production toward that pole. As a result, each chromosome moves to the pole to which its kinetochore is attached.

Attachment is the product of chance encounters. Microtubules grow outward from each pole of the spindle (Fig. 1). If a microtubule happens, by chance, to encounter a kinetochore, it may be captured by the kinetochore (*5*, *6*), and consequently the chromosome becomes attached to the spindle (Fig. 1). The two kinetochores of one chromosome often capture microtubules from opposite poles (Fig. 1B). That desirable outcome is promoted by properties of both microtubules and chromosomes. Microtubules contribute a self-assembly process with the remarkable, perhaps unique, property that energy is used to purchase instability rather than stable bonds (*7*). Consequently, some microtubules shorten and disappear, to be replaced by new ones. Microtubules extending in all directions from each pole are continuously generated, furnishing a plentiful supply of microtubules for capture by kinetochores (*7*). The contribution of chromosomes to proper attachment is their structure, which specifies the position of the kinetochores. Partner kinetochores lie back-to-back, that is, the capture surfaces of partner kinetochores face in opposite directions (Fig. 1). As would be expected, a kinetochore tends to capture microtubules from the pole its capture surface faces (*6*, *8*). Thus, the back-to-back arrangement of partner kinetochores favors their attachment to opposite spindle poles (Fig. 1), as Östergren suggested long ago (*9*).

Chance, Errors, and Error Correction

The chance encounters of microtubules with back-to-back kinetochores secure the proper attachment of most chromosomes. But reliance on chance makes errors in initial attachment inevitable (*10*). Chromosomes are scattered at the time of attachment, so the kinetochores of some chromosomes will happen by chance to face neither pole directly (Fig. 2A). In that circumstance, chance encounters often result in the attachment of both partner chromosomes to the same pole, a "monopolar" attachment (*11*) (Fig. 2B). This is a genetic disaster in the making. Unless the error is corrected, one daughter cell will receive two copies of the chromosome and the other daughter cell will receive none.

Surprisingly, chance is involved in the correction of errors as well as in their origin. The alternative to chance is a precision biochemical machine. Such a machine corrects errors in DNA replication: a protein complex detects the errors with great sensitivity and then corrects them with great precision (*12*). However, errors in chromosome attachment are not corrected by a protein machine, probably because of the scale and nature of the error (*10*). To detect a monopolar attachment (Fig. 2B), a correction machine would have to reach from one kinetochore to its partner, and while reaching out, it would have to unfailingly locate the partner kinetochore rather than the kinetochore of some other chromosome. Instead of a machine, differences in stability are the basis for error correction (*13*). A faulty attachment is unstable and repeatedly changes (Fig. 2, C and D) until, by chance, the one proper attachment is hit upon. Only that attachment (Fig. 2E) is stable, and therefore it alone persists. Thus, error cor-

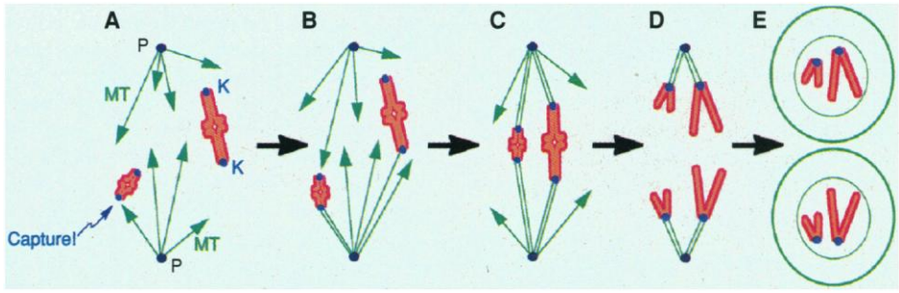

Fig. 1. Chance, attachment, and chromosome transmission. The normal, errorless course of events is illustrated for a cell in meiosis. (**A**) The basic elements are a spindle with two poles (P) and paired chromosomes, each with two spindle attachment sites, kinetochores (K). Microtubules (MT) growing from a pole may by chance encounter a kinetochore and be captured, thereby attaching the chromosome to that pole. (**B** to **D**) If all goes well, the two kinetochores on each chromosome pair become attached to opposite spindle poles; in anaphase, each chromosome pair splits into partner chromosomes that move to opposite poles. (**E**) Each daughter cell has a copy of each chromosome. By metaphase and anaphase (C and D) the number of kinetochore microtubules is generally much greater than shown; 10 to 50 microtubules per kinetochore are typical in multicellular eukaryotes.

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rection depends first on sources of instability and change that generate variations in attachment and second on a source of stability so that the proper attachment persists (*10*).

Correction of faulty attachments requires both the capture of new microtubules and release from the old, improper attachment. Correction of the error shown in Fig. 2 requires the capture of microtubules growing from the upper pole by one kinetochore or the other. That kinetochore must also be free to move—it must have been released from the initial connection that tethered it to the lower pole. Otherwise, the mitotic motors will be unable to move the kinetochore very far, and error correction cannot be completed. Both capture and release are improbable events (6). Capture is improbable because the kinetochores face directly away from the source of appropriate microtubules [the upper pole (Fig. 2, B and C)]. In fact, capture is only possible at all because microtubules that touch the kinetochore at any angle can be captured (*5*, 6). Release is also improbable. Direct tests of release by gently tugging on a chromosome with a micromanipulation needle show that more than half the time, a misattached kinetochore remains tethered to the pole (6). This means that fewer than half of the rare capture events will happen to catch the kinetochore in an untethered state, the condition that will allow movement to continue and error correction to be completed (Fig. 2D). It is not surprising that loss of the old connection is infrequent. Attachment is maintained by a group of several kinetochore microtubules. Release can be viewed as a stochastic process (6): in the absence of tension, individual microtubules come loose at random times. Only occasionally will all the microtubules in the group happen by chance to lose their attachment, and only then will the kinetochore be free to move. And only if capture happens to occur at that time will error correction succeed.

Tension is the source of order in this world of chance. Tension is absent in the improper attachment (Fig. 2B) but present in the proper one (Fig. 2E). Tension as the source of stability has been tested directly, by pulling on an improperly attached chromosome in a living cell with a micromanipulation needle (Fig. 2F). The applied tension makes the unstable, improper attachment stable indefinitely (*6*, *14*).

We do not know how tension stabilizes the attachment of chromosomes to the spindle. Tension could prevent change by stabilizing either the microtubules themselves or the anchorage of microtubules at the kinetochore or at the pole. Stabilization of the polar anchorage is the best bet (6). A particularly interesting possibility is a microtubule motor protein as the link between each microtubule and the pole. Microtubule motors grasp microtubules with a dynamic, not a static, grip: the grip is dependent on conditions (such as the presence or absence of tension, perhaps) rather than permanent (*15*). Some candidates for polar motor-linkers have been identified (*16*, *17*). The sensitivity to tension of would-be linkers can now be tested by using micromanipulation or optical tweezers to pull on the microtubules to which they are attached.

Error Correction as a Darwinian Selection Process

Selection extracts order from disorder, music from noise. Evolution by natural selection begins with random genetic changes, mutations; selection among mutants results in a nonrandom outcome, improved adaptation. Accurate chromosome distribution begins with instability and chance encounters (Fig. 2, B and C), which produce mutant microtubule arrays (Fig. 2D); selection in the form of tension from mitotic forces determines which array persists (Fig. 2E). The result is order, the regular attainment of the one attachment that produces equal chromosome distribution.

Checkpoints and Error Correction

In addition to monopolar attachments, another error commonly occurs—one attachment is missing (Fig. 3). Diverse cells have a quality-control checkpoint that detects such errors (*18*–*24*). The checkpoint delays the onset of anaphase and the completion of cell division, allowing time for the tardy kinetochore to attach to the spindle. The checkpoint is an adaptation to living with chance, an invention that buys time for the capture of microtubules by unfavorably placed kinetochores.

Another use for the checkpoint is found in the spermatocytes of praying mantids (*19*, *22*). Mantid spermatocytes have three sex chromosomes, a Y chromosome and two genetically distinct X chromosomes. Genetic balance requires sperm that carry either the Y chromosome or the two X chromosomes. This desirable state

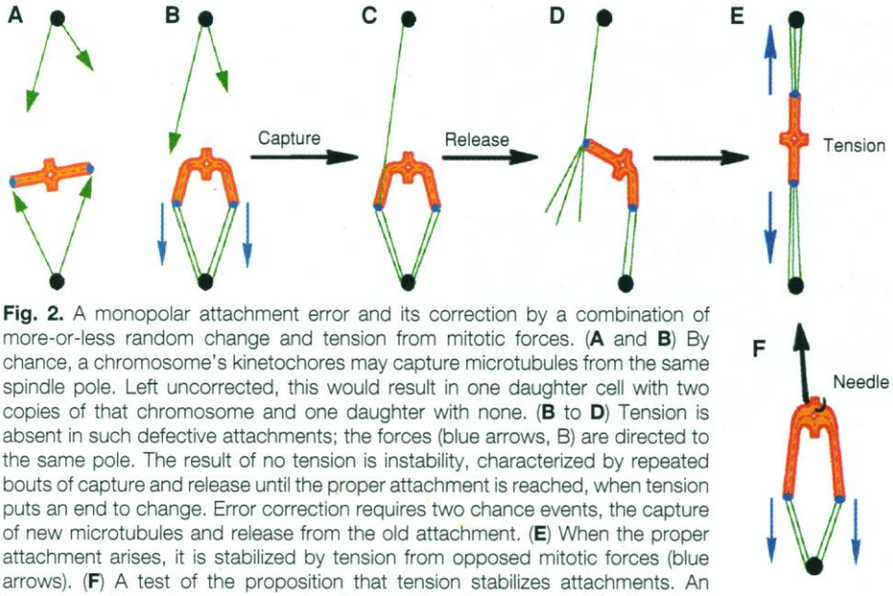

Fig. 2. A monopolar attachment error and its correction by a combination of more-or-less random change and tension from mitotic forces. (**A** and **B**) By chance, a chromosome's kinetochores may capture microtubules from the same spindle pole. Left uncorrected, this would result in one daughter cell with two copies of that chromosome and one daughter with none. (**B** to **D**) Tension is absent in such defective attachments; the forces (blue arrows, B) are directed to the same pole. The result of no tension is instability, characterized by repeated bouts of capture and release until the proper attachment is reached, when tension puts an end to change. Error correction requires two chance events, the capture of new microtubules and release from the old attachment. (**E**) When the proper attachment arises, it is stabilized by tension from opposed mitotic forces (blue arrows). (**F**) A test of the proposition that tension stabilizes attachments. An improperly attached chromosome in a living cell is pulled upward with a fine glass needle, by means of a micromanipulator. The chromosome is stretched, showing that it is now under tension. The misattached chromosome is stabilized by the tension from the microneedle (*6*, *14*). If the experimenter maintains the tension, one daughter cell will get both partner chromosomes and the other daughter will get none (*14*).

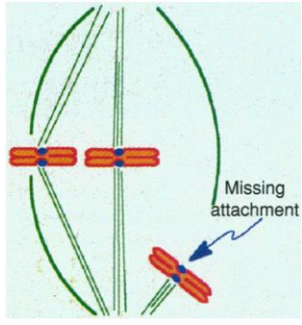

Fig. 3. A second sort of attachment error, illustrated for a somatic cell in mitosis. One kinetochore has failed to capture microtubules.

follows if, in spermatocytes, the Y is attached to one pole and the two X's to the opposite pole (Fig. 4A). Often, however, the three chromosomes fail to remain connected, and one X chromosome is free, not connected to the other two sex chromosomes (Fig. 4B). As often as not, the free X chromosome attaches to the same pole as the Y chromosome (Fig. 4B). The result would be sexually strange mantids in the next generation, mantids with extra or missing sex chromosomes. This does not happen, however. It has been known since the 1950s that cells with free X chromosomes are blocked in division and do not form sperm (*19*). The cost to the organism is the loss of about 10% of the sperm, but sperm are cheap compared to sexually unbalanced offspring.

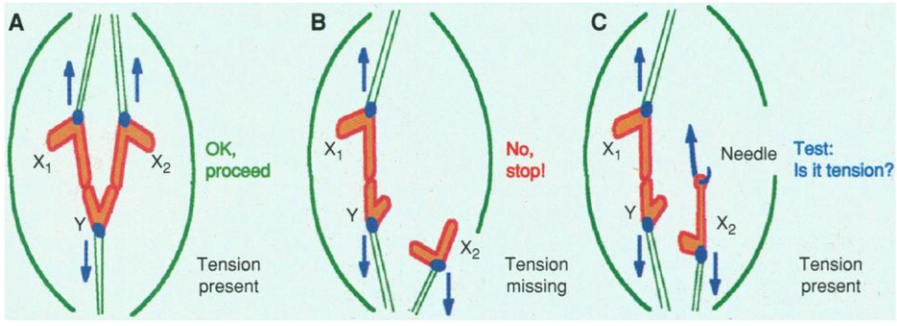

Fig. 4. A checkpoint can detect a single errant chromosome and prevent strange offspring (*19, 22*). (**A**) Praying mantids have three sex chromosomes. Normally, in male meiosis, the sex chromosomes are connected, and the Y chromosome is attached to one pole, whereas the two X chromosomes are attached to the opposite pole. The chromosomes are under tension from opposed mitotic forces (arrows). The cell proceeds promptly to division. (**B**) Sometimes, one X chromosome is free, not connected to the other two sex chromosomes. The free X chromosome experiences mitotic forces (arrow) to only one pole; tension is absent. A checkpoint delays the exit from division. (**C**) Testing the possibility that tension controls the checkpoint. The missing tension force on the free X chromosome is added by snagging the chromosome with a micromanipulation needle and pulling upward. Will the cell now go ahead and divide? [Adapted with permission *Nature* (*22*); copyright 1995, Macmillan Magazines]

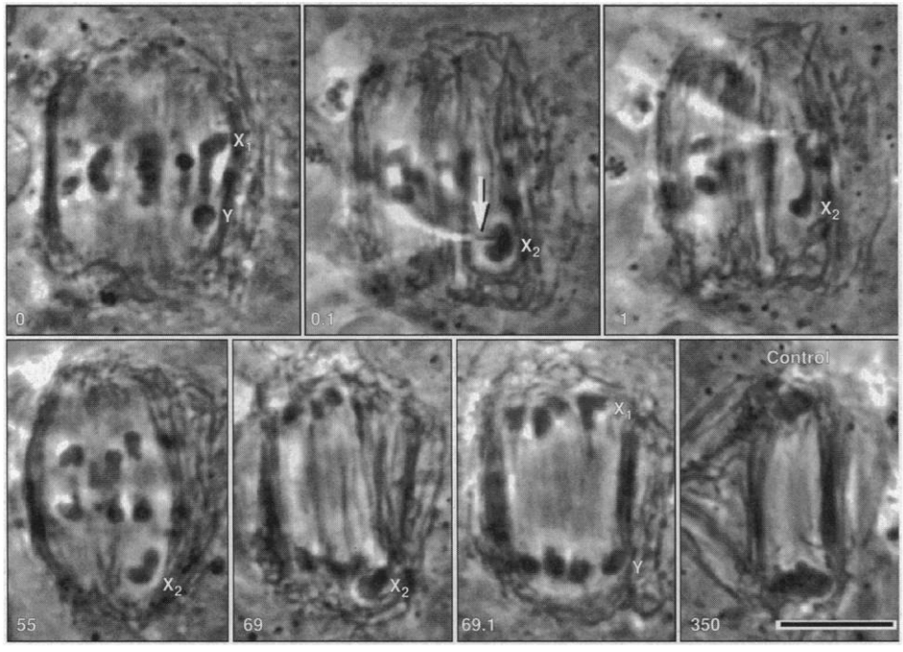

Fig. 5. Tension controls a cell cycle checkpoint (*22*). A living praying mantid cell in male meiosis, as seen by phase contrast microscopy, while it is being manipulated with a fine glass needle. The time (in minutes) is indicated on the lower left of each image. As in Fig. 4B, the three sex chromosomes have separated into an X_1-Y–chromosome pair (0 min image) and a free X_2 chromosome (0.1 min). Owing to the presence of the free X chromosome, the cell has been arrested in mid-division (sister cells with normal sex chromosomes divided about 4 hours earlier). The free X chromosome was impaled with a microneedle (arrow, 0.1 min) and stretched by moving the needle upward (1 min), placing the chromosome under tension. The cell entered anaphase after about an hour (55 to 69.1 min), and the sex chromosomes segregated improperly. An unmanipulated cell with a free X chromosome did not enter anaphase until 5 hours later (Control; 350 min image). Bar, 10 μm. [Reprinted with permission *Nature* (*22*); copyright 1995, Macmillan Magazines]

Different Errors, Different Compromises in Meiosis and Mitosis

Monopolar attachment (Fig. 2) is common in meiosis (*11*, *25*) and uncommon in somatic cell mitosis (*26*). Conversely, missing attachments (Fig. 3) are common in mitosis (*21*) but rare in meiosis. These disparities arise from an important difference in the construction of mitotic versus meiotic chromosomes. The kinetochores of chromosomes in mitosis lie in a pit (Fig. 3) (*27*). Such a configuration decreases the field of view of the kinetochore, so to speak; capture of microtubules occurs only when a microtubule happens to enter the pit. When a kinetochore faces a pole, it readily captures microtubules from that pole, but its sister cannot intercept microtubules from that same pole (Fig. 3). Consequently, monopolar attachment errors are rare. At the same time, however, a kinetochore in a pit can easily lie in a position in which successful encounters with microtubules from either pole are improbable (Fig. 3, right chromosome). The result is that proper attachment is often delayed.

Chromosomes in meiosis, however, have relatively exposed kinetochores (*28*, *29*), which can capture microtubules over a large angle (Fig. 2A). Consequently, a kinetochore can easily attach to either pole, and partner kinetochores often attach to the same pole (Fig. 2, A and B). Hence, monopolar attachment is frequent.

The relatively exposed kinetochores in meiosis make sense as an adaptation to processes at the heart of meiosis—chromosome pairing and recombination. These processes (and what follows after them) result in chromosomes in which the partner kinetochores are linked by long, sometimes convoluted stretches of rather flexible chromatin (*29*). Hence, the partner kinetochores are not rigidly constrained to face in opposite directions, as they are in mitosis, and both may capture microtubules from the same pole. Correction of the error requires that a kinetochore facing one pole somehow must capture microtubules from the opposite pole (Fig. 2B). This improbable encounter is made possible by relatively exposed kinetochores; if the kinetochores were recessed as they are in somatic mitosis, encounters with microtubules from the opposite pole would be very rare, and most

errors would go uncorrected (*29*, *30*).

On this view, kinetochores in meiosis and in somatic cell mitosis illustrate the compromises imposed by reliance on chance encounters for chromosome attachment to the spindle. The cell must strike a balance between hiding and exposing the kinetochores, a balance that minimizes monopolar attachment errors and yet permits the correction of those errors that do occur. In meiosis, coping with chance favors a moderately protuberant kinetochore, which facilitates the correction of monopolar attachment errors. In mitosis, sister kinetochores invariably are back-to-back and the balance is shifted toward a hidden kinetochore, which reduces the frequency of monopolar attachment to a very low level.

Linking Mechanics to Chemistry

Tension controls the checkpoint. What alerts the checkpoint to the presence of a single misattached chromosome? There are several possibilities. Misattached chromosomes lie near a pole, so the distinctive position might be noticed (Fig. 4B). Alternatively, the absence of tension might signal the checkpoint to delay division, as McIntosh (*31*) and, later, Rieder and co-workers (*21*) suggested. The tension proposal can be tested directly simply by using a micromanipulation needle to pull on a misattached chromosome in a living cell (Fig. 4C). The chromosome is stretched out and under tension. The test works: the cell proceeds into anaphase several hours ahead of cells with an unmanipulated, misattached chromosome (Fig. 5) (*22*). Thus, tension makes the misbegotten pass for normal. The checkpoint no longer detects an inhibitory signal, and the cell goes ahead and divides—even though an improper chromosome combination often results (Fig. 5). In an age of molecular biology, such experiments give those of us who manipulate chromosomes a sense of power: a manipulator can control all the complicated chemistry of the cell cycle just by pulling on a chromosome. In some cells, attachment to the spindle by itself (rather than tension following attachment) may suffice to signal the checkpoint that all is well, but tension as the signal remains a possibility even in those cells (*32*).

Tension changes kinetochore chemistry. How does tension signal the checkpoint? The probable answer is tension-sensitive protein phosphorylation. Certain kinetochore proteins in mammalian and insect cells are phosphorylated before the chromosomes attach to the spindle, and they become dephosphorylated after chromosomes attach properly (*33*, *34*). Most significantly for checkpoint control, the kinetochore proteins of misattached chromosomes remain phosphorylated (*33*, *34*).

The effect of tension on kinetochore protein phosphorylation has been determined directly in insect cells by micromanipulation (*34*, *35*). In the absence of experimental intervention, chromosomes with both kinetochores attached to the same pole are relaxed, not under tension (Fig. 2B), whereas properly attached chromosomes are under tension from opposed mitotic forces (Fig. 2E). The kinetochores of misattached, relaxed chromosomes have highly phosphorylated proteins: when immunostained with an antibody specific for the phosphorylated state, they appear much larger and somewhat brighter than the kinetochores of chromosomes under tension (Fig. 6). When such a chromosome is pulled with a micromanipulation needle so that it is visibly stretched and therefore is under tension, the kinetochores become dephosphorylated; they are far less bright after immunostaining than kinetochores of an unstretched, misattached chromosome (compare T_1 and T_2 in Fig. 7, D and E, with M_1 and M_2 in Fig. 6). The dephosphorylation caused by tension from a micromanipulation needle makes immunostained kinetochores indistinguishable from kinetochores subjected to tension from natural mitotic forces (T_1 to T_5 in Fig. 7, D and E).

The effect of relaxing the tension on a chromosome with dephosphorylated kinetochore proteins has also been tested by micromanipulation. The normal tension on properly attached chromosomes can be relieved by detaching them from the spindle (double arrowheads, Fig. 7B). This results in the rephosphorylation of kinetochore proteins (R_1 and R_2 in Fig. 7, D and E) (*34*, *35*).

We do not know how tension produces kinetochore protein dephosphorylation. One possibility is a direct effect on protein conformation, just like an allosteric response to binding a ligand (*34*, *36*). On this view, either experimenters or the cell is pulling on a polypeptide, changing its conformation and hence its activity (*34*, *37*). For example, tension might deform a protein kinase, inactivating it, leading to dephosphorylation of the phosphoprotein.

The evidence that tension-sensitive phosphorylation controls the checkpoint is entirely circumstantial, but it is abundant (*34*, *35*, *38*). Tension, whether from mitotic forces or from an experimenter's tugging, invariably has two effects: kinetochore dephosphorylation and a "go ahead" signal to the checkpoint. Conversely, the absence of tension, whether from natural causes or from micromanipulation, invariably has the opposite two effects: kinetochore phosphorylation and a "wait" signal to the checkpoint. Thus, the absence of tension in an unpaired mantid X-chromosome inhibits the onset of anaphase and is correlated with

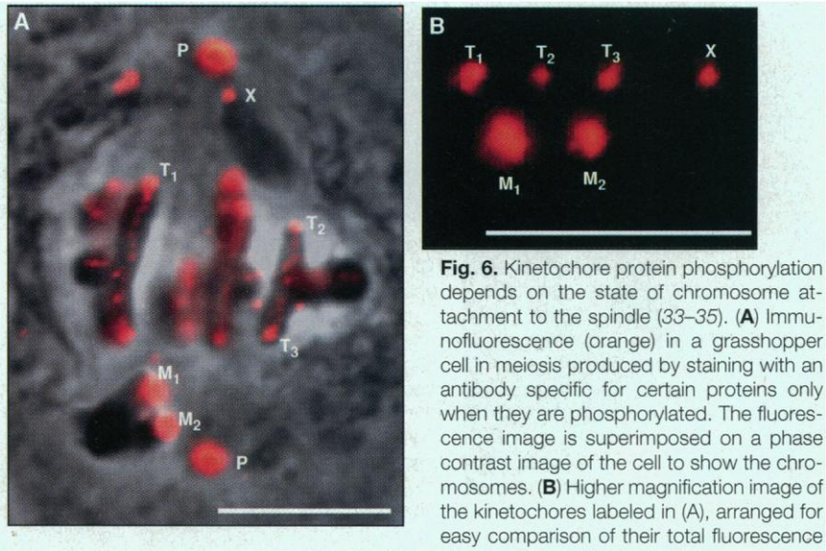

Fig. 6. Kinetochore protein phosphorylation depends on the state of chromosome attachment to the spindle (*33–35*). (**A**) Immunofluorescence (orange) in a grasshopper cell in meiosis produced by staining with an antibody specific for certain proteins only when they are phosphorylated. The fluorescence image is superimposed on a phase contrast image of the cell to show the chromosomes. (**B**) Higher magnification image of the kinetochores labeled in (A), arranged for easy comparison of their total fluorescence (the product of their brightness and their size). The kinetochores of properly attached chromosomes, under tension from mitotic forces, are dimly stained (T_1 to T_3), as is the X chromosome (X); these kinetochores have relatively little phosphorylated protein. In contrast, the kinetochores of a misattached, monopolar chromosome (M_1 and M_2) are large and bright; these kinetochores have large amounts of phosphorylated protein. The antibody recognizes many proteins, and the phosphorylation of most of them is not sensitive to the state of chromosome attachment [for example, the poles (P)]. Properly attached chromosomes show some residual immunofluorescence, but the fluorescence of improperly attached kinetochores is visibly much greater (B), and when measured, the total fluorescence per kinetochore is invariably two to three times greater than that of properly attached kinetochores (*34*, *35*). Bar, 10 μm. [Adapted from (*34*) with permission The Rockefeller University Press]

a phosphorylated kinetochore (*35*). Similarly, relaxed spermatocyte chromosomes with their rephosphorylated kinetochores (Fig. 7) delay the exit from cell division indefinitely (*34*).

A particularly convincing correlation between phosphorylation and the checkpoint response comes from evolutionary differences in sex chromosomes. The X chromosome of some organisms such as grasshoppers is never under tension in male meiosis, yet it does not inhibit the exit from cell division (if it did, no sperm would be formed). An elegant way to achieve this would be to keep the checkpoint but to silence the X chromosome, so that it sends no signal to the checkpoint. If that is indeed the mechanism and if kinetochore phosphorylation is the "delay exit" signal, then the kinetochore of the sex chromosome should be dephosphorylated even though tension is absent. Exactly that is seen: the X chromosome's kinetochore (X, Figs. 6 and 7) is as dim after immunostaining as are the kinetochores of ordinary chromosomes that are under tension from mitotic forces (*34*).

The final, most striking correlation comes from injecting living cells with the antibody that recognizes the phosphorylated kinetochore proteins. Kinetochore dephosphorylation is delayed and the exit from mitosis is correspondingly delayed (*38*).

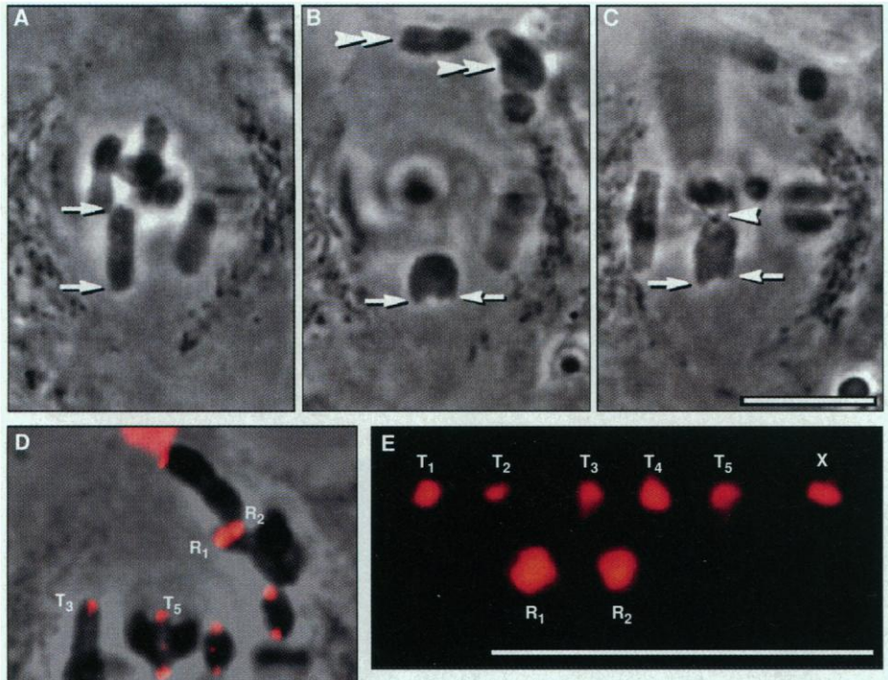

Fig. 7. Tension affects kinetochore chemistry (*34*, *35*). (**A** to **C**) Phase contrast microscopy of a living grasshopper spermatocyte. (A) Before micromanipulation. The cell is nearing metaphase, and all the chromosomes have properly attached to the spindle. (B) By micromanipulation (not shown), two chromosomes (double arrowheads) have been detached from the spindle by pulling sharply on them; they are relaxed, free of tension from mitotic forces. These chromosomes were kept relaxed by redetaching them as necessary until the cell was fixed. In addition, an improperly attached chromosome was manufactured by detaching a chromosome (A, arrows at kinetochores) and bending it (B) so that both kinetochores (arrows) faced the same pole (the lower pole). Such kinetochores promptly capture microtubules growing from the pole they face so that both kinetochores become attached to the same pole. (C) The missing tension was added to the improperly attached chromosome (arrows at kinetochores) by pulling it upward with a micromanipulation needle (arrowhead). The chromosome was kept under tension for 5 min, and then the cell was fixed and immunostained as described in Fig. 6. (**D** and **E**) The stretched chromosome (kinetochores: T_1 and T_2) was released from the needle just before fixation, and it returned immediately to its unstretched length. Two kinetochores of the relaxed chromosomes are in focus (R_1 and R_2). They are large and brightly stained: the tension-sensitive proteins are phosphorylated. All the other kinetochores are under tension (T_1 to T_5). They are dim: the tension-sensitive kinetochore proteins are dephosphorylated in response to tension, whether the tension is from mitotic forces or from a microneedle. Bar, 10 μm. Unpublished images from the study reported in (*34*).

We may soon understand the molecular biology of the tension-sensitive checkpoint, thanks largely to work on a similar or identical checkpoint in budding yeast. Components of the yeast checkpoint include a protein kinase (*24*) and a protein whose phosphorylation by that kinase is implicated in activation of the checkpoint (*39*). Two yeast checkpoint proteins have relatives that are kinetochore components in other cells (*40*–*42*). A particularly enticing candidate is a yeast protein whose vertebrate relative is present at the kinetochore before chromosome attachment and then is lost from the kinetochore after proper attachment is achieved (*41*, *42*). Thus, this protein behaves somewhat like the protein in insect cells whose phosphorylation is sensitive to tension, although it probably is not the same protein (*41*). Beyond the checkpoint, much remains to be learned. After the checkpoint gives the "go ahead" signal, there is a substantial pause before the actual exit from cell division (*34*, *35*), and we do not know what happens during this pause, before the activation of the anaphase-promoting complex (*17*, *43*) and the terminal events in cell division such as cyclin destruction (*44*).

Conclusions

Mitotic forces are needed for the basic act of mitosis, the separation of the chromosomes. Elegantly, those same forces are also used to correct errors (by generating stability differences) and to detect errors (by signaling a checkpoint). The chancy process of chromosome transmission normally works to perfection because the outcome of chance events is monitored by the cell as it generates tension forces.

Sensitivity to mechanical stress is a general cell property (*45*). The common theme is the transduction of mechanical force into chemical change, just the opposite of the transduction of chemical change into mechanical force seen in muscle and other motile systems (*34*). Exactly how mechanical force is transformed into the chemical regulation of a cell's activities is not known in any system. We are in the enviable position in which a cellular capability of obvious significance has been discovered, and yet much of interest remains to be learned.

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RESEARCH ARTICLE

Observation of Interference Between Two Bose Condensates

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Interference between two freely expanding Bose-Einstein condensates has been observed. Two condensates separated by ~40 micrometers were created by evaporatively cooling sodium atoms in a double-well potential formed by magnetic and optical forces. High-contrast matter-wave interference fringes with a period of ~15 micrometers were observed after switching off the potential and letting the condensates expand for 40 milliseconds and overlap. This demonstrates that Bose condensed atoms are "laser-like"; that is, they are coherent and show long-range correlations. These results have direct implications for the atom laser and the Josephson effect for atoms.

The realization of Bose-Einstein condensation (BEC) in dilute atomic gases has created great interest in this new form of matter. One of its striking features is a macroscopic population of the quantum-mechanical ground state of the system at finite temperature. The Bose condensate is characterized by the absence of thermal excitation; its kinetic energy is solely the result of zero-point motion in the trapping potential (in general, modified by the repulsive interaction between atoms). This is the property that has been used to detect and study the Bose condensate in previous experiments. The Bose-Einstein phase transition was observed by the sudden appearance of a "peak" of ultracold atoms, either in images of ballistically expanding clouds (time-of-flight pictures) (*1–3*) or as a dense core inside the magnetic trap (*4, 5*). The anisotropic expansion of the cloud (*1–3*) and the appearance of collective excitations at frequencies different from multiples of the trapping frequencies (*6, 7*) were found to be in quantitative agreement with the predictions of the mean-field theory for a weakly interacting Bose gas (*8–11*). However, similar anisotropic expansion and excitation frequencies have been predicted for a dense classical gas in the hydrodynamic regime (*12, 13*) and are therefore not distinctive features of BEC. Indeed, the nonlinear Schrödinger equation is equivalent to a hydrodynamic equation for superfluid flow, which, in many situations, is very similar to a classical hydrodynamic equation (*9, 13, 14*). Previous BEC studies have mainly concerned the "very cold" nature of the Bose condensate but have not revealed properties that directly reflect its coherent nature, such as its phase, order parameter (macroscopic wave function), or long-range order. In superconductors, the phase of the order parameter was directly observed through the Josephson effect, whereas in superfluid helium the observation of the motion of quantized vortices (*15*) provided indirect evidence.

The coherence of a Bose condensate has been the subject of many theoretical studies. Kagan and collaborators predicted that the Bose condensate will form first as a quasi-condensate consisting of very cold atoms but lacking long-range order, which is only established on a much longer time

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