al decade-long periods of profound drought.

If, as Bond *et al.* (*3*) suggest, the cyclic changes in ice-rafted debris composition reflect oscillations in the strength of the Atlantic's conveyor circulation, one might expect temperature changes in Antarctica to have been opposite in phase to those in the North Atlantic, as was the case during the last deglaciation (*18*). Clow has carried out a deconvolution of the temperature record at the Antarctic Taylor Dome site (*19*). His reconstruction shows that the air temperature was 3°C colder during the time of the Medieval Warm Period than during that of the Little Ice Age. This record suggests that conditions in Antarctica underwent an antiphased oscillation during the Medieval Warm Period–Little Ice Age period.

The Case for a Global Event

The case for a global Medieval Warm Period admittedly remains inconclusive. But keeping in mind that most proxies do not have adequate sensitivity, it is interesting that those capable of resolving temperature changes of less than 1°C yield results consistent with a global Medieval Warm Period. To test whether this is indeed the case, we require Holocene snowline fluctuation records for tropical and Southern Hemisphere sites and continued studies of wood and peat exposed by the continuing retreat of Northern Hemisphere glaciers. As the world's mountain glaciers continue to retreat, ever more evidence for past Holocene warm episodes will be exposed.

One might ask why the strength of the Atlantic's conveyor circulation oscillates on a time scale of one cycle per 1000 to 2000 years. I suspect that it has to do with the export through the atmosphere of water vapor from the Atlantic to the Pacific Ocean. The magnitude of this export has been estimated to be $(0.25 \pm 0.10) \times 10^6$ m^3/s (*20*). If this freshwater loss were not balanced by the export of salt from the Atlantic, the latter's salt content would rise at the rate of about one gram per liter each 1500 years. Such an increase in salt content would densify cold surface water by an amount equivalent to a 4 to 5 K cooling, thereby strongly altering the buoyancy of surface waters in the North Atlantic and hence their ability to sink to the abyss.

I believe that this salt export is not continuous but episodic. The salt content of the Atlantic periodically builds up until a strong conveyor circulation mode is turned on, causing the salt content to drain down. Eventually, a weak circulation mode kicks in, allowing the salt content to build up again. I have suggested previously (*21*) that an apparent mismatch between radiocarbon and chlorofluorocarbon-based estimates of the rate of deep-water formation in the Southern Ocean may reflect a change in circulation after the Little Ice Age.

The geographic pattern of Holocene climate fluctuations remains murky, but several things are clear. The Little Ice Age and the subsequent warming were global in extent. Several Holocene fluctuations in snowline, comparable in magnitude to that of the post–Little Ice Age warming, occurred in the Swiss Alps. Borehole records both in polar ice and in wells from all continents suggest the existence of a Medieval Warm Period. Finally, two multidecade-duration droughts plagued the western United States during the latter part of the Medieval Warm Period. I consider this evidence sufficiently convincing to merit an intensification of studies aimed at elucidating Holocene climate fluctuations, upon which the warming due to greenhouse gases is superimposed.

References and Notes

1. M. E. Mann, R. S. Bradley, M. K. Hughes, *Geophys. Res. Lett.* **26**, 759 (1999).
2. J. M. Grove, *The Little Ice Age* (Methuen, New York, 1988), pp. 1–198.
3. G. C. Bond *et al.*, *Mechanisms of Global Climate Change at Millennial Time Scales, Geophysical Monograph Series*, vol. 112 (American Geophysical Union, Washington, DC, 1999), pp. 35–58.
4. A. Lotter *et al.*, *Palaeogeogr. Palaeoclimatol. Palaeoecol.* **159**, 349 (2000).
5. S. C. Porter, *Quat. Sci. Rev.*, in press.
6. M. Maisch *et al.*, *Die Gletscher der Schweizer Alpen* (Hochschulverlag AG an der ETH Zürich, Zürich, 1999), pp. 221–256.
7. M. Greene, W. S. Broecker, D. Rind, *Geophys. Res. Lett.* **26**, 1909 (1999).
8. H. Holzhauser, in *Paläoklimaforschung Palaeoclimate Research 24, Special Issue: ESF Project* "European Palaeoclimate and Man 16," B. Frenzel *et al.*, Eds. (Verlag, Stuttgart, 1997), pp. 35–58.
9. F. Rothlisberger *et al.*, *Geogr. Helv.* **35/5**, 21 (1980).
10. A. Hormes, *The ^{14}C Perspective of Glacier Recessions in the Swiss Alps and New Zealand* (Verlag, Osnabrück, Germany, 2001), p. 176.
11. A. Hormes, C. Schlüchter, T. F. Stocker, *Radicarbon* **40**, 809 (1998).
12. A. Hormes, B. U. Müller, C. Schlüchter, *Holocene*, in press.
13. E. J. Steig *et al.*, *Science* **282**, 92 (1998).
14. S. Huang, H. N. Pollack, P. O. Snen, *Geophys. Res. Lett.* **24**, 1947 (1997).
15. S. Stine, in *Water, Environment and Society in Times of Climatic Change*, A. S. Issar, N. Brown, Eds. (Kluwer Academic, Amsterdam, Netherlands, 1998), pp. 43–67.
16. The level that would have existed had there been an annual snowmelt-induced overflow.
17. S. Stine, *Nature* **369**, 546 (1994).
18. W. S. Broecker, *Paleoceanography* **13**, 119 (1998).
19. G. Clow, personal communication.
20. F. Zaucker, W. S. Broecker, *J. Geophys. Res.* **97**, 2765 (1992).
21. W. S. Broecker, S. Sutherland, T.-H. Peng, *Science* **286**, 1132 (1999).
22. M. Stuiver *et al.*, *Radiocarbon* **40**, 1041 (1998).

PERSPECTIVES: CELL CYCLE

Centrioles at the Checkpoint

Andrew W. Murray

The cellular organelle called the centriole has been an enigma to biologists for more than a century. Centrioles were first seen as a pair of dots at the center of the cell surrounded by a granular mass (the centrosome) from which radiated arrays of fibers. Subsequent work revealed that these fibers are composed of microtubules assembled from monomers of α- and β-tubulin. The centrosome contains a special form of tubulin (γ-tubulin) that initiates microtubule assembly (a process called nucleation), and the centrioles are composed of highly ordered arrays of short, specialized microtubules. Like DNA, centrioles replicate once during the cell division cycle, but they do so conservatively by forming a completely new centriole (*1*), rather than by distributing the original material between daughter molecules, as DNA does (see the figure). Applying to the centriole the maxim of baseball sage Yogi Berra—"You can observe a lot by watching"—Hinchcliffe, Piel, and their colleagues (*2*, *3*) report on pages 1547 and 1550 of this issue that the centriole regulates key steps in the cell division cycle.

Centrosomes control cell organization and polarity by initiating formation of microtubules, but what is the role of the centrioles that lie within them? Centrioles are not absolutely essential for progression through the cell cycle because some animal oocytes divide successfully despite having destroyed their centrioles early in the meiotic cell cycle, and early embryos can replicate their DNA and pass through mitosis without either centrioles or centrosomes (*4*). Previous (although indirect) attempts to investigate centrosomes in postembryonic cells concluded that centrioles were needed for cells to enter mitosis, the final phase of the cell cycle (*5*).

Hinchcliffe *et al.* (*2*) examined the problem directly. They delicately cut cultured cells in half to separate the centriole from the nucleus and then watched the halved cells for several days with a video microscope. In contrast to earlier results, the abused cells entered mitosis normally and assembled the typical bipolar mitotic spindle. Beyond this point, however, their behavior became increasingly abnormal. There were long delays before the initiation of chromosome segregation, many of

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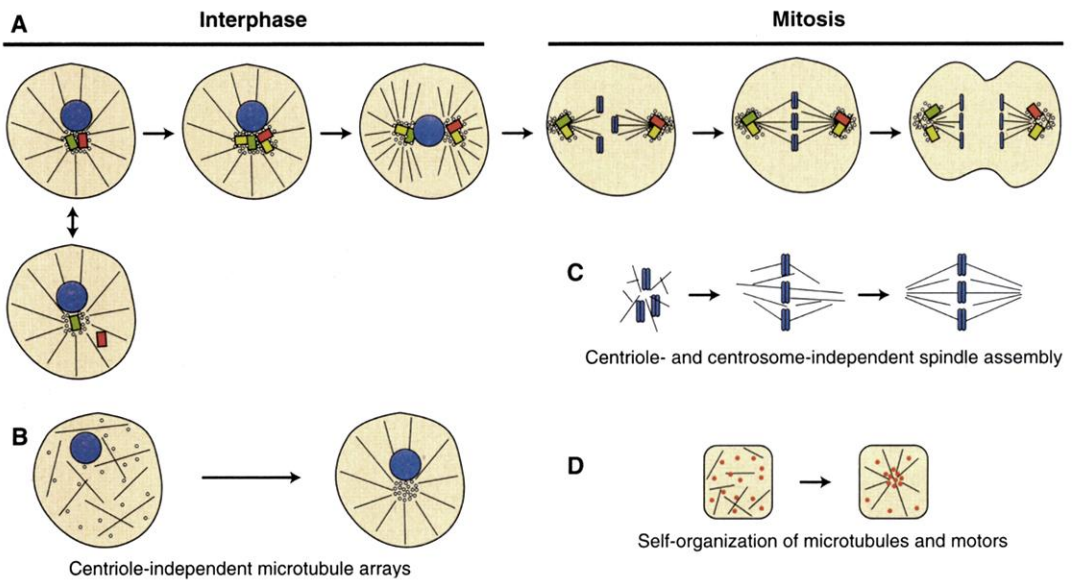
the cells aborted their attempts to divide in two, and none of the cells replicated their DNA after passing through interphase of the next cycle. The mitotic defects are not surprising given that centrioles and centrosomes organize assembly of the mitotic spindle, the array of microtubules that directs chromosome segregation and cell division.

The lack of DNA replication can be interpreted in two ways. The first is that the centriole must activate or concentrate some essential factor needed to induce DNA replication. The second, and more appealing, possibility is that when cells exit mitosis in the absence of a centriole, they activate a regulatory circuit, or checkpoint, that prevents DNA replication. Cells that enter mitosis without centrioles have abnormal mitotic spindles and would be likely to make mistakes during chromosome segregation. Keeping these cells from proliferating would help to prevent them from accumulating chromosomal abnormalities. One plausible explanation for why these cells arrest their cell cycles depends on the spindle checkpoint (*6*, *7*), which delays, but cannot prevent, cells with chromosomes that are incorrectly aligned on the spindle from exiting mitosis. Mouse cells that leave mitosis with the checkpoint still active arrest in G_1 phase of the next cell cycle. This arrest depends on the activity of the p53 tumor suppressor protein (*8*). The absence of centrioles is likely to activate the spindle checkpoint, providing a plausible and testable explanation for why cells without centrioles arrest in G_1, and for why cells with mutations in p53 accumulate abnormal numbers of centrosomes and centrioles (*9*).

Piel *et al.* (*3*) took a slightly different tack. They carefully followed cells whose centrioles had been tagged by attaching green fluorescent protein to centrin, a centrosomal protein. As cells exit mitosis, the cleavage furrow contracts to form the midbody, a narrow, microtubule-filled neck that connects the two daughter cells. At this stage the mother and daughter centriole split from each other and wander around the almost divided cell (see the figure). Strikingly, the completion of cell division is tightly connected with the behavior of the mother centriole. When the mother centriole visits the midbody, the microtubules within the midbody disappear, and when it moves back into the bulk of the cell, the final stage of cell division occurs. Two pieces of evidence suggest that the arrival and departure of the mother centriole trigger the completion of cell division. First, a *Drosophila* cell line that lacks centrioles has profound defects in cell division. Second, altering cell adhesion in ways that prevent the centriole from visiting the midbody impairs cell division. In both cases, cells may divide by the alternative mechanism of simply crawling away from each other until the linkage between them snaps.

Is the centriole directly triggering cell division, or is it releasing the cell from arrest at a checkpoint? Recent results in budding yeast suggest the latter possibility. The delivery of a spindle pole body (the equivalent of centriole plus centrosome) to the daughter yeast cell is required to induce cell division. This dependence is due to a checkpoint, because it can be completely suppressed by removing Bub2, a guanosine triphosphatase–activating protein that normally restrains cell division (*10*–*12*). This phenomenon is analogous to Piel *et al.*'s proposal that the mother centriole must visit the midbody before animal cells can divide, and it will be interesting to see whether the molecular details of this cell-division checkpoint have been conserved. The second point is that blocking centriole duplication appears to keep cells from entering mitosis (*13*), whereas removing the centriole entirely does not. The simple interpretation of these observations is that centrioles are not needed for cells to enter mitosis, but a checkpoint can arrest the cell if it detects abnormalities in centriole number or behavior.

The possible connection between the centriole and cell cycle checkpoints may help to solve the central riddle of the centriole: how an object that lies at the center of the microtubule-organizing center can be dispensed with for many steps in cell division. Centrioles are not essential for assembling spindles, segregating chromosomes, directing cell division, or forming centrosomes. In the absence of centrioles, these processes depend on self-organization—centrosomal components, organelles, and microtubules interact with each other to produce polarized microtubule arrays that resemble centrosomes (*1*, *14*, *15*), and chromosomes and microtubules influence each other's behavior to form spindles (*16*–*18*). In principle, such self-organization requires a very small number of components because mixtures of microtubules and microtubule motors form organized structures when confined to cell-sized enclosures (see the figure) (*19*).



Checking out the centriole. Centrosome behavior during the cell division cycle. (**A**) Cells in G_1 contain a single centriole pair, composed of an old (green bar) and a new (red bar) centriole. Both centrioles are usually located close to the nucleus (blue) and are surrounded by components of the centrosome (yellow dots), which initiate microtubule assembly. The centrioles duplicate conservatively during interphase, producing two pairs each composed of a mother centriole and a daughter centriole (yellow bar). As cells prepare to enter mitosis, the two centrosomes (each containing a centriole pair) move apart to opposite sides of the nucleus, so that they can act as the poles of the mitotic spindle after the nucleus breaks down. In anaphase, the connection between the mother and daughter centrioles is broken. (**B**) Centrosomal components and microtubules can organize themselves into a centrosome-like structure in cells that lack centrioles. (**C**) Chromosomes (blue) can alter the local distribution of microtubules; and chromosomes, microtubules, and microtubule motors can interact to form a bipolar spindle. (**D**) Microtubules and microtubule motors (red dots) can self-organize in glass chambers the same size as cells.

The centriole induces the formation of centrosomes at specific times and in specific places, thus increasing the accuracy and speed of the processes the centrosome directs. For example, the centriole's orderly replication and splitting ensures that each cell inherits a single centrosome as it enters the cell cycle and duplicates this organelle before dividing. Cells lacking centrioles are more likely to make mistakes in chromosome segregation, thus threatening the survival of the cellular cooperatives they belong to. This danger can be prevented by evolving checkpoints that make completing cell division and starting the next round of DNA replication dependent on the presence of centrioles.

I suspect that this pattern is a common theme in the evolution of cellular processes. These processes first appear as slow and inaccurate self-assembly pathways that are governed by very simple rules. Subsequently, speed and fidelity evolve by adding components, such as centrioles, that direct or template what used to be self-assembly. To ensure that the improvements are used, cells evolve checkpoints that make initiating the process dependent on recruiting new components. If the requirements for efficiency are sufficiently high, the new and old components may be merged into the same structure, making both truly indispensable. This appears to have happened in the yeast spindle pole body, which has combined the functions of centrosome and centriole into a single indissoluble organelle. Another example of increasing template dependence is the centromere, the specialized region of the chromosome that attaches it to microtubules. At one extreme, the centromeres of *Drosophila* appear to assemble independently of the DNA sequence and are propagated by a process of self-assembly (*20*); those of mammals appear to be templated by specific DNA sequences under normal conditions but are capable of self-assembly as well. At the other extreme are budding yeast, which are absolutely dependent on specific DNA sequences to direct centromere assembly (*21*).

If the logic of progressive refinement and checkpoint dependence is correct, then many proteins and protein networks may be indispensable only because their absence activates checkpoints designed to guard against error. A checkpoint-independent requirement for other proteins may reflect the fuller integration of these newer components into previously self-sufficient trial-and-error processes. If repeated, such integrations could explain the evolutionary steps that converted the first forms of life into today's complex and sophisticated cells.

References

1. R. S. Kochanski, G. G. Borisy, *J. Cell Biol.* **110**, 1599 (1990).
2. E. H. Hinchcliffe *et al.*, *Science* **291**, 1547 (2001).
3. M. Piel *et al.*, *Science* **291**, 1550 (2001).
4. J. Gerhart *et al.*, *J. Cell Biol.* **98**, 1247 (1984).
5. A. Maniotis, M. Schliwa, *Cell* **67**, 495 (1991).
6. A. Amon, *Curr. Opin. Genet. Dev.* **9**, 69 (1999).
7. J. V. Shah, D. W. Cleveland, *Cell* **103**, 997 (2000).
8. J. S. Lanni, T. Jacks, *Mol. Cell. Biol.* **18**, 1055 (1998).
9. K. Fukasawa *et al.*, *Science* **271**, 1744 (1996).
10. A. Bloecher *et al.*, *Nature Cell Biol.* **2**, 556 (2000).
11. G. Pereira *et al.*, *Mol. Cell* **6**, 1 (2000).
12. Y. Wang *et al.*, *Curr. Biol.* **10**, 1379 (2000).
13. M. Okuda *et al.*, *Cell* **103**, 127 (2000).
14. M. A. McNiven *et al.*, *Cell* **37**, 753 (1984).
15. V. I. Rodionov, G. G. Borisy, *Nature* **386**, 170 (1997).
16. E. Karsenti *et al.*, *J. Cell Biol.* **98**, 1730 (1984).
17. R. Heald *et al.*, *Nature* **382**, 420 (1996).
18. S. Brunet *et al.*, *J. Cell Biol.* **146**, 1 (1999).
19. F. J. Nedelec *et al.*, *Nature* **389**, 305 (1997).
20. X. Sun *et al.*, *Cell* **91**, 1007 (1997).
21. G. R. Wiens, P. K. Sorger, *Cell* **93**, 313 (1998).

PERSPECTIVES: ELECTRONICS

Toward Paperlike Displays

John A. Rogers

Low-cost electronic displays that look and feel like conventional printed paper will dramatically change the way we use and interact with laptop computers, personal digital assistants, and cellular telephones. They will also alter our notions of newspapers, magazines, greeting cards, and even cereal boxes, bumper stickers, and wallpaper.

Such "electronic paper" displays are radically different from traditional electronic systems, which rely on cathode ray vacuum tubes or liquid crystals with silicon-based circuitry on plates of glass. Electronic paper is a thin, high-contrast, reflective display that can be flexed, bent, rolled-up, and folded. A portable computer that uses this technology will resemble a pad of paper more closely than a standard laptop. Future printed paper products will retain the attractive appearance of conventional ink on paper but will be reconfigurable and reusable. A newspaper, for example, will consist of one or several sheets of electronic paper onto which information content, including animated images, will be downloaded through the wireless internet.

The technologies required for paperlike displays are just beginning to emerge from research laboratories in the form of realistic prototypes. The first sheets of electronic paper were recently demonstrated by Bell Labs and E Ink Corporation at the Fall 2000 meeting of the Materials Research Society (*1*). They incorporate the three new technologies that are essential for these types of systems: electronic "inks" for the optical component of the display, mechanically flexible transistors and circuits to drive the ink, and low-cost fabrication techniques to produce the circuits. The Bell Labs/E Ink displays use thin rubber-stamped plastic circuits and electrophoretic inks.

Two types of electronic inks are currently under development for commercial use in large-scale signs. One uses microencapsulated suspensions of charged white particles in a black fluid (*2*); the other relies on tiny rotatable balls that are white on one side and black on the other (*3*). Both are well-suited for electronic paper: They are thin (0.1 to 0.2 mm) and power efficient, they can support high-resolution images (more than 200 pixels per inch), and their contrast is better than newsprint.

To produce electronic paper displays, these "inks" must be laminated onto sheets of active matrix drive circuitry. These types of circuits use transistors at each pixel location to control the electric fields that determine the color of the "ink." They must be mechanically flexible and should be built on thin, low-cost plastic substrates. Meeting these requirements requires materials and patterning techniques that are completely different from those currently used in the microelectronics industry. Most plastics, for example, cannot survive the high-temperature deposition steps that are common for conventional silicon-based circuits. Also, plastic sheets typically have surfaces that are rougher and more uneven than traditional silicon or glass substrates. These and other characteristics make them difficult to process in traditional ways.

Over the last several years, substantial progress has been made toward materials and patterning methods for flexible electronics on plastic. Several classes of semiconductors can now be deposited on plastics at low temperatures: inorganics formed from solution or cast from colloidal suspensions, hybrid inorganic-organic materials, small molecule organics, and even polymers (*4*). A few of them

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