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Do Centrioles Generate a Polar Ejection Force?

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Abstract. *A microtubule-dependent polar ejection force that pushes chromosomes away from spindle poles during prometaphase is observed in animal cells but not in the cells of higher plants. Elongating microtubules and kinesin-like motor molecules have been proposed as possible causes, but neither accounts for all the data. In the hypothesis proposed here a polar ejection force is generated by centrioles, which are found in animals but not in higher plants. Centrioles consist of nine microtubule triplets arranged like the blades of a tiny turbine. Instead of viewing centrioles through the spectacles of molecular reductionism and neo-Darwinism, this hypothesis assumes that they are holistically designed to be turbines. Orthogonally oriented centriolar turbines could generate oscillations in spindle microtubules that resemble the motion produced by a laboratory vortexer. The result would be a microtubule-mediated ejection force tending to move chromosomes away from the spindle axis and the poles. A rise in intracellular calcium at the onset of anaphase could regulate the polar ejection force by shutting down*

the centriolar turbines, but defective regulation could result in an excessive force that contributes to the chromosomal instability characteristic of most cancer cells.

Keywords. Centriole; Centrosome; Polar ejection force; Chromosomal instability; Cancer.

1. INTRODUCTION

In dividing animal cells, the back-and-forth movement of chromosomes during prometaphase is produced by at least two forces. One force tends to pull chromosomes poleward by means of microtubules attached to their kinetochores, and the other tends to push chromosomes as a whole away from the pole. When these forces balance, the chromosomes line up at the metaphase plate, midway between the two spindle poles, in preparation for their separation and poleward movement in anaphase.

Regarding the pushing force, Metz [1933] noted that when chromosomes move away from a spindle pole they “give the appearance of being carried by currents”, though “no true currents are involved” and “the only flowing motion concerned is that of the material immediately around the individual chromosome”. Carlson [1938] attributed this behavior to “repelling forces, whatever their nature, between poles and chromosomes”; Schrader [1947] described it as a “tendency of the spindle body to evict the chromosomes”; and Östergren, Bajer and Molè-Bajer [1960] wrote that it was due to “elimination forces acting on the chromosome arms in the direction away from the centrosomes”. The phenomenon is now known as the “polar wind” or “polar ejection force” (Rieder *et al.* [1986]; Salmon [1989]; Rieder and Salmon [1994]).

The polar ejection force depends on microtubules that extend from the spindle pole. When dividing cells are treated with depolymerizing agents that leave kinetochore microtubules intact but deplete polar microtubules, the ejection force is eliminated and chromosomes move closer to the poles. In cells treated with the microtubule-stabilizing agent taxol, the ejection force increases and chromosomes move farther from the pole (Salmon [1989];

Ault *et al.* [1991]; Cassimeris *et al.* [1994]).

Kinetochore microtubules do not exert a significant pushing force on chromosomes (Rieder *et al.* [1986]; Waters *et al.* [1996]; Khodjakov and Rieder [1996]). It has been suggested that the ejection force may be due to elongating non-kinetochore microtubules (Rieder *et al.* [1986]; Cassimeris *et al.* [1987]), but such pushing is observed in taxol-treated cells of higher plants (Bajer *et al.* [1982]), even though those cells do not possess a pre-anaphase polar ejection force (Khodjakov *et al.* [1996]). Furthermore, Fuge [1997] observed that chromosomes being transported by the polar ejection force appear to be sliding laterally along non-kinetochore microtubules rather than being pushed by the ends of growing microtubules. Fuge concluded that the phenomenon is more likely due to DNA-binding, kinesin-like motor molecules.

One such molecule is the *Drosophila* protein Nod (Zhang *et al.* [1990]; Afshar *et al.* [1995]), which has been proposed as a possible generator of polar ejection forces. But Nod lacks motile properties in microtubule gliding assays, suggesting that the protein provides transient attachments of chromosomes to microtubules rather than directional transport (Matthies *et al.* [2001]).

The *Xenopus* protein Xklp1 contains a kinesin-like microtubule-binding domain, associates with mitotic chromosomes, and is essential for chromosome positioning in egg extracts (Vernos *et al.* [1995]). Klp38B is a *Drosophila* kinesin-like protein that likewise associates with chromosomes during mitosis (Ruden *et al.* [1997]; Molina *et al.* [1997]). It now appears likely, however, that the function of Xklp1 and Klp38B is not to generate a polar ejection force but to establish and maintain spindle bipolarity (Walczak *et al.* [1998]; Antonio *et al.* [2000]; Funabiki and Murray [2000]).

The human protein Kid has a kinesin-like domain that binds to microtubules and another domain that binds to DNA (Tokai *et al.* [1996]). Removing a similar protein, Xkid, from *Xenopus* egg extracts prevents normal metaphase chromosome alignment, and blocking the degradation of Xkid prevents poleward movement of chromosomes at anaphase (Funabiki and Murray [2000]). When anti-Xkid antibodies are added to metaphase spindles with aligned chromosomes, chromosome arms move poleward (Antonio *et al.* [2000]); and in cultured human cells injected with antibodies

against Kid, chromosome arms remain extended toward the spindle poles (Levesque and Compton [2001]). These data are consistent with the hypothesis that Kid and Xkid produce a polar ejection force.

On the other hand, maturing *Xenopus* oocytes depleted of Xkid show no defect in metaphase chromosome alignment during meiosis I (Perez *et al.* [2002]). Furthermore, although a bacterially expressed protein containing a Kid fragment showed motility in a coated bead assay, Kid (like Nod) shows no motile activity in microtubule gliding assays (Yajima *et al.* [2003]). Thus it has not been demonstrated that Kid and Xkid actually move chromosomes.

In any case, if the polar ejection force were due to kinesin-like proteins then one would expect to see chromatin stretched away from the pole along polar microtubules that penetrate or laterally contact it, yet the electron microscopy data do not show this (Rieder and Salmon [1998]). Therefore, although elongating microtubules and kinesin-like proteins may play a role in positioning chromosomes at the metaphase plate, it seems that neither completely accounts for the polar ejection force.

Something more must be involved, and a clue to that something may be the fact that animal cells possess centrioles and a pre-anaphase polar ejection force, while the cells of higher plants possess neither (Luykx [1970]; Pickett-Heaps [1971]; Khodjakov *et al.* [1996]). In the hypothesis proposed here, centrioles produce a microtubule-mediated polar ejection force by generating oscillations in the spindle that resemble the motion of a laboratory vortexer.

2. CENTRIOLE STRUCTURE AND FUNCTION

Except for their role in nucleating cilia and flagella, the precise function of centrioles remains mysterious (Lange and Gull [1996]; Preble *et al.* [2000]). Stubblefield and Brinkley [1967] proposed that movements of the centriole's triplet microtubules turn an internal helix (which they believed to be DNA) to facilitate microtubule assembly. It has since become clear, however, that centrioles

do not contain DNA (Marshall and Rosenbaum [2000]). Bornens [1979] suggested that rapidly rotating centrioles, powered by an ATPase at their proximal ends, function like gyroscopes that provide an inertial reference system for the cell and generate electrical signals to coordinate cellular processes.

Since 1980 there has been relatively little interest in hypotheses about the structure and function of centrioles. This may be due partly to the dominance of neo-Darwinian theory: because all centrioles appear to be equally complex, there are no plausible evolutionary intermediates from which to reconstruct phylogenies (Fulton [1971]), so centrioles have attracted little interest from neo-Darwinian biologists. Furthermore, the reductionist approach to living cells that is implicit in neo-Darwinian theory has focused attention on individual molecules rather than the centriole's overall structure and function.

In structure, centrioles are roughly cylindrical. When mature they typically have a diameter of about $0.2\ \mu\text{m}$ and a length of about $0.4\ \mu\text{m}$. The end of a centriole closest to the center of the cell is called "proximal", and the other end is called "distal". The organelle is composed of nine clusters of microtubules organized as triplets in the proximal half; but the outermost microtubule terminates about halfway toward the distal end, which consists of doublet microtubules (Stubblefield and Brinkley [1967]; de Harven [1968]; Wheatley [1982]; Bornens *et al.* [1987]). The triplet microtubules making up the proximal half form blades that are tilted about 45° relative to the circumference. (The doublet microtubules that make up the distal half are tilted less, about 20° .) The blades are linked at various points by fibrillar braces that connect the outermost microtubule of one blade with the innermost microtubule of the next (Stubblefield and Brinkley [1967]; de Harven [1968]; Wheatley [1982]; Bornens *et al.* [1987]). Various authors, starting with de Harven [1968], have noted that the triplet microtubules have a turbine-like disposition.

What if centrioles really are tiny turbines? This is much easier to conceive if we adopt a holistic rather than reductionistic approach, and if we regard centrioles as designed structures rather than accidental by-products of neo-Darwinian evolution (Wells [2004]). If centrioles really are turbines, then fluid exiting through

the blades would cause them to rotate clockwise when viewed from their proximal ends (Fig. 1).

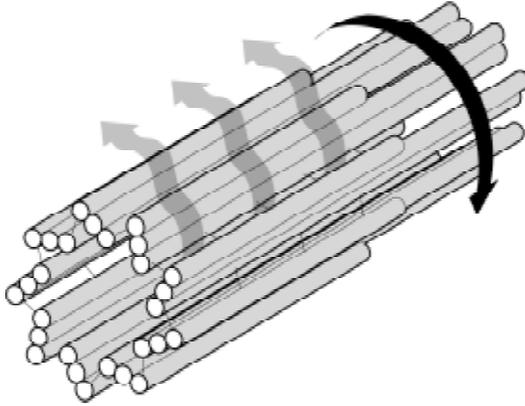


Figure 1 – A centriole viewed from its proximal end. The broad, wavy arrows indicate fluid flow through one of the nine slits between the triplet microtubule turbine blades. The long narrow arrow shows the direction of rotation of the centriole as a whole. (In a real centriole, each blade is slightly twisted so that it lies much flatter at the distal end.)

In order for a centriolar turbine to turn, there must be a mechanism to pump fluid through its blades. The lumen of the centriole appears to be open at the proximal end, and largely filled with dense material at the distal end (Lange and Gull [1996]; Paintrand *et al.* [1992]; Bornens [2002]), so fluid would presumably enter through the former. Helical structures have been observed in the lumens of centrioles (Stubblefield and Brinkley [1967]; Paintrand *et al.* [1992]). Helical structures have also been observed associated with the central apparatus that rotates inside a ciliary or flagellar axoneme (Goodenough and Heuser [1985]; Mitchell [2003]), and axonemes are nucleated by basal bodies that are interconvertible with centrioles (Preble *et al.* [2000]). If the helix inside a centriole rotates like the central apparatus of an axoneme, it could function as an “Archimedes’ screw”, a pump well suited to the low Reynolds number conditions that prevail at sub-cellular dimensions (Purcell [1977]). The pump would draw fluid in through the proximal end and force it out through the triplet-microtubule turbine blades (Fig. 2), causing the turbine to rotate.

This is the reverse of Stubblefield and Brinkley's [1967] idea that the function of the triplet microtubules is to turn the internal helix.

The helical pump could be powered by dynein. As a minus end-directed microtubule motor, cytoplasmic dynein is highly enriched at mitotic spindle poles. It starts to accumulate at centrosomes just before centriole duplication, suggesting recruitment in preparation for mitosis (Quintyne and Schroer [2002]). Dynein produces microtubule-mediated movements in axonemes, though its mode of action in centrioles would have to be different. Cilia and flagella move because of dynein-based sliding between doublet microtubules (Brokaw [1994]; Porter and Sale [2000]); yet centriole microtubules do not slide relative to each other, and there do not seem to be axoneme-like dynein structures between them (Paintrand *et al.* [1992]).

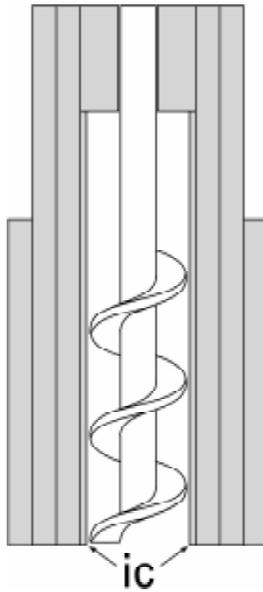


Figure 2 – Cross-section of a single centriole. In the hypothesis proposed here, the helical structure functions as an Archimedes' screw driven by dynein molecules in the internal columns lining the wall of the lumen (ic). The rotating screw would pump fluid in from the proximal end and force it laterally outward between the turbine blades.

Centrioles, however, do contain internal columns with structures consisting of apparently identical subunits. Each subunit possesses a globular domain close to the wall of the lumen and a more extended domain pointing radially inward, suggesting dynein (Paintrand *et al.* [1992]). Dynein molecules in the centriole's internal columns ("ic" in Fig. 2) could drive the Archimedes' screw pump by interacting with its helical blades. If the helix is right-handed (as in Fig. 2), then dynein molecules in the internal columns would not only drive the helix but also start the turbine rotating in the proper direction.

If ϕ and θ are the angular velocity and pitch of the helix, respectively, R_o is the outer radius of the helix blades, R_i is the radius of the central column around which the blades wind, and the thickness of the blades is neglected, then the fluid flow U produced by the rotating helical pump would be

$$U = 4\pi\phi R_o \tan\theta (R_o^2 - R_i^2) \quad (1)$$

The central apparatus of an axoneme rotates once per beat (Smith and Lefebvre [1997]; Omoto *et al.* [1999]), and beat frequencies of flagellar axonemes generally range from 50 to 100 Hz (Cosson [1996]; Porter [1996]). Since the centriolar pump is a small, self-contained structure that does not have to produce flagellar waveforms several micrometers long, its angular velocity could easily be at the high end of this range. Assuming that $\phi = 100$ Hz, $R_o = 0.05 \mu\text{m}$, $R_i = 0.01 \mu\text{m}$, and $\theta = 30^\circ$, the fluid flow into the proximal lumen of a single centriole would be of the order of $U \approx 10^{-19} \text{ m}^3 \text{ sec}^{-1}$.

From U it is possible to derive an order-of-magnitude estimate of the torque produced by a centriolar turbine. The velocity of fluid flow v through the turbine blades is

$$v = U/A \quad (2)$$

where A is the area of the slits between the blades. In cross-sectional photomicrographs (Stubblefield and Brinkley [1967]; de Harven [1968]; Wheatley [1982]; Bornens *et al.* [1987]; Paintrand *et al.* [1992]), the slits between the triplet microtubule blades are

about $0.01 \mu\text{m}$ wide, and the effective length of each slit is about half the length of the centriole, or $0.2 \mu\text{m}$. Since there are nine slits, the total area $A \approx 10^{-14} \text{ m}^2$, so the velocity of the fluid flow would be $v \approx 10^{-5} \text{ m sec}^{-1}$. If ρ_f is the density of the fluid, the mass of fluid passing through the slits per second is

$$m_f = U\rho_f \quad (3)$$

If the fluid has approximately the same density as water, or 10^3 kg m^{-3} , then $m_f \approx 10^{-16} \text{ kg sec}^{-1}$.

This flow is directed against turbine blades that are tilted about 45° relative to the circumference of the centriole. The resulting torque τ is the tangential component of the product of the velocity and mass transport rate multiplied by the distance of the turbine blades from the axis of rotation (Logan [1993]). That distance is the radius of the centriole (R_{CL}), so

$$\tau = (\cos 45^\circ) v m_f R_{CL} \quad (4)$$

Since the radius of a centriole is approximately $0.1 \mu\text{m}$, the torque τ produced by flow from the helical pump through the turbine blades would be of the order of $\tau \approx 10^{-28} \text{ kg m}^2 \text{ sec}^{-2}$.

3. DYNAMICS OF A CENTRIOLE PAIR

Most centrosomes contain a pair of centrioles oriented at right angles to each other, with their proximal ends connected by fibers (Bornens *et al.* [1987]; Paintrand *et al.* [1992]; Bornens [2002]). An isolated centriolar turbine would simply rotate on its long axis, while two centriolar turbines that are orthogonally linked but otherwise unconstrained would tumble around each other. An orthogonally linked pair, however, would behave quite differently if the movement of one centriole were constrained – and this appears to be the case.

The older member (“mother”) of a centriole pair is distinguished from the younger (“daughter”) by various structures (Rieder and Borisy [1982]). Those associated with the mother cen-

triole include “distal appendages” that project at an angle from the distal-most edges of the doublet microtubules, and “subdistal appendages” that form a thick collar around most of the distal half of the mother centriole and serve as an anchor for microtubules that extend into the spindle (Paintrand *et al.* [1992]; Piel *et al.* [2000]). In centrioles isolated under low calcium conditions, the distal appendages are connected to the wall of the centriole while the subdistal appendages are clearly dissociated from it (Paintrand *et al.* [1992]).

These characteristics are consistent with a model in which the subdistal appendages form a bearing connected to the cell’s cytoskeleton, and the distal appendages form a flange. The mother centriole could thus rotate within the bearing provided by its subdistal appendages, as originally suggested by Bornens [1979], while being held in place by the flange formed by its distal appendages (Fig. 3).

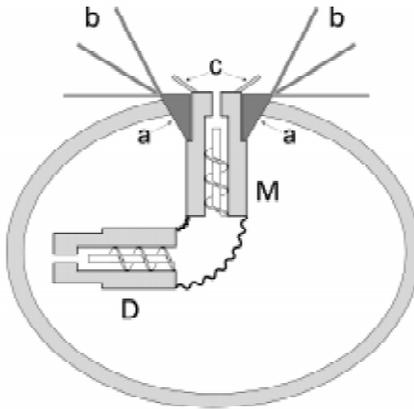


Figure 3 – Cross-section of an orthogonal centriole pair. The mother (M) and daughter (D) centrioles are connected at their proximal ends. The subdistal appendages (a) would function as a bearing around the distal end of the mother centriole and also as an anchor for spindle microtubules (b). The distal appendages (c) would form a flange that holds the mother centriole in place as it rotates. The large ellipse is the centromatrix.

The centriole pair is surrounded by a structural network of 12- to 15-nm diameter filaments called the “centromatrix”

(Schnackenberg *et al.* [1998]). The centromatrix apparently serves as a scaffold for the assembly of a pericentrin- γ -tubulin lattice that plays an important role in nucleating and organizing the microtubule network of the cell (Dictenberg *et al.* [1998]). Although the precise relationship of these centrosomal structures remains to be determined, the centromatrix appears to be innermost, forming a capsule that encloses the centrioles.

The daughter centriole, constrained by its connection to the mother, cannot rotate on its own axis; instead, it would swing bodily around the long axis of the mother centriole (Fig. 4). Nevertheless, the daughter would still function as a turbine, producing a torque that would press the mother centriole laterally against the inner wall of its bearing (open arrow in Fig. 4). The daughter's torque would cause the centriole pair to revolve eccentrically, producing a wobble resembling the motion of a laboratory vortexer.

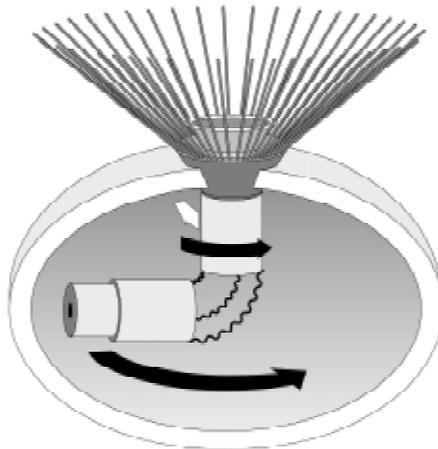


Figure 4 – A three-dimensional view of the centriole pair. The mother centriole would rotate in the direction indicated by the short solid arrow. The daughter centriole would not rotate about its own axis but would revolve around the axis of the mother (long solid arrow). The torque produced by the daughter would press the mother laterally against its bearing (short open arrow, top left), introducing an eccentricity or “wobble” into the revolutions of the pair.

The fluid inside the centromatrix capsule would not remain stationary, but would be stirred in a circle by the revolving daugh-

ter centriole. It might seem that friction against the inner wall of the centromatrix would offer enormous resistance to such movement. Surprisingly, however, the resistance could be quite low. A hydrophobic surface in water tends to be covered by microscopic, pancake-shaped “nanobubbles” with diameters of the order of 200 nm and thicknesses of the order of 20 nm (Tyrrell and Attard [2001]; Steitz *et al.* [2003]; Ball [2003]). Such nanobubbles could render a surface composed of hydrophobic 12-15 nm filaments almost frictionless. With power being continually supplied by the helical pump inside the mother centriole, the centriole pair could thus accelerate to a very high angular velocity inside the centromatrix capsule.

In the hypothesis proposed here, the centriole pair would begin revolving inside the centromatrix capsule at the start of prometaphase. Several live imaging studies have shown that centrioles in prophase cells are stationary within the centrosome (Waters *et al.* [1993]; Piel *et al.* [2000]), but those studies stopped imaging at the beginning of prometaphase – precisely when centriole revolutions would begin.

In the rotational equivalent of Newton’s force law, torque (τ) is the product of moment of inertia (I) and angular acceleration (α), so the angular acceleration of the centriole pair would be

$$\alpha = \tau/I \quad (5)$$

If the only thing rotating were the centrioles themselves, the moment of inertia would be approximately the sum of a cylinder rotating about its long axis (the mother centriole) and a cylinder rotating about an axis perpendicular to one end (the daughter centriole). Assuming that the density of a typical centriole is about 1.1 times that of water, the moment of inertia of the centriole pair would be of the order of $I_{CENTRIOLE\ PAIR} \approx 10^{-30}$ kg m².

Since the intracentrosomal fluid would move with the daughter centriole as it revolves, however, the effective moment of inertia would be higher than this. Assuming that the density of the entire centrosome is 1.1 that of water, its moment of inertia would be of the order of $I_{ENTIRE\ CENTROSOME} \approx 10^{-28}$ kg m². An entire centrosome, however, includes a substantial amount of stationary peri-

centriolar material, so the effective moment of inertia of the revolving centriole pair would be somewhere between 10^{-30} kg m² and 10^{-28} kg m². If the effective moment of inertia of the revolving centriole pair is of the order of 10^{-29} kg m², the angular acceleration (from Equation 5) produced by the torque of the mother centriole (from Equation 4) would be $\alpha \approx 10$ sec⁻².

Assuming negligible friction, this would cause the angular velocity of the centriole pair to increase about 10 Hz every second. Within one minute of starting their turbines the centriole pair would be revolving hundreds of times per second. Ten minutes after start-up the pair would be revolving thousands of times per second, and twenty minutes after start-up it would be revolving more than ten thousand times per second.

4. A POLAR EJECTION FORCE

The subdistal appendages that form the bearing for the revolving centriole pair also anchor microtubules that extend into the spindle (Paintrand *et al.* [1992]; Piel *et al.* [2000]). Other microtubules are anchored in the pericentriolar material surrounding the centromatrix. Just as a vortexer imparts its wobble to a test tube placed in it, so the centrosome would impart its wobble to the microtubules extending from it. Spindle microtubules would thus undergo small amplitude, high frequency oscillations that are mechanical, not electrical as Bornens [1979] proposed.

Spindle microtubules would presumably not transmit this motion as uniformly as the rigid glass walls of a test tube, but microtubules in ordered arrays exhibit more stiffness than would be expected from non-interacting rigid rods (Sato *et al.* [1988]). Objects within the spindle would then undergo high frequency, small amplitude circular movements perpendicular to polar microtubules, as originally proposed by Wells [1985].

Such objects would experience a centrifugal acceleration that is proportional to their radius of rotation and the square of their angular velocity. The radius of rotation of an object surrounded by polar microtubules would be approximately the product of its distance from the centrosome (d) and the tangent of the eccentric-

ity of the centrosome's wobble (ϵ). The object's angular velocity would be the product of the angular acceleration of the centriole pair (α) and the number of seconds that have elapsed since the turbines started (t). So the centrifugal acceleration (β) experienced by an object in the spindle would be

$$\beta = (\alpha t)^2 dt \tan \epsilon \quad (6)$$

If the eccentricity of the wobble is 1° and $\alpha \approx 10 \text{ sec}^{-2}$ (as estimated above), then twenty minutes after turbine startup an object $20 \mu\text{m}$ from the spindle pole would be subjected to a centrifugal acceleration of approximately 50 m sec^{-2} , or about five times the acceleration due to gravity.

Most of this centrifugal acceleration would be perpendicular to a line between the object and the spindle pole. Objects in the middle of a bipolar spindle would thus experience a force laterally away from the long axis of the spindle (large open arrow in Fig. 5). The conical arrangement of spindle microtubules, however, would convert part of this to a component tending to move objects radially away from the pole (small open arrow in Fig. 5).

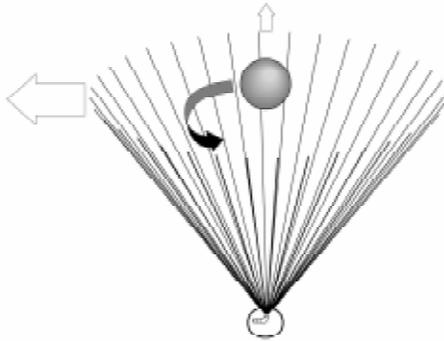


Figure 5 – A cone of spindle microtubules extending from a centrosome. The centriole pair would impart a wobble to the spindle microtubules resembling the motion of a laboratory vortexer. An object within the spindle (solid sphere near top) would be subjected to a small-amplitude rotary motion (solid arrow) and experience a centrifugal force laterally away from the spindle axis (large open arrow to left). The cone-shaped arrangement of the microtubules, however, would produce a component of force directed radially away from the spindle pole (small open arrow, top center). The angle at the vertex of the cone is exaggerated for clarity.

The wobble produced by a revolving centriole pair would thereby generate a polar ejection force that depends on the presence of microtubules but not on microtubule elongation or kinesin-like proteins. The force would originate in spindle poles; it would affect objects in the spindle even if they were not attached to microtubules; and it would make those objects appear to move as though they were being blown or carried by a current – classical characteristics of the polar wind.

5. REGULATION BY INTRACELLULAR CALCIUM

A centriole-generated polar ejection force could be regulated in part by intracellular calcium levels. In dividing animal cells, the onset of anaphase is normally accompanied by a transient rise in intracellular Ca^{2+} concentration (Poenie *et al.* [1986]). This increase could act in three ways to turn off the polar ejection force: (1) by stopping or reversing the direction of the helical pump inside a centriole; (2) by retracting the pump away from the proximal end; and (3) by causing the subdistal appendages to tighten like brake shoes around the mother centriole.

5.1 *Stopping or Reversing the Helical Pump*

Elevated Ca^{2+} concentrations can lead to quiescence in sea urchin sperm flagella axonemes (Brokaw [1987]). This may be due to a Ca^{2+} -induced change in the direction of the power stroke of dynein arms (Ishijima *et al.* [1996]), or to an effect on the central pair apparatus that regulates dynein activity (Bannai *et al.* [2000]). If the helical pump inside a centriole is driven by dynein, then a rise in intracellular calcium concentration could stop its rotation.

5.2 *Retracting the Pump Away from the Proximal End*

Centrin is a 20-kD protein noted for its rapid calcium-modulated contraction and its ability to displace microtubule-based

structures (Salisbury [1995]). It is associated with centrosomes and mitotic spindle poles in a wide variety of organisms (Schiebel and Bornens [1995]), and in human cells the portion of centriin found in centrosomes is concentrated in the distal lumen of centrioles (Paoletti *et al.* [1996]). If the centriin is located in the shaft of the helical pump (Fig. 2), then the rise in Ca^{2+} at the onset of anaphase could cause the pump to retract toward the distal end of the centriole, thereby reducing or eliminating its pumping ability. This would be consistent with electron microscopy evidence showing that the helical structures in centrioles isolated in the presence of millimolar Ca^{2+} concentrations are retracted from the proximal end (Paintrand *et al.* [1992]).

5.3 Brake-like Action of Subdistal Appendages

When centrioles are extracted in the presence of EDTA to lower the Ca^{2+} concentration, the subdistal appendages are clearly dissociated from the centriole wall; but in the presence of millimolar concentrations of Ca^{2+} they are closely associated with it (Paintrand *et al.* [1992]). This suggests that between prophase and anaphase, when the intracellular calcium concentration is low, the subdistal appendages separate from the wall of the mother centriole so that it can rotate freely. The rise in calcium concentration at the onset of anaphase, however, could induce the subdistal appendages to tighten around the body of the centriole like brake shoes. The molecular basis of this contraction is unknown, but it is presumably not due to centriin, which is disrupted by EDTA (Sanders and Salisbury [1994]).

Calcium regulation of the polar ejection force would play an important role in cell division. Once chromosomes have been properly positioned at the metaphase plate, the polar wind is no longer necessary, and reducing or eliminating it would facilitate the poleward movement of chromosomes. In fact, if the revolving centrioles are not shut down they might continue to accelerate, generating a polar ejection force of sufficient magnitude to damage chromosomes.

6. IMPLICATIONS FOR CANCER

An almost ubiquitous finding in cancer cells is chromosomal instability (Lengauer *et al.* [1998]). This instability manifests itself as the gain, loss, or rearrangement of material in single chromosomes (translocation), and in the loss of entire chromosomes or the presence of extra ones (aneuploidy). These defects are typically accompanied by centrosomal defects as well. Indeed, centrosome defects may be the primary cause of chromosomal instability (Brinkley and Goepfert [1998]; Pihan *et al.* [1998]; Lingle and Salisbury [2000]). Although extra centrosomes can form multipolar spindles and lead to aneuploidy, the most important factor in producing chromosomal instability is probably not multiple spindle poles but the presence of extra centrosomes and excess centrosomal material at the poles of normal-looking bipolar spindles (Pihan and Doxsey [1999]; Brinkley [2001]).

If centrioles generate a polar ejection force, the presence of too many centriole pairs at either pole could result in an excessive polar ejection force that subjects chromosomes to unusual stresses and leads to breaks and translocations. Even more serious than the presence of extra centrioles would be a failure of control mechanisms that normally shut down centriolar turbines at the beginning of anaphase, since centriole pairs would continue to accelerate and generate polar ejection forces far greater than normal.

As suggested above, one or more of these control mechanisms could be calcium-regulated. It is worth noting in this regard that recent studies have reported a link between calcium and vitamin D deficiency and various types of cancer. Geographical patterns suggest that reduced exposure to sunlight (resulting in lower vitamin D levels) increases the risk for prostate, colon and breast cancer (Hanchette and Schwartz [1992]; Garland *et al.* [1999]). Dietary calcium supplements can modestly reduce the risk of colorectal cancer (McCullough *et al.* [2003]), and there appears to be an inverse correlation between vitamin D levels and prostate cancer (Konety *et al.* [1999]). Analogs and metabolites of vitamin D inhibit the growth of prostate cancer cells *in vitro* (Krishnan *et al.* [2003]) and *in vivo* (Vegesna *et al.* [2003]), and they have similar inhibitory effects on breast cancer cells (Flanagan *et al.* [2003]). If

centrioles generate a polar ejection force, the correlation between calcium and vitamin D levels and cancer could be a consequence – at least in part – of the role of calcium in turning off centriolar turbines at the onset of anaphase.

7. CONCLUSIONS

The polar ejection force that plays an important role in dividing animal cells could be generated by centrioles. In the hypothesis presented here, these organelles are literally tiny turbines that pump fluid through their triplet microtubule blades with a dynein-powered Archimedes' screw located in their proximal lumens. A mother centriole would rotate about its long axis within a bearing of subdistal appendages, held in place by a flange of distal appendages. A daughter centriole, projecting at a right angle from the mother, would not rotate about its own axis but would revolve around the latter inside the capsule formed by the centromatrix. The daughter would also function as a turbine, however, generating a torque that introduces an eccentricity or "wobble" into the revolutions of the mother-daughter pair.

The resulting wobble, resembling the motion of a laboratory vortexer, would generate a centrifugal-like force several times stronger than the force of gravity, affecting every object within the spindle. Although most of the force would be directed laterally away from the spindle axis, the conical arrangement of microtubules would produce a component directed radially away from the spindle pole. The resulting microtubule-mediated centrifugal-like force could account for many of the characteristics of the polar ejection force observed in dividing animal cells.

This hypothesis is consistent with a large body of evidence. It also makes testable predictions. For example:

A. It predicts that spindle microtubules in animal cells begin to oscillate at the beginning of prometaphase, and that those oscillations rapidly accelerate until metaphase, at which point they decelerate or cease. By metaphase the oscillations may be of such high frequency that they would be difficult to detect, but the lower frequency oscillations early in prometaphase should be detectable by

immunofluorescence microscopy and high-speed camera technology.

B. It predicts that the centriole contains a helical pump powered by dynein molecules located in the inner wall of its lumen. Improved imaging techniques may make it possible to elucidate the complex internal structure of centrioles, characterizing more fully the helical structures in their lumens and determining the precise localization of dynein in their inner walls.

C. It predicts that the polar ejection force is regulated, at least in part, by intracellular calcium concentration. It should be possible to test this by observing chromosome behavior in the spindles of dividing animal cells while artificially raising the concentration of intracellular calcium during prometaphase or blocking its rise at the beginning of anaphase.

If the hypothesis presented here withstands these and other experimental tests, then it may contribute to a better understanding not only of cell division, but also of cancer.

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I CENTRIOLI GENERANO UNA FORZA DI ESPULSIONE POLARE?

Riassunto

Nelle cellule animali si osserva una forza di espulsione polare microtubulo-dipendente che spinge i cromosomi lontano dai poli del fuso durante la prometafase. Tale fenomeno non è osservabile nelle cellule delle piante superiori. I microtubuli o molecole motrici tipo chinesina sono

stati indicati come possibili cause del fenomeno, ma né gli uni né le altre rendono conto di tutti i dati. L'Autore propone che una tale forza di espulsione sia generata dai centrioli, che si trovano negli animali ma non nelle piante superiori. I centrioli consistono di nove triplete di microtubuli disposte come le pale di una minuscola turbina. Turbine centriolari orientate ortogonalmente determinerebbero oscillazioni nei microtubuli del fuso. Si genererebbe così una forza di espulsione mediata dai microtubuli che tenderebbe ad allontanare i cromosomi dall'asse del fuso e dai poli. Un innalzamento della concentrazione intracellulare di calcio all'inizio dell'anafase potrebbe regolare la forza di espulsione polare attraverso la disattivazione delle turbine centriolari. Difetti nella regolazione potrebbero risultare in un eccesso di forza e contribuire così all'instabilità cromosomica tipica della maggior parte delle cellule tumorali.