A Possible Link Between Centrioles, Calcium Deficiency and Cancer

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Abstract

Centrosomal defects leading to chromosomal instability appear to be an early step in the development of major human cancers, though the precise nature of the centrosomal defects remains unknown. An animal centrosome contains two orthogonally oriented centrioles, each composed of nine microtubule triplets arranged like the blades of a turbine. An engineering analysis of centriole ultrastructure based on electron microscope data leads to the hypothesis that these organelles function as dynein-driven turbines to generate a high-speed, small-amplitude oscillation in spindle microtubules that resembles the motion of a laboratory vortexer. Calculations show that the result would be a polar ejection force several times stronger than gravity that would tend to push chromosomes away from spindle poles during prometaphase and metaphase. [*Rivista di Biologia / Biology Forum* 98 (2005): 71-96]. The transient increase in intracellular calcium that normally accompanies the onset of anaphase would shut down the dynein-driven centriolar turbines to permit the unobstructed poleward movement of chromosomes. Under conditions of calcium deficiency or defective calcium regulation, however, centrioles could generate an increasing polar ejection force throughout anaphase that would break chromosome arms and produce chromosomal instability. Several experimental approaches are suggested to test the hypothesis, which if corroborated may contribute to a better understanding not only of cell division but also of cancer.

Introduction

Animal cells possess a microtubule-dependent polar ejection force that pushes chromosomes away from spindle poles during prometaphase. It has been suggested that the force is due to elongating microtubules or to DNA-binding, kinesin-like motor molecules; but neither accounts for all the data. The hypothesis proposed here uses reverse engineering to explain how a polar ejection force could be generated by orthogonally oriented centrioles in the spindle pole of a dividing animal cell. A centriole resembles a tiny turbine, and it appears to contain a helical structure in its lumen that could function as a pump. Molecules resembling dynein line the wall of the lumen, and these could drive the pump. The older ("mother") centriole in a pair is embedded in a bearing-like appendage out of which spindle microtubules emanate. Torque generated by the mother would cause the daughter centriole to revolve around it inside the centrosome, while the torque produced by the daughter would impart an eccentricity to the revolutions of the mother. This would produce a high-speed wobble in spindle microtubules resembling the motion of a laboratory vortexer, and the result would be a polar ejection force several times stronger than gravity. The transient rise in intracellular Ca^{2+} concentration that accompanies the onset of anaphase would shut down the dynein-driven turbines to facilitate the poleward movement of chromosomes.

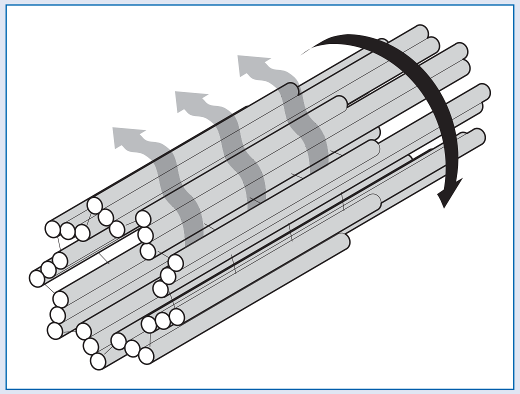

Figure 1. A centriole viewed from its proximal end. The broad, wavy arrows indicate fluid flow through one of the nine slits between the triplet microtubule turbine blades. The long narrow arrow shows the direction of rotation of the centriole as a whole. (In a real centriole, the distal end is plugged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

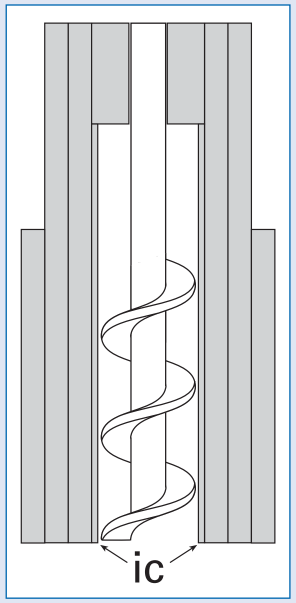

Figure 2. Cross-section of a single centriole. In the hypothesis proposed here, the helical structure functions as an Archimedes' screw driven by dynein molecules in the internal columns lining the wall of the lumen (ic). The rotating screw would pump fluid in from the proximal end and force it laterally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

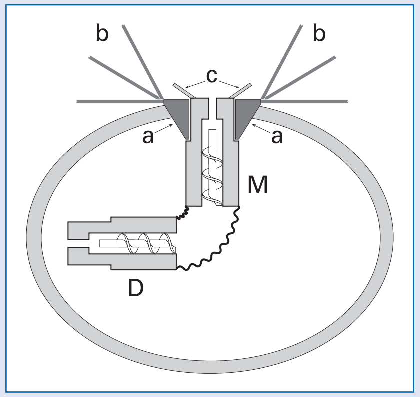

Figure 3. Cross-section of an orthogonal centriole pair. The mother (M) and daughter (D) centrioles are connected at their proximal ends. The subdistal appendages (a) would function as a bearing around the distal end of the mother centriole and also as an anchor for spindle microtubules (b). The distal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

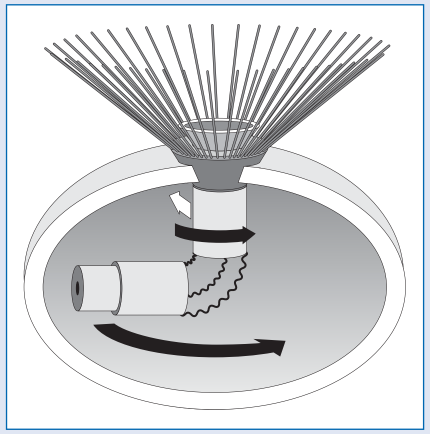

Figure 4. A three-dimensional view of the centriole pair. The mother centriole would rotate in the direction indicated by the short solid arrow. The daughter centriole would not rotate about its own axis but would revolve around the axis of the mother (long solid arrow). The torque produced by the daughter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

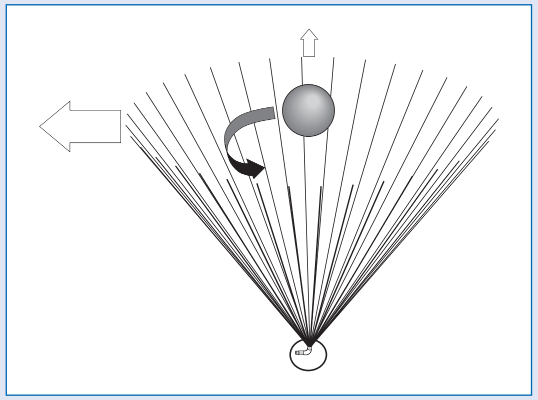

Figure 5. A cone of spindle microtubules extending from a centrosome. The centriole pair would impart a wobble to the spindle microtubules resembling the motion of a laboratory vortexer. An object within the spindle (solid sphere near top) would be subjected to a small-amplitude rotary motion (solid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

CALCULATIONS

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

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

The central apparatus of an axoneme rotates once per beat, and beat frequencies of flagellar axonemes generally range from 50 to 100 Hz. Assuming that ϕ = 100 Hz, R_o = 0.05 μm, R_i = 0.01 μm, and θ= 30°, the fluid flow into the proximal lumen of a single centriole would be of the order of $U \approx 10^{-19}$ m^3 sec^{-1}. Then the velocity of fluid flow ν through the turbine blades is

$$\nu = U/A \qquad (2)$$

where A is the area of the slits between the blades. The total area $A \approx 10^{-14}$ m^2, so the velocity of the fluid flow would be $\nu \approx 10^{-5}$ m sec^{-1}. If ρ_f is the density of the fluid, the mass of fluid passing through the slits per second is

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

If the fluid has approximately the same density as water, or 10^3 kg m^{-3}, then $m_f \approx 10^{-16}$ kg sec^{-1}. The turbine blades 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 times the centriole radius (R_{CL}):

$$\tau = (\cos 45°)\nu m_f R_{CL} \qquad (4)$$

So the torque produced by flow from the helical pump through the turbine blades would be of the order of $\tau \approx 10^{-28}$kg m^2 sec^{-2}. Torque (τ) is the product of moment of inertia (I) and angular acceleration (α), so the angular acceleration of the centriole pair would be

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

If the effective moment of inertia of the revolving centriole pair is of the order of 10^{-29} kg m^2, the angular acceleration would be $\alpha \approx 10$ sec^{-2}. The centrifugal acceleration (β) experienced by an object in the spindle would be proportional to the square of its angular velocity (αt), its distance from the pole (d) and the tangent of the eccentricity of the centrosome's wobble (ε), or

$$\beta = (\alpha t)^2 d \tan\varepsilon \qquad (6)$$

If the eccentricity of the wobble is 1°, then twenty minutes after turbine startup an object 20 μm 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.

Discussion

The chromosomal instability characteristic of cancer cells is manifested 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). Centrosomal defects typically accompany chromosomal instability and may be its primary cause. If centrioles generate a polar ejection force, a failure of control mechanisms that normally shut down centriolar turbines at the beginning of anaphase could lead to continued acceleration, resulting in a polar ejection force far greater than normal. This could subject poleward-moving chromosomes to abnormal stress and lead to chromosomal damage and instability. If centriolar turbines are driven by dynein, one or more of the control mechanisms could be calcium-regulated. It is worth noting in this regard that recent studies have reported a correlation between calcium and vitamin D deficiency and prostate, colon and breast cancer. Analogs and metabolites of vitamin D inhibit the growth of prostate cancer cells *in vitro* and *in vivo*, and they have similar inhibitory effects on breast cancer cells. 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 a centriole-generated polar ejection force at the onset of anaphase.

Conclusions

The hypothesis that centrioles function as dynein-driven turbines to generate a polar ejection force is consistent with a large body of evidence. It also makes testable predictions. For example:

A. It predicts that centriole pairs begin to rotate at the beginning of prometaphase, accelerate rapidly until metaphase, and (in normal cells, at least) cease to rotate at the onset of anaphase. Rotations early in prometaphase should be detectable by fluorescence microscopy and high-speed photography.

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 should make it possible to elucidate the internal structure of centrioles.

C. It predicts that the polar ejection force is regulated, at least in part, by intracellular calcium concentration. It might be possible to block the transient rise in intra-cellular calcium at the onset of anaphase, then observe the damaging effects of an excessive polar ejection force on poleward-moving chromosomes.

If the hypothesis is corroborated by these and other experimental tests, it might aid in the prevention and/or early detection of cancer.

Poster prepared at www.SciFor.com