

## Commentary on “Research on Mitotic Mechanisms”

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### Abstract

Mitosis is the cellular process in which the already duplicated chromosomes are segregated into two identical in preparation for successful cell division. The discovery of mitosis in the late 19th century was made possible by the significant improvements in light microscopes achieved over many preceding decades. Since then, both the descriptions of mitotic phenomena and our understanding of the molecular mechanisms that underlie them has been facilitated at every step by technological advances. The following is a brief account of an open-access chapter that describes many of these advances, recently published as the first part of a ten-chapter book on mitotic mechanism. This open-access, on-line book provides reviews of each of the principal components and events of mitosis, such as kinetochores (the chromosomal specializations that attach each of the sister chromatids to spindle fibers), spindle formation, chromosome congression to the metaphase plate, the checkpoints that assesses quality in spindle formation, the two segments of anaphase chromosome segregation, and the consequences of mitotic errors. Anyone interested in the mechanisms that underly complex cellular processes should find these accounts both interesting and useful.

Mitosis is the process by which eukaryotic cells segregate their already duplicated chromosomes and move them to opposite ends of the cell in preparation for cell division. Its biological importance is seen in the facts that accurate chromosome segregation is essential for successful cell division and mitosis achieves this goal in a huge and diverse group of organisms. Its medical importance follows from multiple facets of the process: 1) The havoc raised when cells lose the ability to segregate chromosomes with precision, as in the aneuploid cells found in most solid tumors. 2) The problems visited upon future generations as a consequence of errors in chromosome segregation during gametogenesis. 3) The encouraging success of chemically diverse pharmaceuticals that retard cancer growth by interacting with components of the mitotic spindle.

This note is a short account an open-access book chapter that charts stages in the growth of our understanding of mitotic mechanism, beginning with the discovery of the process and running up to about 1990 [1]. Most of the other chapters of the book [2] provide a thorough review of progress in more recent years. A theme that runs through all this prose is the significance of technological advances for the discoveries that have moved this field forward. For example, phase microscopy greatly facilitated the description of chromosome motions in live cells. Microscopy with polarized light put to rest a long-standing controversy about the reality of spindle fibers in live cells. Electron microscopy identified spindle fibers as bundles of microtubules and described the structures of both the spindle poles from which most microtubules grow and the kinetochores, which form chromosomal attachment sites for a subset of spindle microtubules. Electron microscopy under the right conditions also revealed the polar orientations of each class of spindle microtubules: those emanating from the poles, those associated with kinetochores and those left behind in the zone between the chromosomes as they separate in anaphase.

This chapter also describes the work of numerous investigators who perturbed spindles in live cells to investigate aspects of their functions in vivo. For example, some students of chromosome motion used glass microneedles, controlled by a micromanipulator, to grab chromosomes in meiotic cells and break their attachments to the spindle. The behavior of these chromosomes as they reattached to the spindle elucidated both the importance of kinetochores for chromosome motion and the role of tension at kinetochores in the formation of stable chromosome-

spindle attachments. Other work described in this chapter revealed the remarkably fast turnover of most spindle microtubules, thanks to the dynamic instability of these polymers in vivo. Still other work used fluorescent tags to follow the motions of the spindle microtubules themselves and chart these motions relative to those of the chromosomes, thereby identifying sites of microtubule polymerization and shortening. Finally, ablation studies, carried out with both ultraviolet and laser microbeams showed the mechanical importance of specific parts of the spindle for different aspects of chromosome motion.

During the decades considered in this chapter, significant progress was also made in understanding the molecular mechanisms of mitotic events, thanks to a combination of technological improvements in microscopy, biochemistry and molecular biology. Microscopy has been of great importance, because spindles are small (<10  $\mu\text{m}$  in most organism), labile and transient, so making useful biochemical preparations of the spindle apparatus has been difficult. Methods for localizing spindle proteins have, however, identified many important spindle parts, such as components of the kinetochores and spindle poles. Both immunolocalization of epitopes and the positions in vivo of spindle proteins engineered as chimeras with fluorescent proteins have allowed the construction of a map of important spindle components onto spindle structure, as seen by either light or electron microscopy. More recent work, described in the later chapters of this book, has built on these initial discoveries, using tagged proteins, affinity chromatography and mass spectrometry to identify protein complexes that reside at either kinetochores or spindle poles.

Another aspect of mitotic mechanism discussed in the initial chapter is the modeling that many investigators have carried out in quest of

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an over-arching idea about how chromosomes move. Very early work included suggestions that electric or magnetic fields acting, on small dipoles, were models for spindle formation, but these sorts of proposals are only mentioned, given that such ideas did not lead to productive experiments. Beginning with the discovery of spindle microtubules, however, investigators began to propose specific hypotheses about force generation based, for example, on the labile association of microtubule subunits. With the discovery of microtubule-dependent motor enzymes, thinking began to shift toward models based on ATP-dependent mechanochemistry, analogous to the action of myosin in muscle contraction. Initial ideas were focused on dynein, the ATPase known to power flagellar and ciliary motions, but after the discovery of kinesin and the development of methods for rapid cloning of wild type genes that rescued mitotic mutants in fungi, several kinesin-like enzymes were shown to be important for spindle formation and function. With the emergence of efficient DNA sequencing, even yeasts have been found to contain 5-8 kinesin-like proteins, many of which are important for mitosis. Thus, ideas about spindle mechanism began to focus on motors.

More recently still, several labs have shown that microtubule dynamics can generate forces. It is no surprise that growing microtubules can push on any load then encounter, but it is intriguing that shortening microtubules too can exert force on a cargo when they are properly attached to it. Some of the most effective attachment factors are proteins that normally reside at kinetochores, so microtubule dynamics has recently come back into favor as a molecular mechanism for aspects of chromosome motion.

In short, the initial chapter [1] and this book as a whole [2] provide the interested reader with access to progress in understanding this age-old problem in cell biology. The combination of the results themselves and the ways in which technology has partnered with exploration science to achieve these advances makes useful and interesting reading.

#### References

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