Mitosis: wisdom, knowledge and information

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The endless cycle of ideas and action,

Endless invention, endless experiment,

Brings knowledge of motion but not of stillness;

Knowledge of speech, but not of silence;

Where is the life we have lost in living?

Where is the wisdom we have lost in knowledge?

Where is the knowledge we have lost in information?

Thomas S. Eliot (*in* The Rock, 1934)

Mitosis is the process responsible for the division of the replicated nuclear material, which in parallel to the division of the cytoplasm during cytokinesis, allows that one cell gives rise to two cells that are exact genetic copies. Since its original discovery and accurate description by Walter Flemming in 1879 [1], mitosis has been one of the most active research topics in the cell biology field. However, despite being so heavily scrutinized by more than a century, mitosis researchers have yet to provide a full picture of the molecular and biophysical principles that orchestrate the correct distribution of the genetic information every cell division.

Cells are driven into mitosis as result of the activity of cyclin-dependent kinases (CDKs), which phosphorylate a number of important protein substrates that dictate the necessary changes in nuclear and cytoskeleton architecture that lead in one hand to the condensation of DNA and the formation of individual chromosomes, and on the other hand to the assembly of a microtubular mitotic spindle. In the basis of a correct distribution of chromosomes during mitosis is precisely their capacity to interact with the mitotic spindle, which in vertebrates is made possible due to the transient disassembly of the nuclear

envelope. At the heart of the chromosome-spindle interface there is a minute structure known as the kinetochore [2,3], which is responsible for the two forms of directed chromosome motion observed during mitosis: 1) the stochastic alignment/congression of individual chromosomes at the spindle equator during prometaphase; and 2) the synchronous poleward migration of sister-chromatids during anaphase. While the goal of anaphase can be easily deduced even for non-specialists, the meaning of establishing a metaphase plate before separating sister-chromatids remains an intriguing problem. In Daniel Mazia's own words, which are still largely applicable in the present days, "*we know practically nothing about what happens during the usual pause at metaphase except that something is happening!*" [4]. An appealing possibility is that the establishment of a high-order state of metaphase would ensure that all chromosomes separate essentially from the same axial position with similar poleward velocities (if one assumes a uniform distribution of forces), thereby ensuring the fidelity of chromosome segregation [5].

Given its essential role in chromosome segregation, mitotic spindle assembly in animal cells is a highly conserved and redundant process that involves multiple parallel pathways. The classic "text book" pathway is the one relying on the centrosome, which nucleates dynamically unstable microtubules that "search-and-capture" chromosomes after nuclear envelope breakdown [6]. However, it seems clear that a mechanism solely relying on microtubule dynamic instability would be insufficient, for instance in the case of human cells, to capture 92 kinetochores within the observed kinetics of mitosis [7]. Another mechanism, known as the chromatin pathway, was originally identified in acentrosomal Xenopus meiotic oocytes and shown to involve the formation of a RanGTP gradient around chromosomes that promotes the nucleation of microtubules, which are subsequently organized into a bipolar structure by motor proteins [8]. Curiously, animal somatic cells that normally have centrosomes were shown to form a functional spindle after genetic or physical removal of centrosomes [9-12], indicating that a centrosome-

independent pathway for spindle assembly exists in animal cells. However, the underlying molecular and structural requirements behind acentrosomal spindle formation in animal somatic cells remain largely unknown.

Mitosis research can be separated by at least three distinct periods: the *conceptual era* from Flemming until 1980s/1990s where the major microscopical events behind mitosis have been identified, described and eventually explained (some classic references include [4,13-16]); the *genetic/genomic era* from 1980s until the present days, which led to the massive identification of the main molecular players driving mitosis; and the *molecular biophysics era* that we are just entering to, where the biophysical mechanisms of mitosis may eventually be unravelled and controlled with molecular resolution and reproduced by the simple manipulation of mathematical variables. Since the overproliferation of cells is in the basis of many human cancers, controlling mitosis would probably mean controlling cancer through the development of more effective therapies [17]. The times ahead are therefore exciting times for mitosis research.

More than providing a molecular update, here we intended to critically review and integrate the outstanding issues of mitosis from a mechanistic or even conceptual perspective. As so, it is deliberate that each individual contribution in this multi-author review series is a deep intellectual exercise, which attempts for a rigorous historical reference to ground-breaking ideas and seminal experiments, but also challenges current paradigms while dissecting the facts from the remaining questions. Accordingly, Kops, Saurin and Meraldi start by addressing the problem of chromosome congression and the respective relationship with the initial contacts between microtubules and kinetochores, how these contacts get converted into stable attachments leading to chromosome bi-orientation, and how erroneous attachments are prevented/corrected. These authors focus on the molecular regulation of the microtubule-kinetochore interface, while highlighting future directions. This is accompanied by a review by McEwen and Dong on the structural

basis of microtubule-kinetochore interactions and how kinetochores may harness the energy released from microtubules to generate the force required to move chromosomes during mitosis. Next, Debec, Sullivan and Bettencourt-Dias revisit the role of centrioles/centrosomes in mitosis and question their value as “organs for cell division” by taking an integrated comparative approach in different cells, tissues and species. This discussion is followed by a paradigmatic case study of spindle assembly by Müller-Reichert and colleagues in the one-cell embryo from *C. elegans*. At this stage, both meiotic and mitotic spindles are sequentially assembled in the same cytoplasm within one hour, the first being totally acentrosomal, whereas the latter relies entirely on the presence of centrioles.

One of the most exciting recent findings in mitosis research was the link established between the nuclear transport machinery and their recycling for specific mitotic functions. While in many aspects this evolving relationship only now is starting to become understood, there is already substantial data that must be put in context with the state-of-the art of mitosis research. This challenging task has been taken by Wozniak, Burke and Doye who review how components of the nuclear transport machinery are linked with key mitotic processes, such as spindle assembly, kinetochore function and the spindle assembly checkpoint.

Finally, two review articles discuss biophysical and molecular models associated with force generation and chromosome motion during anaphase. The first, by Civelokoglu-Scholey and Scholey deals with great depth with theoretical considerations of force-velocity relationships by microtubule motors in the spindle. The second, by me and my colleague Lince-Faria provides a wider and critical perspective of present models and mechanisms of force-production during chromosome segregation in anaphase. Overall, as in the words of the poet, I expect that in a time where massive information makes the headlines of scientific literature this review series can help to distinguish knowledge and

hopefully provide some wisdom to such an enigmatically beautiful field. My deep gratitude goes to all colleagues that made this review series possible.

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