Mitosis, its regulation and disturbances

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Mitosis is the process in which a eukaryotic cell nucleus splits in two, followed by division of the parent cell into two daughter cells. Once mitosis is complete, the entire cell divides in two by way of the process called cytokinesis. During this multistep process, cell chromosomes condense and the spindle assembles. The duplicated chromosomes then attach to the spindle, align at the cell equator, and move apart as the spindle microtubules retreat toward opposite poles of the cell. Each set of chromosomes is then surrounded by a nuclear membrane, and the parent cell splits into two complete daughter cells. Mitosis consists of five morphologically distinct phases: prophase, prometaphase, metaphase, anaphase, and telophase.

1. Prophase

During prophase, the parent cell chromosomes — which were duplicated during S phase — condense. Each duplicated chromosome consists of two identical sister chromatids joined at a point called the centromere. Several DNA binding proteins catalyze the condensation process, including cohesin and condensin. Cohesin forms rings that hold the sister chromatids together, whereas condensin forms rings that coil the chromosomes into highly compact forms. The nucleoli disappear. The mitotic spindle begins to form. It is composed of the centrosomes and the microtubules that extend from them. The centrosomes move away from each other, propelled partly by the lengthening microtubules between them.

2. Prometaphase

During prometaphase, phosphorylation of nuclear lamins by M-CDK causes the nuclear membrane to break down into numerous small vesicles. As a result, the spindle microtubules now have direct access to the genetic material of the cell. Each microtubule is highly dynamic, growing outward from the centrosome and collapsing backward as it tries to locate a chromosome. Eventually, the microtubules find their targets and connect to each chromosome at its kinetochore, a specialized protein structure at the centromere. The chromosomes have become even more condensed. Some of the microtubules attach to the kinetochores, becoming “kinetochore microtubules,” which jerk the chromosomes back and forth. Nonkinetochore microtubules interact with those from the opposite pole of the spindle.

3. Metaphase

The centromeres of chromosomes are now in alignment on a single plane at the center of the cell. An imaginary plane is called the metaphase plate. The chromosomes align along the cell equator. At this point, the tension within the cell becomes balanced, and the chromosomes no longer move back and forth. In addition, the spindle is now complete, and three groups of spindle microtubules are apparent. Kinetochore microtubules attach the chromosomes to the spindle pole; interpolar microtubules extend from the spindle pole across the equator, almost to the opposite spindle pole; and astral microtubules extend from the spindle pole to the cell membrane.

4. Anaphase

Anaphase is the shortest stage of mitosis, often lasting only a few minutes. It begins when the cohesin proteins are cleaved. This allows the two sister chromatids of each pair to part suddenly. In the first part of anaphase — sometimes called anaphase A — the kinetochore microtubules shorten and draw the chromosomes toward the spindle poles. Then, in the second part of anaphase — sometimes called anaphase B — the astral microtubules that are anchored to the cell membrane pull the poles further apart and the interpolar microtubules slide past each other, exerting additional pull on the chromosomes. The cell elongates as the nonkinetochore microtubules lengthen. By the end of anaphase, the two ends of the cell have equivalent—and complete—collections of chromosomes.

5. Telophase

During telophase, the chromosomes arrive at the cell poles, the mitotic spindle disassembles, and the vesicles that contain fragments of the original nuclear membrane assemble around the two sets of chromosomes. Phosphatases then dephosphorylate the lamins at each end of the cell. This dephosphorylation results in the formation of a new nuclear membrane around each group of chromosomes. The nucleoli reappear. The chromosomes become less condensed. Any remaining spindle microtubules are depolymerized.

Cytokinesis

Cytokinesis is the physical process that finally splits the parent cell into two identical daughter cells. a) In animal cells -> The cleavage furrow forms just as anaphase draws to a close. The cleavage furrow deepens when a band of actin filaments (the contractile ring) slowly forms a circular constriction between the two daughter cells. As the actin and myosin filaments move past each other, the contractile ring becomes smaller. When the ring reaches its smallest point, the cleavage furrow completely bisects the cell at its center, resulting in two separate daughter cells of equal size. b) In plant cells -> Plant cells are not able to undergo the same process because they have a

rigid, inflexible cell wall. These cells divide by forming a new piece of cell wall in their center. A small, flattened disk appears between the two daughter plant cells near the site where the metaphase plate once was. The cell plate is simply newly formed plasma membrane that expands outward until it reaches the old plasma membrane and fuses with this membrane. The new membrane releases molecules that form the new plant cell walls. Regulation of mitosis -> Mitotic cyclin-CDK complexes, which are synthesized but inactivated during S and G2 phases, promote the initiation of mitosis by stimulating downstream proteins involved in chromosome condensation and mitotic spindle assembly. A critical complex activated during this process is a ubiquitin ligase known as the anaphase-promoting complex (APC), which promotes degradation of structural proteins associated with the chromosomal kinetochore. APC also targets the mitotic cyclins for degradation, ensuring that telophase and cytokinesis can proceed. Mitotic disturbancies -> Mitotic nondisjunction in somatic cells contributes to genetic disease. Nondisjunction soon after fertilization, either in the developing embryo or in extraembryonic tissues like the placenta, leads to chromosomal mosaicism that can underlie some medical conditions, such as a proportion of patients with Down syndrome. Further, abnormal chromosome segregation in rapidly dividing tissues, such as in cells of the colon, is frequently a step in the development of chromosomally abnormal tumors, and thus evaluation of chromosome and genome balance is an important diagnostic and prognostic test in many cancers.