Interphase - Part 1

Objectives

After going through this lesson, the learners will be able to understand the following:

- Cell Cycle
- Phases of Cell Cycle
- Interphase
    - G1 phase
    - G2 phase
    - G3 phase
    - G0 phase

Content Outline

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- Phases of Cell Cycle
- Interphase
    - G1 phase
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Introduction

Are you aware that all organisms, even the largest, start their life from a single cell? You may wonder how a single cell then goes on to form such large organisms. Growth and reproduction are characteristics of cells, indeed of all living organisms. All cells reproduce by dividing into two, with each parental cell giving rise to two daughter cells each time they divide. These newly formed daughter cells can themselves grow and divide; giving rise to a new cell population that is formed by the growth and division of a single parental cell and its progeny. In other words, such cycles of growth and division allow a single cell to form a structure consisting of millions of cells.

Cell Cycle

Cell division is a very important process in all living organisms. During the division of a cell, DNA replication and cell growth also take place. All these processes, i.e., cell division, DNA replication, and cell growth, hence, have to take place in a coordinated way to ensure correct division and formation of progeny cells containing intact genomes. The sequence of events by which a cell duplicates its genome, synthesises the other constituents of the cell and eventually divides into two daughter cells is termed cell cycle. Although cell growth (in terms of cytoplasmic increase) is a continuous process, DNA synthesis occurs only during one specific stage in the cell cycle. The replicated chromosomes (DNA) are then distributed to daughter nuclei by a complex series of events during cell division. These events are themselves under genetic control.

Phases of Cell Cycle

A typical eukaryotic cell cycle is illustrated by human cells in culture. These cells divide once in approximately every 24 hours. However, this duration of cell cycle can vary from organism to organism and also from cell type to cell type. Yeast for example, can progress through the cell cycle in only about 90 minutes. The cell cycle is divided into two basic phases:

Interphase

Before mitosis, meiosis and cytokinesis, a cell must go through a process known as Interphase. Interphase has four stages; G1, S, G0, and G2. For cell division, a cell has to progress through the G_1 phase. If not then it enters to G_0 where it is still living but on hold and may be again gone through the interphase at later stage. The cell has to be passed through various checkpoints during interphase to be either progressed or denied further development. The S (Synthetic) phase includes the replication of genetic material. G2 marks the gap2 phase of the cell before it enters into M phase. The M phase can be either mitosis or meiosis depending on the type of cell. Germ cells undergo meiosis, while somatic cells will undergo mitosis. After the cell proceeds successfully through the M phase, it may then undergo cell division through cytokinesis. The control of each checkpoint is controlled by cyclin and cyclin dependent kinases. The progression of interphase is the result of the increased amount of cyclin. As the amount of cyclin increases, more and more cyclin dependent kinases attach to cyclin signaling the cell further into interphase. The peak of the cyclin attached to the cyclin dependent kinases this system pushes the cell out of interphase and into the M phase, where mitosis, meiosis, and cytokinesis occur.

M Phase (Mitosis phase)

The M Phase represents the phase when the actual cell division or mitosis occurs and the interphase represents the phase between two successive M phases. It is significant to note that in the 24 hour average duration of cell cycle of a human cell, cell division properly lasts for only about an hour. The interphase lasts more than 95% of the duration of the cell cycle.

The M Phase starts with the nuclear division, corresponding to the separation of daughter chromosomes (karyokinesis) and usually ends with division of cytoplasm (cytokinesis). The interphase, though called the resting phase, is the time during which the cell is preparing for division by undergoing both cell growth and DNA replication in an orderly manner.

The interphase is divided into three further phases:

- G1 phase (Gap 1)
- S phase (Synthesis)
- G2 phase (Gap 2)

G_1 Phase (First Gap)

G1 phase is the first stage of the four phases that takes place in a Eukaryotic cell during cell division. Although very little changes are visible in this stage but cell is quite active biochemically. During this stage of interphase, the cell grows in size, synthesizes mRNA and the proteins associated with it required for DNA synthesis; and reserves the sufficient energy required to replicate chromosomes in the nucleus. G_1 phase terminates when the cell proceeds to S phase. Duration of the G1 phase is different among various cells, like Human somatic cells take 18 hours to complete a cell cycle and G1 phase required $1/3^{rd}$ of it while in *Xenopus, Drosophila* and sea urchin embryo it barely existed.

Limiting growth factors such as temperature, nutrient supply etc, also affects the G1 or other phases. G1 phase is particularly important in the cell cycle because it determines whether a cell commits to division or to leaving the cell cycle. If a cell is signaled to remain undivided, instead of moving onto the S phase, it will leave the G1 phase and move into a state of dormancy called the G0 phase. Most non proliferating vertebrate cells will enter the G0 phase.

S Phase (Synthesis phase)

Throughout interphase, nuclear DNA remains in a semi-condensed chromatin configuration. In the S phase, DNA replication can proceed through the mechanisms that result in the formation of identical pairs of DNA molecules—sister chromatids—that are firmly attached to the centromeric region. The centrosome is duplicated during the S phase. The two centrosomes will give rise to the mitotic spindle, the apparatus that orchestrates the movement of chromosomes during mitosis. At the center of each animal cell, the centrosomes of animal cells are associated with a pair of rod-like objects, the centrioles, which are at right angles to each other. Centrioles help organize cell division. Centrioles are not present in the centrosomes of other eukaryotic species, such as plants and most fungi.

S phase (**synthesis phase**) is the part of the cell cycle in which DNA is replicated, occurring between G_1 phase and G_2 phase. Precise and accurate DNA replication is necessary to prevent genetic abnormalities which often lead to cell death or disease. Due to the importance, the regulatory pathways that govern this event in eukaryotes are highly conserved. This conservation makes the study of S-phase in model organisms such as *Xenopus laevis* embryos and budding yeast relevant to higher organisms.

The major event in S-phase is DNA replication. The goal of this process is to create exactly two identical semi-conserved chromosomes. The cell prevents more than one replication from occurring by loading pre-replication complexes onto the DNA at replication origins during G1 phase which are dismantled in S-phase as replication begins. In synthesis, the enzyme helicase unwinds the DNA double helix, and the enzyme DNA polymerase re-binds free-floating nucleotides to the separate DNA single strands in accordance with the complementary base pairing rule. DNA synthesis can occur as fast as 2000 nucleotides/second and must create fewer than 2 errors (I.e., wrong bases) in 10^{10} nucleotide additions.

G2 Phase (Second Gap)

In the G2 phase, the cell replenishes its energy stores and synthesizes proteins necessary for chromosome manipulation. **Some cell organelles are duplicated, and the cytoskeleton is dismantled to provide resources for the mitotic phase. There may be additional cell growth during G2. The final preparations for the mitotic phase must be completed before the cell is able to enter the first stage of mitosis.**

G2 phase, or **Gap 2 phase**, is the second subphase of Interphase in the cell cycle directly preceding mitosis. It follows the successful completion of S phase, during which the cell's DNA is replicated. G_2 phase ends with the onset of prophase, the first phase of mitosis in which the cell's chromatin condenses into chromosomes.

G2 phase is a period of rapid cell growth and protein synthesis during which the cell prepares itself for mitosis. Curiously, G2 phase is not a necessary part of the cell cycle, as some cell types (particularly young *Xenopus* embryos and some cancers) proceed directly from DNA replication to mitosis. Though much is known about the genetic network which regulates G2 phase and subsequent entry into mitosis, there is still much to be discovered concerning its significance and regulation, particularly in regards to cancer. One hypothesis is that the growth in G2 phase is regulated as a method of cell size control. Fission yeast (*Schizosaccharomyces pombe*) has been previously shown to employ such a mechanism, via Cdr2-mediated spatial regulation of Wee1 activity. Though Wee1 is a fairly conserved negative regulator of mitotic entry, no general mechanism of cell size control in G2 has yet been elucidated.

Biochemically, the end of G2 phase occurs when a threshold level of active cyclin B1/CDK1 complex, also known as Maturation promoting factor (MPF) has been reached. The activity of this complex is tightly regulated during G2. In particular, the G_2 checkpoint arrests cells in G2 in response to DNA damage through inhibitory regulation of CDK1.

G0 Phase Not all cells adhere to the classic cell cycle pattern in which a newly formed daughter cell immediately enters the preparatory phases of interphase, closely followed by the mitotic phase. Cells in the G0 phase are not actively preparing to divide. The cell is in a quiescent (inactive) stage that occurs when cells exit the cell cycle. Some cells enter G0 temporarily until an external signal triggers the onset of G1. Other cells that never or rarely divide, such as mature cardiac muscle and nerve cells, remain in G0 permanently.

The **G_0 phase** describes a cellular state outside of the replicative cell cycle. Classically, cells were thought to enter G0 primarily due to environmental factors, like nutrient deprivation, that limited the resources necessary for proliferation. Thus, it was thought of as a ***resting phase***. It's now known that G_0 cannot be painted with a single broad brushstroke. For example, most adult neuronal cells, among the most metabolically active cells in the body, are fully differentiated and reside in a terminal G_0 phase. Neurons reside in this state, not because of stochastic or limited nutrient supply, but because it's part of their internal genetic programming.

G1 phase together with the S phase and G2 phase comprise the long growth period of the cell cycle called interphase that takes place before cell division in mitosis (M phase).

Examples of Various Situations Where Mitosis Occurs.

- **Cut in hand** – while cutting vegetables in the kitchen, by accident if we cut our finger after providing the first aid we will notice a cut mark in the finger. After a few days we would notice that the mark is slowly disappearing, the reason for this is **Mitosis.**
- **Growth of a leaf from a seed** – when we sow a seed in the soil and water it regularly for a couple of days or more the first thing we observe is the growth of a small leaf. The reason for the development of the new leaf is **Mitosis.**
- **Development of zygote to fetus** – Every living organism develops from a single cell (zygote). It is the mitotic division of zygote that eventually develops into a young one.

Summary

G1 phase corresponds to the interval between mitosis and initiation of DNA replication. During the G1 phase the cell is metabolically active and continuously grows but does not replicate its DNA. S or synthesis phase marks the period during which DNA synthesis or replication takes place.

During this time the amount of DNA per cell doubles. If the initial amount of DNA is denoted as 2C then it increases to 4C. However, there is no increase in the chromosome number; if the cell had diploid or 2n number of chromosomes at G1, even after S phase the number of chromosomes remains the same, i.e., 2n. In animal cells, during the S phase, DNA replication begins in the nucleus, and the centriole duplicates in the cytoplasm. During the G2 phase, proteins are synthesized in preparation for mitosis while cell growth continues.

Some cells in the adult animals do not appear to exhibit division (e.g., heart cells) and many other cells divide only occasionally, as needed to replace cells that have been lost because of injury or cell death. These cells that do not divide further exit the G1 phase to enter an inactive stage called the quiescent *stage (G0)* of the cell cycle. Cells in this stage remain metabolically active but no longer proliferate unless called on to do so depending on the requirement of the organism.

In animals, mitotic cell division is only seen in the diploid somatic cells. Against this, the plants can show mitotic divisions in both haploid and diploid cells. From your recollection of examples of alternation of generations in plants (Chapter 3) identify plant species and stages at which mitosis is seen in haploid cells.

Important terms

- **Anaphase:** stage of mitosis during which sister chromatids are separated from each other
- **Cell cycle:** ordered series of events involving cell growth and cell division that produces two new daughter cells
- **Cell plate:** structure formed during plant cell cytokinesis by Golgi vesicles, forming a temporary structure (phragmoplast) and fusing at the metaphase plate; ultimately leads to the formation of cell walls that separate the two daughter cells
- **Centriole:** rod-like structure constructed of microtubules at the center of each animal cell centrosome
- **Cleavage furrow:** constriction formed by an actin ring during cytokinesis in animal cells that leads to cytoplasmic division
- **Condensin:** proteins that help sister chromatids coil during prophase
- **Cytokinesis:** division of the cytoplasm following mitosis that forms two daughter cells.
- **G0 phase:** distinct from the G1 phase of interphase; a cell in G0 is not preparing to divide
- **G1 phase:** (also, first gap) first phase of interphase centered on cell growth during mitosis
- **G2 phase:** (also, second gap) third phase of interphase during which the cell undergoes final preparations for mitosis
- **Interphase:** period of the cell cycle leading up to mitosis; includes G1, S, and G2 phases (the interim period between two consecutive cell divisions)
- **Karyokinesis:** mitotic nuclear division
- **Kinetochore:** protein structure associated with the centromere of each sister chromatid that attracts and binds spindle microtubules during prometaphase

- **Metaphase plate:** equatorial plane midway between the two poles of a cell where the chromosomes align during metaphase
- **Metaphase:** stage of mitosis during which chromosomes are aligned at the metaphase plate
- **Mitosis:** (also, karyokinesis) period of the cell cycle during which the duplicated chromosomes are separated into identical nuclei; includes prophase, prometaphase, metaphase, anaphase, and telophase
- **Mitotic phase:** period of the cell cycle during which duplicated chromosomes are distributed into two nuclei and cytoplasmic contents are divided; includes karyokinesis (mitosis) and cytokinesis
- **Mitotic spindle:** apparatus composed of microtubules that orchestrates the movement of chromosomes during mitosis
- **Prometaphase:** stage of mitosis during which the nuclear membrane breaks down and mitotic spindle fibers attach to kinetochores
- **Prophase:** stage of mitosis during which chromosomes condense and the mitotic spindle begins to form
- **Quiescent:** refers to a cell that is performing normal cell functions and has not initiated preparations for cell division
- **S phase:** second, or synthesis, stage of interphase during which DNA replication occurs
- **Telophase:** stage of mitosis during which chromosomes arrive at opposite poles, decondense, and are surrounded by a new nuclear envelope.