MITOSIS AT A GLANCE

NEOPLASM is an abnormal and un-coordinated growth of tissue, which is categorized by WHO (World Health Organization) as benign tumors, in-situ tumors, malignant tumors, and neoplasms of uncertain or unknown behavior.[1]

Cancer is a malignant tumor featuring abnormal cell growth and cellular division resulting in excessive cellular proliferation, with the potential to invade or spread to other parts of the body.[2,3] Dysplasia is linked to altered tissue architecture, with one of the reasons being excessive cellular proliferation, leading in all probability to malignant transformation if not treated.[4]

The cell cycle, or cell-division cycle, is the series of events that take place in a cell leading to its division and duplication (replication) that produces two daughter cells.[5]

Cell division occurs in defined stages, which together comprise the cell cycle [Figure 1]. There are two types of cell division: Meiosis and Mitosis.

• MEIOSIS: Occurs during formation of the gametes, the number of chromosomes reduced to half in reproductive cell[6]
• MITOSIS: Mitosis is the process in which a eukaryotic cell nucleus splits in two, followed by division of the parent cell into two daughter cells.[6]

CELL CYCLE: Divided into two major events,[5]

• Interphase- Cell increases in size and replicates its genetic material
• Mitosis
• G0 phase- A resting phase where the cell has stopped dividing[5]

INTERPHASE:
• G1 phase- Cells increase in size in Gap 1.

Figure 1: Cell cycle illustration with duration, regulation, and inhibitors
The G1 checkpoint control mechanism ensures that everything is ready for DNA synthesis\(^5\)
- S phase- DNA replication occurs during this phase\(^5\)
- G\(_2\) phase- During the gap between DNA synthesis and mitosis, the cell will continue to grow. The G2 checkpoint control mechanism ensures that everything is ready to enter the M (mitosis) phase and divide\(^5\)
- MITOSIS is subdivided into
- PROPHASE- This is the first stage of mitosis. In this phase, chromosomes are distinctly seen and centrioles move apart. Nuclear membrane disappears\(^7\) [Figure 2]
- METAPHASE- Chromosomes are lined up along the metaphase or equatorial plate\(^7\) [Figure 3]
- ANAPHASE- Sister chromatids separate and begin to migrate to opposite poles of the cell and a cleavage furrow begins to develop\(^7\) [Figure 4]
- TELOPHASE- Terminal phase of mitosis and characterized by cytokinesis, reconstitution of nucleus and nuclear envelope, disappearance of mitotic spindle, and unwinding of chromosomes into chromatin.\(^7\) [Figure 5]

NORMAL MITOSIS:\(^7\)
Mitosis occurs in the following circumstances:
- Development and growth
- Cell replacement, repair, and regeneration
- Asexual reproduction in some micro-organisms.

The turnover rate of oral mucosa ranges from 14 - 24 days depending on the site (buccal mucosa, floor of the mouth, etc.). Oral mucosa is a highly dynamic tissue that rapidly replaces its structure and contributes to oral health by maintaining an intact barrier that protects the underlying tissues from environmental stress. Mucosal renewal and repair depends on stem cells or basal or mother cells. Only stem cells have the ability to continuously generate new cells for whole lifetime and when they divide they both renew themselves and produce hierarchies of other cells that differentiate for tissue function.\(^9\)

ABNORMAL MITOSIS
Defects of mitosis result in various nuclear abnormalities, namely, micronuclei, binucleation, broken egg appearance, pyknotic nuclei, and increased numbers of and/or abnormal mitotic figures.\(^9\)

These abnormal mitotic figures (MFs) are commonly seen in oral epithelial dysplasia and squamous cell carcinoma. Location and increased numbers of and/or abnormal mitotic figures are important criteria that carry increased weightage in the grading of dysplasias.\(^9\)

Mitotic activity remains restricted to somatic stem cells that eventually repair injuries, and to committed stem cells that substitute for tissue turnover.\(^4\)

The following are the criteria that characterize aberrations from regular mitotic activity in the soma:\(^4\)
- Dislocated divisions with relentless persistency
Mitosis at a glance

- Multipolar anaphase distortion [Figures 6 and 7]
- Centromere defects and chromosome misaggregation resulting in multiple mitotic figures
- Spindle defects- Aberrant cellular divisions
- Genome instability (Failures in check points and apoptotic system) resulting in proliferation and aberrant chromosome division figures (CDFs)
- Chromosome mutations- Acquisition of successive mutations leading to tumor initiation or syndromic manifestations
- Interphase aneuploidy
- Chromosome division figures- Pathologic mitosis with aberrant DNA content.

The hypothesis on the understanding of mitosis is as an equational bipartition of the hereditary substance (Fleming 1879; Roux 1883). True mitoses guarantee the constancy of terminally differentiated tissues.

**Cellular division can be:**

1. Symmetric
2. Asymmetric

Stem cells are capable of two types of symmetric divisions: A proliferation division resulting in the creation of two stem cells, and a differentiation division resulting in the creation of two differentiated cells[10] [Figure 8].

Asymmetric cell division [Figure 8] is suspected to play an important role in cancer, in particular with respect to the cancer stem cell hypothesis. The hypothesis states in essence that each tumor contains a relatively small population of cells capable of initiating and maintaining tumor growth. This hypothesis has enormous therapeutic implications, but also raises the possibility that defects in stem cell lineages may lead to tumor formation. Cancer stem cells as well as normal embryonic and adult stem cells are defined by both their ability to make more stem cells, a property known as self-renewal, and their ability to produce cells that differentiate. One strategy by which cancer stem cells can accomplish these two tasks is asymmetric cell division. Asymmetric division is a key mechanism to ensure tissue homeostasis.[10]

In normal stem and progenitor cells, asymmetric cell division balances proliferation and self-renewal with cell-cycle exit and differentiation. Disruption of asymmetric cell division leads to aberrant self-renewal and impairs differentiation, and could therefore constitute an early step in the tumorigenic transformation of stem and progenitor cells and result in formation of atypical/multipolar mitosis (According to studies done by Arnold (1879), von Hansemann (1890), Mendelsohn). The pathology of premalignant and malignant tumors is the given homeland for the pathology of mitosis.[11]

Stroebel (1892) described asymmetric mitosis occurrence in carcinoma and sarcoma and in normal regenerating and inflammatory tissues.[11]

Stains to visualize CDFs and atypical and typical mitotic figures include H and E, Crystal violet, toluidine blue, Giemsa.

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**Figure 6:** (a) Photomicrograph (H&E stain, ×400) (b) hand drawn illustration showing abnormal mitosis with tripod formation

**Figure 7:** (a) Photomicrograph (H&E stain, ×400) (b) hand drawn illustration showing abnormal mitosis with tetrapod formation

**Figure 8:** Types of cell division - asymmetric and symmetric cell division
stain and fluorescent microscopy. Newer prognosticators like immunohistochemistry, flow cytometry, autoradiography, and DNA ploidy measurements are now on the forefront.\[9\]

The immunohistochemical labeling of MFs with the mitosis-specific antibody anti–phosphohistone H3 (PHH3) has been suggested as a promising method.\[12\]

Anti-PHH3 antibodies specifically detect the core protein histone H3 only when phosphorylated at serine 10 (Ser10) or serine 28 (Ser28). The phosphorylation of histone H3 is a rare event in interphase cells but a process almost exclusively occurring during mitosis.\[12\]

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