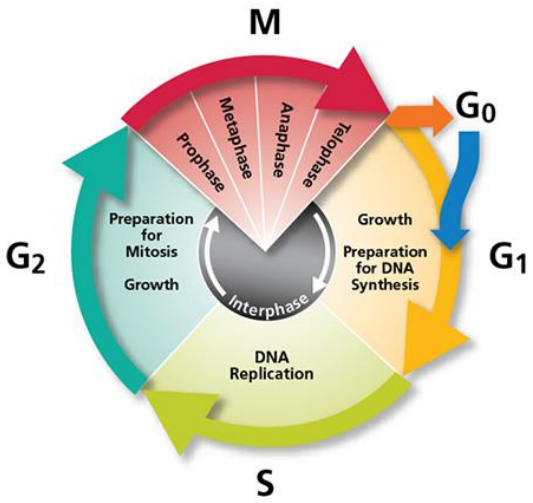
Unit I – Problem 9 – Molecular Biology: Regulation of The Cell Cycle

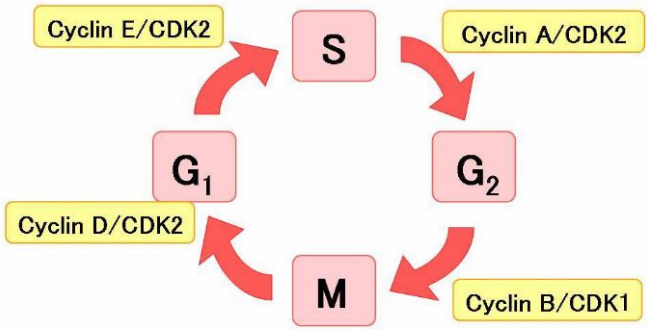
- **There are two phases of the cell cycle:**
  - **Interphase**: it is the stage in which a typical cell spends most of its life. During this phase, the cell copies its DNA in preparation for mitosis. This phase includes the following:
    - ✓ G1 phase (in which the cell grows and functions normally) or G0 phase (in which the cell does not divide again).
    - ✓ S phase: in which the cell duplicates its DNA.
    - ✓ G2 phase: in which the cell resumes its growth in preparation for division. The mitochondria divide and cell continues to grow until mitosis begins.



  - **M phase**: it consists of nuclear division (karyokinesis), cytoplasmic division (cytokinesis) and it is a relatively short period of the cell cycle. This phase is complex and highly regulated. This phase is subdivided into the following phases:
    - ✓ Prophase: nucleolus fades and chromatin condenses into chromosomes.
    - ✓ Prometaphase: breakdown of nuclear envelope.
    - ✓ Metaphase: alignment of all chromosomes in one plane at the center of the cell.
    - ✓ Anaphase: daughter chromosomes are pulled apart and move to the cell poles.
    - ✓ Telophase: Daughter chromosomes are at the poles; the spindle fibers that pulled them apart disappear.
- **Regulation of the cell cycle:**
  - A balance between cell death (programmed or pathological) and generation of cell from progenitor.
  - Uncontrolled growth of cells must be regulated otherwise malignancy would occur!
  - Notice that some cells retain the ability to divide throughout their life span. Some have rapid turnover as part of their job thus they need continuous replacement. Some cells immediately leave the active phases of the cell cycle after differentiation and enter the G0 phase (such as neurons which are known as senescent cells).
  - **Cell cycle regulation is represented by:**
    - ✓ Check points:
      - ❖ *Restriction point in G1 is a check point*: the progress of the cell cycle depends on external stimuli by growth factors till the restriction point, thereafter the cell cycle continue without further stimulation. G1 check point checks for: cell size, nutrients, growth factors and DNA damage.
      - ❖ *G2 check point checks for*: cell size and DNA replication.
      - ❖ *Spindle assembly checkpoint checks for:* chromosome attachment to spindle.
    - ✓ Cyclins and Cyclin-Dependent Kinase (CDKs):
      - ❖ These have kinases activity which can be inhibited by cyclin-dependent kinases inhibitor (CKI).
      - ❖ Cyclins are categorized as: D, E, A or B cyclins.
      - ❖ Each of these cyclins is expressed to regulate a specific phase of the cell cycle. Their concentrations rise and fall during the cycle due to synthesis and degradation via proteosomal pathway.

- D-type cyclins (D1, D2, D3) are G1 phase regulators. They are critical for progression through restriction point.
- S phase regulators include E and A cyclins.
- G2/M cyclins include B and A.
- CDK are found in constant amounts during the cell cycle. Some cyclins complexes with CDK to stimulate their kinase activity. Then, the cyclin-CDK complex phosphorylate its substrate at Ser and Tyr residues, changing the activity of the substrate. Such changes of the regulatory proteins allows initiation of the next phase.
  - Active CDK2 activates target proteins involved in S phase transition (G1 to S) and for initiation of DNA synthesis.
  - Active CDK1 activates target proteins critical for initiation of mitosis (M phase).

  The image below shows the cell cycle and cyclin-CDK complexes:



✓ <u>Tumor suppressor proteins (retinoblastoma, p53 and CKI):</u>

- They normally function to halt the cell cycle progress within G1.
- Mutations encode proteins that permit the progression of the cycle at inappropriate times leading to cancer.
- *G1 checkpoint proteins: these are regulators that ensure G1 is completed before S phase:*
  - Retinoblastoma (Rb) protein: it halts cell cycle at resting or G1 phase. Hereditary retinoblastoma (inherited eye disorder) is due to (Rb) gene mutation.
  - p53: nuclear DNA damage results in activation of p53 which will enhance the production of p21 protein thus halting cell cycle progression to allow DNA repair (if the damage cannot be repaired, p53 triggers apoptosis). Mutated p53 gene can produce protein unable to arrest cell cycle and growth. About 50% of cancers were found to be associated with p53 mutations.
  - CKI: two classes are known and they halt cell cycle and growth.
- *G2 checkpoint: ensuring completion of DNA replication in S phase before initiation of mitosis:*
  - CDK1 activity: It controls entry into mitosis. After activation by dephosphorylation, CDK1 binds cyclin B stimulating progression of the cell cycle through remainder of the cycle.
  - cdc25C phosphatase: permitting formation of CDK1-cyclin B complex which moves into the nucleus to activate mitosis.