Control of the Cell Cycle & Cancer Cells

Packet #10

**It is of the upmost importance that students watch the video animations that go along with this packet in order to fully understand sequential steps for the various processes.**
Introduction

- Cell Cycle
  - An ordered sequence of events in the life of a dividing eukaryotic cell and is a cellular asexual reproduction.
  - The contents of the parent’s cell nucleus is duplicated and two new, identical nuclei are produced.
    - Two daughter cells are produced the parent cell.
Cell Cycle
Three General Phases

- **Interphase**
  - G1 phase
  - Gap phase #1
  - S phase
  - DNA synthesis {replication}
  - G2 phase
  - Gap Phase #2

- **M Phase**
  - Mitotic phase

- **Cytokinesis**
Introduction I

- Within a eukaryotic organism, composed of eukaryotic cells, there must be a balance of **cell generation and cell death**.
  - Cell generation, proliferation, occurs via the **cell cycle**.
  - Cell death occurs via **apoptosis (programmed cell death)**.
  - Apoptosis occurs because of a series of enzymatic reactions carried out by **proteases (enzymes that hydrolyze peptide bonds that link amino acids together)**.
Cells, through **cell-to-cell communication** with each other, help evaluate whether they must continue dividing or die.
Introduction III

- **Why must cells die?**
  - Cells, that have reached the point of no longer being useful, damaged or abnormal, are programmed to die (apoptosis).
  - During the development of a baby in the womb, the programming of cells to die is important.
  - Very important in the development of fingers and toes for example.
Introduction IV

- To accomplish the production of cells (cell cycle) or the destruction of cells (apoptosis) different control mechanisms are used.
Introduction V

Types of Controls

Cell Cycle
- Intracellular
  - Negative: Stops cell cycle
  - Positive: Promotes cell cycle
- Extracellular
  - Negative: Stops cell cycle
  - Positive: Promotes cell cycle

Apoptosis
- Intracellular
  - Negative: Blocks apoptosis
  - Positive: Activates apoptosis
- Extracellular
  - Negative: Blocks apoptosis
  - Positive: Activates apoptosis
Introduction VI

- The cell cycle is in-part controlled by a **series of genes and proteins/enzymes that work sequentially**.

- These genes, working in sequence, can be considered to be **proto-oncogenes/oncogenes**.

- The sequential pathway is often started by a signal called **growth factors**.
Control of the Cell Cycle

Intracellular Control
Intracellular Controls I

- The steps of the cell cycle must occur in sequence and before the process can proceed to the next step, a checkpoint must be passed.

- There are checkpoints for:
  - Cell size
  - Determination of whether DNA replication is complete
Intracellular Controls II

- These checkpoints are, in general, regulated by various means
  - **Growth factors (extra cellular)**
    - MPF
      - Mitotic phase promoting factor
        - Signals from other cells
        - Turns on/off the intracellular controls allowing cell to divide.
  - **Protein kinases**
    - Enzymes
      - Phosphorylate
    - Cyclin-dependent protein kinases (Cdk)
  - **Proto-oncogenes/Oncogenes**
    - These are genes that are coded to make the growth factors and/or protein kinases.
The Big Picture

The Steps of Proliferation

Growth factor signals

growth factor

cell surface receptor

protein kinase cascade

nuclear membrane

nuclear pore

cytoplasm

cell division

chromosome

nucleus

E2F

Cdk

P

Rb

E2F
Cell Cycle Intracellular Positive Controls

Remember, positive intracellular controls advance the cell cycle and promote cell division.

G1/S Phase Checkpoint
Tumor Suppressor Genes

Activation of E2F {General Description}
Activation of E2F
{General Description}

- Initially, the Rb protein and E2F protein are joined together.
- E2F, when separated from Rb, allows the cell to continue dividing.
Activation of E2F
General Description II

- Cyclin (protein) and CDK (protein) join together to form the CDK-cyclin complex.
- Cyclin activates the CDK.
- Remember, CDK is short for cyclin dependent kinase.
- The CDK complex carries out the work of a protein kinase (phosphorylyating other enzymes/proteins).
The CDK complex, being a protein kinase, phosphorylates the Rb protein.
Activation of E2F
General Description IV

- Rb separates from E2F.
- E2F is activated.
- The cell cycle continues.
Production of CDK
Cell Cycle Intracellular Positive Control
Production of CDK I

- Remember, from the discussion on the activation of E2F, cyclin and CDK must unite together to form the CDK complex in order to remove Rb from E2F.

- Therefore, if there is no CDK protein, the cell cycle cannot continue.

- The sequence for the production of CDK is more detailed than the process for the activation of E2F.
Production of CDK II

- Growth factor binds onto a cell surface receptor.
- The binding of the growth factor, activates a phosphorylation cascade and eventually causes the regulatory protein to become phosphorylated.
Production of CDK III

- Meanwhile, the Rb protein (yes once again involved), is attached to the protein myc.

- When the phosphorylated regulatory protein enters the nucleus, Rb becomes phosphorylated and releases from myc.
Production of CDK IV

- myc, once free and activated, behaves as a transcription factor for the CDK gene (the gene that will be used to produce the CDK protein).

- CDK is produced.

- As long as the production of CDK continues, allowing CDK-cyclin complexes to form without any “inhibitions,” CDK, cyclin and the **CDK-cyclin complex** all “act” as positive intracellular controls.
Cell Cycle Intracellular Negative Controls

Remember, negative intracellular controls stop the cell cycle and promote apoptosis.

G1/S Phase Checkpoint
Introduction I

- To control these sequential pathways, **tumor suppressor genes are in place to shut off the pathway and stop the cell from dividing out of control.**

- One of the most famous tumor suppressor genes is **p53**.
  - Keep in mind, that the information about to be covered is tied to the two previous discussions on positive intracellular controls.
Inactivation of the CDK Complex
Cell Cycle Intracellular Negative Control
Inactivation of the CDK Complex I

- During the S phase, if the DNA is damaged, the p53 gene becomes activated and produces the p53 protein.

- The p53 gene protein stimulates transcription of the gene (p21 gene) that codes for a **CDK inhibitor protein**.
  - The p53 gene protein behaves as a transcription factor.

- The **CDK inhibitor protein** (p21 inhibitor protein) **binds onto** the S phase **cyclin-Cdk complex and inactivates them**.
  - This means that the **cyclin-CDK complex can no longer behave as a kinase**.

[Diagram showing the inactivation process]
Inactivation of the CDK Complex II

- The CDK inhibitor protein (p21 inhibitor protein) **inhibits CDK complex** and **stops** the complex from activating E2F.
- **The CDK inhibitor protein does not allow the cyclin-CDK complex to phosphorylate the Rb protein.**
- **This keeps E2F inactive.**

- **When E2F is inactive, the cell cycle stops.**
Side Note

- The genes that are used to make the proteins cyclin, CDK, Rb and E2F, are all considered tumor suppressor genes.
Extracellular Controls—Signals From Other Cells
Extracellular Controls

- The extracellular signal molecules that regulate cell size and cell number are generally either soluble secreted proteins, proteins bound to the surface of cells, or components of the extracellular matrix.
The factors that promote organ or organism growth can be operationally divided into three major classes:

- **Mitogens (cell cycle positive extracellular control)**, which stimulate cell division, primarily by relieving intracellular negative controls that otherwise block progress through the cell cycle.

- **Growth factors (cell cycle positive extracellular control)**, which stimulate cell growth (an increase in cell mass) by promoting the synthesis of proteins and other macromolecules and by inhibiting their degradation.

- **Survival factors (apoptosis negative extracellular control)**, which promote cell survival by suppressing apoptosis.
Survival Factors

- **Survival factors allow cells to “survive”** and if cells are deprived of them, cells will then activate intracellular suicide programs.
  - Programmed cell death
  - Apoptosis

- Survival factors help prevent necrosis (tissue death).
Survival Factors II

- What are the roles of survival factors in regards to fetal development?
  - Fetal development
    - The development of hands and feet occur in part due to an “inactivation” of survival factors—which allow apoptosis to occur in the correct cells/areas.
  - Metamorphosis
    - The same process is exhibited during metamorphosis
      - Tadpole → frog
Survival Factors III
Cancer Cells

- The presence of survival factors allow cancerous cells to keep dividing—hence promoting the cell cycle.
Side Note...

- The only checkpoint investigated in the packet is the G1/S phase checkpoint...there are other checkpoints...
Cancer Cells
Cancer Cells

- Many of the genes, in which mutations cause cancer, are those which contribute either directly or indirectly to the normal control of growth and differentiation mechanisms in the cell.

- Cancer cells develop because of mutations that directly/indirectly impact the “proliferation control system.”
  - Faulty control system
  - **Mutant proliferation genes are called oncogenes**
    - Cancer promoting genes.
    - Mutations in genes such as myc, p53 and p21 allow those genes to become oncogenes.
Review