Neoplasia 1

Lecture 8
Pathology and Clinical Science 1 (BIOC211)
Department of Bioscience

Text Reference:

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Session Learning Outcomes

This session aims to understand and discuss:

- Causes of tumour formation and DNA mutation
- Risk factors involved in cancer formation
- The three step model of carcinogenesis
- Epidemiology of cancer
Understanding Cancer

- Cancer is a group of diseases characterised by uncontrolled growth and spread of abnormal cells, and if the spread is not controlled it can result in death.

- When cells in some areas of the body divide without control, the excess tissue that develops is called a neoplasm (neo = new; plasia = growth) (or a tumour).

- Neoplasia is uncontrolled cell division leading to new growths. To understand how a cell loses control of its cell division it is important to understand the processes involved when a cell divides.

- These processes are called mitosis and cytokinesis, which together form parts of the cell cycle.
During cell development from a stem cell to a fully differentiated cell, cells in the body alternately divide (mitosis) and then "appear" to be resting (interphase). This sequence of activities is called the Cell Cycle.

Interphase, which appears to the eye to be a resting stage between cell divisions, is actually a period of diverse activities. Those interphase activities are indispensable in making the next mitosis possible.
Overview of the Normal Cell Cycle

- Each cell has a basic cell cycle of growth and replication.
- The cell cycle has distinct phases including mitosis where it reproduces to two daughter cells.
- These phases are strictly regulated to ensure cells divide at periods appropriate to cellular size and DNA status.
- Cell replication is largely controlled by chemical factors (e.g., hormones) in the micro-environment.
- Different cells complete their cell cycle at different times.
Overview of the Normal Cell Cycle

- Control over the cell cycle is genetic and orchestrated via DNA-specific chromosomes and genes exist to control the cell cycle.

- Control = rate, timing and differentiation (specialisation).

**Genes either:**

- TURN ON cell division and replication = proto-oncogenes.

- TURN OFF or SLOW DOWN cell division and replication = Tumour suppressor genes.
Mitosis

- The events that describe what happens to a cell’s DNA or chromosomes when a cell divides into 2 identical daughter cells

- There are a number of phases:
  - Interphase – including S phase
  - Prophase
  - Metaphase
  - Anaphase
  - Telophase

## Control of cell destiny

A cell has three destinies:
- Remain alive and function
- To grow and divide
- To die

When there is a balance between cell proliferation and cell death there is homeostasis.

Maturation Promoting Factor (MPF) induces cell division.
### Apoptosis

- Throughout the life time of an organism, cells undergo genetically programmed cell death.

- APAF-1 is activated causing cell death (apoptosis).

- *Recall:* Necrosis is the pathological type of cell death from tissue injury.

- Certain genes regulate both cell division and apoptosis.
Necrosis vs. Apoptosis

NORMAL

NECROSIS

APOPTOSIS

Apoptotic body

Phagocyte

**Apoptosis**

- Different cells have different life spans
- Cellular aging occurs naturally and cells eventually enter apoptosis
- The processes of cellular aging and the subsequent loss of cell control systems are not fully understood
- Current theories focus on the presence of a programmed number of cell cycles (different for different cells) after which, programmed cell death occurs
- Normal mammalian cells are only able to undergo a finite number of cell divisions
Mutations

- Specific damage can occur in a cell’s DNA
- DNA damage can occur on any chromosome.
- DNA damage is related to a number of diseases
- If the DNA is altered in the parent cell, this is passed onto the daughter cell
- Mutations can arise spontaneously during mitosis or can be induced through exposure to DNA damaging agents
- Rapid rates of mitosis increase the chance of errors and mutations occurring
- Specific mutations at specific locations in the chromosomes that control the cell cycle, may lead to the development of neoplasia.
Proto-oncogenes

- Often proto-oncogenes are involved in signalling cells in normal situations.
- Mutations or the presence of additional copies of these genes results in overactivity (= oncogene) which in turn increases the rate of mitosis and adds to the loss of control of the cell cycle.
- This overactivity is due to the fact that expression of these genes mimics persistent growth factor stimulation.
**Oncogenes**

- An oncogene is the term given to a gene that has been mutated to cause uncontrolled cell growth.

- Genes that normally control the cell cycle are:
  - Proto-oncogenes
  - Tumour suppressor genes

- When these genes are damaged they lead to:
  - Overactivity of a proto-oncogene
  - Loss of function of a tumour suppressor gene
### Mutations and oncogenes

- Every cell has proto-oncogenes that carry out normal growth and development.
- When mutation occurs, proto-oncogenes are changed to oncogenes.
- Oncogenes contribute to cancer formation.
- Oncogenes are dominant over the proto-oncogenes.
### Tumour suppressor genes

- Proteins from tumour suppressor genes can act to prevent rapid mitosis from taking place and aid in controlling the rate of the normal cell cycle.

- Tumour suppressor genes can, as a normal function, induce apoptosis of the cell to prevent any damage from being passed on to the daughter cells.

- A single mutation in a tumour suppressor gene is usually insufficient to initiate oncogene formation. A second mutation has to occur in the second copy of the gene.
## Carcinogenesis

- The generation of cancerous cells from normal cells (tumour formation)

- Results from specific damage to the DNA that controls normal cell cycle patterns and thus a potential loss of cell cycle control

- Loss of cell cycle control results in a neoplasm (new growth)

- Neoplastic cells are transformed (altered) as they continue to replicate, ignoring normal cellular controls

- In common medical terminology a neoplasm is often referred to as a tumour
Aetiology of Tumour Formation

- Tumours result from a sequence of changes over a relatively long period of time
- Can be from a combination of factors or repeated exposure to a single factor
- Some cancers have well established risk factors such as lung cancer (Bronchogenic Carcinoma) and cigarette smoking

http://images.radiopaedia.org/images/382214/a280a19796be7dc5ae90deec5887b7.jpg
Aetiology (Continued)

- Often difficult to determine aetiology as multiple factors are involved and it takes many years to develop

- Most mutations that arise occur in somatic genes and therefore are not passed onto offspring, however there are a few cancers where an inherited genetic predisposition occurs, e.g:
  - Familial Adenomatous Polyposis
  - Retinoblastoma
Familial Adenomatous Polyposis

From *Essential Pathology* (3rd ed), by Rubin E. 2000. Lippincott, Williams & Wilkins
Retinoblastoma

From *Essential Pathology* (3rd ed), by Rubin E. 2000. Lippincott, Williams & Wilkins
The Causes of Cancer

Damage to DNA can occur as a result of:

- spontaneous mutation during mitosis
- exposure to chemicals
- exposure to viruses
- exposure to radiation
- exposure to other hazards such as trauma which increases mitotic rate and increases the risk of errors during DNA replication

This initial change does not result in an active neoplasia but instead generates an oncogene.
## Tumour Formation

Carcinogenesis involves a three step process:

- **Initiating factors**
  - cause the first irreversible change to the DNA

- **Promoters**
  - later exposure causes additional damage to the DNA

- **Additional changes to DNA and cell structure**
  - result in tumour formation
## Initiating Factors - 1st Step

- The cell cycle normally has molecular checkpoints to prevent uncontrolled replication

- Initiating factors in carcinogenesis cause damage to one or more of these checkpoints

- This damage is the first irreversible damage to the DNA of the cell

- Can be genetic or from environmental exposure
# Promotion – 2\textsuperscript{nd} Step

Exposure to promoters results in further changes to the DNA in adapted cells

- **Examples of promoters include:**
  - Hormones (eg. oestrogen)
  - Chemicals (eg. food additives)
  - UV radiation (eg. Dental x-rays)

- **Outcomes of promotion are:**
  - Less differentiation and an increased rate of mitosis
  - Further adaptation towards neoplasia
  - Cell death
Continual Damage to DNA - 3rd Step

- Continued exposure and further changes in the DNA of the adapted cell results in a malignant tumour.

- The prolonged time interval and multiple factors involved complicate efforts in identification of initiators and promoters and their specific relationship to cancer types.
First Hit - Initiation
Irreversible damage
Generation of oncogene
UV, viral, radiation,
inherited, spontaneous mutation

Second Hit - Promotion
Exposure to promoters
Hormones, chemicals,
Industrial factors

Third Hit - Cancer
Continued exposure to
Damaging stimuli

NEOPLASIA
“Cancers grow by progressive infiltration, invasion, destruction and penetration of the surrounding tissue”

*Kumar, Cotran, Robbin, Basic Pathology, 7th Ed, 2003*

As the mass enlarges the innermost cells are frequently deprived of nutrients and die

- Many tumour cells trap nutrients depriving normal cells and therefore preventing tissue regeneration
- Inflammation and the loss of normal cells leads to a progressive loss in organ function
- For the tumour to be able to grow beyond 1-2 mm in diameter it must be vascularised
## Angiogenesis

- Branches extend from pre-existing capillaries to generate new blood vessels (neovascularisation).

- This is a normal process which is important in tissue healing and regeneration; developing alternate routes of microcirculation at sites of ischemia.

- This process can be induced and when this occurs facilitates tumour growth by allowing nutrient supply to growing tumour cells.

- Tumours are capable of synthesising additional growth factors which promote angiogenesis to supply the tumour with nutrients.
Angiogenesis Cascade

http://medicalart-work.co.uk/wordpress/wp-content/gallery/gallery/angiogenesis-01.jpg
### Pathophysiology of Cancer

- A tumour manifests as an enlarging space-occupying mass
- Expansion compresses the local area and local structures including blood vessels
- Lack of blood flow leads to necrosis and therefore inflammation around the tumour site
- Malignant cells can break free from the tumour and infiltrate local tissue, blood vessels and lymphatics (metastasis)
- Some neoplasms develop in this way very quickly whereas others take a lot longer and offer better diagnostic and treatment potential
Readings and Resources

Resources:

- **Set Textbooks:**

- **Additional textbooks:**
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