# STUDY UNIT 5 : CANCER NOTES

## Pathologic basis of disease Chapter 7 and Psychoneuroimmunology Chapter 11

### CANCER INITIATION

**Tumorigenesis**

- Multi-step process
- Consisting of genetic and epigenetic alterations which lead to alterations of normal cells into malignant cells

**Cell alterations**

- Acquired from viral infections
- New genes introduced into the host cell (viral oncogene)
  - Kaposi sarcoma (HIV) Human immunodeficiency virus
  - Cervical cancer (HPV) Human papillomavirus

**Physical damage to cellular DNA**

- Alterations of human gene (carcinogen)
- Radiation (damage to human genome)
- Arsenic
- Asbestos

Alteration in cell physiology (hallmarks of cancer) include:

1. **Self-sufficiency in growth signals**
- Tumours have the capacity to proliferate without external stimuli, usually as a consequence of oncogene activation.
2. **Insensitivity to growth inhibitors**
- Inactivation of tumor suppressor genes that encode for sections of the growth inhibitory pathways
3. **Altered cellular metabolism**
- Tumour cells undergo metabolic switch to aerobic glycolysis (Warburg effect), which allows synthesis of macromolecules, which are needed for rapid cell growth.
4. **Evasion of apoptosis**
- Tumors are resistant to programmed cell death
5. **Limitless replication potential (immortality)**
- Avoid cellular senescence and mitotic catastrophe
6. **Sustained angiogenesis**
- Tumour cells need a vascular supply to bring nutrients and oxygen and remove waste products- Tumours must induce angiogenesis.
7. **Tissue invasion and Metastasis**
- The ability is intrinsic to tumour cells and factors initiated in the tumour microenvironment contribute.
8. **Evade host immune response**
- Cancer cells exhibit alterations that allow them to evade immune response

### 1. SELF-SUFFICIENCY IN GROWTH SIGNALS

- Genes that promote autonomous cell growth in cancer cells are called oncogenes
- **Proto oncogenes**- Normal gene codes for proteins that regulate growth and differentiation (unmutated counterpart to oncogenes)

- **Oncogenes**- mutated proto-oncogene that has lost dependence on normal growth promoting signals, which encodes oncoproteins.
  - Promote cell growth in the absence of normal growth promoting signals, does not depend on external signaling
  - Cells expressing oncoproteins are freed from checkpoints (G1/S, G2M) that limit growth and due to this they proliferate excessively

- The normal cell response to growth factors:

1. Growth factors bind specific receptors
2. Transient and limited activation of the receptor activates cytoplasmic signal-transducing proteins.
3. Transduced signal is transmitted to the nucleus (via cytoplasmic effector proteins and second messengers or by a cascade of signal transduction molecules) where it initiates DNA transcription
4. Expression of factors promotes progression of the cell into the cell cycle, which results in cell division.

## 2. INSENSITIVITY TO GROWTH INHIBITION

- Oncogenes drive the proliferation of cells; the products of **tumour suppressor genes** apply brakes to cell proliferation.
  - Abnormalities in these genes leads to failure of growth inhibition, which is a hallmark of carcinogenesis.

- **Tumour suppressor proteins:**
  - Form network checkpoints that prevent uncontrolled cell growth
  - P53 recognizes genotoxic stress and responds by shutting down proliferation.
  - Expression of an oncogene in normal cells with intact tumor suppressor genes leads to permanent cell arrest (quiescence) rather than uncontrolled proliferation.
  - Some impact multiple cancer phenotypes

- **P53**
  - Critical role in prevention of cancer development.
  - Affects cell cycle progression
  - Affect genomic stability
  - Enhance susceptibility to cell death
  - Affect cell metabolism

## 3. CHANGED CELLULAR METABOLISM

- **Warburg effect (aerobic glycolysis)**
  - Even in the presence of ample oxygen, cancer cells opt for metabolism of high glucose uptake and an increased conversion of glucose to lactate via the glycolytic pathway (2 ATP molecules per glucose molecule)
  - Instead of oxidative phosphorylation (36 ATP molecules per glucose molecule)

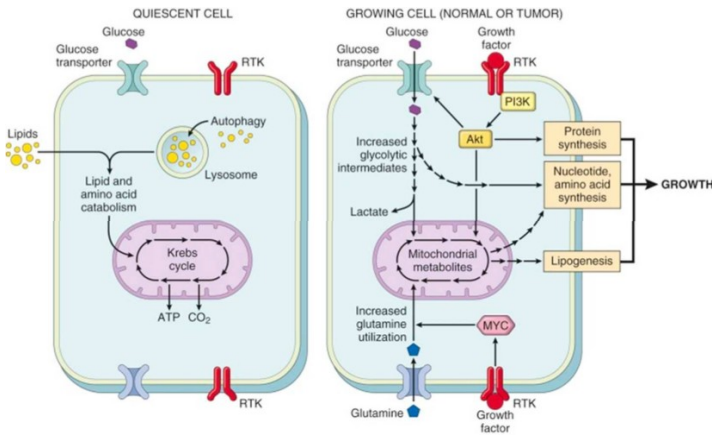


**Figure 7-32** Metabolism and cell growth. Quiescent cells rely mainly on the Krebs cycle for ATP production; if starved, autophagy (self-eating) is induced to provide a source of fuel. When stimulated by growth factors, normal cells markedly upregulate glucose and glutamine uptake, which provide carbon sources for synthesis of nucleotides, proteins, and lipids. In cancers, oncogenic mutations involving growth factor signaling pathways and other key factors such as MYC deregulate these metabolic pathways, an alteration known as the *Warburg effect*.