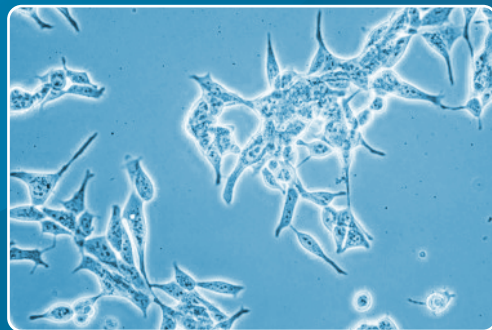


Oncology Basics

Tutorial 1 Cancer Primer



Tutorial 1 Cancer Primer

Tutorial 1: Cancer Primer is an introduction to the basic characteristics and biology of cancer – a group of over 200 different diseases. Key terms and tumour classifications are also defined. All this is necessary grounding for tutorials two to five in the Oncology Basics program.

Goals and Objectives

Upon completion of this program you will be able to:

- Describe the key characteristics of cancer cells.
- Define the following key terms – neoplasms, benign tumours, malignant tumours, anaplasia, hyperplasia, dysplasia, metastasis.
- Identify the cells of origin in the following tumour classifications – carcinoma, adenocarcinoma, squamous cell carcinoma, sarcoma, glioma, astrocytoma.
- Describe the different phases of the cell cycle.
- Describe how tumour cell growth differs from normal cell growth.

DEFINITION AND CHARACTERISTICS OF CANCER CELLS

Cancer cells are typically characterized by abnormalities in growth, division and location.

UNCONTROLLED PROLIFERATION

Cells in normal tissues have constraints or feedback mechanisms to regulate growth. They proliferate until there are enough cells to maintain the physiologic needs of the tissue or organ. Cancer cells lack or fail to respond to normal homeostatic mechanisms that control cell division or cell growth. *The capacity for persistent, uncontrolled proliferation is the distinguishing property of malignant cells.* Without intervention, cancerous tissues grow in an unrestrained manner, leading to tissue invasion, metastasis and ultimately death. Some cancers are composed of rapidly dividing cells while others are composed of cells that divide more slowly than normal. This differs from the old belief that cancer cells simply divide more rapidly than do normal cells.

Cell growth associated with carcinogenesis involves two classes of genes: 1) *oncogenes*, and 2) *tumour suppressor genes*.

- **Oncogenes** develop from protooncogenes, which are present in all cells and serve as regulators of the cell cycle. Protooncogenes mutate when exposed to carcinogenic agents such as radiation, chemicals or viruses, or as a result of inherited factors. Activation of oncogenes results in dysregulation of normal cell growth, which produces excessive cellular proliferation.
- **Tumour suppressor genes** regulate and inhibit inappropriate cellular growth and proliferation. Mutation of these genes results in loss of control over normal cell growth.

INAPPROPRIATE ABILITY TO INVADE SURROUNDING TISSUES

Cell populations that make up body tissues normally remain segregated (i.e. one type of cells does not invade physiologic structure belonging to a different type of cells). In contrast, malignant cells lack the constraints that inhibit invasive growth. As a result, cells of a solid tumour can penetrate adjacent tissues, allowing the cancer to spread.

DECREASED CELLULAR DIFFERENTIATION AND OTHER CELLULAR CHANGES

Most normal cells evolve through the process of differentiation, which means that they develop from a primitive cell with few specialized properties into a cell with more specific morphology and physiologic functions. Cancer cells have generally lost some or all of these differentiated characteristics and cannot perform the intended physiologic functions of their tissue of origin.

Malignant cells are also genetically unstable and lose the normal cell structure and function typical of the cells of their origin.

Cancer cells may also show changes in the cell membrane, and exhibit different protein and enzyme content, different shapes and appearances, and chromosomal abnormalities. Pathologists use all of these characteristics to distinguish between malignant and benign cells, and to classify cancers to specific tumour types. Cancer treatment, especially chemotherapy and radiotherapy, exploits the differences in growth patterns between cancer cells and normal cells. Some drugs also capitalize on other biochemical differences between normal and malignant cells.

METASTASIS: ABILITY TO ESTABLISH NEW GROWTH AT DISTANT SITES

Cancer cells have a unique ability to “break away” and metastasize, or spread to distant sites of the body. Cancer cells which break away from the original tumour mass frequently travel via the blood or lymphatic system, establishing a new secondary tumour (metastasis) elsewhere.

Most tumour cells that detach from the primary tumour do not survive in the systemic circulation. Survival of these tumour cells depends on three factors:

- The tumour cells or cell aggregates must receive the necessary nutrients at the distant site
- The host immune system must be overcome
- Angiogenesis (new blood vessel formation) must be initiated

Angiogenesis has been recognized as an important step in primary tumour growth and metastasis. It has become a target for the development of new anticancer drugs.

Key Sites and Characteristics of Metastasis

Local metastases generally invade the lymphatic system. Distant metastases commonly involve the brain, lung, bone and liver. Each cancer has a distinct pattern of metastasis (e.g. prostate cancer commonly metastasizes to the bone, but rarely to the brain). Metastasis can occur at any time in the growth of a cancer, and may occur before or after removal of the primary tumour. A cancer cell that has metastasized retains many of the characteristics of the original cancer cells. For example, a patient with breast cancer that has metastasized to the liver does NOT have liver cancer. This is often misunderstood by the patient. The breast cancer cells are growing in the liver, and the disease is treated with regimens against the original malignant breast tumour cells.

CANCER TERMINOLOGY: KEY TERMS IN ONCOLOGY

Neoplasms or **tumours** (terms used interchangeably) are masses of newly formed tissue characterized by new and abnormal cell development. They may be benign or malignant. (Note: Neoplasm means “new growth.”)

Benign tumours are generally encapsulated and slow growing. They usually resemble the cells from which they developed, generally do not metastasize, and rarely recur if removed. Benign tumours are not often harmful, but can cause harm and even death if the growth exerts pressure or occupies space required for vital organ functioning.

Malignant or **cancerous tumours** are defined as “uncontrolled growth of cells” which manifest as:

- Rapid proliferation
- Decreased cellular differentiation
- Invasion of surrounding tissues
- Ability to metastasize

A diagnosis of “malignant” versus “benign” cancer is made at the microscopic level through pathology review. Under the microscope, cancer cells typically show evidence of mitotic activity and abnormal cellular structure and organization. As a result, cancer cells cease to perform their normal functions. The loss of structure and function is referred to as **anaplasia**; this ultimately leads to death unless the process is halted.

Hyperplasia is an increase in the number of cells in a tissue or organ. It may precede the development of neoplasms by several months to years.

Dysplasia is an abnormal change in the size, shape or organization of cells in a tissue. Dysplastic changes may precede development of neoplasms by months or years.

Metastasis is the process by which malignant tumour cells spread to distant parts of the body. Metastasis is the cause of most cancer-related deaths.

Did You Know

The word “cancer” arose from early descriptions of malignancies in which claw-like projections extended from the central tumour. These claws resembled those of a crab – the symbol of the astrological sign of cancer.

CLASSIFICATION OF TUMOURS

Benign tumours are named by adding the suffix, “-oma”, to the name of the cell type (e.g. lipoma is a benign growth in fat tissue).

Malignant tumours are classified by their tissue of origin. It is critical to know the cancer’s tissue of origin because each type of cancer cell responds differently to therapy and the prognosis from different cancer cell types varies significantly.

Malignancies are classified into hematologic and solid tumours.

- 1) *Hematologic malignancies* include acute and chronic leukemias, multiple myeloma and lymphomas.
- 2) *Solid tumours* are further classified by the cells of origin: epithelial cells (*carcinomas*); connective tissues such as bone, fat, cartilage and muscle (*sarcomas*); neural tissues; and gonadal tissues.
 - *Carcinomas* are subdivided into tumours that are predominantly glandular or ductal in origin (*adenocarcinomas*), and those that derive from stratified squamous epithelium (*squamous cell carcinomas*).
 - *Carcinoma in situ* is a malignant cancer limited to the site of origin and has not yet invaded the basement membrane. *Carcinoma in situ* is a pre-invasive stage of malignancy and can be cured with complete surgical removal of the tumour (e.g. *carcinoma in situ* of the cervix). *Most carcinomas have progressed beyond this stage at the time of diagnosis.*
 - *Neural tumours* are classified based on the cells from which they arise. For example, a brain tumour arising from a *glial cell* is called a *glioma*; a brain tumour from an *astrocyte* is called an *astrocytoma*.

GRADING AND STAGING OF MALIGNANT TUMOURS

At the time of diagnosis, the pathologist will determine the tissue type of origin, the tumour grade and the stage of the cancer. These parameters offer important prognostic information and will guide the selection of treatment. Different cancer types have different staging and grading systems.

Tumour grade reflects the histology of the cancer cells. It is based on the degree of differentiation of the tumour cells and their mitotic activity (an estimate of the tumour growth rate). *The less a tumour cell appears to resemble a normal cell and the greater the number of cells active in cell division, the higher the grade.* A higher grade generally correlates with a more aggressive tumour and a poorer prognosis.

The stage of a cancer signifies the extent of the disease. Most solid cancers are classified into stages 0 to IV – stage 0 indicates carcinoma *in situ*; stage IV indicates metastatic disease. The TNM staging system is the most common staging system, and includes the evaluation of three variables:

- Size of the primary lesion (**T**)
- Involvement of regional lymph nodes (**N**)
- Presence of distant metastases (**M**)

Once treatment has begun, staging may be repeated to evaluate the effectiveness of the treatment.

MOLECULAR BIOLOGY OF CANCER: SIGNAL TRANSDUCTION

Protooncogenes are genes that normally code for growth factors and/or their receptors. Examples include:

- Epidermal growth factors
- Vascular endothelial growth factors
- Epidermal growth factor receptors
- Vascular endothelial growth factor receptors

Protooncogenes can become **oncogenes** (genes that evoke abnormal cell growth) when they undergo mutations or increased expression. The activation of oncogenes can potentially lead to the development of cancer.

SIGNAL TRANSDUCTION PROCESS

Signal transduction refers to a process whereby extracellular signaling molecules activate a membrane receptor, eliciting an intracellular response. It often involves a number of phosphorylation reactions within the cell. The signal alters gene expression and results in an increased production of proteins that control cell function. For example, a growth factor will bind to and activate its receptor, thereby eliciting an activation signal that is then conveyed to a series of other proteins, and eventually to the nucleus.

Protein kinase enzymes (mainly tyrosine kinases) are often involved in the phosphorylation process. These enzymes are the targets of many new anticancer treatments. Examples of tyrosine kinase inhibitors include erlotinib and gefitinib.

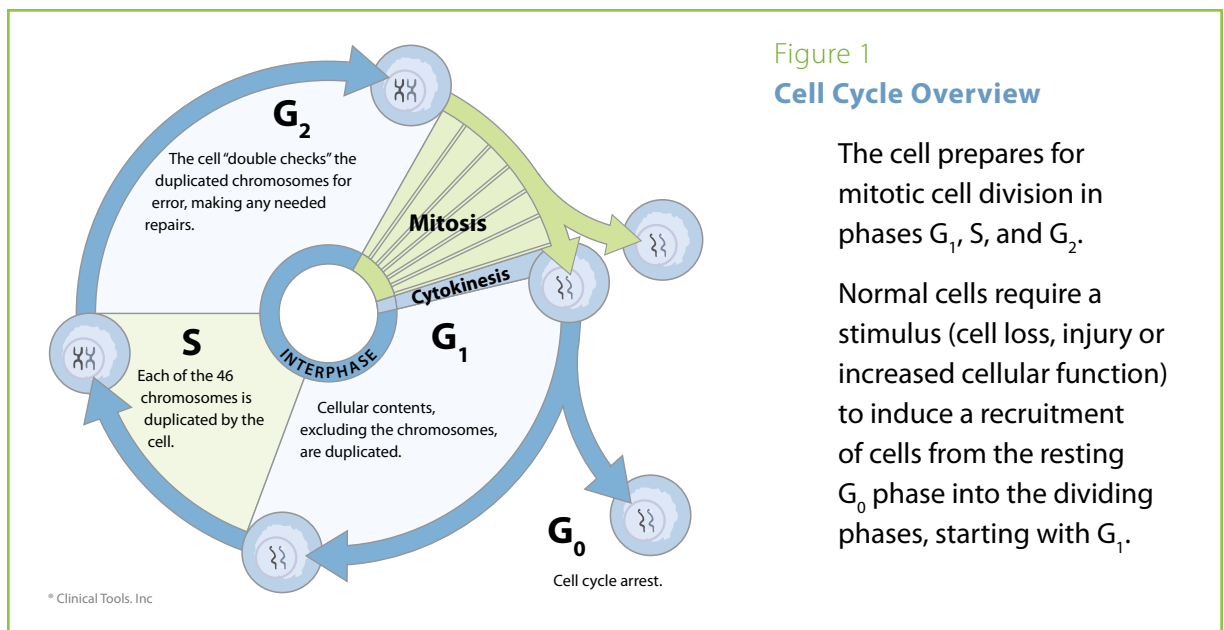
MOLECULAR BIOLOGY OF CANCER: THE CELL CYCLE

All cells reproduce in a multi-phase cell cycle. Increases in signal transduction can lead to increased stimulation of cell replication and uncontrolled cell growth. Understanding how normal cells and cancer cells grow leads to better understanding of: 1) the pharmacology of antineoplastic drugs in the treatment of cancer; and 2) the toxicities associated with these agents. Radiotherapy and many anticancer drugs reduce the level of uncontrolled cellular growth that is the hallmark of cancer cells.

PHASES OF THE CELL CYCLE

As illustrated in Figure 1, the cell cycle includes four key stages: Gap₁ (G₁), Synthesis (S), Gap₂ (G₂) and Mitosis (M). Following cell division in mitosis, cells are destined to either:

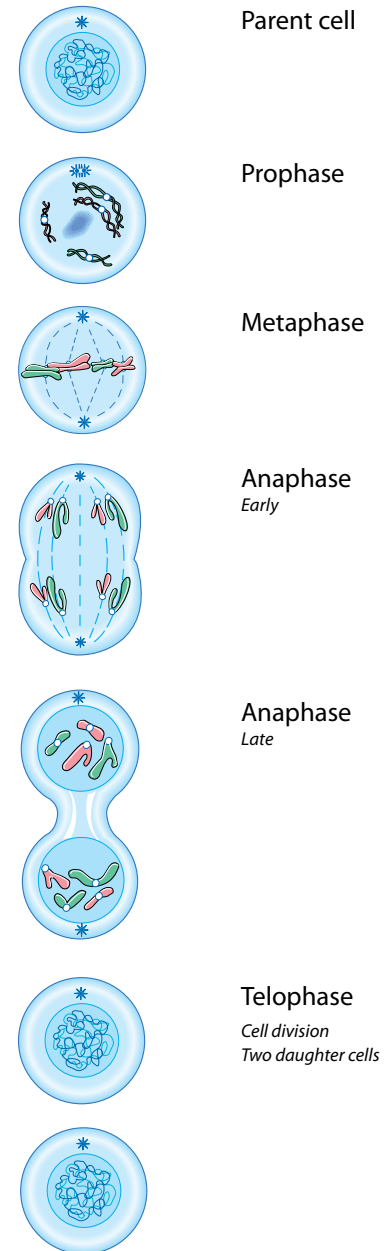
- Go back into the cell cycle at the G₁ phase, or
- Enter a dormant or resting phase G₀ where cells can rest, proceed to cellular differentiation, or die. This stage is not considered part of the cell cycle as cells are not undergoing active division. Most normal human cells exist predominantly in the differentiated G₀ phase, during which they perform the work for which they are intended (e.g. kidney cells filter urine). Because chemotherapy mainly targets rapidly dividing cells, *cancer cells in the G₀ phase are not as susceptible to the toxic effects of chemotherapy as in other cell cycle phases.*



MULTI-PHASE CYCLE, BEFORE AND DURING CELL DIVISION

- G₁ Phase** Enzymes for Deoxyribonucleic acid (DNA) synthesis are manufactured.
- S Phase** In the Synthesis Phase DNA replication occurs. The DNA coil unwinds, and an identical strand of DNA is synthesized with the help of the enzyme DNA polymerase. When DNA replication is complete, new and old DNA strands coil to form double-stranded DNA.
- G₂ Phase** This is a short, pre-mitotic phase during which Ribonucleic acid (RNA) and specialized proteins are produced to form the mitotic spindle.
- M Phase** As illustrated in Figure 2, mitosis or the cell division phase is further categorized into four sub-phases:
 - Prophase**
The nucleus of the cell disintegrates, releasing chromosomes into the cytoplasm, and the protein spindle structure is synthesized.
 - Metaphase**
Chromosomes line up along the centre of the cell.
 - Anaphase**
Chromosomes separate and migrate to opposite ends of the cell along the mitotic spindle.
 - Telophase**
Two new nuclei are formed and cell division takes place, producing two identical daughter cells.

Figure 2
Cell Cycle Mitosis



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MANY ANTICANCER DRUGS TARGET RAPIDLY PROLIFERATING CELLS

Many anticancer drugs are designed to target the cell cycle. *Drugs with activity in a particular phase of the cell cycle are called cell cycle phase-specific.* For example, antimetabolites are active during the S Phase. At any time, tumour cells can be at various phases of the cell cycle. Chemotherapy agents that are cell cycle phase-specific should be given as a continuous infusion or in multiple repeated fractions in order to capture as many cells that are entering into the cell cycle as possible.

In contrast, *cell cycle phase-non-specific agents* have activity in multiple phases of the cell cycle. The tumour activity of these agents are dose-dependent. Cell cycle phase-non-specific agents include alkylating agents such as cyclophosphamide and melphalan. Interestingly, some anticancer drugs (e.g. endocrine therapy) have activities that are not related to the cell cycle events at all.

MOLECULAR BIOLOGY OF CANCER: KINETICS OF TUMOUR CELL GROWTH

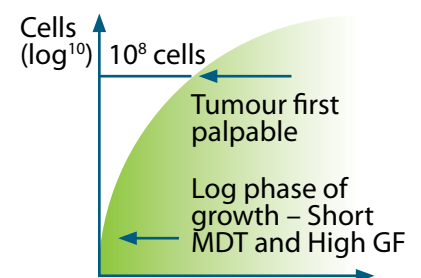
The study of tumour growth led to the development of many basic principles of cancer chemotherapy. Tumour growth can be modeled through “*Gompertzian kinetics*,” named after Gompertz, a German insurance agent who developed a mathematical model to describe the relationship between an individual’s current age and expected age of death. As illustrated in Figure 3, this model also describes expected tumour cell growth.

“GROWTH FRACTION” IN A TUMOUR

In both normal tissue and malignant tumours, some cells are going through the cell cycle while others are “resting” in the G_0 phase. *The ratio of proliferating cells to G_0 cells in a tumour mass is called the Growth Fraction (GF). In other words, the growth fraction signifies the percentage of proliferating cells in a tumour mass.*

Tumours with a high growth fraction are likely to be more susceptible to chemotherapy compared to tissues with a low growth fraction. Most chemotherapy agents directly interfere with the synthesis and/or function of DNA during the process of mitosis.

Figure 3
Gompertzian growth curve



MDT
Minimum Detection Time

GF
Growth Fraction

Reprinted with permission of the World Small Animal Veterinary Association from Blackwood L. How antitumour drugs work. WSAVA 2008 Dublin World Congress Proceedings

INITIAL TUMOUR GROWTH IS VERY RAPID

Early phase growth is exponential, so it is better to give chemotherapy in this phase since the growth fraction is very high (i.e. most of the cells are dividing). *Cells are very susceptible to chemotherapy in the high growth period.* As the tumour grows, the growth fraction decreases and the rate of growth starts to plateau. At this time, there are fewer cells dividing. Slower growth in a large tumour may be due to decreased availability of oxygen, nutrients and hormones. Also, toxic metabolites and wastes accumulate, because the vascular supply to the large tumour cannot support growth of all the cells.

PREDICTIVE VALUE OF THE GROWTH FRACTION

Knowing the growth fraction can help predict how a tumour will respond to chemotherapy.

- *As a rule, solid tumours (e.g. breast, lung, colon and prostate) have a lower growth fraction and, therefore, will not respond as well to chemotherapy as haemopoietic cancers (such as leukemias and lymphomas) which have a higher growth fraction.*
- Knowing the growth fraction and sensitivity to anticancer drugs can help predict which normal tissues will be most affected by treatment.
- Tissues which are rapidly proliferating and have a high growth fraction will be most affected by anticancer drug treatments (e.g. bone marrow, GI epithelium, hair follicles, etc.). Toxicities are greatest in those tissues because the rapidly proliferating cells will be highly targeted by the therapy.

DIAGNOSIS AND TREATMENT

Unfortunately, most cancers are diagnosed when a patient already has symptoms, or the tumour has reached a sufficient size to be clinically detected by physical or radiological examination.

At the point of diagnosis, the cancer cell number may already be very large (e.g. one billion cells present in a tumour of about 1 cm in diameter). Also, the Gompertzian growth curve will have already progressed to the plateau phase, meaning a lower growth fraction and fewer cells that are highly susceptible to chemotherapy.

Initial treatment for many cancers is aimed at decreasing tumour size, usually with surgery (e.g. debulk tumour) or radiotherapy, which stimulates cells to reenter the cell cycle (i.e. recruitment). The idea is to get tumour growth to shift downward on the Gompertzian growth curve so that the growth fraction increases as cells begin dividing and the tumour cell population becomes more sensitive to drug therapy. At this time, chemotherapy is administered.

MOLECULAR BIOLOGY OF CANCER: APOPTOSIS

Apoptosis or “programmed cell death” is an orderly process of cell death in which the cell shrinks away from surrounding cells and forms apoptotic bodies to degrade its nuclear DNA. This process usually occurs without damaging surrounding cells.

A number of chemotherapy agents work by inducing DNA damage that stimulates cancer cell apoptotic death.