Cancerous growth and classification

Cancer cells are characterised by two distinct heritable properties, which discriminate them from normal cells.

First, they and their progeny reproduce despite the normal constraints that inhibit cell division and proliferation. Cancer cells proliferate more than the surrounding normal cells and so eventually crowd out and damage the local tissue.

A tumour or neoplasm is a relentless growing mass of abnormal cells.

Second, cancer cells invade and colonize territories normally reserved for other cells.

The invasion of cancer cells into other cellular territories is called **"metastasis"** and it may be local or distant.

Third, cancel cells are genetically unstable.

Fourth, cancer cells evade limitations to cell proliferation escaping replicative senescence.

Fifth, cancer cells have lost the ability to differentiate.

Cancer may be classified into two types **benign** or **malignant**

As long as the cancer cells remain clustered together in a single mass enclosed in a fibrous connective tissue or capsule the tumour is classified as **benign** and may be completely cured by surgical excision (assuming it is accessible surgically).

A tumour is classified as **malignant**, if its cells have the ability to invade the surrounding tissue. Such cells may break loose and enter the blood stream or invade draining lymph nodes. The more widely and rapidly a cancer spreads or metastasises the more difficult it may be to treat.

Cancers are classified according to their tissue and cell type of origin.

Cancerous growth and classification (cont)

Cancers arising from epithelial tissues are called **"carcinomas"**

Cancers arising from connective tissues or muscle are called **"sarcomas"**

Cancers arising from hematopoietic tissue are called **"leukaemia"**

Cancers arising from lymphoid cells and tissues are called **"lymphomas"**

Each cancer cell often demonstrates features that reflect the cell of origin, however, as cells become more and more malignant this may become increasingly difficult for the pathologist to discriminate by microscopy alone.

Identification of Type of Cancer by Pathologist

Pathologists are able to identify the relative stages in cancer development from biopsy specimens that are obtained.

Histopathology and **specialized stains** enable the identification of normal cells, low-grade cancer lesions through to high-grade tumours, and in many cases the cell of origin can be identified.

These various pathological classifications for the most part reflect the cell of origin of the cancer, and are extremely important in predicting disease outcome and prognosis, likelihood and sites of metastasis and are essential for appropriate treatments i.e. no treatment versus local treatment, versus chemotherapy plus or minus radiotherapy.

There are various sub-sets of the benign tumours including **adenomas**, which is a benign epithelial tumour, which may undergo **malignant transformation** to become an **adenocarcinoma.**

Identification of Type of Cancer by Pathologist (cont)

The surgeon/physician will use the histopathology of a benign or malignant tumour to decide whether the lesion has been completely excised and if it is likely to further metastasise.

The majority of human cancers are carcinomas of various different sub-types.

Each carcinoma may arise from a distinct cell type and follow an extremely different disease profile and outcome.

In low-grade lesions of epithelial tumours the cancer cell may clearly resemble the cell or origin, but may have started to proliferate and the dividing cells may escape the basal layer of the epithelium. In high-grade lesions, (that is moderate to severe cancer), the cells appear much more undifferentiated and demonstrate a highly variable cell and nuclear size and shape.

Abnormal mitotic figures are frequently seen, evidence of genetic instability of the tumour. The transformation of the cell from a low-grade lesion to a high-grade lesion arises by successive cycles of DNA mutation and natural selection.

The acquisition of additional DNA mutations generates a selective advantage of the mutated cell over its normal neighbours, facilitating increased proliferation, overcoming natural barriers to growth in the surrounding tissue.

Many successive rounds of genetic mutation are required, as cells contain many distinct regulatory systems, which inhibit abnormal cell proliferation. Tumour proliferation and expansion requires maintenance of its own oxygen and nutrients and the ability to overcome physical barriers at both the local site and at distant metastatic sites.

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Identification of Type of Cancer by Pathologist (cont)

Pathologists and scientists have developed special stains, antibodies to surface proteins and key components of the cytoskeleton and signalling pathways, together with chromosomal and DNA analysis to help to identify specific cancers and various subtypes.

This is important as the cancer type and the cell of origin dictates specific therapies.

The change from a normal cell to a cancer cell is called **"cell transformation".**

Cancer cells lack the structural features and cellular functions of normal cells. Cancer cells typically show an enlarged nuclei, dense DNA and changes to the cytoskeleton, so that the cell is unable to maintain its normal shape.

Pathologists have long recognized that there is **spectrum of histological features** that correlate with the progression of cancer. These include abnormal cellular morphology and presence of mitoses, or "mitotic index" and assessment the degree of invasiveness of the tumour.

There is now strong evidence that these histological and clinical characteristics have a molecular basis. There is much data to suggest that cancer develops and becomes more malignant, as multiple genetic abnormalities accumulate in the cell.

By the time of clinical presentation most cancer cells will demonstrate evidence of genetic instability. This will include the inability of the cancer cell to repair DNA damage, or correct replication errors in specific nucleotides. Many cancer cells are unable to maintain the integrity of their genome.

Identification of Type of Cancer by Pathologist (cont)

This genetic instability increases the likelihood that a cancer cell will experience a mutation in a gene such as a proto-oncogene or a tumour suppressor gene, which plays an important role in either promoting or inhibiting cell proliferation.

These genes are critical genes that regulate cell growth and the cell cycle. As the tumour becomes increasingly malignant, through the successive acquisition of mutations in the DNA, evidence of genetic instability becomes more apparent. Chromosomes can be seen to have abnormalities in structure and number, in preparations of metaphase chromosomes of tumour cells.

It is probable that cells, which maintain an optimum level of genetic instability, may be the most likely tumour cells to survive

In normal cells, genetic instability is rare. The presence of genetic instability in tumour cells makes it increasingly likely that at least one cell within the tumour cell acquires a mutation. This may allow the cancer cell to overcome certain selection barriers, which include the ability of the cell to proliferate under less than optimum conditions, such as under low oxygen conditions, or in the absence of specific growth factor stimulation.

However, if the level of genetic instability becomes too high and serious mutations occur, this may lead to extinction of the abnormal cell. Thus for a cancer cell to survive it requires some level of genetic instability, so that it has survival advantage, but does not acquire so many mutations that it becomes extinct.

Cells that are more rapidly cycling through the cell cycle are more likely to acquire DNA mutations and there is less time during S phase for repair.

Escaping Cell Senescence

Senescence: loss of a cell's power of division and growth.

Normal highly differentiated cells do not divide. This ability to stop proliferating is called **"Cell Senescence".**

This may be a mechanism to prevent cancer development. Cell senescence in human cells is mediated by the shortening of telomeres, which are the repetitive DNA sequences and associated proteins that cap the end of each chromosome.

The enzyme "Telomerase" maintains these repetitive telomeric sequences. In adult human cells the gene encoding for the catalytic subunit telomerase is switched off, or not fully activated, therefore the telomeres in these cells tend to become a little shorter with each successive cell division, and eventually the telomeric cap on the chromosome can become dangerously shortened, arresting the cell cycle preventing cell division, as long as the cell contains broken or inadequate DNA.

In normal cells that still produce functional p53 and have intact cell cycle checkpoints, this shortening of the telomerase results in an arrest of cell division, i.e., **"replicative senescence"**

In cancer cells or pre-cancer cells, which have acquired mutations in p53 or specific cell cycle checkpoint proteins, the shortening of the telomerase and the signal generated maybe ignored, and the cell cycle progresses resulting in massive chromosomal damage. The accumulated mutations may promote cancer development.

Normal cell growth and differentiation

The number of cells in a multicellular organism is usually tightly controlled with a balance existing between the rate of cell division and differentiation, and the rate of cell death.

In the fully developed human body, the total number of differentiated functional cells making up a particular tissue does not change significantly, with most tissue cell populations being subject to slow turnover through cell division or differentiation, and cell death.

As cancer is caused by disruption of the control of cell growth and differentiation, it is important to understand the molecular mechanisms that regulate the normal cell cycle and control cell death.

Some cells persist throughout the lifetime of the organism without cell division. These include nerve cells, heart muscle cells, sensory receptor cells for light and sound, and lens fibres.

Cells of other tissues, lost through cell death or damage, are replaced either by mature cell division, or differentiation of stem cells.

The liver is an example of a tissue subject to slow turnover. Following liver damage, cells simply divide to produce daughter cells of the same type. In tissues such as the intestinal epithelium, the hematopoietic system, or the skin, which have a very rapid turnover, damaged cells are rapidly replaced by adult stem cell differentiation.

Stem cells by definition are not terminally differentiated and have the ability to divide throughout the lifetime of an organism. Pools of stem cells yield some progeny that will differentiate into more specialized cells and others that remain stem cells with the capacity to self renew.

Normal cell growth and differentiation (cont)

Terminal differentiation of these progenitor cells is stimulated by growth factors and cytokines resulting in cellular specialization in terms of cell structure and function, specific for the tissue type. These highly differentiated cells that make up a functional tissue will, in general, retain their specific properties, even when placed in a novel environment and will not interconvert to another cell type.

Failure in the regulation of cell division and differentiation or cell death results in serious effects on the tissue or organ function.

Cancer is a product of uncontrolled proliferation of a single cell and often results from loss of control of cell division coupled with a lack of **apoptosis** – (programmed cell death)

Each phase of the cell cycle is tightly controlled and has a specific set of checkpoints at which time the cell cycle can stop.

The **major checkpoints** in a cell cycle are the checkpoint G1, just before entry into S-phase and the checkpoint at G2, just before entry into mitosis.

When environmental circumstances forbid cell division, most cells will stop at G1, as this is the point if the cell does not stop it will initiate S-phase DNA replication.

The G1 and G2 checkpoints can be regulated by both specific intracellular proteins and extracellular stimuli. In most eukaryotic cells, cell cycle checkpoints at G1 and G2 are times in which the cell cycle can be arrested, if the previous cell cycle events have not been completed.

The G1 checkpoint will prevent entry into the S or synthetic phase, if DNA mutations or errors are detected.

Normal cell growth and differentiation (cont)

Progression from the G2 checkpoint into mitosis may be prevented if the DNA has not been adequately and completely replicated, or chromosome separation in mitosis is delayed due to incomplete attachment chromosomes to the mitotic spindle.

Regulation by specific Protein Kinases

The family of cyclin dependent kinases, CDKs, regulate progression of the cell cycle by phosphorylating selected proteins on serine and threonine residues.

he cyclin dependent kinases themselves are regulated by complex formation with specific proteins known as cyclins, which bind the kinases and regulate their activity

The are two subsets of cyclins:

The G1 cyclins, which bind to the CDKs during G1 and regulate entry into S-phase

The mitotic cyclins which bind the cyclin-dependent kinases during the G2 phase and regulate entry into mitosis.

One of the characteristics of the cyclins is the level of cyclins go up and down, i.e., oscillate during the cell cycle.

In contrast the levels of the cyclin-dependent kinases do not change. The cyclin-dependent kinases associate with specific cyclins to trigger various events in the cell cycle. The activity of cyclin-dependent kinases is usually terminated as a result of degradation of the cyclin.

Specific cyclins act in each phase of the cell cycle, for example, there are S-phase cyclins and M-phase cyclins, which in turn form complexes with the cyclin-dependent kinases and trigger cell specific cell cycle events.

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Regulation by specific Protein Kinases (cont)

In addition to the regulation of cyclin-dependent kinase activity via complex with the cyclins, additional mechanisms exist which regulate cyclin dependent kinase activity.

The cyclin-cyclin-dependent kinase complex can be inhibited by phosphorylation via a protein kinase.

In contrast dephosphorylation of CDK by CDC25 increases cyclin-dependent kinase activity. In addition, the cyclin-cyclin-dependent kinase complexes can also be regulated by binding of a specific inhibitors known as CDK inhibitor proteins.

These inhibitory proteins act primarily in the control of the G1 and S-phase entry. As previously noted, the cyclin-cyclin-dependent kinase complexes are regulated by proteolysis of the cyclins at specific stages of the cell cycle. Cyclin destruction is mediated by ubiquitin-dependent mechanisms, resulting in proteolysis of the cyclin via the proteosome. The transfer of ubiquitin onto the cyclin is mediated by enzymes known as ubiquitin ligases.

There are 4 specific classes of cyclins, which are defined by the stage of the cell cycle at which they bind their respective cyclin-dependent kinases.

hese are the G1/S cyclins, which work at the end of G1 and commit the cell to DNA replication

the S cyclins, which bind the cyclin-dependent kinases during S-phase, and initiate DNA replication

the M cyclins, which promote entry into and the events of mitosis

Many cells also contain a fourth class of cyclin known as the G1 cyclins which promote entry through the restriction point in late G1.

Cell Cycle Control System

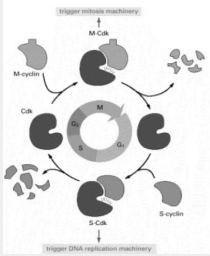

Figure 17-16. A simplified view of the core of the cell-cycle control system.
Cdk associates successively with different cyclins to trigger the different events of the cycle. Cdk activity is usually terminated by cyclin degradation. For simplicity, only the cyclins that act in S phase (S-cyclin) and M phase (Mcyclin) are shown, and they interact with a single Cdk; as indicated, the resulting cyclin-Cdk complexes are referred to as S-Cdk and M-Cdk, respectively.

The Cell Cycle and Cancer

The control of G1 progression into S-phase is important because if there is damage to the DNA the cell cycle must pause to allow time for the DNA to be repaired, prior to its duplication in S-phase.

The control of G1 progression and the initiation of S-phase is often abnormal in cancer cells. If the G1 checkpoint is lost this leads to unrestrained entry into the cell cycle and consequent cell proliferation.

Several important tumour suppressor genes, including the retinoblastoma gene product and the tumour suppressor gene p53 function to regulate G1 to S-phase progression. The retinoblastoma gene product Rb is an inhibitor of cell cycle progression, during G1, Rb binds to the transcription factor E2F and blocks the transcription of S-phase genes.

Cell cycle progression is also regulated by p53. DNA damage leads to activation of the gene regulatory protein known as p53, which regulates the transcription of many important genes, including the cyclin-dependent kinase inhibitory protein p21, which regulates the cyclin-dependent kinases, thereby blocking entry into S-phase.

The Cell Cycle and Cancer (cont)

This delay in entry into S-phase allows the cell time to repair DNA damage, prior to replication of the DNA in S-phase. Should the function of p53 be lost, as occurs in many cancers, over the long term there will be an accumulation of genetic damage. **Mutation of p53 has been detected in more than 50% of all human cancers.**

The **G1 checkpoint is a critical checkpoint of no return**, cancer cells often abandon the controls, which are present in normal cells, which regulate the G1-S-phase entry.

Once cells exit G1 and progress into S-phase, the cell cycle is automatic.

M-Phase

M-phase, “mitosis” is a phase of nuclear division, which takes approximately 1 hour.

During this time the chromosomes are segregated and two nuclei form.

In cytokinesis cytoplasmic division occurs and the whole cell splits into two. M-phase is characterized by progressive compaction of the chromatin (DNA and bound proteins). The DNA is replicated not as bare DNA, but as complex with tightly bound proteins called histones. The condensed chromosomes segregate onto the mitotic spindle. During mitosis the nuclear envelope breaks down, the nucleus condenses to visible chromosomes and microtubules condense onto the mitotic spindle.

In the middle of mitosis the cell cycle pauses briefly and the duplicated chromosomes are aligned on the spindle ready for segregation. This may quite often be seen in highly proliferative and also malignant cells as mitotic figures. The mitotic index can be used as a marker of the degree of malignancy of the tumour.

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M-Phase (cont)

During mitosis, mitotic spindles radiate from a body known as the “centrosome”, which is the major microtubule organising centre in the cell. During interphase the centrosome is typically located to the side of the nucleus, embedded within the centrosome are the centrioles. During mitosis the centriole splits into two and the daughter centrosomes move to opposite sides of the nucleus. Mitosis is organised by the microtubule asters, which form around each of the two centrosomes. In mitosis the mitotic spindle aligns the chromosomes, then each chromosome separates into two daughter chromosomes.

Each chromosome is aligned by the spindle to the opposite spindle pole. Following mitosis cytokinesis occurs during which time the contractile ring of actin forms beneath the plasma membrane and as the ring contracts it pulls the membrane inward to divide the cell into two.

Apoptosis

Apoptosis is a physiological form of cell death associated with distinct set of biochemical and physical changes involving the cytoplasm, nucleus and plasma membrane.

Apoptosis is an important inducible form of cell death involved in the sculpture of structures during development ie., digits, killing of viral infected cells by cytotoxic T cells, the removal of cells that have unsuccessfully completed mitosis or have unrepairable DNA damage, and in general the adjustment of cell numbers.

Apoptosis (cont)

The balance between the level of cell division and apoptosis is an important determinant in cancer. Billions of cells die from apoptosis, and in some cancer cells the level of apoptosis is decreased. For example, billions of cells die in the bone marrow and intestine every hour, in adult humans. In the healthy adult cell death exactly balances cell division resulting in no nett change in organ or tissue size. Some novel therapeutic experimental strategies aim to increase apoptosis in cancer cells.

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