Oncology

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1 Definition

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body.

2 Features of malignant transformation

2.1 Establish an autonomous lineage

Cells develop **independence** from the **normal signals** that control supply and demand (**grow** and **proliferate** in the absence of **external stimuli)**.

Tumorigenesis is proposed to have **three steps**: **initiation, promotion, and progression**. **Initiating** events such as **gain of function of genes known as oncogenes** or **loss of function of genes known as tumor-suppressor genes** may lead a single cell to acquire a distinct growth advantage. **The initiating events** are **usually genetic** and occur as ***deletions of tumor-suppressor genes or amplification or mutation of oncogenes.*** **Subsequent events** can lead to **accumulations** of additional deleterious mutations in the clone. Most tumors go through a **progression** from benign lesions to in **situ tumors to invasive cancers** (e.g., atypical ductal hyperplasia to ductal carcinoma in situ to invasive ductal carcinoma of the breast).

2.2 Obtain immortality

Normal cells are permitted to undergo only a **finite number of divisions**. For humans this number is between **40 and 60**. The limitation is imposed by the **progressive shortening of the end of the chromosome (the telomere)** that occurs

each time a cell divides. Telomeric shortening is like a **molecular clock** and, when its **time is up, the lineage will die out**. **Cancer cells can use the enzyme telomerase to rebuild the telomere at each cell division; there is no telomeric shortening, and the lineage will never die out**. The cancer cell has achieved immortality.

2.3 Evade apoptosis

Cells that find themselves in the wrong place normally die by apoptosis and this is an important **self-regulatory mechanism** in growth and development: cells in the web space of the embryo die by apoptosis, as do lymphocytes that could react to self. **Genes, such as p53, that can activate apoptosis function as tumour suppressor genes**. Loss of function in a tumour suppressor gene will contribute to malignant transformation. Cancer cells will be able to evade apoptosis, ***which means that the wrong cells can be in the wrong places at the wrong times***.

2.4 Acquire angiogenic competence

A mass of tumour cells cannot, in the absence of a blood supply, grow beyond a diameter of about 1 mm. However, the mass of tumour cells is able to **attract or to construct a blood supply** then it is able to quit its dormant state and behave in a far more **aggressive fashion**. The ability of a tumour to **form blood** vessels is termed '**angiogenic competence'** and is a key feature of malignant transformation.

2.5 Acquire ability to invade

They acquire the ability to **breach** the **basement membrane** and gain direct access to **blood** and **lymph** vessels. Cancer cells use **three main mechanisms** to facilitate **invasion**: (1) they cause a **rise in the interstitial pressure** within a tissue; (2) they

secrete **enzymes** that **dissolve extracellular matrix**; and (3) they become **mobile**.

2.6 Acquire ability to disseminate and implant, evocation of inflammation

Once cancer cells gain **access** to **vascular and lymphovascular spaces**, they have acquired the potential to use the body's natural distribution system. This is not, of itself, sufficient to cause tumours to develop at distant sites. The cells also need to **acquire the ability to implant**. As Paget pointed out over a century ago, there is a crucial relationship here between the seed (the tumour cell) and the soil (the distant tissue). Most of the cancer cells discharged into the circulation probably do not form viable metastases: circulating cancer cells can be identified in patients who never develop clinical evidence of metastatic disease. **Clumping may be important in permitting metastases, the outer cells protecting the inner cells from immunological attack.** These outer protective cells may, on occasion, be normal lymphocytes. Cancer can spread in this **embolic fashion** but can also spread when **individual cells migrate and implant**. Whether spread occurs in groups or as individual cells there is still the problem of crossing the vascular endothelium (and basement membrane) to gain access to the tissue itself. Cancer cells probably **implant themselves** in distant tissues by **exploiting, and subverting, the normal inflammatory response**. By expressing inflammatory cytokines the cancer cells can fool the endothelium of the host tissue into becoming activated and allowing cancer cells access to the extravascular space. **Activated endothelium expresses receptors** that bind to **integrins and selectins** on the surface of cells, **allowing them to move across the endothelial barrier**.

2.7 Evade detection/elimination

Cancer cells are simultaneously **both 'self' and 'not self'**. Although derived from normal cells ('self') they are, in terms of their genetic makeup, behavior and characteristics, foreign ('not self'). As such, they ought to provoke an immune

response and be eliminated, and it is entirely possible that malignant transformation is a more frequent event than the emergence of clinical cancer. **Cancer cells**, or at least those that give rise to clinical disease, appear to **gain the ability to escape detection by the immune system**. This may be through **suppressing expression of tumour associated antigens** or it may be through a**ctively co-opting one part of the immune system to help the tumour escape detection** by other parts of the immune surveillance system.

2.8 Jettison excess baggage

Cancer cells are geared to excessive and remorseless proliferation. They **do not need to develop or retain those specialized function**s that make them good cellular citizens. **They can therefore afford to repress or permanently lose those genes that control such functions**. Subvert communication to and from the environment/milieu

2.9 Develop ability to change energy metabolism

Blood flow in tumours is often sporadic and unreliable. As a result, cancer cells may have to spend prolonged periods starved of oxygen – in a state of relative hypoxia. Compared with the corresponding normal cells, some cancer cells may be better able to survive in hypoxic conditions. This ability may enable **tumours to grow and develop despite an impoverished blood supply**. Cancer cells can **alter their metabolism even when oxygen is abundant**; they **break down glucose** but do not, as normal cells would do, send the resulting pyruvate to the mitochondria for conversion, in an oxygen-dependent process, to carbon dioxide. This is the phenomenon of **aerobic glycolysis**, or the **Warburg effect**, and leads to the **production of lactate**. In an act of symbiosis, **lactate-producing cancer cells** may provide lactate for **adjacent cancer cells** which are then able to use it, via the citric

acid cycle, for energy production. This cooperation is similar to that which occurs in skeletal muscle during exercise.

3 Malignant transformation

The characteristics of the cancer cell arise as a result of mutation. O**nly very rarely is a single mutation sufficient to cause cancer**; **multiple mutations are usually required**. **Mutations must be acquired in a specific sequence**. Cancer is usually regarded as a clonal disease. Once **a cell** has arisen with all the mutations necessary to make it **fully malignant**, it is capable of giving rise to an **infinite number of identical cells,** each of which is fully malignant. overall clinical behaviour of a tumour. **Two mechanisms** may help to **sustain** and **accelerate** the process of **malignant transformation**: **genomic instability** and **tumour-related inflammation**.

3.1 Genomic instability

Cancer is in a genetic ferment. Cells are dividing without proper checks and balances. Mutations are arising all the time within tumours and some of these mutations, particularly those in tumour suppressor genes, may have the ability to encourage the development and persistence of further mutations. This gives rise to the phenomenon of genomic instability – as it evolves, **cancer contains an increasing variety and number of genetic aberrations**. The greate**r the number of such abnormalities**, the greater the chance of increasingly deviant behavior, and the pace of malignant transformation accelerates.

3.2 Tumour-related inflammation

If a tumour provokes an inflammatory response then the cytokines and other factors produced as a result of that response may act to promote and sustain malignant

transformation. **Growth factors, mutagenic ROS (reactive oxygen species), angiogenic factors and antiapoptotic factors may all be produced as part of an inflammatory process and all may contribute to the progression of a tumour**.

4 The growth of a tumour

The growth of a typical human tumour can be described by an exponential relationship, **the doubling time of which increases exponentially – so-called Gompertzian growth**. This Gompertzian pattern has several important implications for the diagnosis and treatment of cancer.

The implications of Gompertzian growth

- The majority of the **growth** of a tumour occurs **before** it is clinically detectable
- By the time they are detected, tumours have passed the period of **most rapid growth**, that period when they might be most sensitive to antiproliferative drugs
- There has been plenty of time, before diagnosis, for individual cells to detach, invade, implant, and form distant metastases. In many patients cancer may, at the time of presentation, be a systemic disease
- 'Early tumours' are genetically old, yielding many opportunities for mutations to occur, mutations that might confer spontaneous drug resistance (a probability greatly increased by the existence of cell loss)
- The rate of regression of a tumour will depend upon its age (the Norton–Simon hypothesis extends this: chemotherapy results in a rate of regression in tumour volume that is proportional to the rate of growth for an unperturbed tumour of that size).

5 The causes of cancer

The interplay between nature and nurture: Both inheritance and environment are important determinants of cancer development. Neither influence is totally dominant. Using a familiar example, not all smokers develop lung cancer; lung cancer can occur in people who have never smoked. The debate concerning the relative importance of the two factors has recently become polarized. Knowledge about the causes of cancer can be used to design appropriate strategies for prevention or earlier diagnosis. As we find out more about the genes associated with cancer, genetic testing and counselling will play an increasing role in the prevention of cancer.

The following factors may suggest the presence of a hereditary cancer:

1. Tumor development at a much younger age than usual

2. Presence of bilateral disease

3. Presence of multiple primary malignancies

4. Presentation of a cancer in the less affected sex (e.g., male breast cancer)

5. Clustering of the same cancer type in relatives

6. Occurrence of cancer in association with other conditions such as mental retardation or pathognomonic skin lesions

6 The management of cancer

6.1 Prevention

The World Cancer Research Fund has published an extensive view of the evidence on the preventable causes of cancer; their conclusion is that many cancers could be prevented if people ate sensibly and exercised more.

6.2 Screening

Screening involves the **detection of disease in an asymptomatic population in order to improve outcomes by early diagnosis**.

6.3 Diagnosis and classification

An unequivocal diagnosis is the key to an accurate prognosis. **Only rarely can a diagnosis of cancer be confidently made in the absence of tissue for pathological or cytological examination**. Cancer is a disease of cells, and, for accurate diagnosis, the abnormal cells need to be seen.

Grading of tumors: Different tumours are classified in different ways: most **squamous epithelial tumours** are simply classed as **well (G1), moderate (G2) or poorly (G3) differentiated**.

6.4 Investigation and staging

It is not sufficient simply to know what a cancer is; its site and extent must also be known. If it is **localized**, then **locoregional treatments** such as **surgery and radiation** therapy may be curative. If the disease is **widespread** then, although such local interventions may contribute to cure, they will be insufficient and systemic treatment, for example with **drugs or hormones**, will also be required.

Staging is the process whereby the extent of disease is mapped out. Stage 0 mainly denotes in-situ component of the disease, Stage I usually an early disease, Stage II represent a transition between early and Stage III which is a locally advanced disease, while metastatic disease considered as Stage IV. This applied to majority of the malignancies, the staging system is defined to each tumor according to the characteristics of tumor size, lymph node status and distant metastasis (TNM

staging). Some types of malignant tumors the grade of the disease included in the staging system such as sarcoma (TNM-G)

6.5 Therapeutic decision making and the multidisciplinary team

As the management of cancer becomes more complex, it becomes impossible for any individual clinician to have the intellectual and technical competence that is necessary to manage all patients presenting with a particular type of tumour. Teams should not only be multidisciplinary, but they should also **be multiprofessional**.

6.6 Prognostic and Predictive Tissue Markers

A tumour marker is a substance reliably found in the circulation of a patient with neoplasia which is directly related to the presence of the neoplasm, disappears when the neoplasm is treated and reappears when the neoplasm recurs.

Tumour markers may be

- **Hormones**, e.g. beta-human chorionic gonadotropin (βHCG), calcitonin
- **Enzymes**, e.g. prostate-specific antigen (PSA), placental alkaline phosphatase (ALP), lactate dehydrogenase (LDH)
- **Oncofetal antigens**, e.g. α-fetoprotein, carcinoembryonic antigen (CEA), CA-125, CA19-9
- **Serum and tissue proteins**, e.g. thyroglobulin

The possible uses of tumour markers

- Diagnostic purposes
- Prognostic information (tumour load)
- Monitoring response to treatment
- Surveillance to detect recurrence

- Screening

Examples of tumor markers:

Hormones

Markers	Associated Cancers
Human chorionic gonadotropin	Trophoblastic tumors, nonseminomatous testicular tumors
Calcitonin	Medullary carcinoma of thyroid
Catecholamines	Pheochromocytoma

Oncofetal Antigens:

Markers	Associated Cancers
Alpha-Fetoprotein	Liver cell cancer, nonseminomatous germ cell tumor of testis, lung cancer
CEA	Adenocarcinoma of the colon, pancreas, lung, breast, ovary, prostate

Specific Proteins:

Markers	Associated Cancers
Immunoglobulins	Multiple myeloma and other gammopathies
PSA and prostate specific membrane antigen	Prostate cancer

Mucins and Other Glycoproteins

Markers	Associated Cancers
CA-125	• Cancer of ovary, fallopian tube, endometrium cervix, breast, lung, pancreas and colon
CA-19-9	o Colona cancer, pancreatic cancer