Cancer

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Cancer is a potentially fatal disease caused mainly by environmental factors that mutate genes encoding critical cell-regulatory proteins. The resultant aberrant cell behaviour leads to expansive masses of abnormal cells that destroy surrounding normal tissue and can spread to vital organs resulting in disseminated disease, commonly a harbinger of imminent patient death.

Overview

Cancer is a complex genetic disease that is caused primarily by environmental factors. The cancer-causing agents (carcinogens) can be present in food and water, in the air, and in chemicals and sunlight that people are exposed to. Since epithelial cells cover the skin, line the respiratory and alimentary tracts, and metabolize ingested carcinogens, it is not surprising that over 90% of cancers occur in epithelia.

The causes of serious ill-health in the world are changing. Infection as a major cause is giving way to noncommunicable diseases such as cardiovascular disease and cancer. In 1996 there were 10 million new cancer cases worldwide and six million deaths attributed to cancer. In 2020 there are predicted to be 20 million new cases and 12 million deaths. Part of the reason for this is that life expectancy is steadily rising and most cancers are more common in an ageing population. More significantly, a globalization of unhealthy lifestyles, particularly cigarette smoking and the adoption of many features of the modern Western diet (high fat, low fibre content) will increase cancer incidence.

Tobacco use and diet each account for about 30% of new cancer cases, with infection associated with a further 15%; thus, much of cancer is preventable. No individual can guarantee not to contract the disease, but it is so strongly linked to diet and lifestyle that there are plenty of positive steps that can be taken to reduce the chances: eat more fruit and vegetables, reduce the intake of red meat and definitely do not smoke. Carcinogens interact with the individual’s constitution, both inherited and acquired, determining vulnerability to cancer induction. This vulnerability is based on how an individual deals with the carcinogens, ideally eliminating them in a harmless form before they do any genetic damage or being able to repair that damage.

The science of classical epidemiology has identified populations at high cancer risk (e.g. users of tobacco products). However, many lifelong smokers do not get cancer, perhaps because of the way they handle potential carcinogens metabolically, and the relatively new science of molecular epidemiology attempts to identify high-risk individuals within populations, such as smokers. Many issues concerning diet and cancer are controversial (e.g. fat intake and breast cancer). This may be because only certain polyunsaturated fatty acids generate damaging free radicals; furthermore, the intake level of antioxidant vitamins that can scavenge these harmful radicals is a confounding factor. Reducing infection, particularly in the poorer countries, will lead to reductions in cancer incidence. Infectious agents associated with increased cancer risk include hepatitis B virus (liver), certain subtypes of human papillomavirus (cervix), the bacterium Helicobacter pylori (stomach) and human immunodeficiency virus (many sites).

The management of patients with cancer is costly, but there is the daunting prospect that 70% of tomorrow’s patients are likely to live in countries that between them have only 5% of global resources. Huge steps in improving the prognosis of patients with cancer are almost immediately achievable with present-day technology and sufficient financial resource, and all essentially relate to early detection. Cancer does not develop overnight, instead often evolving over many years with detectable premalignant lesions presaging the development of full-blown malignancy. Malignant tumours not only invade surrounding tissue, but are able to colonize other, often vital, organs, a process known as metastasis. Widespread metastatic disease is usually a harbinger of imminent patient death. Thus, immediate referral to the oncologist after detection of any suspicious lump or symptom is paramount; in many parts of the world with poor health education patients present with very advanced disease. In the same vein, cancer screening programmes are designed to detect not only early asymptomatic malignant tumours but also premalignant lesions. Even in the richer countries, such programmes are a significant financial burden, and the more cost-effective programmes target the higher-risk groups denoted by age (e.g. cervical screening, mammography, colonoscopy) or occupation (e.g. blood in the urine of dye workers for bladder cancer).
Classification

In terms of behaviour, tumours are either ‘benign’ or ‘malignant’. Benign tumours are generally slow-growing expansive masses that compress rather than invade surrounding tissue. As such they generally pose little threat, except when growing in a confined space like the skull, and can usually be readily excised. However, many so-called benign tumours have malignant potential, notably those occurring in the large intestine, and these should be removed before malignancy develops.

Malignant tumours are usually rapidly growing, invading surrounding tissue and, most significantly, colonizing distant organs. The ability of tumour cells to detach from the original mass (the primary tumour) and set up a metastasis (secondary tumour) discontinuous with the primary is unequivocal proof of malignancy. Tumours are also classified according to their tissue of origin; recognition of the parent tissue in a lymph node metastasis could establish the location of a hitherto undiagnosed primary tumour.

Nomenclature

The suffix ‘oma’ usually denotes a benign tumour, and tumours of glandular epithelia are called ‘adenomas’ (e.g. colonic adenoma). Tumours of surface epithelia are called ‘papillomas’ (e.g. skin papilloma). However, carcinoma and sarcoma refer to malignant tumours of epithelia and connective tissue respectively, qualified by the tissue of origin (e.g. prostatic carcinoma). There are numerous exceptions to this systematic nomenclature; leukaemias and lymphomas are malignant tumours of bone marrow and lymphoid tissue respectively, and malignant melanoma derives from the melanin-producing cells of the skin.

Clinical assessment

The management of a patient with cancer is dependent upon a number of pieces of information that can be gathered about the tumour:

- the tissue of origin
- benign or malignant
- tumour grade
- tumour stage

Benign tumours can normally be removed by surgery. Malignant solid tumours will, if possible, be surgically resected, probably followed and even preceded by other treatment modalities. More diffuse tumours such as leukaemias with circulating tumour cells require systemic chemotherapy. A histopathologist will ‘grade’ the tumour in terms of its state of differentiation on a scale from well, through moderately to poorly differentiated. For example, normal colonic epithelial cells form simple tubular glands; cancerous colonic cells largely organized into glandular structures, albeit in a disorderly fashion, would be graded as well differentiated (low grade). At the other end of the spectrum, poorly differentiated (high grade) tumours show little if any resemblance to the tissue of origin. Poorly differentiated tumours tend to be more aggressive, growing faster and more likely to have metastasized before the patient has presented. Thus, patients with poorly differentiated tumours tend to have a worse prognosis and might be selected for more aggressive treatment.

Tumour ‘staging’ is a semiquantitative assessment of the clinical gravity of the disease. A complete profile can be built up from knowing the size of the primary tumour, the extent of local lymph node involvement and the presence or absence of distant metastasis. In this tumour node metastasis (TNM) staging, the larger the primary tumour and the more local nodes involved then the more advanced the stage with a concomitantly poorer prognosis. Significantly, the presence of metastatic disease immediately assigns the patient to the most advanced stage, irrespective of the size of the primary tumour, highlighting the importance of early detection and intervention to patient survival.

Treatment

Cancer treatment is usually a combination of a number of different modalities. If the tumour is amenable to surgery, then surgery is the single most effective tool in the anticancer armamentarium. Targeted radiotherapy is another option, as are combinations of anticancer drugs. Most conventional anticancer drugs have been designed with deoxyribonucleic acid (DNA) synthesis as their target. Therein lies the problem, in that tumour cells are not the only proliferating cells in the body; cells that line the alimentary tract, bone marrow cells that generate red blood cells and cells to fight infection, and epidermal cells including those that generate hair are all highly proliferative. Thus, patients with cancer receiving chemotherapy commonly suffer unwanted (hair loss) and sometimes potentially life-threatening (anaemia and proneness to infections) side effects that limit treatment.

The new generation of drugs have targets removed from the direct synthesis of DNA; they affect the signals that promote or regulate the cell cycle, growth factors and their receptors, signal transduction pathways and pathways affecting DNA repair and apoptosis. Each of these pathways may be affected by activating mutations that predispose to cancer and, thus, offer the potential as a target for inhibition. Other strategies focus on either attempting to target tumour cells specifically by conjugating cell toxins to tumour-specific antibodies (magic bullets), or slowing down cancer progression by affecting cell adhesion, proteolytic enzyme activity and angiogenesis.
Cell Signalling

Much of cell behaviour (division and differentiation) is governed by the effects of polypeptide growth factors which, because of their water-soluble nature, cannot diffuse through the plasma membrane of the cell, instead interacting with membrane-bound glycoprotein receptors that transduce the first message (the growth factor or ligand) into a series of intracellular signals that promote or inhibit the transcription of specific genes. Operationally there are three principal signalling strategies between cells. In endocrine signalling the producer cells and the target cells are distant from one another, whereas in paracrine signalling they are very close; normal and cancer cells can employ both these pathways. Autocrine signalling, however, is almost exclusively the preserve of cancer cells, signifying the ability of cells both to produce growth factors and to be stimulated by them through bearing the appropriate receptors. Having an autocrine stimulatory loop explains the ability of cancer cells to grow autonomously in culture devoid of growth factors, and bestows upon them some independence from normal growth restraints.

Apart from polypeptides, lipophilic hormones such as steroids, retinoids and thyroid hormones are potent regulators of cell behaviour, and many cancers of their target tissues are hormone-dependent and responsive to hormone ablation therapy (e.g. testosterone-dependent prostate cancer). Hormones are targeted to their respective tissues by intracellular receptors after they have diffused through the plasma membrane. The occupied receptors translocate to the nucleus, bind to hormone-response elements and modulate transcription at those sites. In the prevention or treatment of breast cancer, steroid hormone analogues such as tamoxifen are used to mimic the action of the natural oestrogen, eliciting a much weaker oestrogenic response.

Cell Cycle Regulation

Ligand occupancy of plasma membrane-bound receptors brings about receptor activation, commonly through phosphorylation of tyrosine residues, triggering downstream signal transduction pathways that produce phosphorylated molecules to act as transcription factors modulating gene expression (Figure 1). Mutational activation of any of the component molecules in these cascades can lead to constitutive signalling in the absence of binding ligand, and so contribute to tumour development. The eukaryotic cell cycle is regulated by periodic activation of different cyclin-dependent kinases (Cdks), heterodimers of a protein kinase catalytic subunit, the Cdk, and a cyclin-activating subunit. Different Cdk–cyclin complexes are required to catalyse the phosphorylation of proteins that drive the cell cycle. Cyclin D plays a central role (Figure 1); its expression is regulated by growth factors, and once the retinoblastoma protein (pRb) is phosphorylated by cyclin D–Cdk4, then E2F–DP transcription factors are free to mediate transcription of a number of genes encoding proteins that drive the cell cycle. Thus, once activated, cyclin D acts as a starter of the cell cycle motor; it refuels itself and induces cyclins for cell cycle progression later on.

Brakes on the cell cycle motor are provided by the Cdk inhibitors (CKIs), seven proteins belonging to either the Kip/Cip (kinase inhibitor protein/Cdk interacting protein) family or the Ink4 (inhibitor of Cdk4) family. Ink4 proteins, particularly p16\(^{ink4A}\), compete with cyclin D to bind Cdk4/6 and so block phosphorylation of pRb. Thus, the Rb–cyclin D–Cdk4–p16 pathway is a major fuse-box of growth control. Brakes on the cell cycle are also provided by the transcription factor p53, upregulated by a variety of cellular stresses, inducing p21\(^{Cip1}\), a potent inactivator of cyclin–Cdk complexes, and transforming growth factor β inducing p27\(^{Kip1}\).

DNA Repair and Genetic Instability

The ability to maintain genome integrity in the face of DNA damage is critical for healthy survival. At a cellular level cancer is a very rare disease given that an individual has many millions of cells, so normally the repair and/or elimination mechanisms of damaged cells must be very efficient, akin to having a ‘caretaker’ function. The pathway to malignancy involves the accumulation of many genetic alterations, achieved through successive rounds of alteration and clonal expansion (see Multistage Carcinogenesis). To account for the multiple mutations in cancer cells, attention has become focused on the mechanisms of DNA metabolism that maintain genome integrity, looking for the so-called ‘mutator phenotype’. If the mechanisms of DNA repair are faulty, this leads to ‘genetic instability’, facilitating an increased rate of alterations in the genome. Most cancers probably are genetically unstable, providing the genetic plasticity to drive the stepwise progression of genetic changes required for the development of malignancy. This relaxation in genome stability is due to alterations in genes involved in DNA replication, repair, telomere stabilization and chromosome segregation, and could lead to point mutations, deletions or additions of a few nucleotides, translocations, and even losses or gains of whole or parts of chromosomes.

The importance of repair processes can be appreciated by studying the rare chromosomal instability syndromes, autosomal recessive diseases where homeostatic mechanisms fail, resulting in multisystem effects including a predisposition to malignancy and immunodeficiency. In Bloom syndrome, the defect is in a DNA helicase; while heterozygotes do not have an increased cancer risk,
homozygotes commonly develop lymphomas and leukemias in their twenties. Ataxia telangiectasia homozygotes have a 30–40% lifetime risk of malignancy, and the ataxia telangiectasia mutated protein is a member of a family of protein kinases. Cells from patients with ataxia telangiectasia cannot effect cell cycle arrest after irradiation-induced DNA damage, referred to as radiation-resistant DNA synthesis. Patients with xeroderma pigmentosum suffer from a defect in nucleotide excision repair, becoming highly sensitive to ultraviolet light-induced damage with a 2000-fold increased risk of developing skin cancer.

Firm support for a ‘mutator’ phenotype being important for cancer development comes from patients with hereditary nonpolyposis colonic cancer (HNPCC) who are very prone to cancer development. As in the other recessive diseases, individuals suffer from the consequences of defects in DNA repair once the wild-type allele is inactivated during tumorigenesis, accumulating the mutations in proto-oncogenes and tumour suppressor genes (TSGs) that are characteristic of cancer. In HNPCC, mutations are present in mismatch repair enzymes, enzymes that recognize and repair distortions of the double helix resulting from a ‘misfit’ of noncomplementary base pairs. Defects in these enzymes are indicated from examining ‘microsatellites’, regions of chromosomes in which a single base (e.g. A) or a small number of bases (e.g. CA) is tandemly repeated a number of times. Microsatellites are relatively constant in normal cells, but can vary greatly in tumours, so-called ‘microsatellite instability’, a marker of mismatch repair defects in a cell.

**Figure 1** Overview of cell cycle regulation. Growth factor binding leads to receptor dimerization and phosphorylation, activation of Ras and the mitogen-activated protein kinase (MAPK) signal transduction pathway leading to cyclin D production. Many of the genes encoding growth factors, receptors, components of the signal transduction pathway and cyclins are proto-oncogenes, genes that when activated by mutation (now oncogenes) can contribute to cancer development. pRb, p53 and the cyclin-dependent kinase inhibitors (CKIs) all act as a brake on cell cycling and are the products of tumour suppressor genes (TSGs); when inactivated by mutation, loss or viral proteins, they also contribute to cancer development. The phosphorylation of pRb is necessary for the release of E2F–DP dimers that promote the transcription of cell cycle-associated genes. pRb can be inactivated by virally encoded oncoproteins such as adenovirus E1a and human papillomavirus (HPV) E7. p53 is negatively regulated by Mdm2, an enzyme required to produce a polyubiquitinated p53 for degradation by the proteasome. p53 can be disabled by adenovirus E1b and HPV E6. The *Ink4a* locus also encodes p14ARF; whose function is to activate p53 by binding to and inactivating Mdm2, making ARF another TSG. DNA, deoxyribonucleic acid; DHFR, dihydrofolate reductase; TGFβ, transforming growth factor β.
Telomerases

Most somatic cells have a ‘molecular clock’ that limits the number of times they can divide. This is known as the ‘Hayflick limit’, and in most cells this is between 50 and 70 doublings, after which cells enter a state of senescence and cease dividing. The molecular clock is telomere shortening. Telomeres are protective caps on the ends of chromosomes, commonly composed of short, tandemly repeated, sequences that are guanosine-rich (e.g. (GGGTTA)n). The conventional DNA replication machinery which replicates the middle regions of chromosomes cannot replicate the ends, and replication here depends on a ribonucleoprotein enzyme called ‘telomerase’. This enzyme is a ribonucleic acid (RNA)-dependent DNA polymerase that can extend one strand of telomeric repeats by having a short RNA template (e.g. CCCAAT). These extensions are then a template for synthesis of complementary DNA by DNA template (e.g. CCCAAT). These extensions are then a template for synthesis of complementary DNA by DNA polymerase ζ. The catalytic subunit of telomerase is known as TERT for telomerase reverse transcriptase (a reverse transcriptase makes DNA from complementary RNA). Although telomeric DNA constitutes less than 1/10 000th of total euchromatic chromosomal DNA, without telomeres chromosomes are recognized as damaged DNA and display aberrant behaviour such as fusing together.

Apart from germ cells, normal cells have a very low level of telomerase, resulting in progressive telomere shortening with each round of cell division, which limits the cellular lifespan. Cancer cells are immortalized cells and, although the cell of origin of some cancers may have sufficient telomerase activity to prevent significant telomere erosion, most cancers probably originate in a telomerase-negative cell but they escape eventual cellular death by reactivation of telomerase. Expression of the c-myc gene, like telomerase activity, is positively correlated with cell proliferation, and the Myc protein will activate telomerase. Moreover, c-myc is transcriptionally activated by β-catenin when APC (the gene associated with adenomatous polyposis coli) is mutated, providing another means through which telomerase is reactivated in cancer cells.

Apoptosis

Cell death in tumours, particularly carcinomas, is very common. Much of this death is a passive degradative reaction known as necrosis, most likely due to inadequate angiogenesis within the tumour. Apoptotic cell death, on the other hand, is controlled by a number of gene families, and to manipulate proapoptotic pathways specifically in tumours is something of a holy grail for oncology. Net tumour growth is due to the cell production rate through mitosis exceeding the cell loss rate through cell death. In a type of skin tumour there is the paradox of a high mitotic rate, yet low overall growth rate, resolved by finding a high incidence of tumour cell death taking the form of affected cells shrinking, fragmenting and being phagocytosed by neighbouring cells. Originally called ‘shrinkage necrosis’ it was renamed ‘apoptosis’ (Gk. meaning ‘dropping off’, as leaves from trees) to suggest its counterbalancing role to mitosis.

Apoptosis is often viewed as an altruistic cell suicide process: when DNA is damaged, signals go to both repair and apoptotic pathways, and if repair cannot be effected then the cell undergoes apoptosis – ‘better dead than wrong’. Due to the disordered genomes in many tumours, potentially harmful genetic damage can often be tolerated because of uncoupling of these two pathways. In particular, cells harbouring mutant p53 will have a survival advantage over normal cells. In response to damage, normal cells upregulate p53 which acts as a transcription factor for cell cycle arrest and apoptosis, p53-mutant cells cannot carry out this protective arrest or apoptosis and might survive with what otherwise would be lethal genetic damage, perhaps explaining why p53 mutations are so common in human cancers.

The decision to die is largely played out on the mitochondrial surface between three major families: the so-called ‘three horsemen of apoptosis’. Proteases called caspsases are the final executioners cleaving critical substrates such as DNA repair enzymes and cytoskeletal proteins, but they are stored aszymogens bound to an apoptotic adenosine triphosphatase, apoptosis-activating factor 1 (Apaf-1), the mammalian homologue of the nematode Caenorhabditis elegans cell death protein, Ced-4. In turn, Apaf-1 is held in check if bound to antiapoptotic Bcl-2 proteins located in the outer mitochondrial membrane. However, proapoptotic Bcl-2 family proteins such as Bax (upregulated by p53) can activate apoptosis by releasing cytochrome c (cyt c) from mitochondria which in turn activates Apaf-1.

Cell Adhesion

Changes in expression of cell adhesion molecules (CAMs) appear crucial to many aspects of tumour behaviour. The integrins are a large family of receptors mediating adhesion between the cell membrane and either the extracellular matrix (ECM) or other CAMs. Each molecule is composed of two noncovalently associated α and β subunits, and at least 20 heterodimers exist. Integrin expression is diverse in tumours. In primary tumours, downregulation of the type IV collagen and laminin receptors is common, indicating that loss of cell attachment from the basement membrane is important for invasion. Conversely, expression of particular integrins may be crucial for metastasis. Members of the immunoglobulin superfamily are CAMs that can mediate the interaction of leucocyte integrins with endothelium during inflammation. Likewise, upregulation
of integrins on tumour cells may facilitate adhesion to endothelium (e.g. malignant melanoma cells expressing the \( \alpha_4\beta_1 \) integrin interact with vascular cell adhesion molecule (VCAM)-expressing endothelium. Integrons are not merely transmembrane rivets linking the cell to the ECM; ECM binding may directly stimulate signalling pathways such as the mitogen-activated protein kinase (MAPK) pathway, and failure to bind ECM can lead to apoptosis, in this instance called ‘anoikis’ (Gk. ‘homeless’).

Epithelial cells are held together by various junctional complexes; adherens-type junctions depend on \( \text{Ca}^{2+} \)-dependent interactions between E-cadherin molecules that span the plasma membranes of adjacent cells. The development of most carcinomas is associated with reduced expression of E-cadherin, facilitating cell detachment from the primary tumour mass, invasion and metastasis. Apart from being an intercellular glue, E-cadherin molecules are linked to the actin cytoskeleton through E-cadherin-associated undercoat proteins called catenins, and one catenin in particular, \( \beta \)-catenin, also functions as a signalling molecule. Normally tethered to E-cadherin in the adherens junction, any free \( \beta \)-catenin is phosphorylated by glycogen synthase kinase-3 in combination with the APC protein, and then degraded by the ubiquitin–proteasome pathway. However, when the \( \text{APC} \) gene is mutated, as it is in the majority of colonic cancers, \( \beta \)-catenin accumulates and binds to the TCF/LEF family of transcription factors, translocates to the nucleus and switches on the \( c\text{-}\text{myc} \) gene, a gene associated with cell cycle progression. Thus, normal \( \text{APC} \) protein performs a ‘gatekeeper’ function, blocking excessive stimulation of \( \text{myc} \) by \( \beta \)-catenin.

### Angiogenesis

Avascular tumours cannot grow beyond a size of 2–3 mm\(^3\) without vascularization. This vasculature is derived from the surrounding ‘normal’ tissue; thus, the endothelial cells that line the blood capillaries can be considered ‘gatekeepers’ of tumour expansion. The growth of new capillaries is called angiogenesis, and a failure of tumour cells to stimulate angiogenesis may be responsible for long-term dormancy of some primary and metastatic tumours. Many peptide growth factors stimulate angiogenesis including the family of vascular endothelial growth factors and acidic and basic fibroblast growth factors. The process is summarized in Figure 2.

Since a tumour’s vasculature can be considered an Achilles heel, targeting the vasculature is an attractive proposition. It is also appealing for other reasons:

- **Angiogenesis is primarily a developmental process; antiangiogenic therapy should have minimal side effects.**
- **Because angiogenesis is a physiological host response, pharmacological blockade should not lead to the development of resistance since normal endothelial cells lack the genetic instability of cancer cells that is responsible for the emergence of drug-resistant clones.**
- **As each capillary in a tumour supplies many hundreds of tumour cells, targeting the endothelium will lead to a potentiation of the antitumour effect.**
- **Therapeutic agents have direct access to the endothelium.**

The action of inhibitors ranges from blocking endothelial proliferation, antagonizing growth factor receptors, suppressing proteolytic enzyme secretion, to blocking integrin expression so making cells marooned from the ECM and consequently undergoing apoptosis. However, not all tumours are angiogenesis dependent: in some lung cancers the tumour cells grow around the richly vascularized air sacs (alveoli) and there is no new capillary growth.

### Tumour Metastasis

A metastasis is a tumour implant discontinuous with the primary tumour. The formation of a metastasis is a multifactorial process (Figure 3). Metastases are the major cause of death from malignant disease because widespread metastatic disease is difficult to treat. Pivotal to the invasive process is the action of proteolytic enzymes to clear a path...
The development of a malignant tumour begins with a mutation in a long-lived cell, probably a stem cell. That mutation gives the cell a growth advantage over its normal neighbours and it undergoes clonal expansion. Other mutations that give any progeny a growth advantage lead to successive rounds of mutation and clonal expansion until the malignant genotype is acquired. In many cases, one of the first mutations is likely to be in a ‘caretaker’ gene that maintains genome integrity. The malignant phenotype is likely to be a manifestation of disturbances in the control of cell proliferation, cell death and cell adhesion. CAM, cell adhesion molecule; TERT, telomerase reverse transcriptase.

(b) Malignant tumours can (1) invade beyond normal tissue boundaries, (2) detach from the primary tumour mass and (3) enter vascular or lymphatic vessels before (4) adhesion to suitable endothelium and exit from the circulation. Establishment of the metastasis requires (5) local tissue invasion and (6) induction of angiogenesis.

through the ECM. Serine proteases such as urokinase-type plasminogen activator (uPA) and matrix metalloproteinases (MMPs), including the type IV collagenases (gelatinases) and interstitial collagenases, are important players. uPA is activated by binding to its receptor, catalysing conversion of plasminogen to plasmin, a proteolytic enzyme capable of degrading many proteins, and activating the zinc-dependent zymogenic MMPs; the effect of blocking MMPs is being explored in clinical trials.

The distribution of some metastases can be explained on mechanistic grounds: tumour cells that are shed into the blood vascular system lodge in the first capillary network they meet downstream. For example, the lung is the most favoured site in patients with primary tumours draining into the systemic veins. Also determining patterns of
metastasis may be the ‘stickiness’ of the endothelium, in that endothelia in particular organs have organ-specific CAMs that determine which cell–cell interactions occur. In particular, members of the immunoglobulin superfamily such as VCAM on endothelia may react with specific integrins expressed on tumour cells.

**Multistage Carcinogenesis**

Most cancers have defects in many aspects of cell behaviour as a result of multiple genetic alterations, and this has crystallized into the multistage theory of carcinogenesis (Figure 3). The founder cell is probably a stem cell since, for example, a mutation in a cell within the most superficial layers of the epidermis would not be expected to give rise to cancer because the affected cell would normally be sloughed off within a short period of time. Finally, not all cancers need the same number of mutations: a cancer of the colon may need mutations in six or seven proto-oncogenes and TSGs, whereas a childhood leukaemia may require perhaps only one significant alteration.

**Further Reading**


