The principles of neoplasia and oncology

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Abstract

Cancer is a result of a series of complex events leading to uncontrolled cell growth. A number of key events need to occur in a single cell in order to lead to cancerous growth. These include overcoming the key regulators of the cell cycle, invasion of local tissue, establishment of a blood supply and potential spread to distant sites. A potential role for cancer stem cell in the process of invasion and spread is becoming apparent. Additionally, the role of some viruses and infections in causing certain cancers is now well understood and has led to effective vaccine strategies. The interplay of cancer biology and the immune system is an area of particular recent interest. A role of innate immune cells such as monocytes in driving cancer processes is now appreciated, while the potential of T cells in cancer surveillance has led to significant advances in medical therapy.

Keywords Angiogenesis; cancer; cancer stem-cell; check-point; immunotherapy; inflammation; metastasis; oncogene; tumour-suppressor gene

The potential for dysregulated cell growth leading to cancer is an inherent feature of multicellular organisms. The earliest written descriptions of cancer appear in ancient Egypt. The term 'cancer' is attributed to Hippocrates who used the description *carcinos* to describe the cut surface of a solid tumour where the blood vessels entering and leaving on all sides resembled a crab's legs. With key advances in the prevention and treatment of infectious diseases and cardiovascular disease, cancer has emerged as the leading cause of death in the UK, accounting for 28.5% of all deaths in 2015. This article will focus on the key molecular and cellular events leading to the development and spread of cancer and explore how a better understanding of these processes has led to new advances in therapy.

An introduction to cancer biology

This article will first discuss the molecular mechanisms and genetics responsible for the pathogenesis of cancer. As it is a highly heterogeneous disease and there are hundreds of associated genes, it is important to initially consider the factors thought to be fundamental to the underlying biology of cancer. These factors have been described as the following six hallmarks of cancer[1] — (1) self-sufficiency in growth signals; (2) insensitivity to growth inhibitory signals; (3) evasion of cell death; (4) limitless replicative potential; (5) development of sustained angiogenesis; and (6) the ability to invade and metastasize. The dysregulation of genes involved in some or all of these processes is found in every cancer.

The origin of a cancer within the body is described as being due to a single renegade cell in which mutated genes confer a survival advantage and allow it to outcompete normal cells in the tissue. A single mutation is not sufficient to allow a cancer cell to acquire all of the hallmarks necessary to successfully grow and so it is theorized that multiple genetic hits are required for a cancer to develop. These hits may be in the form of inherited gene mutations, or genetic damage due to exogenous influences. The most important mutations that must occur are those that regulate cell growth and those that are involved in cell cycle regulation and DNA repair.

The genes involved in the regulation of cell growth encode proteins that function as growth factors, their receptors and many downstream signalling molecules that drive the cell to begin replication. Each is a potential site at which a mutation could distort these processes and lead to excessive cell growth. When mutated, these genes are called oncogenes. Of the oncogenes promoting production of growth factors, there are two main methods by which they avoid the controls on replication rate normally present in the cell cycle. Ordinarily, cells that produce growth factors do not possess the receptors for their own factors; however, in several glioblastoma types, oncogenes cause the secretion of platelet-derived growth factor (PDGF) and its receptor, creating a positive-feedback loop. The other method is a variation of this in which cancer cells activate their surrounding stroma to produce excess growth factor. Alternatively, oncogenes are also known to produce growth factor receptor proteins that stay active in the absence of their substrates as well as causing overexpression of the receptors that allows the growth pathway to be activated at a reduced concentration. The latter is the case in some types of breast cancer where the HER2/NEU receptor for epidermal growth factor (EGF) is overexpressed.

Oncogenes also increase the expression of several downstream signalling molecules. One of the most common mutated genes involved encodes the G protein RAS. Whereas other mutations lead to positive-feedback loops promoting growth, the RAS oncoprotein removes a natural negative-feedback mechanism. RAS is ordinarily an inactive signalling molecule when bound to guanosine diphosphate (GDP) nucleotides. When it is activated by upstream growth factors, GDP is exchanged for guanosine triphosphate (GTP) and a signal is emitted but is then rapidly deactivated by the intrinsic GTPase ability of RAS, which converts GTP back to GDP. The RAS oncoprotein, however, lacks this enzymatic function and is constitutively active.

Oncogenes can also influence the regulation of nuclear transcription factors and a common example is dysregulation of the *MYC* gene as a result of a t(8;14) translocation in Burkitt's lymphoma. The MYC oncoprotein simultaneously promotes the expression of cyclin-dependent kinases (CDKs) which advance the cell into the cell cycle, and down-regulate CDK inhibitors to promote cell division.

The second hallmark of cancer is insensitivity to growth inhibitory signals. This is acquired through mutations to tumour suppressor genes and understanding their function sheds light on a further mechanism in cancer pathogenesis. Retinoblastoma

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gene *RB* is a tumour suppressor gene involved in preventing entry to the cell cycle. As its name suggests, when mutated it is involved in the pathogenesis of retinoblastoma as well as breast, lung and bladder cancers. The Rb protein is crucial for integrating signals in cells to determine whether the cell moves from G_1 of the cell cycle into the S phase or G_0 (Figure 1). In G_0 the cell is removed from the cell cycle until signals direct that it re-joins it or senesces and dies. In the S phase, the cell replicates its DNA and is obligated to replicate. While in G_1, Rb is active and bound to E2F transcription factors, inhibiting them by preventing transcription of cyclin E, which is required to initiate DNA replication. When growth factors are detected, a cyclin kinase complex is activated, which phosphorylates Rb to deactivate it and cause the release of E2F. When both alleles of *RB* become mutated, the Rb protein is permanently inactive and cells pass uninterrupted into S phase.

The other important tumour suppressor gene implicated in the development of cancer is *TP53*. It encodes the protein p53, which responds to internal factors affecting the cell such as damage to the DNA and oncoprotein activity. It protects cells by upregulating genes that cause the cell to enter G_0 and allow DNA repair mechanisms to restore normal function to the genome and prevent the mutations being passed on to other cells. If the damage is unable to be repaired, then other genes are upregulated to cause cell senescence and apoptosis. Mutations of *TP53* are implicated in up to 70% of cancers. Both copies of the gene are required in order for this to lead to cancer formation and while most of this mutations are acquired, some people are born with a mutation in one copy, which is a condition known as Li Fraumeni syndrome. Having one mutant copy of *TP53* means only one additional genetic hit is required for cancer development and accordingly these patients experience a far greater incidence of cancer.

Cancer cells evade death as well as promote growth and one of the most direct methods of doing so is by circumventing cellular pathways for apoptosis. Apoptosis can be initiated by external signals such as Fas ligand binding to its receptor and leading to a signalling cascade of caspase activation resulting in the activation of caspase-3 which cleaves DNA to cause cell death. It can also be triggered by internal stressors such as radiation, chemicals or mutated DNA. Via the aforementioned p53 protein, DNA damage leads to upregulation of proteins BAX and BAK, which form pores in the mitochondria and cause cytochrome C to leak out, which again triggers activation of caspase-3 and cell death. In many B cell lymphomas, a gene translocation causes overexpression of another protein called BCL2 which inhibits the actions of BAX and BAK. This prevents cell death in response to DNA damage and so allows cancer cells to proliferate.

Another method for evading death is to stop cellular ageing, preventing the cells from triggering apoptosis in the first place. Normal human cells typically replicate fewer than 70 times before they enter senescence in a process governed by the length of telomeres — non-coding regions at the end of chromosomes. Telomeres usually shorten with each replication until they reach a length that triggers senescent processes. In cells with mutated *TP53* or *RB* as discussed, these pathways cannot be activated and instead chromosomes get joined together in a non-homologous manner, which introduces new genomic instability. Ordinarily this would trigger a mitotic crisis; however, in nearly all cancer types, mutations also lead to the upregulation of the enzyme telomerase, which is responsible for telomere length. Telomerase restores the length of the telomere such that it no longer triggers senescence and the cancer cell survives.

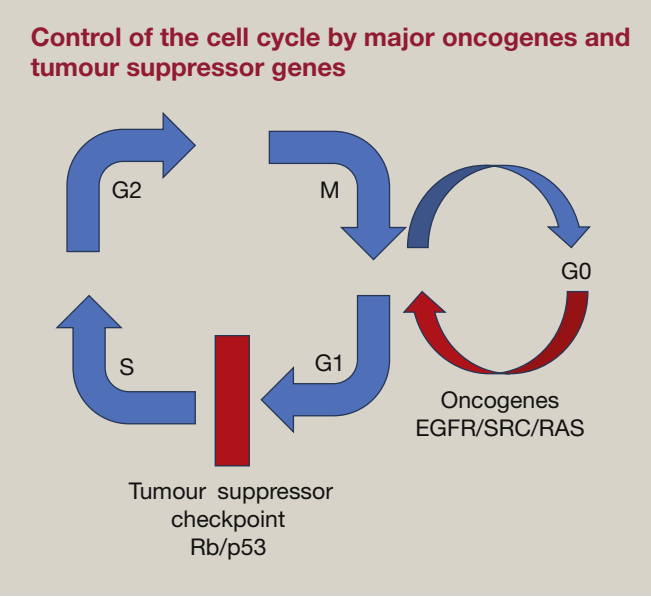

Figure 1

The spread of cancer

The attributes of cancer described so far have concerned the mechanisms by which cells become cancerous; however, there is another key feature that contributes to the devastating nature of this condition that is the ability of cancer cells to spread and metastasize. This is generally divided into two related processes — the invasion of local tissue and the distant spread via the blood stream to other tissues, in a process often termed the invasion-metastasis cascade.[2]

Local invasion involves a series of changes that allow the cancer cells to move from their original tissues and into the blood stream from which they can access distant sites. A particularly important change found in many metastatic cells is the down-regulation of E-cadherin, a cell—cell adhesion molecule crucial for maintaining order and structure in epithelial tissues. This allows cancer cells to free themselves from their original tissue. The cells must then move through the interstitial connective tissue surrounding them and this requires them to degrade various proteins such as collagen and laminins that would impede them, including the epithelial basement membrane. This typically involves the secretion of proteases such as matrix metalloproteinases (MMPs) by the cancer cells. This has an added advantage to their ability to spread in that several of the products of the protease activity act as growth factors and chemotactic agents that aid the movement of the cells. Benign tumours have been shown to express far less of these proteases than related malignant cells.

In addition to navigating the intracellular matrix (ICM), cancer cells have also been shown to secrete their own chemotactic

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