

# The hallmarks of cancer

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Cancer cells are able to proliferate in an uncontrolled fashion; - their ability to divide and spread is unbounded. Cancer cell growth destroys first the tissue from which they arise and - eventually the person in which they are present. In order to survive, divide, invade and spread, cancer cells have to acquire a number of characteristics. No one characteristic is sufficient and not all characteristics are absolutely necessary. These features, based on articles by Hanahan and Weinberg, are given in Summary box 12.1. Establish an autonomous lineage Cells develop independence from the normal signals that control supply and demand. The healing of a wound is a physiological process; the cellular response is exquisitely coordinated so that - proliferation occurs when it is needed and ceases when it is no - longer required. The whole process is controlled by a series of - Maurice Hugh Frederick Wilkins, 1916–2004, of Summary box 12.1 Features of malignant transformation /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF signals telling cells when, and when not, to divide. Cancer cells escape from this normal system of checks and balances: they grow and proliferate in the absence of external stimuli and regardless of signals telling them to desist. Oncogenes are genes with the potential to cause cancer if mutated and expressed at high levels; they are key factors in carcinogenesis. Most oncogenes are normally involved in physiological processes, i.e. cell growth, but if mutated they can predispose a cell to cancer and in concert with other oncogenes can enable cancer cell survival and development of an established tumour. The implication is that we all carry the seeds of our own destruction: genetic sequences that, through mutation, can turn into active oncogenes and thereby cause malignant transformation. Indeed, through study of the timing of key genetic events in adult cancer development, a handful of cells develop the founder mutations of cancer development several decades prior to diagnosis. If the individual is unfortunate enough to accumulate further mutations in key driver genes, that cell becomes malignant and, if it proliferates, a cancer may develop. Only very rarely is a single mutation sufficient to cause cancer; multiple mutations are usually required. Colorectal cancer provides the classical example of how multiple mutations are necessary for the complete transformation from normal cell to malignant cell. Vogelstein and his colleagues identified the genes implicated and also postulated that it is necessary to have mutations in all the relevant genes; they also noted that these mutations must be acquired in a specific sequence for malignant transformation to occur. Obtain replicative immortality According to the Hayflick hypothesis, 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; eventually the lineage will die out. Cancer cells utilise the enzyme telomerase to rebuild the telomere at each cell division, such that there is Bert Vogelstein, b.1949, molecular biologist, Johns Hopkins Hospital, Baltimore, MD, USA. Leonard Hayflick, b.1928, while working at the Wistar Institute in Philadelphia in 1962, he noted that normal mammalian cells growing in culture had a limited, rather than an indefinite, capacity for self-replication. cancer cell hence develops immortality. Evade apoptosis Apoptosis, taken from the Greek for 'leaf fall', is a

form of programmed cell death that occurs as the direct result of internal cellular events instructing the cell to die. Unlike necrosis, which is a form of traumatic cell death resulting from acute cellular injury, apoptosis is an orderly and internally driven process. The cell dismantles itself neatly for disposal (Figure 12.1). There is minimal inflammatory response. Apoptosis is a physiological process. Cells that are redundant normally die by apoptosis and this is an important self-regulatory mechanism in growth and development, i.e. cells in the web space of the embryo die by apoptosis, or lymphocytes that could react to self. Genes, such as p53, that can activate apoptosis function as tumour suppressor genes. Mutation in such genes causes a loss of this inhibitory function, which will contribute to malignant transformation as apoptosis is evaded; this means that the wrong cells can be in the wrong places at the wrong times.

Acquire angiogenic competence A mass of cancer cells cannot, in the absence of a blood supply, grow beyond a diameter of about 1 mm. This places a severe restriction on the capabilities of the tumour (note that the word tumour means swelling and does not mean the lesion is malignant, although 'tumour' is often taken by patients to be synonymous with cancer). It cannot grow much larger or spread widely within the body. If, however, the mass of cancer 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

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Acquire ability to disseminate and implant Once cancer cells gain access to vascular and lymphovascular spaces, they can be readily distributed systemically throughout the body. 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; presumably these cells die if they cannot implant or they are destroyed by the patient's immune system. Cancer can spread as individual cells or cell clumps that 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

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Tumour-related inflammation A malignancy can provoke an inflammatory response and the cytokines and other factors produced as a result of that response may act to promote and sustain malignant transformation. Growth factors, mutagenic reactive oxygen species, angiogenic factors and anti-apoptotic factors may all be produced as part of an inflammatory process and all may contribute to the progression of a cancer.

- Evade detection/elimination Although derived from normal cells ('self') cancer cells are, in terms of their genetic make-up, behaviour and characteristics, foreign ('not self'). As such, they ought to provoke an immune response and be eliminated. It is entirely possible that malignant transformation is a more frequent event than the emergence of clinical cancer. The possible role of the immune system in eliminating nascent cancers was proposed by Paul Ehrlich in 1909 and revisited by both Sir Frank McFarlane Burnet and Lewis Thomas in the late 1950s. 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 actively co-opting one part of the immune system to help the tumour escape detection by other parts of the immune surveillance system. This hallmark has been exploited in recent years in the development of T-cell checkpoint inhibitors, which 'take the brakes' off the immune system to re-enable T-cell killing of cancer cells, e.g. in renal cell carcinoma, lung cancer and melanoma.

Loss of specialist cell function Cancer cells are geared to excessive proliferation. They do not need to develop or retain those specialised functions that prior to malignant transformation were their physiological function. These cells can therefore afford to repress or permanently lose those genes that control such functions. The longer term disadvantage to this process is that cancer cells are vulnerable to external stressors, which may, in part, explain why some cancer treatments work.

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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. The hallmarks of cancer

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