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Cancer—a degenerative disorder?

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Cancer is primarily a disease of ageing epithelia, and of ageing individuals. We now possess detailed insights into the changes in cell regulatory genes and DNA repair systems which accumulate with time and which manifest in malignancy. These demonstrate how cancer is frequently characterized by degenerative change in the genotype, from the most subtle base pair mutations to gross aneuploidy, and by deterioration in cell and tissue regulatory control, be it of proliferation, programmed cell death or signalling.

Cancer may thus be as much a phenomenon of loss or deterioration of normal genomic control as of the acquisition of new, neoplastic functions. This distinction may be more than semantic, not least because it governs our approach to the search for therapeutic strategies. This essay considers the concept of cancer as a degenerative disease and its implications, and proposes the neologism *aldoplasia* to describe this phenomenon of cancer biology.

Key words: **neoplasia; degeneration; genome; regulation; aldoplasia.**

A model of cancer

The distinction of neoplasia, or new growth, from other forms of disease, such as inflammation, infection or degeneration, is deeply embedded professional dogma. The terminology defines our intellectual approach to the search for remedies, and determines the form of our clinical practice. The terms which we use in association with cancer, for example invasion and implantation, help to reinforce the image of a cancer cell as a contaminant whose alien persona and genetic characteristics, when eventually defined, will lead us to a 'cure'. We have come to regard neoplastic, cancerous change as the *acquisition* of new and damaging properties by cells. Twentieth century expectations for cancer therapy have largely been conditioned by the control of microbial infection by antibiotics, which act through well-defined molecular mechanisms. However, despite the dramatic progress which has been made during the past century in the fields of cell, tissue and molecular biology, progress towards the control of established malignancy by non-surgical techniques has been slow. Effective new therapies remain elusive.

If science has failed so far to identify the cure for cancer, then may it be in part because we are viewing cancer from the wrong perspective. Cancer is a disease of genetic disorder as well as of tissue disorganization. Cumulative genomic damage explains the aetiology of many malignancies. We may thus hypothesize that degenerative change in the genome is sufficient to explain neoplasia. We may consider the deterioration in gene *structure* as *degenerative*, while the consequences for altered gene *function* on cell behaviour are *neoplastic*, conferring disordered growth regulation, invasion and metastasis upon cancer cells.

In the acquisitive scenario, the product of acquired genetic abnormalities, for example, discrete 'cancer' proteins and cell markers, should be identifiable and targetable. Thus, for example, evolutionarily discarded genes lying dormant in the mass of inactivated DNA in the human genome may be activated by neoplastic stimuli, and there may be an immunological response to acquired, novel pathogenic characteristics.

In the degenerative scenario, the gradual accumulation of dysfunction through genetic damage leads to the neoplastic phenotype through reversion to less regulated and ordered behaviour. Such changes are less easy to identify, because they involve a subtle functional realignment of existing molecular processes. The distinction between the acquisition of new genetic characteristics and the degeneration of existing genetic information to a less regulated state may thus be important.

At the limit, acquired and generative cell and genetic dysfunction converge in the abnormal expression of the genome. However, as this position may be reached by a number of different routes, so the implications for the design and likely success of various adjuvant therapeutic strategies will vary. The objective of this article is to consider the concept of cancer as a class of degenerative diseases of the genome, and to consider the implications of such a hypothesis.

Time and genetic aging

Longer life expectancy increases the risk of cancer, for which we have abundant evidence. In the past 200 years, mean

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life expectancy in the developed world has increased by some 30 years. Time ages the body and the genome, measured in cell and tissue terms by cell replication and the passage of cell generations.

Cell replication confers age upon the cell by repeated mitosis. The telomerase enzyme provides the vehicle for an elegant hypothesis as to how simple, repetitive process may have profound consequences for the DNA of replicating cells.[1-3] Chromosomes shorten with each replication in normal cells with the loss of short repeat sequences of DNA primer fragments from the telomeric complexes at each end of the chromosomes. This mechanism imposes a limit on the number of divisions that a cell can make before replication is terminally damaged. Telomere shortening may confer a biological clock, and a proliferative lifespan, upon normal cells. Telomerase restores the length of telomeres and transforms stem line and neoplastic cells such that they acquire an extended proliferative potential, which at the limit is immortalization in neoplasia, as in testicular germ-line cells. Evidence for this has been derived from cell lines, and from ovarian, retinoblastoma, haematogenous and other malignancies, using the indirect telomerase assay of terminal restriction fragment (TRF) length. Telomerase does not appear to be expressed in normal human somatic cells. In a cohort of colorectal cancers and tissues, telomerase was not found to be expressed in biopsies of normal tissue or in pre-cancerous adenomas, but was expressed in most cancer samples.[4]

The incidence of most forms of cancer increases progressively with age. Malignancy is primarily a disease of epithelium (skin, aerodigestive and urogenital tract). These epithelia share two important general features, in that they are proliferative, and that they are relentlessly exposed to environmental events (solar radiation, dietary constituents and toxins, and excretory products) which can cause genetic damage. In consequence, highly proliferative tissues will acquire a greater risk of damage, DNA instability and misreplication with time. Genetic damage and mutation appears to accumulate with repeated cell division, particularly in the proliferative epithelia. At various and variable points in the life of an organism or tissue, the loss or disruption of regulatory functions within component cells moves the tissue nearer to malignant behaviour.

General evidence for genomic degeneration

Cumulative, successive defects rather than immediate, single-step genetic damage are the key to the malignant genotype. The genetic disturbances in malignant cells may be classified as cumulative point mutations in regulatory genes and oncogenes, chromosomal disorder through mechanisms such as gene amplification, DNA methylation and chromosome duplication, or amplification of DNA sequences and chromosomes. Many critical genes specifying key cell regulatory processes are highly conserved through evolution and therefore are found throughout the natural world. Structural genetic disorder at the level of single base pair mutations in such genes demonstrably leads to regulatory protein dysfunction and to malignancy. Conserved genes display considerable point mutational heterogeneity within populations, but many of the mutations may be functionally neural. However, some functional mutations or allelic losses lead to dysfunction associated with malignancy in key processes, including proliferation, apoptosis and signalling. There are many excellent reviews on these mechanisms.[5-8]

The p53 protein system is one such example.[9-12] The protein product of the p53 gene may have a regulatory role in the cell cycle and in programmed cell death, or apoptosis. Point mutations change the normal (wild-type) protein to a mutant variant. More than 2600 point mutations have been recognized.[13] In general terms, normal p53 appears to prevent progression through the cell cycle of genetically damaged cells, while mutant p53 allows uncontrolled cell cycle progression and impairs apoptosis. Seemingly minor 'degenerative' changes in the genome may thus have profound consequences for cancer development.

Genetic damage gives rise to pluripotentiality of gene function and expression. The emergence of the malignant phenotype (invasion, metastasis) may thus be a reversion to a less highly regulated and a more disordered state of cell function and interrelationship. It may be that only the most immunologically evasive and subtly abnormal cells will survive to exhibit the features of uncontrolled proliferation, deregulated cell death, invasion and metastasis. Malignancy may then be the statistical and biological price to be paid for massive and rapid cell and tissue turnover throughout life.

Mechanisms of degenerative damage

Degenerative DNA damage may rise spontaneously in the course of normal molecular processes. This damage is likely to account in large part for the natural ageing of the body, and for the induction of many tumours as natural defences become less effective with time. DNA repair imparts reproduction continuity and fidelity upon cells, and may protect against a much higher incidence of cancer in the natural world. It has been estimated that the DNA of each cell, comprising 4×10^9 bases, temporarily loses 10,000 nucleotide bases each day from spontaneous DNA damage alone. There is a predicted efficiency of only three mistakes per 3 billion base pairs during DNA copying, in each of the 10^{14} cells in the human body, and in up to 10^{14} cell generations per human lifespan in stem cell lines (such as the haematopoeitic system). Not only is the existence of such a DNA repair capability remarkable, but it highlights a profound problem in cancer therapy, because such an evolutionarily stable process possesses considerable redundancy against DNA damage induced by therapeutic manoeuvres.[14]

The covert, irresistible and unavoidable force of nature so far as DNA is concerned is ionizing radiation. This includes cosmic particles and natural terrestrial sources. Radiation damage may cause single base mutations, or grosser forms of genetic damage, such as the disruption of chromosomes. Radiation damage to the genome is cumulative. Environmental hazards also include chemicals and carcinogens which may induce genomic damage through deliberate (chemotherapy) or inadvertent use.

Gatekeeper (DNA repair) and caretaker (housekeeping) genes

Cells have developed sophisticated DNA repair mechanisms for ionizing and other forms of DNA damage.[15-17] The topoisomerase and DNA ligase family of proteins[18,19] are nuclear, DNA-associated conformational enzymes with housekeeping functions such as the repair of strand breaks, and the facilitation of chromosome cleavage and segregation. Gatekeeper genes are those genes which control cell proliferation, for example through proteins acting as check points in the cell cycle, growth inhibitors or apoptosis regulators. Examples include the retinoblastoma and APC genes. Both copies must be inactivated to promote cancer development. Individuals with hereditary mutation in these genes are at a high risk of developing malignancies.

Genetic instability has recently been shown to arise in two forms: the recessive traits of DNA mismatch repair deficiency leads to nucleotide sequence (microsatellite) instability, while the dominant chromosomal instability pathway produces aneuploidy.[20] Lengauer *et al.*[21] have thus suggested that persistent genetic instability may be critical for the development of all colorectal cancers, for example. Other regulatory genes are broadly classified as having tumour-promoter and tumour-suppressor functions. Many have interrelated functions. Their products include nuclear, cytoplasmic and membrane associated molecules. Detailed understanding of the growth factor and growth inhibitor initiated cell cycle[22,23] and cell signalling pathways has revealed the extent and complexity of the interrelated roles of the oncoproteins. Malignant change may be mediated through a number of newly recognized mechanisms at various sites in the cell, including: cell-surface receptor pathways (such as via protein-tyrosine kinase, PTK); signalling pathways to the nucleus (including the TGF-beta and Ras oncoprotein systems); the actin cytoskeleton (which plays a key role in signalling, adhesion, binding and regulatory processes); and at the nucleus (including transcription factors and regulators, and chromatin regulatory proteins).

Dysfunction in 'caretaker' genes, such as the DNA repair genes, which regulate the integrity of the genome, increases genonic degeneration and leads to more genetic damage across all types of genes, including gatekeeper genes. A number of other DNA associated proteins and enzymes contribute to DNA synthesis and repair. Examples include the DNA strand mismatch repair gene hMSH2, defects of which are significantly associated with the emergence of colorectal cancer in the hereditary non-polyposis colorectal cancer syndrome (HNPCC).[24] Protection against cell damage by ultraviolet light is afforded by the nucleotide excision repair (NER) pathway, abnormalities in which are found in xeroderma pigmentosum. NER mechanisms may also repair cytotoxic drug-induced damage in target cells. Cellular detoxification mechanisms also affect the capacity for cells to sustain drug and radiation damage and effect repair. Glutathione metabolism is one example.[25]

Genotypic modulation of many other critical cell functions may produce the malignant phenotype. Such processes include intra- and intercellular signalling, cell adhesion, angiogenesis, and metastatic behaviour.[26-30] Conversely the immense subtlety and complexity of cell regulation may limit intrinsic and extrinsic (e.g. cytotoxic drug) damage. Disruption of one molecular system or functional pathway may lead to complex readjustments and 'workarounds' in other pathways, endowing considerable resilience upon the cell.

Genetic differences between the parent genotype and the cancer also vary with time, with growth and with site within the lesion. Moreover, there is no one point at which a cancer site can be considered to have achieved its definitive genotype. Genetic instability may lead to many different cell lines, or clones, which may have better or worse survival characteristics. The ageing of the genetic and molecular machinery of the cell may manifest as aneuploidy in cancerous cells.[31,32] The absolute or functional loss of alleles is a commonly reported genetic correlate of malignant change.

Cell loss and the ageing, damaged genome

Cell loss is a key process in tissue and tumour biology. It may be inadvertent, through hypoxia, immunological response, therapeutic action, exfoliation or shedding, or deliberate. Apoptosis, or programmed cell death,[33-36] is a fundamental cause of cell loss. The balance between cell production and cell loss, and hence between tissue or tumour growth, steady state stability, or regression, can be very subtle. Apoptosis allows the recognition and elimination of cells damaged genetically, either through faulty replication or because of environmental factors. Many genes and signals mediate apoptosis, including p53, cmyc, bcl2, max and bax. Other genes, such as BCL2, protect against apoptosis. Genomic damage may be an important cause of dysfunctional apoptosis. This may prevent the elimination of abnormal cells and hence of cancer genesis and growth.[37] A link is thus indicated between genomic damage of key regulatory genes and dysfunctional tissue and cancer growth.

Clinical models of genomic degeneration and malignancy

The importance of a cascade of genetic changes leading to the malignant genotype is now recognized in several classes of cancer. These changes may occur at random and without immediate effect in individual stem cells, for example in intestinal mucosa or bone marrow, at any time in life. However, their sequential accumulation with time produces genomic dysfunction. At least 20 hereditary cancer syndromes have now been described.[38] Hereditary genetic defects seem able to bypass some of the stages in carcinogenesis, thus accelerating the stages of molecular degeneration and promoting the early development of malignancy.

Colorectal cancer is perhaps the best studied model of sequential genetic change from normal tissue to malignancy.[39] The list of defective genes include the adenomatous polyposis coli gene (APC) and mismatch repair loci. HNPCC patients display high mutation rates in short repeating sections of DNA (microsatellites)

and mutations in genes believed to have a 'caretaker' function.[20,21] Genetic defects identified in sporadic cancers include mutations in the p53, APC, and MCC (mutated in colorectal cancer), ras, and DCC (deleted in colorectal cancer) genes.[40]

Breast cancer also results from progressive and cumulative genetic aberrations which correlate with morphology. The BRCA1 and BRCA2 tumour suppressor genes have a role in hereditary and sporadic breast cancer, for which more than 100 mutations are now recognized.[41,42] The expansion of knowledge of the molecular genetics of other tumour classes continues, including, for example, urological tumours,[43] and pancreatic tumours,[44] and we may expect continuing insights into mutational deficits in many tumour types. Clinical cancer development is thus a staged progression of genetic and functional changes in the cell which may be accelerated by environmental interactions and by hereditary genetic changes.

Implications of the degenerative concept of cancer aetiology

Evolutionary and reproductive pressures and natural selection refined over aeons have determined the emergence of the complex biological processes within cells, tissue and organs. They have improved higher degrees of order and specialist function upon biological systems to ensure life, reproduction and specimen survival. It is difficult to conceive of the pressures that would favour the selection or acquisition of the malignant genotype, a very damaging event for individuals. It is somewhat easier to conceive of cancer resulting from degenerative change in the genome.

Malignancy may simply be the statistical and biological price to be paid for rapid cell and tissue turnover throughout life, particularly in the blood and epithelia. Given the huge numbers of cells produced by proliferative tissues, dysfunctional cells are likely to be generated frequently throughout life, although most do not survive. Only the most immunologically evasive, and subtly abnormal cells will survive to exhibit the features of uncontrolled proliferation, deregulated cell death, invasion and metastasis. Thus, as the human body ages, the emergence of malignancy through cumulative genetic damage may be unavoidable intrinsic process, rather than a disease superimposed from without upon innocent tissues.

Degenerative genomic damage may thus help explain why nature has not eliminated cancer as a harmful biological process through the power of evolutionary natural selection. Most cancers arise in the post-reproductive years, at which time there has not been evolutionary or genetic survival pressure to develop resistance mechanisms to malignancy. Consequences are evident for the development of therapeutic strategies for cancer. In the therapy of infections, antibiotics assist well-rehearsed body defences to attack targets which are immunologically and functionally distinct from normal tissues. In the case of cancer, the very blandness and similarity of cancer cells to normal cells consequent upon subtle degenerative genomic changes hinders anti-cancer strategies.

In summary, our genes represent completely continuous, continually evolving lineages over more than a thousand million years. Some highly conserved genes guarantee absolute certainty and continuity of cell homeostasis and reproduction. Others provide powerful defence mechanisms (DNA repair systems) to protect against DNA damage. Where this cannot be compensated, damaged cells eliminate themselves through apoptosis. When cells become malignant, the key processes of cell function, regulation and division are preserved, or else the cell would stop cycling and self-destruct. Subtle changes in the balance of regulation, of proliferation and apoptosis can have very significant consequences for abnormal growth. So far as the neoplastic properties of invasion and metastasis are concerned, we are not yet sure whether these represent reacquisition of function of completely suppressed or dormant genes which confer less ordered behaviour, or whether they result from degenerate modulation of normal regulatory genes. The truth may lie within a combination of these various states.

The term *aldoplasia*, which we may thus introduce to describe genomic deterioration with time, may help describe the degenerative aspects of the malignant process and to identify the challenges and complexities in ageing genes, cells and tissues.

References

1. Lundblad V, Wright WE. Telomeres and telomerase: a simple picture becomes complex. *Cell* 1996; **87**: 369–75.
2. Lundblad V. The end replication problem: more than one solution. *Nature* 1997; **3**(11): 1198–9.
3. Wynford-Thomas D, Kipling D. Cancer and the knockout mouse. *Nature* 1997; **389**: 551–2.
4. Rennie J. Immortal's enzyme. *Sci Am* 1994; **271**: 8–9.
5. Bishop M. Oncogenes. *Sci Am* 1982; **246**: 69–78.
6. Dang CV. c-Myc oncoprotein function. *Biochim Biophys Acta* 1991; **1072**: 103–13.
7. Miden MD, Pawson AJ. Oncogenes. In: Tannock I, Hill RP (eds) *The Basic Science of Oncology*, 2nd edn. New York: McGraw Hill, 1992; 61–87.
8. Hunter A. Oncoprotein networks. *Cell* 1997; **88**: 333–46.
9. Vile RG. p53: a gene for all tumours? *Br Med J* 1993; **307**: 1226–7.
10. Donehower LA, Bradley A. The tumour suppressor p53. *Biochim Biophys Acta* 1993; **1155**: 181–205.
11. Harris CC. p53: at the crossroads of molecular carcinogenesis and risk assessment. *Science* 1993; **262**: 1980–1.
12. Levine AJ. p53, the cellular gatekeeper for growth and division. *Cell* 1997; **88**: 323–31.
13. Soussi T, Caron de Fromentel C, May P. Structural aspects of the p53 protein in relation to gene evolution. *Oncogene* 1990; **5**: 945–52.
14. Koshland DE. Molecule of the year: the DNA repair enzyme. Editorial. *Science* 1994; **266**: 1925–7.
15. Modrich P. Mismatch repair, genetic stability and cancer. *Science* 1994; **266**: 1957–8.
16. Hanawalt PC. Transcription-coupled repair and human disease. *Science* 1994; **266**: 1957–8.
17. Sancar A. Mechanisms of DNA excision repair. *Science* 1994; **266**: 1954–6.
18. Liu LF. DNA topoisomerase poisons as antitumour drugs. *Ann Rev Biochem* 1989; **58**: 351–75.
19. Smith PJ. Topoisomerase inhibitors: new twists to anticancer drug action. *Oncol Today* 1991; **3**: 4–9.
20. Kinzler KW, Vogelstein B. Gatekeepers and caretakers. *Nature* **386**: 761–3.

21. Langauer C, Kinzler RW, Vogelstein B. Genetic instability in colorectal cancer. *Nature* 1997; **386**: 623–6.
22. Hartwell LH, Kastan MB. Cell cycle control and cancer. *Science* 1994; **266**: 1821–8.
23. Peters G. Cell cycle: stifled by inhibitions. *Nature* 1994; **371**: 204–5.
24. Lynch HT, Smyrk TC, Watson P, *et al.* Genetics, natural history, tumour spectrum, and pathology of hereditary non-polyposis colorectal cancer. *Gastroenterology* 1993; **104**: 1535–49.
25 Hedley DW. Flow cytometric assays of anticancer drug resistance. *Ann NY Acad Sci* 1993; **677**: 341–53.
26. Garrod DR. Cell to cell and cell to matrix adhesion. *Br Med J* 1993; **306**: 703–5.
27. Menger MD, Vollmar B. Review: adhesion molecules as determinants of disease: from molecular biology to surgical research. *Br J Surg* 1996; **83**: 588–601.
28. Fidler IJ, Ellis LM. The implications of angiogenesis for the biology and therapy of cancer metastasis. *Cell* 1994; **79**: 185–8.
29. Folkman J. Angiogenesis in cancer, vascular and rheumatoid disease. *Nature Med* 1995; **1**: 27–31.
30. Jiang WG, Puntis MCA, Hallett MB. Molecular and cellular basis for cancer invasion and metastasis: implications for treatment. *Br J Surg* 1994; **81**: 1576–80.
31. Rew DA. Significance of aneuploidy. *Br J Surg* 1994; **81**: 1416–22.
32. Rew DA. Heterogeneity, biodiversity and bioperversity in human solid tumours. *Eur J Surg Oncol* 1996; **22**: 469–73.
33. Kerr JFR, Wyllie AH, Currie AH. Apoptosis, a basic biological phenomenon with wider implications in tissue kinetics. *Br J Cancer* 1972; **26**: 239–45.
34. Nagata S. Apoptosis by death factor. *Cell* 1997; **88**: 355–65.
35. Wyllie AH. Apoptosis. *Br J Cancer* 1993; **67**: 205–8.
36. Duke RC. Ojcius DM, Young JD. Cell suicide in health and disease. *Sci Am* 1996; **Dec**: 48–55.
37. Williams GT. Programmed cell death: apoptosis and oncogenesis. *Cell* 1991; **65**: 1097–8.
38. Fearon ER. Human cancer syndromes: clues to the origin and nature of cancer. *Science* 1997; **278**: 1043–50.
39. Vogelstein B, Fearon ER, Hamilton SR, *et al.* Genetic alterations during colorectal tumour development. *New Engl J Med* 1988; **319**: 525–32.
40. Stanbridge EJ. Identifying tumour suppressor genes in colorectal cancer. *Science* 1990; **247**: 12–3.
41. Ford D, Easton DF. The genetics of breast and ovarian cancer. *Br J Cancer* 1995; **72**: 805–12.
42. Greene MH. Genetics of breast cancer. *Mayo Clin Proc* 1997; **72**: 54–65.
43. Maher ER. Genetics of urological cancers. *Br Med Bull* 1994; **50**: 698–707.
44. Flanders TY, Foulkes WD. Pancreatic adenocarcinoma: epidemiology and genetics. *J Med Genet* 1996; **33**: 889–98.