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What are Cancer Genes, and how do they Upset Cell Behaviour?

J.R. Yarnold

Some of the cellular changes underlying the presentation of cancer in a patient can already be understood in terms of mutations affecting specific gene functions. So far, only a few of the mutated genes responsible for carcinogenesis have been identified and these are chiefly involved in deregulation of cell growth rather than with the processes of invasion and metastasis. Proto-oncogenes are important cellular genes which can acquire gain in function mutations as random events in somatic cells. In their mutated, activated forms they are called cellular oncogenes or c-oncs. This distinguishes them from homologous DNA sequences captured by viruses from host cells in the course of retroviral evolution that cause cancers in animal hosts (viral oncogenes or v-oncs). In recent years, loss of function mutations have been identified in regulatory genes that normally serve to constrain cell growth. These are called tumour suppressor genes. Loss of function mutations may be transmitted in the germline, as in hereditary retinoblastoma, or arise *de novo* in somatic cells. The normal molecular mechanisms disrupted by mutations in tumour suppressor genes include processes regulating progression through the cell cycle.
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SOMATIC MUTATION THEORY AND MULTISTAGE CARCINOGENESIS

SOME OF the cellular changes underlying tumour growth, invasiveness and metastatis can already be understood in terms of altered function in a tiny percentage of the several tens of thousands proteins coded in the human genome. Altered gene function arises from altered DNA sequences (mutations) which arise either spontaneously, e.g. from uncorrected errors in DNA replication, or from exposure to exogenous carcinogens. For example, the benzopyrene content of cigarette smoke is probably responsible for point mutations that alter the p53 gene sequence and activity in many lung cancers [1]. Mutational events in critical genes presumably confer some kind of survival or growth advantage on the affected cells, so that descendants accumulate genetic damage over successive generations [2, 3].

Progressive alterations in cell morphology and tissue organisation can be observed for several years before the appearance of invasive disease, e.g. epithelial hyperplasia, epithelial dysplasia and carcinoma *in situ*. The molecular mechanisms underlying these pathological changes are best described in colon cancer where the accumulation of mutations in several genes correlates with progression via epithelial dysplasia, adenoma and carcinoma *in situ* to frank malignancy [4–6]. Colon cancer offers the best illustration so far of multiple somatic mutations underlying multistage carcinogenesis. As we shall see later, the inheritance of mutations in the germ-line also contribute in some individuals with cancer.

Mutational (genetic) events in cancer cells are not the only factors affecting cancer development; its just that they are easier to identify than environmental (epigenetic) influences that also affect the evolution of malignancy. As evidence of this, the

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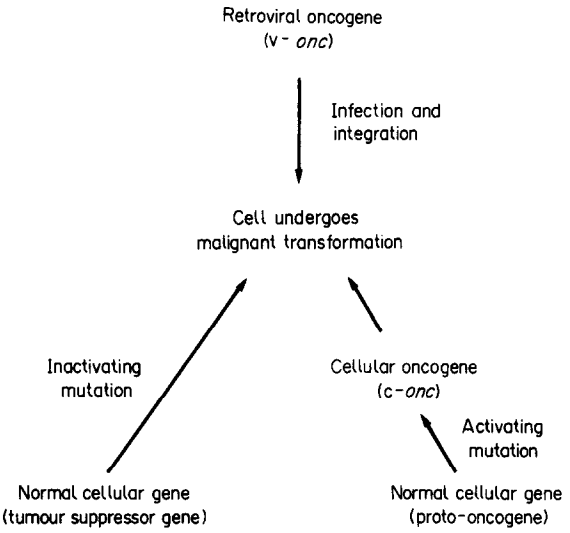

Fig. 1. Schema of terminology used to describe cancer genes.

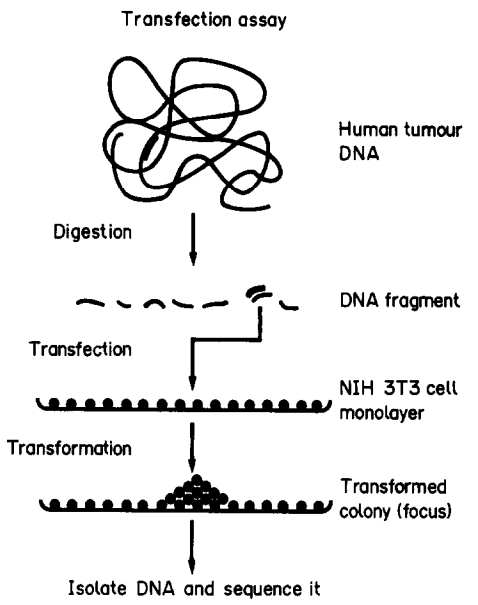

Fig. 2. Schema of transfection assay.

pattern of metastases in solid tumours is strongly influenced by the normal tissue environment, presumably reflecting the nature of the intercellular matrix and local growth factors.

THE ORIGINS AND DEFINITIONS OF CANCER GENES

Somatic mutations

Until the last decade there were virtually no experimental approaches to the identification of human cancer genes, but two advances revolutionised this state of affairs [7]. First, the genes carried by animal RNA tumour viruses (retroviruses) provided vital clues. It was known since early in the century that Rous sarcoma in chickens was caused by an infectious particle, later identified to be a retrovirus. By 1980, it was clear that the viral gene sequences (viral oncogenes) responsible for malignancy in the animal host were truncated or otherwise modified sequences of normal cellular genes already known to have an important role in the regulation of cell growth. The spectacular hypothesis remains that viral RNA sequences responsible for cancers in the animal host (viral oncogenes, v-oncs) were captured, or transduced, from infected cells during viral evolution. Normal cellular genes with sequence similarities (homologies) to v-oncs are called proto-oncogenes, see Fig. 1. Proto-oncogenes themselves are normal but they can undergo mutations in the cell that result in activation. Proto-oncogenes activated *in situ* by mutation are called cellular oncogenes or c-oncs to distinguish them from their viral counterparts. Mutations can also inactivate genes that normally suppress malignancy (tumour suppressor genes) but these are not represented among retroviral oncogenes for reasons that will be discussed later.

The second approach that revolutionised the identification of human cancer genes was the transfection assay. The transfection assay offers a direct way of testing the actions of potential cancer genes on cell cultures [8]. It involves the introduction (transfection) of human tumour DNA fragments into the culture medium overlying rodent fibroblasts, which take up DNA fragments by endocytosis and integrate them into the rodent genome, see Fig. 2. The fibroblasts (NIH 3T3 cells) are not normal in that they do not senesce and die in culture after several generations, but are already immortalised as a result of acquiring rare, spontaneous mutations. In this state, the cells are part-transformed (v.i.) whilst retaining some normal characteristics such as anchorage dependent growth and contact inhibition. Fibroblasts that integrate segments of DNA containing c-onc sequences undergo a process called transformation. This involves loss of anchorage dependence and contact inhibition, leading to multi-layered heaps or 'foci' of malignant-looking cells in a monolayer background.

The existence of c-oncs in human cancer was first demonstrated in a human bladder carcinoma cell line [9]. In the case of the bladder carcinoma, the transformed clones of 3T3 cells contained human DNA fragments coding for a member of the **ras** gene family [10]. Since then, many other c-oncs have been identified in a wide range of human cancers using the transfection assay. Some, but not all, have viral homologues. For example, the bladder cancer c-ras gene had striking sequence similarities to the v-onc of the Harvey strain of murine sarcoma virus, hence its abbreviated name H-c-ras. Transformed cells in culture sometimes grow into tumours when implanted subcutaneously into immune-deprived mice. This test of c-onc action is called a tumourogenicity assay.

Whereas RNA viruses are very rare causes of human cancer [e.g. human T cell leukaemia virusl (HTLV1) causes a cutaneous T cell lymphoma], oncogenic DNA viruses are a most important cause of cancer worldwide [11, 12]. For example, hepatitis B and papilloma viruses are implicated in human hepatocellular carcinoma and cancer of the cervix respectively. Quite different mechanisms are involved compared to those of retroviruses and they will be mentioned later.

Germ-line mutations

Most human cancers arise purely from an accumulation of somatic mutations, but more than 20 years ago it was predicted that mutations transmitted in the germ-line would also contribute to the evolution of human malignancy. Furthermore, it was expected that such mutations would result in the inactivation of cancer-associated genes, rather than the activating mutations characteristic of c-oncs [13, 14]. Large family pedigrees with multiple members affected by cancer are of enormous value to geneticists because segregation analysis offers an important route to isolating genes involved in a wide range of malignancies.

Examples of diseases where an inherited gene defect has been identified includes retinoblastoma, Wilm's tumour and von Recklinghausen's disease [15–19].

Germ-line mutations are transmitted to every somatic cell in the affected individual. He or she also accumulates random somatic mutations in cells of one or more tissues which presumably confer some kind of survival or growth advantage to their descendants. Retinoblastoma is the paradigm for hereditary cancer, see Fig. 3. Hereditary retinoblastoma is almost always bilateral and occurs at a younger age than its sporadic counterpart because every retinoblast already contains one of the relevant mutations [13]. There are only two rate-limiting events, one germ-line inactivation of the retinoblastoma gene locus and a subsequent somatic inactivation of the opposite allele in band 14 of the long arm of chromosome 13 (13q14), often by deletion of a large section of chromosome. Retinoblasts are only susceptible to malignant transformation during fetal development, after which they differentiate into a fixed cell population. Given that there are thought to be at least one million susceptible retinoblasts in the developing eye, the chances are virtually 100% that a somatic mutation involving the normal retinoblastoma locus occurs at least once in a fetus during development. Thus, hereditary retinoblastoma is inherited as a Mendelian autosomal dominant disease with a high degree of penetrance.

In sporadic retinoblastoma, unilateral tumours develop in a slightly older age group. This is because one susceptible retinoblast has to sustain two somatic mutations to inactivate both retinoblastoma loci. Although the shapes of the age-incidence curves of hereditary and sporadic retinoblastoma are consistent with two rate-limiting genetic events as the minimum necessary for the development of the disease, it is almost certain that the full evolution of retinoblastoma involves a number of other non-rate-limiting mutations yet to be identified.

It has already been mentioned that germline mutations characteristically inactivate the gene product, unlike the c-oncs which are activated by mutation. Activating mutations in the germline are presumably incompatible with embryonal development. In germ-line mutations of potential cancer genes, the inactivation of one allele is associated usually with no detectable change in embryonal development because sufficient gene product is available from the homologous allele on the other chromosome. Germ-line mutations usually contribute to the development of cancer only after the homologous allele is inactivated by a somatic mutation. Because this cause of malignant behaviour depends on loss of gene function from both alleles, the genes are called tumour suppressor genes [20]. The retinoblastoma gene was the first tumour suppressor gene to be isolated but

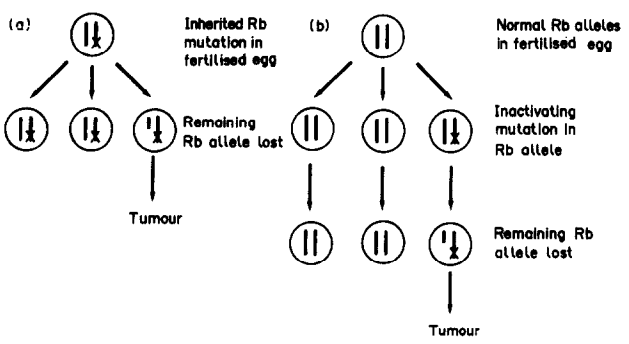

Fig. 3. Schema of representing development of (a) hereditary and (b) non-hereditary retinoblastoma (Rb).

Table 1. A classification of human cancer cells with selected examples

Cancer gene	Chromosomal location	Protein product	Cellular location	Cellular function	Chemical function /structure
H-c-*ras*	11p	Mutated	Plasma membrane	Proliferation	GTP binding protein
c-*myc*	8q	Over-expressed	Nucleus	Proliferation	?
c-*erb*B2	17q	Over-expressed	Plasma membrane	Proliferation	Growth factor binding
BCL-2	18q	Over-expressed	Mitochondrion	Delays apoptosis	?
NM-23	?	Mutated/ deleted	?	Metastasis suppressor	NDP kinase
Rb	13q	Mutated/ deleted	Nucleus	Cell cycle control	Transcription factor
NF1	17q	Mutated/ deleted	Unknown	?	GTPase activating protein (GAP)
DCC	18q	Mutated/ deleted	Plasma membrane	? Cell adhesion	Membrane glycoprotein

there are now many other candidate suppressor genes implicated in almost every cancer type studied so far. Tumour suppressor genes are sometimes referred to as recessive oncogenes because both alleles have to be lost for a phenotypic effect, but there are disadvantages with this classification which will be explained later.

Adult patients with an inherited predisposition typically present at an earlier age than average because one of the critical mutations is already present in the germline. The presence of this mutation in every cell offers a genetic explanation for the predisposition to multiple primary tumours, e.g. in young women with familial breast cancers presenting with multicentric or bilateral tumours.

CELLULAR FUNCTIONS OF CANCER GENES

Many c-oncs and tumour suppressor genes exert their effects in cancer by upsetting (deregulating) cell growth control [21]. Experimental assays for cancer genes introduce a bias here because the effects of mutations on cell proliferation are one of the things that can be studied in cell cultures. On the other hand, genetic events responsible for invasion and metastasis are virtually impossible to study *in vitro* because they involve interactions with host tissues.

The best known group of c-oncs are plasma-membrane receptors for growth factors (Table 1) [22]. For example, c-*erb*B1 (EGFR) is a human homologue of v-*erb*, a retroviral oncogene causing avian erythroblastosis. c-*erb*B1 (EGFR) is structurally similar to c-*erb*B2, both of which are over-expressed in a minority of primary breast cancers. Both over-expressed gene products are structurally normal proteins that transmit growth signals from growth factors (first messengers) across the cell membrane. Each receptor recognises and binds its own specific growth factor(s). Growth factor binding on the outside of the cell

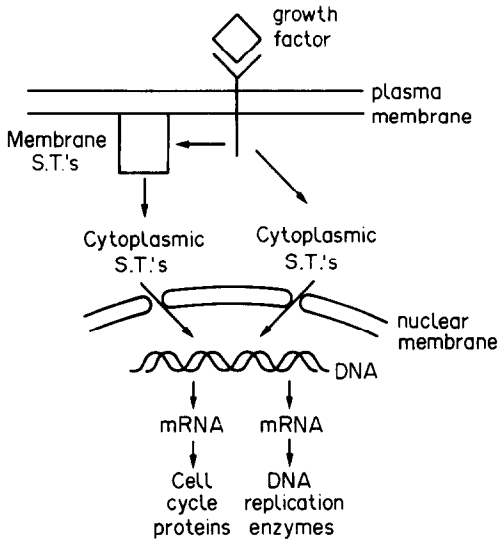

Fig. 4. Signal transduction pathways. S.T. = signal transducer.

activates an enzymic activity on the intracellular portion (domain) of the receptor molecule which in turn activates second and subsequent messenger molecules. These transmit (transduce) signals to nuclear proteins including transcription factors which regulate DNA replication and cell division [23].

Although most c-oncs upset cell growth by stimulating proliferation, the BCL-2 gene is unusual in that it upsets cell growth by postponing programmed cell death [24]. This seems to account for the vast accumulation of terminally differentiated malignant B cells in nodular lymphoma. Other manifestations of cancer, such as invasiveness and metastasis, have been much more difficult to study. For example, animal models of metastasis have been relatively uninformative but the recent isolation of a putative metastasis-suppressor gene may change this. A gene missing from a metastasising variant of hamster melanoma has been identified by comparing the mRNAs produced by metastasising and non-metastasising clones [25, 26]. A causal link is suggested by experiments showing that transfection of the normal gene sequence into metastasising variants coincides with a reduction in metastasising ability [27, 28]. The human homologue of this gene (NM23—the 23rd non-metastasising clone studied) is inactivated by mutation in a proportion of women with breast cancer who have higher than normal rates of positive lymph nodes and relapse.

MOLECULAR MECHANISMS OF CANCER GENES

Cellular functions of cancer genes in their normal (wild-type) and mutated forms will eventually be understood in terms of the molecular mechanisms involved. Already, these are very varied but the best studied involve pathways that transmit proliferative signals from outside the cell to the nucleus via growth factors (e.g. c-sis), growth factor receptors (c-*erb*B1, c-*erb*B2), membrane associated signal transducers (e.g. G proteins such as c-ras), cytoplasmic second messenger molecules (e.g. c-mos), as well as nuclear phosphoproteins and transcription factors (e.g. Rb, p53, c-jun, c-fos), see Fig. 4, [23]. The separate steps in a signal cascade are needed not only to span the plasma membrane, but also to amplify the signal, to provide several levels of negative feedback control and to provide multiple points of interaction with other chemical pathways. There is currently still a chemical gap to be bridged between the cytoplasm and the nucleus with unidentified signal transducer molecules.

There are many different signal pathways originating at the plasma membrane depending on cell type which offer potential sites of activating and inactivating mutations. Proliferation signals of different origins converge on a final common chemical pathway which has direct control of the cell cycle, and which is also susceptible to mutation. For example, the retinoblastoma (Rb) gene product in its unphosphorylated form appears to prevent cells from entering the S phase. Phosphorylation of the Rb protein, or inactivation of the unphosphorylated form as a result of deletion or point mutation releases this restraint on cell growth [29]. The proteins coded by some DNA viruses deregulate cell growth by binding and inactivating the host cell's normal Rb and p53 gene products. This is probably the spectacular mechanism of action for the E7 and E6 oncoproteins of human papilloma viruses in cancer of the cervix, and the E1A and E1B oncoproteins of adenovirus [30, 31].

The retinoblastoma gene product is expressed in all dividing tissues and its special link to tumours of the eye cannot yet be explained. In other cancers, a link with a particular cancer gene is easier to understand. For example, a candidate Wilm's tumour suppressor gene is normally expressed only in the embryonic tissues of the urogenital tract [32].

DOMINANT AND RECESSIVE CANCER GENES

It is common to hear cancer genes described as either dominant or recessive oncogenes. Dominance or recessiveness cannot be interpreted here strictly in the Mendelian sense, which refers to the interaction between two alleles opposite each other on homologous chromosomes. One allele is said to be dominant if the phenotype it specifies is observed in the organism, and recessive if it is not. On this definition, retinoblastoma is inherited in the patient as an autosomal dominant disease. At a cellular level, both alleles need to be inactivated for cancer to develop and hence its described as a recessive gene. This use of the nomenclature can therefore be confusing [33, 34].

Similarly, activating mutations that lead to overexpression of gene product, e.g. c-*erb*B2, H-c-ras etc are often described as dominant mutations. However, c-*erb*B2 involvement in breast cancer is nearly always associated with many extra copies of the gene amplification. Increased cell proliferation is an observable phenotype in these cancers but because there are so many copies of the gene and a high level of gene protein product, dominance does not relate directly to Mendelian genetics.

A last word on tumour suppressor genes; the loss of a single allele is not always completely silent as it appears to be in retinoblastoma. For example, the inheritance of an inactivating germ-line mutation at the familial adenomatous polyposis coli locus on chromosome 5 is associated with polyclonal hyperplasia of the colonic epithelium. This is an interesting exception to the simple rules already outlined for the action of tumour suppressor genes.

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Differentiation and Cancer

M.D. Mason

NORMAL DIFFERENTIATION AND STEM CELLS

NORMAL TISSUE growth and renewal depends on cellular differentiation from a pool of stem cells, undifferentiated cells which are the origin of the mature cells that characterise an individual tissue. This system certainly exists in the haemopoietic system, in most common epithelia, and may even exist in some other non-epithelial tissues although this is not established [1]. Similarly, malignant tumours may also, as a 'tissue', be based on a stem cell system [2]. In some tumours, the stem cell population will predominate and no differentiated elements will be apparent under light microscopy. In others, mixtures of undifferentiated cells and more mature cells may give a malignant tumour its characteristic morphology.

The term determination refers to a heritable undertaking by a cell, usually during embryonic development, to follow a particular pathway of specialised development at some stage in the future. Differentiation implies that a cell acquires certain structural and functional characteristics that endow it with the ability to undertake a specialised task, e.g. to carry oxygen, or to absorb nutrients. Differentiation may involve, for example, the secretion of certain specialised molecules that are not produced by the undifferentiated cell, and therefore determination must by definition precede differentiation. Commitment implies that a cell has entered the programme of differentiation, though it has not yet completed the process. According to classical dogma, once a cell is committed it will remain faithful to one lineage pathway of differentiation only—a committed intestinal epithelial precursor cell will not turn into a red blood cell,

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