Pergamon

European Journal of Cancer Vol. 30A, No. 13, pp. 1942–1946, 1994
Elsevier Science Ltd
Printed in Great Britain
0959-8049/94 $7.00+0.00

0959-8049(94)00384-X

The Genetics of Childhood Cancer

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INTRODUCTION

OVERWHELMING EVIDENCE implicates a complex interaction of abnormal intra- and extracellular genetic events in the development of cancer. Neoplasia is a dynamic multistep process that ultimately drives a normal cell to proceed towards malignant transformation. The number of steps, their chronological order and the nature of particular genetic events specific to each tumour type are objectives of ongoing studies. Childhood cancers are unique in that their early age of onset suggests that underlying inherited constitutional genetic defects might provide a strong predisposing influence. For example, childhood cancers are common in single-gene disorders, such as neurofibromatosis type I and Beckwith–Wiedemann syndrome, as well as in DNA breakage sydromes, including Fanconi's anaemia and Bloom's syndrome, in which the ability to repair damaged DNA is impaired as a result of deficiencies or defects of specific inherited repair enzymes. The pedigree of a child with cancer often demonstrates other affected family members, suggesting that vertical transmission of a defective or altered gene from generation to generation plays a causative role in cancer development. Various poorly-defined environmental factors may interact with the underlying genetic background of the host to determine the precise phenotype of such childhood and familial cancers. Nevertheless, in only a small percentage of cases of human cancer does evidence for hereditary or familial influences exist [1].

This review outlines the roles of the "dominant" oncogenes and "recessive" tumour suppressor genes known to be involved in the formation of paediatric malignancies. Table 1 indicates well characterised genes associated with paediatric tumours. In addition, the genetics of familial cancer syndromes and genomic imprinting will be discussed as they apply to childhood cancer. The clinical relevance of genetic factors in the aetiology of paediatric cancer is discussed, as well as issues surrounding the role of predictive genetic testing for this population of cancer patients.

Initiation, promotion, progression and metastasis represent the stepwise stages of human carcinogenesis. At each of these stages, one or several genetic events occur in what are thought to be critical normal cellular growth regulatory pathways. Knudson's original "two-hit" hypothesis of carcinogenesis [2] suggests that both alleles of one gene need to be altered for tumour formation to occur in tissues with relatively few genetic checkpoints and controls, and the paradigm for this hypothesis is retinoblastoma. The model has now been expanded to encompass tumours, such as Wilms' tumour and neuroblastoma, with more complex and numerous mitotic controls [3]. Intermediate types of tissues that require more than one genetic alteration to disturb cell growth are also within the realm of paediatric malignancies that include the leukaemias, lymphomas, germ cell tumours and soft tissue sarcomas. Carcinomas appear to arise from the accumulation of multiple genetic events in association with multifactorial exogenous signals, and tend to occur beyond paediatric ages; they include cancers arising in the lung, breast, colon, prostate and other primarily epithelial organs. Presumably these tissues have evolved numerous levels of cell cycle control that need to be overcome by genetic events in order for malignant transformation to occur, and it is probably the time required for acquiring such genetic alterations that

Table 1. Oncogenes and tumour suppressor genes associated with paediatric cancers

Gene	Chromosome site	Associated malignancies
Dominant oncogenes		
C MYC	8q24	Burkitt's lymphoma Neuroepithelioma
N MYC	2p23-24	Neuroblastoma
ABL	9q34	Chronic myelogenous leukaemia Acute lymphoblastic leukaemia
REL	11q14	Rhabdomyosarcoma
ETS1	11q23-24	Ewing's sarcoma Neuroepithelioma
N RAS	1p13	Thoracic neuroblastoma Carcinomas, leukaemia
H/K-RAS	11p14-15/12p12	Neuroblastoma, rhabdomyosarcoma Carcinomas
SIS	22q13	Glioblastoma
SRC	20q	Rhabdomyosarcoma, osteosarcoma leukaemia, Ewing's sarcoma, neural tumours
ERBB	7pter-q22	Glioblastoma
Tumour suppressor genes		
TP53	17p13	Leukaemias, osteosarcoma, Rhabdomyosarcoma, Ewing's sarcoma, Glioma, lymphoma
WT1	11p13	Wilms' tumour
RB1	13q14	Retinoblastoma, osteosarcoma

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results in this group of tumours occurring only very rarely in childhood.

DOMINANT ONCOGENES

Inappropriate activation of normal growth potentiating genes, or cellular proto-oncogenes, plays a significant role in the development of many childhood cancers. Activation from proto-oncogenes to oncogenes can occur through various mechanisms, including viral insertion, point mutation, insertional mutagenesis, chromosomal translocation or gene amplification. Historically, oncogenes were first identified at genomic sites where integration of specific retroviral sequences led to the induction of neoplastic changes, through activation during viral replication. The oncogenes, therefore, often bore the names of the viruses from which they were first identified.

When one considers the network of genetic events that is required to control growth in any given cell, it becomes apparent that the presence of a single genetically altered protein product at any one of these steps can lead to catastrophic results. The cellular pathways of growth regulation include growth factors and their receptors on the cell surface membrane, which in turn interact with cytoplasmic messengers that pass information to nuclear relgulatory factors. Oncogenes are a heterogenous class of genes that encode many of these regulatory proteins. Structural alterations or overexpression of any of these proteins can activate the pathways that stimulate cellular growth and proliferation, potentially resulting in neoplasia. The ability to convert a cell to malignancy by the alteration of only one of the two proto-oncogene alleles suggests a dominant Mendelian pattern of genetic function.

Several examples of dominant oncogene activation associated with the development of paediatric tumours are known. The human proto-oncogene *C MYC*, located on the long arm of chromosome 8, is involved in the t(8;14) translocation commonly found in Burkitt's lymphoma [4]. The *MYC* oncogenes encode a family of structurally related nuclear phosphoproteins that include c-myc, N-myc, l-myc, B-myc, and r-myc which have been linked to cellular proliferation and differentiation [5]. In Burkitt's lymphoma, the functional consequences of the chromosomal translocation is to bring the *C MYC* gene under the influence of the immunoglobin heavy chain enhancers at the breakpoint region on chromosome 14. The *C MYC* gene is deregulated by virtue of both damage to its own regulatory region and its juxtaposition to regulatory sequences derived from one of the immunoglobulin loci [6]. Altered *C MYC* transcription maintains the expanded population of B-cell progenitors in a proliferative state, making them susceptible to further genetic alterations, resulting in tumour formation.

The *N MYC* oncogene, located on chromosome 2, has been identified in paediatric neuroblastoma and has been found to be commonly amplified, particularly in late stage disease [7]. Amplification of this gene is virtually always associated with translocation to chromosome 1, usually with development of double minute chromosomes, homogenously staining regions or loss of regions of the short arm of chromosome 1 [8]. This latter karyotypic observation appears to be the most common chromosomal abnormality found in neuroblastoma, occuring in up to 80% of neuroblastoma tumours and cell lines [9]. It is not clear what role N MYC plays in the aetiology and biological behaviour of neuroblastoma. N MYC can independently drive proliferation of tumour cells, and down-modulation of N MYC results in loss of this proliferative capacity [10]. However, proliferation is not linked to N MYC expression; that is, N MYC expressing tumours do not necessarily demonstrate aggressive clinical behaviour, unlike N MYC amplified tumours [11]. Because N MYC amplification, if it is going to occur, is usually present at diagnosis, it appears to be an intrinsic biological property of those tumours [12].

Another cytoplasmic oncogene, whose functional significance is not yet known, has been shown to be a useful marker in Ewing's sarcoma and peripheral neuroepithelioma. This gene, termed *ETS1*, is localised to chromosome 11q23-24. When juxtaposed to the region of chromosome 22q12, which contains a gene encoding a protein that bears homology to proteins that interact with double-stranded nucleic acids, such as eukaryotic polymerase II, the expression of the *ETS1* gene becomes variable [13]. The fusion gene can be ascertained in histological samples obtained at diagnosis, and is a useful marker of the pathological histiotype of the tumour. Although *ETS1* is a member of a family of transcription factors, its role in tumorigenesis is not yet understood.

Several other oncogenes have been found to be associated with paediatric tumours. Alterations of specific members of the *RAS* family of oncogenes are seen in neuroblastoma, leukaemias, rhabdomyosarcoma and rare paediatric carcinomas. These genes encode for proteins that are involved in the signal transduction pathway, and yet are not as commonly found in paediatric tumours as in many common epithelial adult-onset tumours [14].

At least 100 proto-oncogenes [15] are thought to be involved in the control of cell growth and differentiation. In many instances, little is known of the precise function of the proteins encoded by many of the oncogenes. The study of the molecular biology of paediatric tumours is potentially important in the elucidation of these functions as the complicating influence of accumulated external stimuli are less likely to be manifest in the young hosts.

TUMOUR SUPPRESSOR GENES

While oncogenes appear to behave in a dominant fashion (i.e. only one allele needs to be altered to result in aberrant cellular growth and proliferation), studies have indicated that some inherited forms of cancer are the result of genes behaving in a recessive fashion (i.e. both alleles must be altered, inactivated or deleted).

The paradigm of this in the paediatric population is retinoblastoma, a rare tumour of the eye, which arises as the result of functional inactivation of the retinoblastoma susceptibility gene (*RB1*) on chromosome 13q14. Abnormalities of both copies of the *RB1* gene are necessary and probably sufficient to yield both hereditary and non-hereditary forms of retinoblastoma [16]. The gene product of *RB1* is a protein that, when hypophosphorylated in the early G1 phase of the cell cycle, inhibits cellular proliferation [17]. If absent, altered or physically bound to another protein product, such as the E1a oncoprotein product of adenovirus, the phosphorylation potential of *RB1* may be affected, leading the cell into unchecked proliferation. Children inheriting a germline mutation are at increased risk of developing other primary tumours, particularly osteosarcomas [18], as well as a propensity to the development of second malignant neoplasms following the treatment of their primary tumour.

Another tumour supressor gene that has been the focus of much study in the last decade is the *TP53* gene located on human chromosome 17p13. The p53 protein product is involved in several cellular functions, including DNA repair, DNA replication, activation of transcription of other growth regulatory

genes and apoptosis, or programmed cell death [19]. It appears to act as a cell cycle regulator central to the restriction checkpoint control that allows cells to arrest in G1 phase. This permits DNA that has sustained damage secondary to gamma-irradiation or chemical carcinogens to be repaired prior to further DNA synthesis. If repair does not occur, the cell undergoes apoptosis. Absent, altered or physically bound and subsequently inactivated p53 protein might allow a cell that carries damaged DNA to divide and therefore propogate altered genetic information to the daughter cells [20]. This DNA damage may well be an initiator or promoter of carcinogenesis.

Alterations of the *TP53* gene and its encoded protein are the most frequently observed genetic lesions in sporadic human cancers [21, 22]. Inherited germline *TP53* mutations are associated with the cancer susceptibility Li–Fraumeni Syndrome (LFS) [23, 24] reviewed by Birch in this issue. The diverse tumours, which include breast cancer, sarcomas, osteosarcoma, brain tumours, leukaemia and adrenocortical carcinoma, commonly develop at unusually early ages [25]. Although mutations of the *TP53* gene are common in many adult-onset tumours, alterations of this gene or protein are only infrequently encountered in paediatric cancer. Several studies suggest that the frequency of *TP53* gene alterations in solid paediatric tumours, including Wilms' tumour, rhabdomyosarcoma, Ewing's sarcoma and neuroblastoma, is less than 10 per cent [26–28]. Immunohistochemical staining of these tumours often demonstrates overexpression of p53 protein, although it is not clear whether this represents stabilised normal or mutant forms. The role of *TP53* in the development of sporadic paediatric malignancy has yet to be defined.

Wilms' tumour, or nephroblastoma, is an embryonal malignancy that arises from remnants of immature kidney and affects approximately 1 in 10 000 children. It is frequently associated with specific congenital abnormalities, including genitourinary anomalies, sporadic aniridia, mental retardation and hemihypertrophy [29]. In addition, genetic predisposition to Wilms' tumour is recognised in two distinct syndromes with urogenital malformations (Wilms-aniridia-genitourinary anomalies-retardation, WAGR syndrome and Denys–Drash syndrome), as well as in Beckwith–Wiedemann syndrome (BWS), a congenital overgrowth syndrome characterised by growth abnormalities and a predisposition to several embryonic neoplasms, including Wilms' tumour [30]. Thus, the genetic associations of Wilms' tumour are striking. The congenital defects have been linked with specific genetic loci implicated in Wilms' tumorigenesis. The WAGR locus at chromosome 11p13 encompasses several contiguous genes, including the Wilms' tumour suppressor gene *WT1*. The WT1 protein contains functional domains which indicate that it is a transcription factor, acting to regulate the expression of other genes [31]. Deletions of the *WT1* gene or mutations which destroy the DNA binding activity of the protein are associated with tumour development.

A second putative gene *WT2*, mapped to chromosome 11p15, is implicated in BWS, and is thought to be a Wilms' tumour suppressor gene [32]. In fact, both the clinical and genetic association between BWS and Wilms' tumour are sufficiently strong that even patients exhibiting a forme fruste phenotype of BWS (e.g. isolated hemihypertrophy) may be routinely screened for the occurrence of Wilms' tumour by frequent abdominal ultrasound examinations. The pattern of inheritance of *WT2* and BWS is not obviously recessive, and another genetic model, known as genomic imprinting, is felt to play an important role in the genesis of this paediatric tumour.

A third gene involved in the development of Wilms' tumour has been postulated to exist on the long arm of chromosome 16, based on observations of loss of this region in approximately 20 per cent of Wilms' tumours [33]. Recent evidence suggests that alterations of chromosome 16q are associated with poor outcome, independent of tumour stage or histology [33]. This observation implies that abnormalities of this Wilms' tumour-associated gene probably reflect progression of malignancy. Because linkage studies have excluded the 16q locus in "familial" Wilms' tumour, it seems likely that at least a fourth Wilms' tumour gene also exists [34].

To conclude this review of tumour suppressor genes in paediatric cancer, a discussion of the development of colon cancer is warranted. Although this tumour does not typically manifest itself in the paediatric age group, an estimated 7–10 per cent of cases occur in an inherited form that may manifest itself by the presence of polyps or extracolonic features characteristic of Gardner's syndrome, Turcot's syndrome, familial adenomatous polyposis or hereditary non-polyposis colon cancer. These conditions are reviewed by Hall and Bishop in this issue. Familial adenomatous polyposis is a autosomal dominantly inherited disorder with high penetrance, associated with an inherited defect in the adenomatous polyposis coli (*APC*) gene located on chromosome 5q21 [35]. This disorder is characterised by the development of multiple benign polyps of the colorectum that, in approximately 90 per cent of patients, will ultimately become malignant. The *APC* gene is located in close proximity to the *MCC* (mutated in colorectal cancer) gene and, in fact, the two may interact at a cellular level in the same growth regulatory pathway. Although the exact functions of *APC* and *MCC* are not known, one hypothesis suggests a dosage effect model whereby hemizygous deletion of *APC* results in decreased *APC* function and subsequent increase in the proliferation zone of the colonic crypts [36]. The functional interaction of *MCC* and *APC*, presumably in the context of other growth regulatory genes, dictates the colon cancer phenotype. The ability to identify defects in these "colon cancer genes" in childhood would be advantageous to the early detection of disease in early adulthood.

The spectrum of tumours in paediatric oncology that are associated with alterations of tumour suppressor genes indicates the importance of this family of genes in the development of childhood cancers. Identification of inherited germline mutations of these genes in childhood may be helpful in ascertaining which individuals are at risk of developing cancer. Further guidelines and recommendations for screening and prevention may then prove fruitful. In addition, as our understanding of the role these genes play in the growth regulatory pathways of normal cells improves, the significance of alterations to their function in the development of sporadic childhood cancers will become apparent.

CHILDHOOD CANCER AND GENETIC IMPRINTING

Mendelian genetics suggests that the mode of transmission of an inherited trait can be determined by the number of altered alleles required to establish the phenotype, and whether or not the allele resides on a sex or autosomal chromosome. A particular trait can be either dominant or recessive, autosomal or X-linked. The concept of genetic (genomic) imprinting implies that there is a parent of origin-dependent modification of the genome [37]. The activity or expression of a gene may be dependent on which parent denotes (or imprints) it. A gene may be inherently

normal, but is inactive only because it was inherited from a particular parent.

Evidence has accumulated to demonstrate that, at least in some cases, tumorigenesis may in fact be invoked by imprinting. This association has been particularly associated with bilateral retinoblastoma, Wilms' tumour, osteosarcoma and rhabdomyosarcoma. In the vast majority of these cases, the paternal allele is retained in the tumour [37]. This paternal allele is then inactivated, either as a result of a mutation or other genetic alteration, or simply because it was derived from the father. The phenotypic sequela of unrestricted cellular growth arises from a non-functioning allele and a potentially altered gene product.

FAMILIAL AGGREGATIONS OF CANCER

Because of the high frequency of sporadic cancer in the general population, it is often difficult to determine whether a particular occurrence in a family is based on the presence of an underlying genetic predisposition or as the result of chance occurrence. Recognition of genetic susceptibility within a family may be based on a variety of features including the presence of two or more first-degree relatives with the same tumour or with rare tumours, or three or more relatives with cancers at associated histopathological sites. The presence of multifocal neoplasms, tumours associated with other genetic traits or congenital defects, or tumours diagnosed at young ages are characteristic features of hereditary malignancy [38]. Approximately 10 per cent of children with cancer have at least one affected first-degree relative.

A number of syndromes are associated with chromosomal instability as a result of DNA breakage. In most of these cases, specific nucleic acid repair enzymes are either deficient or defective, and although cellular checkpoint control mechanisms may be in place, inappropriate DNA repair occurs, leading to cellular aneuploidy and ultimately malignant transformation. It is, therefore, not unexpected that individuals affected by these disorders develop cancer and often do so early in life. These diseases, including Fanconi's anaemia, Bloom's syndrome and ataxia-telangectasia, are commonly inherited in an autosomal recessive manner with the homozygotes expressing the disease.

Fanconi's aplastic anaemia was originally described as a set of clinical features most frequently including small stature and head circumference, hypoplasia or aplasia of the thumb and/or radius, pancytopenia, splenic hypoplasia, brownish skin pigmentation, small genitalia in males and increased chromosomal breakages. This chromosomal fragility, as demonstrated in *in vitro* cultured lymphoblasts from affected patients, is probably related to their propensity to develop leukaemia and/or other tumours (up to 20 per cent). Furthermore, treatment for their malignancy or aplastic anaemia requires the use of cytotoxic agents and/or gamma-irradiation, which themselves have been shown to potentiate DNA damage and accelerate the appearance of secondary malignancies.

Bloom's syndrome is another chromosomal fragility disorder that is commonly associated with growth deficiency, microcephaly and telangiectatic erythema, together with other craniofacial irregularities and immunoglobulin deficiencies. One quarter of patients develop malignancies, the most common begin leukaemia. *In vitro* studies demonstrate the tendency to chromosomal breakage and rearrangements. The specific defect in Bloom's syndrome appears to be the lack of DNA ligase I, which acts to splice in new DNA to replace damaged DNA.

Ataxia-telagiectasia syndrome (A-T) is another autosomal recessive disorder that demonstrates a set of phenotypic abnormalities in homozygotes, including growth deficiency, progressive ataxia and degeneration of the central nervous system, skin and conjunctival telangiectasia, respiratory complications and immune deficiencies. There is also a propensity to develop lymphoreticular malignancies, and a high frequency of chromosomal breakages occur in cultured leucocytes, as described in the previous two syndromes. Patients with A-T are particularly sensitive to the DNA damaging effects of ionising radiation as a result of the DNA repair defects they harbour.

Distinct from these chromosomal breakage syndromes are the familial cancer syndromes that result from the inherited transmission of altered tumour susceptibility genes. Many of these syndromes are described in detail elsewhere in this issue, and are only mentioned here to highlight the fact that for many, the initial manifestations of disease occur during childhood. In addition, cancer frequently develops in children in affected families.

Although familial cancer clusters have been reported over many decades, only within the last few years have molecular biological techniques become sophisticated enough to elucidate the molecular basis of inheritance in some of these syndromes. The study of rare childhood tumours has led to the recognition of some of the earliest molecular alterations that lead to these familial cancer aggregations as well as to the genetic changes required for sporadic malignant transformation.

CLINICAL RELEVANCE AND FUTURE DIRECTIONS

Where does our knowledge of the genetic basis for cancer lead the clinical oncologist in the ultimate management of paediatric malignancies? Can *in vitro* studies and animal models of carcinogenesis be applied to the complex multifactorial nature of human cancers? Currently, descriptive histopathology is being augmented by the introduction of molecular biological markers of diagnostic relevance, such as the detection of chromosomal translocation and fusion genes in lymphomas, leukaemias, sarcomas and others. These markers increase the specificity and accuracy of the diagnoses. These advances will lead to improved treatment protocols that may then be modified according to more accurate classifications, based on cellular and genetic characteristics of the tumour. Such decisions are already being made if certain genetic aberrations exist. For example, the existence of *N MYC* amplification in neuroblastoma suggests advanced stage disease and warrants aggressive treatment.

The ultimate short-term and intermediate goals in recognising molecular alterations would be to classify patients' tumours. In the long-term, novel approaches utilising gene therapy in attempts to manipulate the genetic foundation of malignant cells may lead to tumour-specific curative therapy. The possibility of reducing the significant loss caused by the death of a young child from cancer makes research efforts into the genetics of childhood cancer highly worthwhile.

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Pergamon

European Journal of Cancer Vol. 30A, No. 13, pp. 1946–1956, 1994

0959–8049/94 $7.00+0.00

0959-8049(94)00385-8

The Genetics of Colorectal Cancer

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INHERITED SUSCEPTIBILITY TO COLORECTAL CANCER

CLINICALLY, we recognise a number of distinct syndromes which predispose to colorectal cancer. The majority of these syndromes are inherited as autosomal dominant genes, which means that a parent carrying a mutation passes on his mutation to, on average, half of his or her children. Offspring who inherit this mutation then have a high chance of developing colorectal cancer. Three broad groups of syndromes are seen (Table 1):

1. Those which predispose to large numbers of adenomatous polyps, each of which has some malignant potential and through which mechanism the increased risk of colorectal cancer is presumably attributable.
2. Syndromes which do not have associations with large numbers of adenomatous polyps, but for which the adenomas appear to have an increased malignant potential.
3. Syndromes associated with hamartomatous (non-adenomatous) polyps and which are associated with less dramatic increases in risk than those whose premalignant lesion is an adenoma.

The recognition and classification of these syndromes has followed many years of careful clinical observation, while the

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