

Inherited Cancer Syndromes

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Abstract: There are various factors that contribute to the development of neoplasia. Among the most important factors are the genetic and environmental factors. One of the strongest pieces of evidence for the genetic basis of cancer at the cellular level is the observation that nearly all cancers are monoclonal in origin that is all of the cancer cells in an individual patient can be shown to have arisen from a single original precursor cell.

Key words: Genetic factors, neoplasia, monoclonal, environment factors, cellular level, cancer

INTRODUCTION

There are several lines of evidence to support the genetic contribution to cancer. The evidence for a genetic origin of cancer at the somatic level includes:

- The evidence using the X-linked polymorphic glucose-6-phosphate dehydrogenase marker for a clonal origin of cancer at the cellular level
- The occurrence of specific chromosomal changes in particular forms of cancer
- The fact that many carcinogens are also mutagens which in many cases can be shown to act through their interactions with DNA
- The observation that inherited syndromes involving deficiencies in the ability to repair defects in DNA, leading to increased mutation rates are associated with increased tumour incidence (Barrett, 1987)

During the past 20 years, cancer researchers have made dramatic progress in identifying large number of genes that when mutated can contribute to the development of the cancer cell. From this large body of work, the general picture of cancer pathogenesis is beginning to emerge (Mueller and Young, 2002).

INHERITED CANCER SYNDROMES

Though in any individual the development of cancer cannot usually be ascribed to a single inherited gene abnormality at the cellular level cancer is fundamentally a genetic disease (Gelehrter *et al.*, 2000).

Each human cell carries a very complex and highly regulated genetic programme that controls normal cellular growth and differentiation. Cancer results from a disruption of this normal regulatory pattern, leading to

uncontrolled cellular growth and proliferation that is recognised as a malignant tumour. The development of cancer requires the accumulation of multiple, sequential genetic mutations within a somatic cell. These somatic mutations are restricted to the tumour and are not found in the normal cells of the individual. In contrast a germ line mutation is present all throughout the cells of the individual and may be passed on to subsequent generations (Gelehrter *et al.*, 2000).

Several hereditary conditions are associated with an increased risk of cancer. For some, this susceptibility has been demonstrated by comparing rates among relatives of cancer patients with the rates in the general population. For others, the increase is so dramatic that it is evident after the evaluation of only a few affected families.

Recently developed techniques of molecular biology are being applied to locate the gene responsible for the development of cancers. The knowledge of gene location can be applied to the early diagnosis and prevention of inherited cancer. Hereditary cancer syndromes for which the chromosomal location is known include hereditary retinoblastoma, Familial Adenomatous Polyposis (FAP), the Cancer Family Syndrome (CFS) or lynch syndrome, Li-fraumeni syndrome, Multiple endocrine neoplasia type 1 and 2, dysplastic naevus syndrome, neurofibromatosis type 1 and 2 and Von hippel lindau disease (Tomatis and Aitio, 1990).

THE GENETICS AND CLINICAL ASPECTS OF RETINOBLASTOMA

Retinoblastoma is a relatively rare, highly malignant childhood cancer of the developing retinal cells of the eye which usually occurs before the age of 5 years. The first clue to the location of the retinoblastoma gene was provided by rare individuals who developed bilateral

retinoblastomas and had multiple congenital anomalies and developmental impairment. Retinoblastoma, the prototype of diseases caused by mutation of RB1 gene has an incidence of 1 in 20,000 live births. Unlike other tumours, retinoblastoma is detected at a relatively early stage of tumour development because its easily detected by ophthalmoscopy. At the time of clinical detection, most retinoblastoma tumours are confined to the retina and vitreous body. Invasive growth into the optic nerve, sclera and orbits or metastases occurs only at advanced stages. The prognosis of patients with metastatic disease is poor unlike the early stage retinoblastoma which carries a good long term outcome (Horsthemke, 1992).

About 40% of cases of retinoblastoma are of the heritable form, in which the child inherits one mutant allele, the Retinoblastoma locus (RB1) through the germline (Nissbaum *et al.*, 2004). A somatic mutation or other alteration in a single retinal cell leads to loss of function of the remaining normal allele, thus initiating development of a tumour.

The inherited susceptibility gene, RB1 gene, according to Knudson's two mutation hypothesis is dominant because having inherited one abnormal gene, the probability of a second event occurring is sufficiently high so that this gives the individual with the single abnormal gene an almost certain chance of developing retinoblastoma. This occurs because the large number of primordial retinoblasts and their rapid rate of proliferation make it very likely that a somatic mutation will occur in one of the retinoblasts. At the cellular level, however, the necessary genetic change is recessive since both copies of the gene must be inactivated for the tumour to develop (Horsthemke, 1992).

The other 60% of cases of retinoblastoma are sporadic. In these cases both RB1 alleles in a single retinal cell have been inactivated by independent somatic mutations. Because this is a rare event, the retinoblastoma that develops in this case is unilateral and the average age of onset is later than the infants with the heritable form (Horsthemke, 1992).

RB1 GENE STRUCTURE AND FUNCTION

Chromosome13-specific DNA markers and positional cloning techniques were used to identify the RB1 gene (Fung *et al.*, 1987). The retinoblastoma protein is a phosphoprotein that is hypophosphorylated and hyperphosphorylated at different stages of the cell cycle.

In its hypophosphorylated state, it blocks cell cycle progression at the boundary between the G1 and S phase, thereby inhibiting entry into the S phase by binding to and inactivating transcription factors (Chellappan *et al.*,

1991). As the RB1 protein becomes progressively more heavily phosphorylated, it releases its protein binding partners, allowing entry of the cell in the S phase. Loss of the RB1 gene deprives cells of an important mitotic checkpoint and allows uncontrolled proliferation (Chellappan *et al.*, 1991).

FAMILIAL COLON CANCER

Familial polyposis coli is a rare autosomal dominant form of colon cancer that can be readily distinguished from sporadic colon cancer. Its prevalence is approximately 1:10,000 (Anderson, 1978). Familial polyposis patients have a normal colon at birth but during the first 20 years of life hundreds of small polyps appear in the colon and occasionally elsewhere in the intestinal tract. Although, these polyps are asymptomatic their major significance is in the risk of progression to colon cancer which approximates 100% by age of 50 years in a patient with this disease. A pancolectomy in early adulthood prevents this outcome. As this condition is autosomal dominant, making the diagnosis in one individual obligates the physician to investigate the rest of the family, as there may be no other warning signs of the disease until the appearance of malignancy. Because surgical therapy is so successful, individuals at risk should be evaluated with DNA testing and colonoscopy if indicated by the age of 20 years (Gelehrter *et al.*, 2000).

Though the gene for familial adenomatous polyposis, referred to as APC gene (adenomatous polyposis coli gene) was first cloned in 1991, clues to its function have have only recently begun to emerge (Gelehrter *et al.*, 2000). The APC gene functions by interacting with a family of proteins involved in cell adhesion, regulating subsequent signalling to the nucleus. APC fulfills the criteria for a classic tumour suppressor gene with the second hit in familial polyposis patients eliminating expression of the remaining normal allele. Loss of the APC gene expression in a colonic mucosal cell gives rise to a clonal benign tumour proliferation resulting in a polyp.

Though this single event does not by itself produce cancer, it is the first step that appears to markedly predispose the cell to the effects of other genetic events which eventually accumulate to produce a frank colon cancer.

This mechanism also appears to operate in sporadic colon cancer with at least 80% of sporadic tumours exhibiting somatic mutation of the APC locus (Winawer *et al.*, 1985). these and other studies on colon cancer have resulted in perhaps, the clearest example of the multiple genetic steps required for progression from a normal cell to full blown cancer. Loss Of Heterozygosity

studies (LOH) on colon cancer identified a sequential pattern of genetic loss on chromosomes 5q,17p and 18q (Gelehrter *et al.*, 2000). The gene on chromosome 5q turned out to be the *APC* gene and the gene on 17p is the *p53* gene. The *18q* gene, named the *DCC* gene for deleted in colon cancer is still of unknown function and germline mutations in this gene have not yet been identified. For colon cancer to develop mutations in the ras oncogene also occur. Colon cancer cells undergo other types of changes and DNA modifications such as DNA methylation that may also contribute to the malignant phenotype (Gelehrter *et al.*, 2000).

HEREDITARY NON POLYPOSIS COLON CANCER

Although, familial polyposis accounts for <1% of colon cancer, familial clustering of colon cancer without polyps is frequently observed. These families often also have features associated with familial cancer syndromes such as younger age of onset and association with other specific tumours such as younger age of onset and association with other specific tumours such as ovarian and endometrial cancer. This syndrome is referred to as hereditary non polyposis colon cancer-HNPCC or Lynch syndrome (Freed, 1988).

Using the methods of positional cloning, the first gene responsible for a subset of HNPCC families termed MSH2 was identified in 1993 (Gelehrter *et al.*, 2000). This gene is closely related to a family of genes in bacteria and yeast involved in the repair of DNA sequence mismatches. Three other genes subsequently identified in HNPCC families also appear to be involved in the same DNA repair pathway (Lynch, 1980). Though the DNA mismatch repair genes appear to account for the majority of HNPCC families, additional genes probably remain to be identified.

BREAST CANCER

Human breast cancer is usually caused by genetic alterations of the DNA of the somatic breast ductal epithelial cells but occasionally susceptibility to the disease is inherited (Sattin *et al.*, 1985). A family history of breast cancer is reported to increase woman's risk two fold to three fold. Among woman with a family history of breast cancer, those that have a first degree relative with bilateral or premenopausal breast cancer especially if they develop breast cancer before the age of 40 years are especially at high risk of developing breast cancer (Bain *et al.*, 1980).

Other breast cancer risk factors such as menopausal status, age at menarche, parity, age at first full term

pregnancy and history of benign breast disease have all been studied to determine their possible influence on the risk of breast cancer. The younger the age at first full term pregnancy and the higher the multiparity the lower is the risk of breast cancer. However, except for parity and age at first full term pregnancy, different studies which analysed the other risk factors have yielded conflicting results especially on the relationship between the oral contraceptive pill and breast cancer (Brinton *et al.*, 1982).

Breast cancer has been the subject of an impressive number of studies which have all shown without exception a two to three fold increased risk of breast cancer in 1st degree relatives of patients with breast cancer (Anderson *et al.*, 1958). These results are indicative of a strong polygenic mechanism involvement of many genes exerting small effect acting in concert with environmental or non genetic factors which have a stronger and more important effect. In fact it is now thought that breast cancer is heterogenous i.e., breast cancer is due to mutations at different loci in different families.

Breast cancer has long been recognised as being complex. Epidemiological studies have indicated a difference in the susceptibility between women developing the disease before menopause and those developing the disease post menopausal. The premenopausal type of disease is considered to involve excessive ovarian estrogenic activity, while the postmenopausal type is considered to involve estrogens of adrenocortical origin (De Waard *et al.*, 1964).

A genetic difference between the premenopausal and postmenopausal types of disease has been demonstrated. Various studies have shown that the risk for breast cancer increases significantly in first degree relatives of patients with premenopausal breast cancer but does not increase in post menopausal patients. The risk of breast cancer increases five fold in relatives of patients with bilateral disease but those with unilateral disease the risk of developing breast cancer in 1st degree relatives is much less. When the disease is both premenopausal and bilateral, the risk increases nine fold while the post menopausal and unilateral patients exhibit only a 1.2 fold increase. The results of such studies suggest a genetic difference between the two types of breast cancer and a much stronger genetic effect in the premenopausal and bilateral type of disease than in the post menopausal and unilateral type (Anderson, 1974).

LI FRAUMENI SYNDROME

Families with Li fraumeni syndrome are at increased risk of developing a number of tumours especially soft

tissue sarcomas in children and young adults and early onset breast cancer in their mothers and other close relatives. Brain tumours, leukemia, laryngeal and lung cancer, adrenocortical tumours and osteosarcomas also occur with increased frequency in patients with Li Fraumeni syndrome which is inherited in an autosomal dominant way (Glendon *et al.*, 1990).

It has been suggested that the retinoblastoma susceptibility gene, located at the chromosome 13q 14 is involved in Li Fraumeni syndrome as well. Other possible gene locations include chromosome 11 and 17p which have been shown to be involved in the development of both sarcomas and breast cancers (Koufos *et al.*, 1985).

Families with Li Fraumeni syndrome are rare but nevertheless recognition of such families is important in identifying individuals at risk who may benefit from genetic counselling and screening. Of wider importance, such families provide a model of cancer susceptibility not only to rare cancers such as soft tissue sarcomas but also to the very common malignancies such as carcinoma of the breast. Collaborative interdisciplinary studies of the Li Fraumeni syndrome may lead to important insights into the aetiology and histogenesis of a variety of cancers (Birch, 1990).

The mutation in Li Fraumeni syndrome involves the p53 tumour suppressor gene. The p53 regulates the cell cycle and is involved in a lot of anti cancer mechanisms. It activates DNA repair mechanisms when DNA has sustained damage or else it initiates apoptosis if DNA has sustained damaged beyond repair. So Li Fraumeni patients who inherit only one functional copy of the p53, develop multiple tumours at an early age.

CONCLUSION

Although, genetic factors play a role in the aetiology of most of the neoplasms, there are certain neoplasms where the genetic contribution plays the dominant role. As we have considered, these include retinoblastoma, Li Fraumeni syndrome, hereditary breast cancer, hereditary non polyposis colon cancer. To make a diagnosis of these relatively rare syndromes, special criteria are available, as recognition of such families is important in identifying individuals at risk who may benefit from genetic counselling and screening.

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