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Feature Articles

Familial and Genetic Aspects of Colorectal Carcinogenesis

Rodney J. Scott and Hansjakob Müller

There is abundant clinical and pathological evidence which suggests that colorectal cancer arises in a sequential manner through a series of events that can be followed during the progression of the disease from early adenoma through to metastatic disease. The molecular events that are associated with the initiation and progression of the disease are gradually being unravelled. As the molecular characterisation of colorectal cancer continues, new mechanisms by which the disease progresses are becoming evident. In this short review, a brief description of current knowledge of colorectal cancer development is presented.
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INTRODUCTION

COLORECTAL CANCER (CRC) is the second most common malignancy in European countries, with similar incidence rates for both men and women. Epidemiological studies imply that environmental factors play a significant role in the aetiology of the disease [1]. For example, the incidence of CRC is very much higher in countries where the diet is rich in fat and low in fibre [2,3]. In addition, there exist a number of distinct genetic syndromes which predispose people to the development of CRC, these are listed in Table 1. From this table, there are two genetic entities, familial adenomatous polyposis (FAP) and hereditary non-polyposis CRC (HNPCC) which predispose persons to an extremely high risk of developing CRC at a young age. In addition to CRC, other neoplasia and symptoms tend to aggregate in these families, implying that the effects of the predisposition are not restricted to the colon alone. However, not all

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Table 1. Inherited predispositions to colorectal cancer

Syndromes with pre-existing polyposis	
Familial adenomatous polyposis (FAP)	Colonic polyposis
Gardner's syndrome	Colonic polyposis in association with extra colonic lesions
Oldfield's syndrome	With sebaceous cysts
Turcot syndrome	Malignant tumours of the central nervous system in association with polyposis of the colon
Carroli's disease	Bile duct and renal anomalies
Syndromes with pre-existing hamartomatous polyps	
Peutz–Jeghers syndrome	Abnormal pigmentation on the lips and buccal mucosa
Ruvalcaba–Myhre–Smith syndrome	Macrocephaly, pigmented macules on the penis
Juvenile polyposis	Cystic harmatomatous polyps
Cowden's syndrome	Multiple harmatomatous lesions, primarily on the mucocutaneous tissue
Syndromes without pre-existing polyposis	
Hereditary non-polyposis colorectal cancer (HNPCC) (Lynch type I and type II syndromes)	Few if any polyps, CRC tends to be site-specific
Muir-Torre's syndrome	Lynch type II syndrome with dermatological lesions and laryngeal cancer

signs of disease are necessarily malignant nor are they always readily apparent. People carrying a genetic predisposition do not initially have CRC but they have the susceptibility to develop it. The trigger that initiates the development of CRC is not known, but it is believed that the colonic environment plays a crucial role. Thus, CRC is not in itself inherited, but the susceptibility which favours its development is.

The genetic model of CRC

The development of CRC from normal tissue through hyperplasia, adenomas, pre-invasive, invasive and finally metastatic disease is much more apparent than in any other common malignancy, such as breast or lung cancer. The molecular genetics of colorectal cancer are probably the best understood of the common malignancies because it is relatively easy to obtain premalignant and malignant tissue at various stages of neoplastic development. This, and the fact that familial forms of CRC exist, has allowed for detailed molecular investigations to be performed. In this review, a description of the molecular genetic events that appear to underlie the development of this disease shall be presented.

One of the most significant findings was the discovery that not only in sporadic CRC but also in FAP, CRC appeared to arise from the clonal expansion of a particular subset of cells that had acquired a particular growth advantage after a somatic mutation [4]. Additional support for the clonal expansion of cells in human CRC came from parallel studies in mice, which were fed dietary carcinogens, and subsequently developed CRC [5]. Such findings are in direct contrast to normal mucosa, which is polyclonal even in the normal mucosa of patients with FAP [6]. Taken together, these results imply that a somatic mutational event is necessary before adenoma development can proceed. This is of particular relevance with respect to the inherited forms of CRC as these, therefore, also require an additional, somatic mutational event before adenoma development [6]. This implies a "second hit" which is consistent with Knudson's "Two Hit" hypothesis [7]. This has been modified extensively since the discovery of tumour suppressor genes, as the original model implied that the second hit was at an entirely different site to that of the first [8].

Over recent years significant advances have been made in our understanding of the molecular genetic events associtated with CRC due to intensive investigations into FAP. This is an autosomal, dominantly inherited disease, and accounts for approximately 1% of all observed CRC cases and has a prevalence of approximately 1 in 10 000 [9, 10].

The first advance in the understanding of the molecular nature of this disease occurred after the discovery by Herrera *et al.* [11] of a mentally retarded male with Gardner's syndrome, and an interstitial deletion of the long arm of chromosome 5q. Thereafter, it was quickly established, using linkage analysis, that FAP was related to a gene on the long arm of chromosome 5 [12, 13]. Within 5 years, the gene responsible for FAP was identified simultaneously by two groups and is now commonly known as the APC gene (adenomatous polyposis coli gene) [14–17]. The APC gene contains an 8538 base pair (bp) open reading frame, and consists of 15 exons, the first 14 being relatively short, and the fifteenth being one of the largest discovered, spanning over three quarters of the entire coding sequence (6577 bp) of the gene. A differential splicing site is present in exon 9 which gives rise to two different mRNA transcripts, one being approximately 300 bases longer than the other, with the largest being the most abundant [15, 18].

The APC gene encodes a 2843-amino acid protein which is expressed in many tissues and, interestingly, contains coiled coil regions which are indicative of oligomerisation. The localisation of the full length APC protein indicates that it is neither nuclear nor membrane bound, and that it appears in the non-soluble fraction of the cell. Truncated forms of the protein appear both in the soluble and insoluble fractions of the cell, indicating that they may be oligomerising with the full length protein, as predicted by the presence of heptad repeats which are necessary for protein–protein interactions [19].

The role of APC in the development of FAP is not, as yet, clearly defined but it appears that the presence of a germline mutation is sufficient for small adenoma formation, since analysis of adenomas from FAP patients has thus far revealed few examples of allelic loss [20–23]. Other mechanisms may be involved, such as changes in methylation which result in aberrant gene expression [24], and consequently, loss of normal cellular control. However, it has been shown that adenocarcinomas from FAP patients have undergone loss of heterozygosity at the FAP locus. In comparison, 35–60% of adenomas taken from patients with no known familial predisposition to CRC have allelic losses at chromosome 5q, making this one of the most frequently detected genetic changes in small early adenomas [20, 22, 25].

Besides the APC gene, the 5q region also contains an additional gene which has been shown to be mutated in several cases of sporadic CRC, and which is called the MCC (mutated in colorectal cancer) gene. The MCC gene encodes an 829-amino acid protein that contains within it a short region that has similarities to the G protein-coupled acetylcholine receptor. Due

to the loss of this gene in CRC, it is presumed to be a tumour suppressor gene, although how it controls the cell remains unknown. Other genes, including oncogenes, have also been shown to be altered in neoplastic tissue taken from CRC patients. Mutations of the K-*ras* gene are observed in approximately 50% of CRC [26, 27] and in a high percentage (90%) of adenomas that are greater than 1 cm in diameter. Interestingly, *ras* gene mutations have been shown to occur in fewer than 10% of adenomas less than 1 cm in diameter [22]. Taken together, these observations indicate that *ras* gene mutations may be associated with the progression of disease such that adenomas that have acquired a *ras* gene mutation are able to progress to a larger more dysplastic type.

It is clear, however, that *ras* gene mutations alone are not sufficient to initiate CRC development, and that certainly in addition to APC mutations others are required. A small proportion of CRC has been associated with mutations in other oncogenes, such as *src*, *myc* or *neu*/Her2 [28, 29]. The *myc* oncogene has been shown to be involved in cellular proliferation, differentiation and mitogenesis [30], and is found to be overexpressed in the majority of CRC cases. Of particular interest is the finding that deregulated *myc* expression has been related to allelic loss of chromosome 5q [29]. The development of CRC has been associated with the phenomenon of loss of heterozygosity [31] which appears to affect primarily regions on chromosomes 17 and 18 and, to a lesser extent, chromosome 5 [32]. Interestingly, 17p is the region where the tumour suppressor gene p53 resides, and 18q is the site where another tumour suppressor gene, known as DCC (deleted in colorectal cancer), is found [33]. Allelic loss of chromosome 17 has been shown to occur in 68–80% of sporadic CRC but much less often in adenomatous polyps [34, 35]. The DCC gene shows partial homology to neural cell adhesion molecules, is expressed in most tissues [36], and is reduced or absent in 70–75% of CRC. Evidence implies that DCC loss precedes p53 loss, as with the latter the course of the disease seems to be much more rapid and aggressive than seen with DCC loss alone.

More recently, chromosomal analysis of adenomas taken from FAP patients were compared to non-inheritable CRC. In both groups of patients, additional copies of chromosomes 7 and 13 were seen in a significant percentage of adenomas, indicating that genes reside on these chromosomes [37] which are beneficial to increased growth when present in additional copies, but are not capable of transformation when present at their normal copy number. The results indicate that adenomas from patients with FAP tend to have fewer structural abnormalities compared to sporadic adenomas, and that numerical changes are the most common cytogenetic observation, which suggests that the mechanism by which loss of heterozygosity occurs operates at a stage lower than that of the whole chromosome [37, 38]. Other chromosome changes commonly seen in CRC development include 1p, 2p, 4p, 6p, 8q, 9q, 14q and 22q. Karyotypic analysis indicates that there are certain specific abnormalities associated with CRC development, and that most of these occur in the premalignant adenoma stage [39–42]. More recent cytological studies consistently show that chromosome 1 is specifically affected in tumour progression and in *in vitro* immortalisation of adenoma cells, indicating that this event may represent a crucial role in the progression to neoplasia [43]. When considered together, it appears that it is the accumulation of changes and not the order of changes that are associated with the development of malignancy.

Very recently, Thibodeau *et al.* [44] proposed that instability of the dinucleotide repeats (CA)*n* may be the underlying cause of CRC in sporadic disease, as they observed, in a significant number of colorectal tumours, changes in $(CA)_n$ repeats on human chromosomes 5q, 15q, 17p and 18q. Chromosome 15q was chosen as it has a low frequency of loss in CRC [32] and, therefore, represents a useful control with respect to changes that may occur in microsatellite DNA that has not been associated with disease. Chromosomal instabilities appeared as either a gross alteration in length (not always an increase, decreases were also observed) or a minor change representing the loss of two base pairs. This implies that loss of heterozygosity may not necessarily be the only mechanism by which colonic epithelium becomes deregulated. These results are interesting in the light of a new gene that has been found on chromosome 2 [45, 46], and which appears to be linked to HNPCC, otherwise known as Lynch syndrome I or II, depending whether it is associated with other malignancies, notably endometrial cancer [47]. This gene has been tentatively called the FCC (familial colorectal cancer) gene which is associated with microsatellite DNA on chromosome 2 [46].

The FCC gene has been shown to have very tight linkage to

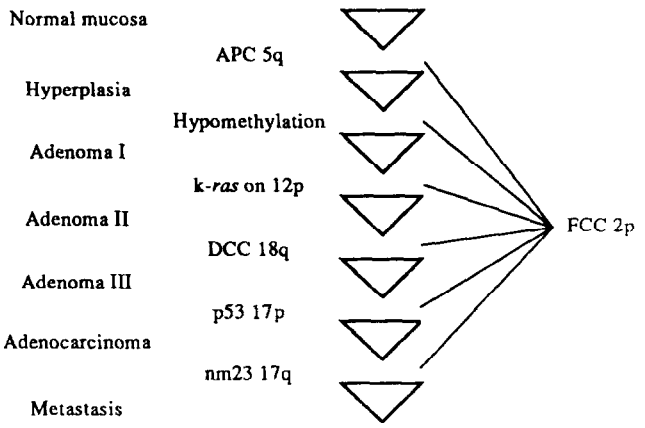

Fig. 1. Schematic representation of a model for colorectal tumorigenesis. The FCC gene is shown on the right and is depicted as being able to affect all stages of colorectal cancer development (adapted from [50]).

the disease phenotype in two large kindreds from New Zealand and North America [45]. At the time of writing, the gene has not been sequenced but is believed to represent a new type of gene, with respect to tumour development, as it is neither a tumour suppressor gene nor an oncogene. It was observed that the dinucleotide repeat (CA)*n* within the FCC locus increased in size in tumour DNA compared to normal DNA, and that loss of heterozygosity was not observed at the chromosome 2 locus, implying that the mechanism by which CRC developed was not dependant upon the loss of a tumour suppressor allele [45, 48, 49].

It has been postulated that the gene localised to chromosome 2 represents a defective replication factor that could increase the mutation rate during the progression of disease, and has hence been termed a "mutator mutation" [49]. Interestingly, there are similarities between sporadic CRC and HNPCC, in that genomic instability is observed in CRC coming from persons who have no familial predisposition to the disease. Therefore, this newly described phenomenon of genomic instability may well represent a general mechanism by which CRC development is not only initiated but also progressed, as its affects could occur anywhere in the previously described pathway of CRC development [50], as shown in Fig. 1.

In addition to a genetic predisposition to develop CRC, other factors exist which may predispose persons to the development of disease. There is evidence that the acetylation status of a person may alter their predisposition to develop the disease. Rapid acetylation has been associated statistically with CRC [51, 52], whereas the slow acetylation phenotype may be protective in the colon but predisposes to the development of bladder cancer. It is known that, in the bladder, there are high levels of *N*-acetyltransferase and low levels of *O*-acetyltransferase [53], whereas in the colon both are high. This difference may be important as it may shed light on the relationship between rapid acetylation and CRC. In the colon of rapid acetylators there is a greater capacity to activate *N*-hydroxy-arylamines to form arylamine-DNA adducts, which are capable of initiating CRC, whereas in the bladder *N*-acetyltransferase inactivates carcinogenic amines [51, 54].

CONCLUSION

It is widely accepted that colorectal cancer develops as a result of a progressive series of genetic alterations in oncogenes and tumour suppressor genes. More recently, dynamic mutations have been described which could conceivably explain how losses of specific genes occur during the progression of disease. There remains, however, a considerable number of questions that need to be answered as little is known about the normal physiological role of the genes that have been identified to date, let alone their role in the pathogenesis of disease. Once the mechanisms which underlie the development of this common malignancy are elucidated, a better rationale for the treatment of the disease may be forthcoming, and with it better patient care via more specific therapies, and hence lower mortality.

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