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Genetics of hereditary colon cancer — a basis for prevention?

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Abstract

Hereditary colorectal cancer syndromes are among the best *in vivo* models to study colorectal carcinogenesis and the influence of putative modifiers of the cancer risk. The present knowledge regarding the wide range of colorectal cancer (CRC) susceptibilities and the histological and molecular changes they elicit is leading to a very dynamic and integrated concept of tumorigenesis in the colon and to new views about prevention and early treatment of cancer.

Keywords: Hamartoma polyposis syndromes; Familial adenomatous polyposis; Hereditary non-polyposis colorectal cancer; Colon cancer prevention

1. Introduction

Approximately 5–10% of colon cancers can be explained by autosomal-dominantly inherited susceptibilities. One such condition is familial adenomatous polyposis (FAP) (Fig. 1). Affected persons develop hundreds or even thousands of adenomatous polyps in the colon and rectum which, if left untreated, will almost certainly develop into colorectal cancer (CRC). Although not associated with a generalised polyposis, hereditary non-polyposis colorectal cancer (HNPCC) is another genetic condition that is associated with an increased risk for colorectal cancer. Patients with both predispositions tend to develop neoplasms also in other organs. The rare inherited hamartoma polyposis syndromes are characterised by the presence of gastrointestinal hamartomatous polyps and an increased risk of gastrointestinal malignancy. Considerable progress has been made towards the understanding of the molecular basis leading to these colorectal cancer syndromes which is a prerequisite for the development of prevention strategies. However, most of the familial cases of CRC cannot be attributed to these genetic entities. Future research has, therefore, to focus on identifying and characterising low penetrance genes, modifier genes, epigenetic mechanisms leading to cancer, and especially on the interaction of predisposing genes, i.e., their mutated proteins with environmental carcinogenic factors. This paper summarises progress in the understanding of the molecular and genetic aspects of colorectal carcinogensis in the established hereditary cancer syndromes which are among the best *in vivo* models to study carcinogenic influences on the colon by providing a uniform aetiological basis.

2. Inherited hamartoma polyposis syndromes

The hamartoma polyposis syndromes comprise Cowden syndrome (CS) and its variant the Bannayan-Riley-Ruvalcaba syndrome (BRR), together with the juvenile polyposis syndrome (JPS) and the Peutz-Jeghers syndrome (PJS). CS is characterised by hamartomas in various organs, including gastrointestinal hamartomatous polyps and a increased risk of neoplasms of the thyroid, breast, uterus and skin. BRR patients suffer from macrocephaly, hamartomatous polyposis, lipomatosis and freckled penis. Germ line mutations in tumour suppressor gene (*PTEN*) which encodes an ubiquitously expressed dual-specificity phosphatase have been found in CS, BRR and JPS conditions [1,2]. Patients with JPS have numerous polyps in the colon and small intestine which can be distinguished from those occurring in FAP by pathology, location and age of onset. There seem to be several causes of JPS, but two could be attributed to mutations of the *PTEN*- [3] and also the *SMAD4* gene [4]. Patients with JPS caused by mutations of the *PTEN*

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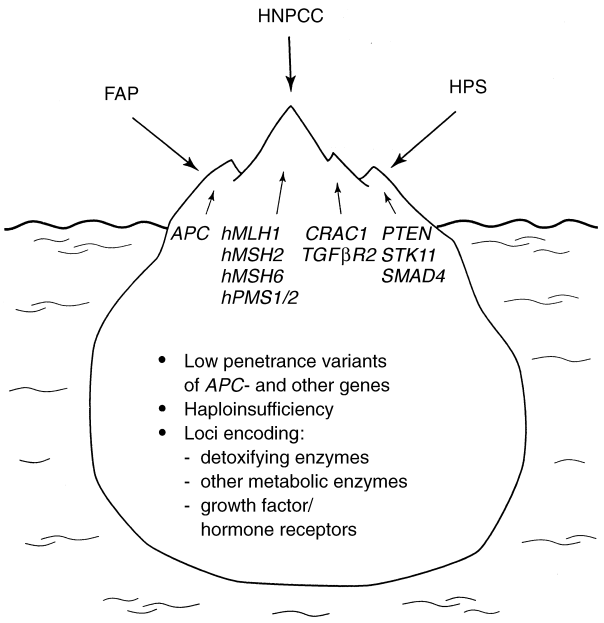

Fig. 1. The iceberg of genes which predispose to colorectal cancer. FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal cancer; HPS, hamartoma polyposis syndromes; *PTEN*, *MMAC1*; *STK11*, *LKB1*; *SMAD4*, *MADH4*/*DPC4*.

gene are rarer and seem to have higher risk for thyroid and breast cancers, whilst those with JPS caused by *SMAD4* alterations have a higher risk for colon and pancreatic cancers. PJS is characterised by the development of primarily benign polyps with typical histological features occurring throughout the gut but mainly in the small intestine. Hamartomas of the small intestine cause most of the clinical symptoms, including anaemia and also blockages that require surgery. In the stomach and colon they should be monitored endoscopically since they have a tendency to become malignant. PJS is marked by hyperpigmentation (freckling) of the lips and sometimes other parts of the face which become noticeable within the first 5 years of life and often fading during adulthood. The mucocutaneous pigmention on the lips and oral mucosa may lead to the suspected diagnosis of the generally well known PJS in children. However, periungual hyperpigmentations also occur as symptoms of other clinical entities not related to cancer such as the Laugier-Hunziker syndrome [5]. Germ line mutations of the *LBK1* or *STK11* gene, encoding a serine threonine kinase have been found to cause many cases of PJS [6,7].

Many phenotypic features are shared by several hamartoma syndromes, a fact that often makes difficult the clinical diagnosis and exact classification of these disorders in a given patient. However, it is important to distinguish the various hamartoma syndromes, since the cancer risk and the types of cancer might be quite different among them. Therefore, the possibility of a molecular genetic evaluation as an extension of the clinical diagnosis is already of considerable practical relevance, with respect to the prevention of cancer.

With a view to prevention, it is now a matter of deciphering the genetic pathways associated with the hamartoma polyposis syndromes and leading to CRC, as well as of identifying their connections with those of FAP and HNPCC. Whether a distinct 'hamartoma-carcinoma' sequence exists is as yet uncertain [8]. Dysplastic juvenile polyps have been shown to harbour adenomatous polyposis coli *APC* mutations [9], whereas mutations of the *STK11* and *PTEN* genes rarely occur in sporadic CRC. Therefore, it is possible that a loss of function mutation of the hamartoma genes has a modifier effect on *APC* which is expedient to tumour development [8].

3. Familial adenomatous polyposis (FAP)

3.1. Severity of the intestinal symptoms

The APC protein which is a member of the Wnt pathway has a prominent position in colorectal carcinogenesis. Somatic inactivation of this protein is involved in up to 80% of sporadic colorectal cancers (CRC). Furthermore, APC or other proteins of the Wnt pathway, such as β-catenin or T cell factor (Tcf)4, are frequently targeted in colorectal tumours which grow on the basis of mismatch repair deficiency (replication error phenotype, RER-positive) [10–12], e.g. in HNPCC patients. Finally, if mutated in the germ line *APC* gives rise to an autosomal dominant disorder, familial adenomatous polyposis (FAP), characterised by multiple intestinal polyps which represent precursors of colorectal carcinomas developed later during the lifetime. Interestingly, although harbouring mutations within the same gene, the severity of intestinal polyposis, characterised by the number and the age of onset, varies considerably among FAP patients. As it definitely correlates with carcinoma occurrence, it is of a predominant importance to study which factors influence differences in the disease severity.

In general, the number of polyps within the gastrointestinal tract in FAP patients seems to follow a gradient character, increasing from the stomach towards the colon, independently of the site and type of the *APC* mutation [13]. Upper gastrointestinal polyps were previously reported to occur in 23–56% of FAP patients [14]. Recent data, however, estimate that though gastric polyps develop in approximately 10–30% of patients, using optimal screening methods nearly all FAP patients will develop duodenal adenomas [15]. Fundic gland polyps are the most common gastric lesions in FAP and although they generally have little potential for malignant transformation, a few cases of gastric adenocarcinoma associated with fundic gland polyposis

have been described [16]. Duodenal cancer incidence has thus far been relatively low, reaching approximately 5% [15,17], however, upper gastrointestinal malignancy occurring mostly in the antrum and duodenum is after colectomy the main cause of death in FAP patients [15,18]. In contrast to colonic polyps, it seems that the occurrence and number of gastric and/or duodenal polyps is not associated with the specific type or localisation of the *APC* mutations.

As it is the primary phenotypic feature of the disease, significantly more data are available on polyposis developed in the colon of FAP patients. It is generally accepted that the variability in terms of the number of polyps in colorectum is considerable and has wide implications for the therapy and survival of patients. Though the total numbers vary even among patients within the same family, several 'rules' may be established with respect to the association of the polyp number and the site of the mutation within the *APC* gene. In summary, the most profuse polyposis is almost invariably observed if the *APC* mutation occurs between codons 1250–1330 [19] and particularly in carriers of the 1309 mutation who manifest a significantly higher number of adenomas compared with carriers of all other *APC* mutations [20,21]. On the contrary, milder colonic polyposis develops if a patient carries a germ line mutation at the very 5′ end of the *APC* gene [22] or at the 3′ end beyond codon 1520 [13,23–26].

The correlation between the polyp number in the colorectum and the site of the germ line *APC* mutation could be explained by at least two, mutually not excluding, hypotheses. (1) The first one is based on a direct influence of the germ line mutation on the function of mutated protein and/or its ability to interrupt the wild-type protein originating from the healthy allele. (2) The second hypothesis relies on an indirect influence of the germ line mutation on the probability that a second (somatic) mutation is, in combination with the first one, sufficient in terms of developing a polyp.

Hypothesis (1) as the APC protein functions as a dimer, stable truncated proteins result in a dominant negative effect with respect to the interrupting the function of the wild-type protein and are associated with the most severe disease phenotypes such as those for codon 1309. If the truncated protein is for some reason unable to dimerise and thus interrupt the wild-type protein, the polyposis tends to be milder. Thus, *APC* mutations towards both ends of the gene which have been shown to result in an undetectable protein correlate with less polyps developed in the colon [25,27,28]. However, as these mutations still cause the disease to develop, the maintenance of even 50% of the normal APC function in the cell is clearly insufficient to take over the APC function properly (haploinsufficiency). Finally, milder variants of polyposis arise if the function of resulting mutated protein can at least partially fulfil its original function: a/ mutations localised in alternatively spliced regions within the *APC* gene (exons 1–4 and 9) which result in splicing out of the mutation site in a portion of transcripts [29–33], b/ truncations at the very 3′ end of the *APC* gene [23,26,34] analogous to the situation in the *APC*1638T mouse model which, even in homozygous state, remains compatible with life and does not develop tumours in adulthood [35], c/ missense germ line *APC* mutations, such as polymorphisms I1307K or E1317Q, and missense mutations in exons 8-15 predisposing its carriers to develop a decreased number of polyps (up to 30), and carcinoma at a higher age [36,37].

Hypothesis (2) an alternative hypothesis favours the combination of two *APC* hits being decisive in terms of the disease severity. As recently shown [38] inactivation of the APC protein is sufficient for the initial growth of colorectal adenomas, however, such inactivation needs to be specific. Several lines of evidence show that the β-catenin regulation domains (codons 1020 to around 1700) are the crucial ones with respect to polyp development and that at least one of the two *APC* mutations (germ line or somatic) has to be localised within this region to give rise to a polyp growth. This gives a germ line *APC* mutation localised within this region a considerable selective advantage as the second somatic event can in such cases can occur in virtually any position within the *APC* gene to initiate adenoma development. On the contrary, only specific somatic events precisely localised in the β-catenin regulatory region (representing less than 10% of the whole coding region) can take over the same function if the first germ line hit lies within an area other than β-catenin regulatory domain. Finally, should both hits be localised outside this region, a third hit is probably needed to interrupt the APC function sufficiently in terms of adenoma development [39–41].

3.2. Modifiers

Although correlation between the severity of the intestinal disease in FAP and the site of the *APC* mutation is often found, exceptional cases exist, e.g. patients originating from the same family and displaying different disease severities. Beside the influence of environment, further genetic factors, so-called modifier genes, have to be considered. Several candidate modifiers have been proposed based on the FAP mouse models, e.g. secretory phospholipase A2, cyclooxygenase 2 or DNA-methyltransferase. However, no clear association has been confirmed for any of those in humans [42–44].

3.3. Locus heterogeneity in FAP

Approximately 25% of FAP patients remain without an identified *APC* mutation (*APC*-negative) and using a detailed analysis they seem to differ phenotypically from

the classical FAP patients in terms of lower polyp number, later age at diagnosis and lower occurrence of extraclonic manifestations [14,45]. Although the incomplete sensitivity of methods used to identify *APC* mutations in FAP patients causes a certain amount of false-negative cases, it can not alone explain such a high percentage of *APC*-negative families. Definitely, alterations in the *APC* gene expression which are not based on mutations within the coding region could cause the typical FAP phenotype to develop. Indeed, Laken and colleagues [46] using a new technique of analysis of monoallelic *APC* expression showed that the majority of their *APC*-negative patients expressed a significantly reduced dose of the APC protein. All analysed patients in this study, however, displayed the very typical FAP phenotype with >100 polyps in the colon and positive family history of the disease, and are thus not equivalent to the *APC*-negative patients determined by other groups [14,45]. Moreover, a few reports revealed an absence of linkage to the *APC* locus within FAP families [47,48] supporting the hypothesis that other genes might be responsible for a phenotype very similar to FAP.

The potential candidates lie preferentially within the Wnt pathway, however, β-catenin has been excluded in several studies [49,50] suggesting that its fluctuations at the germ line level might not be relevant. Interestingly, another candidate which might contribute to APC's tumour suppressive effect and serves as a potential transcription target of the Wnt pathway is the homeobox gene caudal (*Cdx2*). *Cdx2* heterozygote mutant mice develop multiple intestinal adenomatous polyps upon inactivation of the second allele of *Cdx2*. Moreover, a truncating mutation in *Cdx2* has been observed in colorectal cancer cell line lacking *APC* and *β-catenin* mutations [51] and both alleles of *Cdx2* have been mutated in a RER+ colorectal tumour [52]. Further candidates, identified similarly according to the intestinal polyp phenotype in the deficient mouse, is the *Tcf1* gene which is physically linked to the *APC* gene on chromosome 5q and believed to cooperate with APC to suppress malignant transformation of epithelial cells [53]. Contrastingly, should the regulation of β-catenin represent the crucial function of APC with respect to carcinogenesis, all alternative pathways which increase the level of β-catenin or its activity in transcriptional activation could potentially serve as candidates for the FAP-like phenotype. Very recently, one of the first reports of an APC-independent increase of β-catenin-mediated transcription in intestinal cell lines has been described through the activation of protein kinase C by the phorbol ester PMA [54].

Table 1
Amsterdam Criteria I (ACI)

There should be at least 3 relatives with CRC. All the following criteria should be present:
One should be a first-degree relative of the other 2.
At least 2 successive generations should be affected.
At least 1 CRC should be diagnosed before age of 50 years.
Familial adenomatous polyposis should be excluded.
Tumours should be verified by pathological examination.

4. HNPCC

The autosomal dominantly inherited HNPCC syndrome is thought to account for between 2 and 10% of all colorectal cancers and, thus represents one of the most common inherited cancer predisposition syndromes [55,56]. The penetrance of the HNPCC-predisposition is high, with an 80–85% lifetime risk of colorectal cancer and a 40–50% risk of endometrial cancer by the age of 80 years [57–59]. Furthermore, HNPCC patients are at an increased risk to develop a typical spectrum of other extracolonic malignancies, such as cancer of the small bowel, stomach, hepatobiliary tract, renal tract, ovary and brain.

4.1. Genotype-phenotype correlations

The initial observation of expansions and contractions of short repetitive DNA sequences, the so-called microsatellite DNA, in the genome of colorectal tumours coming from HNPCC patients, termed RER or microsatellite instability (MSI), established the link with the DNA mismatch repair (MMR) system [60,61]. In contrast to the gatekeeper concept illustrated by the *APC* gene in FAP, the DNA MMR genes belong to the so-called 'caretakers', which when inactivated do not directly promote tumorigenesis, but rather lead to genetic instability and thus, by increasing the genome-wide mutation rate, indirectly promote tumour growth [62]. The evolutionarily highly conserved MMR genes function as 'guardians of the genome' by detecting and initiating repair of base:base mispairs and insertion/deletion mispairs which occur during replication and by preventing recombination between divergent sequences [63,64]. Inactivation of the MMR system through mutation of one of its components consequently leads to genomic instability, as illustrated by microsatellite instability in tumours from HNPCC patients.

Linkage studies in HNPCC families fulfilling the stringent Amsterdam Criteria (ACI) (Table 1) finally led to the discovery of two human MMR genes, termed *hMSH2* (human MutS homologue 2) and *hMLH1* (human MutL homologue 1), which account for 45–86% of all classical HNPCC families, for review see [56]. Interestingly, phenotype-genotype correlations in HNPCC point to a higher risk of *hMSH2* mutation carriers to develop extracolonic cancers, in particular endometrial cancer, compared with *hMLH1* mutation carriers [58,65]. To date, several other mismatch repair

genes have been assigned to the aetiology of HNPCC, namely *hPMS1* (human post-meiotic segregation 1), *hPMS2* and *hMSH6* accounting for approximately 2–7% of HNPCC kindreds [66–70]. *hMSH6* germ line mutations appear to predispose to late-onset, familial colorectal cancer not necessarily fulfilling the ACI. Recently, Wijnen and colleagues [69] have shown that endometrial cancer represents the most common clinical manifestation of HNPCC among female *hMSH6* mutation carriers and that CRC cannot be considered an obligate requisite to define HNPCC. Meanwhile, the ICG-HNPCC has adopted new research criteria, the so-called Amsterdam criteria II (ACII), which besides CRC also includes endometrial, small bowel and upper renal tract cancers (Table 2) [71]. Applying the modified AC on their Dutch cohort, 73/83 mutation-positive families, originally described as 65 ACI positive and 18 ACI negative, were found to fulfil the ACII, illustrating the usefulness of the new criteria [69].

In approximately 10–40% of all HNPCC kindreds fulfilling the Amsterdam criteria, however, no pathogenic germ line mutation in one of the MMR genes can be identified. This failure could be due to the limitations of the conventional mutation detection techniques, as recently demonstrated by Yan and colleagues [72] who used a diploid-to-haploid conversion method on 10 classical HNPCC kindreds previously without any detectable germ line mutations and, thus, were able to identify disease-causing alterations in either *hMLH1* or *hMSH2* in all families. Alternatively, other genes such as *CRAC1* [73] or the transforming growth factor β-Receptor II (*TGFβRII*) [74] may be responsible for a subset of HNPCC kindreds (Fig. 1).

4.2. Modifiers of disease expression in HNPCC

Although cancer is essentially a genetic disease, environmental factors clearly play an important role in carcinogenesis, especially in the case of the colon which is constantly exposed to xenobiotic substances confering continuous genotoxic stress on the colonic epithelium. According to reports from the World Health Organization (WHO), approximately 80% of all human cancers arise as a consequence of exposure to environmental agents [75]. As an adaptive response to environmental insult, a number of enzyme superfamilies, including the cytochrome P450s, glutathione S-transferases (GSTs) and N-acetyltransferases (NATs), have evolved in order to metabolise and consequently detoxify the foreign compounds [76]. Any alteration in the activity of these enzymes is therefore likely to result in an altered susceptibility to cancer. As detoxifying enzymes are often genetically polymorphic, resulting in different kinetic activities, they represent good candidate modifiers. A modifier (locus) can be defined as an inherited genetic variation, distinct from the disease locus, that leads to a quantitative or qualitative difference in any aspect of the disease phenotype [77].

Table 2
Amsterdam Criteria II (ACII)

There should be at least 3 relatives with an HNPCC-associated cancer (CRC, cancer of the endometrium, small bowel, ureter, or renal pelvis).
One should be a first-degree relative of the other 2.
At least 2 successive generations should be affected.
At least 1 CRC should be diagnosed before age of 50 years.
Familial adenomatous polyposis should be excluded in the CRC case(s) if any.
Tumours should be verified by pathological examination.

Inter- and intrafamilial differences in the age of onset and cancer occurrence in MMR gene mutation carriers could be explained by altered enzyme activities and, thus, altered metabolisation of environmental agents which result in different susceptibilities to cancer, as seen in the association between occupational bladder cancer and the slow acetylation activity of the *NAT2* gene [78]. Since *hMLH1*/*hMSH2* mutation carriers show considerable phenotypic variability with respect to age at diagnosis, cancer site and cancer occurrence, modifying genes may account in part for the variation in disease expression.

Moisio and colleagues [79], who investigated polymorphisms in the *NAT1* and *GSTM1* and *T1* genes in 2 large Finnish HNPCC kindreds harbouring *hMLH1* founder mutations, reported the *NAT1* allele 10 to be associated with lower median age of onset of colorectal cancer and the combined null genotype of *GSTM1* and *GSTT1* was associated with a proximal tumour location. In a recent study of ours, we screened 21 Swiss HNPCC families for specific genetic polymorphisms in *GSTM1*, *GSTT1* and *NAT2* known to enhance, reduce or abolish the activity of their respective proteins. Through comparison of 26 unaffected and 52 cancer-affected mutation carriers, the NAT2 slow acetylators were found to be significantly more prevalent in the latter group ($P < 0.04$), suggesting a protective effect of the NAT2 rapid acetylator phenotype on colorectal cancer development [80]. In view of the clear association with occupational bladder cancer and recent studies on acetylator status in CRC, however, it seems conceivable that the rapid acetylator phenotype may indeed confer a protective effect in *hMLH1*/*hMSH2* mutation carriers. By analogy to bladder cancer, rapid acetylators may detoxify arylamine substrates faster (by N-acetylation) and thus prevent carcinogen activation (e.g. N-oxidation by CYP1A2) and aromatic amine-DNA adduct formation [78,81]. The acetylation activity of the NAT2 enzyme is expressed in colorectal mucosa in a phenotype-dependent manner indicating that this tissue has the capacity to participate in local bioactivation of dietary and environmental aryl- or heterocyclic amine carcinogens

[82]. Thus, it remains a potentially important regulator of genotoxic insult to colonic crypt cells. Additionally, recent large epidemiological studies using the genotyping approach (in contrast to older studies which assessed the acetylator status phenotypically, e.g. hydrazine metabolism) failed to observe any association between acetylator status and colorectal cancer risk [83]. Interestingly, slow *NAT2* acetylator genotypes were more common in CRC patients under 70 years of age than in controls suggesting that slow acetylation is a risk factor for CRC in younger people.

4.3. Considerations concerning CRC prevention

Traditional colon cancer treatment — chemotherapy, radiation, surgery, are expensive, unpleasant and also damage healthy tissue. It is, therefore, desirable to avoid the need for cancer treatment by preventing the malignancy in the first place.

This urgently raises the question of whether, and if so to what extent, the current knowledge of the genetic predispositons to CRC can be used in the development of effective preventive measures, particularly since persons with a greatly elevated risk level are a group who warrant special attention in this respect.

It can be seen from the proceeding parts of this paper that molecular genetics has gained considerable importance in the identification of persons with an increased CRC risk due to a mutated cancer gene, allowing their systematic medical surveillance and the early detection of tumour development. As yet, however, it is not easy to say definitively whether this knowledge can be used for the derivation of the strategies for prevention of the initiation of CRC or if it may make greater sense to try to suppress generally the clinical onset of CRC.

Fearon and Vogelstein [84] have established a model in which the histopathological process of colorectal carcinogenesis is linked with circumscribed genetic changes during each of its individual steps. In view of the present knowledge regarding the wide range of CRC susceptibilities and the histological changes they elicit, the so-called 'Vogelgram' needs to be expanded. The inclusion of these aspects leads to a dynamic and integrated concept of colorectal carcinogenesis. Two mechanisms influence the course of this process: (1) The accumulation of various mutations at a rate which is typical for tumour tissue or at an increased rate due to a mismatch repair deficiency as well as due to another type of genetic instability such as chromosomal instability [85]. Mutational alterations causing genetic instability are gaining scientific interest since they might be necessary for cancers to progress beyond the initial benign stage. (2) The selection of certain clones within the tumour due to their acquiring certain characteristics as a result of mutation or epigenetic influences, including possibly also mutations of individual DNA microsatellites. Rüschoff and colleagues [86] recently observed that the administration of non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin and sulindac resulted in the suppression of microsatellite instability in a subset of MMR-deficient CRC cell lines (*hMLH1* -/-, *hMSH2* -/-, *hMSH6* -/-). This time- and dose-dependent effect on the induction of apoptosis results in genetic selection for cells that retain stable microsatellites, rather than due to the antiproliferative properties of NSAIDs.

On the basis of the analysis of the *APC* gene which is commonly mutated in CRC, it can be assumed that mutated genes which lead to a growth advantage are more commonly to be found in the first steps of tumour formation than those which cause increased genetic instability. In FAP, the inherited pathogenetic germ line mutation of the *APC* gene is related to the type of the somatic mutation of the second *APC* allele which can be interpreted as evidence of a selective advantage for the cells thus affected [87]. In HNPCC caused by an inherited mutation of a mismatch-repair gene, both *APC* genes have also to be mutated in the cells leading to CRC. This occurs later in life in somatic cells which are obviously prone to mutation. If selection before the occurrence of *APC*-mutations is important in HNPCC needs further clarification. In connection with DNA-repair, it must also be taken in account that there is a degree of overlap between different repair systems, the nucleotide excision repair system for the repair of UV damage is capable of independently rectifying certain mismatches and thus serving as a kind of safety net for the mismatch repair system [88].

Possible approaches in the prevention of CRC are first the impediment of somatic mutations leading to carcinogenesis or second the induction of selection barriers which arrest the outgrowth of cancerous cell clones. A possible alternative pathway would be making malignant cells genetically so unstable that they exceed the threshold of viability so that apoptotic pathways are activated and cell death ensues. Apoptosis related to mismatch repair could be a starting point to proceed in such a form of cancer prevention. Research into the number and overlaps of the different pathogenetic pathways initiated by the different CRC-susceptibilities and also into apoptosis should provide information as to why tissues other than the colonic endometrium are prone to becoming neoplastic. Obviously, in the hereditary CRC syndromes prevention measures cannot only be limited to the gut. With regard to prevention, consideration must also be given to other options that persons at risk could take on their own initiative, such as changes in their dietary habits or physical activity.

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