

Review

Molecular Genetics of Small Bowel Cancer

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Abstract

Although the molecular genetic changes that take place during carcinogenesis in the large bowel have been well elucidated, very little work has been done on the carcinogenesis process in the small bowel where this phenomenon is much rarer. The few studies that have been done suggest that certain oncogenes, *i.e.*, *erbB2*, *K-ras*, *cyclin D1*, and *p53*, are all altered in ways and in frequency similar to these phenomena in large bowel cancer. Some tumor markers have been noted to occur in malignant carcinoid tumors as well. Given the overall similarities in the epidemiology and the role of the adenoma-carcinoma sequence for both small bowel adenocarcinoma and colorectal adenocarcinoma, it is highly likely that the same molecular genetic changes play a major role. Further work is needed to confirm this. If true, a potentially important area of future research would be to determine why these molecular genetic changes occur so much less frequently in the small bowel as compared to the large bowel.

Introduction

Although the small intestine or bowel contains almost 90% of the mucosal surface area of the gastrointestinal tract, cancer of the small intestine has an incidence rate which is one-fiftieth that of the large intestine (1). This is despite the fact that there are many similarities in the epidemiology of cancer in these two organs: they tend to covary in different countries (2); patients with small bowel adenocarcinoma are at elevated risk for large bowel adenocarcinoma and *vice versa* (3); both arise from adenomatous polyps (4); and both are increased in individuals with familial adenomatous polyposis (4).

Before proceeding, it is important to understand the histological categories of small bowel cancer. There are four major types of small bowel cancer. These are adenocarcinoma, malignant carcinoid tumors, lymphoma, and leiomyosarcoma. In the United States, adenocarcinoma is the most common histological subtype, whereas carcinoid tumors come in a close second with sarcomas and lymphomas representing <20%

overall. The adenocarcinomas primarily cluster in the duodenum, whereas malignant carcinoid tumors primarily occur in the ileum (5).

Relatively little research has been done on specific risk factors for small bowel cancers. Two things, familial adenomatous polyposis and Crohn's disease, are known to be powerful risk factors for small bowel adenocarcinoma. In particular, Crohn's disease may increase the risk of small bowel adenocarcinoma by >100 (5–11). This effect is mainly localized to the ileum, where Crohn's disease is more prominent, in opposition to the duodenum, which is where most small bowel cancers occur in general. Several studies have shown an elevated risk for small bowel adenocarcinoma in patients with familial adenomatous polyposis (4, 12–15). In familial adenomatous polyposis patients, small bowel cancer has been the most common cancer following colon cancer itself. The relative risk for small bowel adenocarcinoma in these patients has been described as being >100 (15). Two studies (16, 17) have also suggested an elevated risk of small bowel cancer in patients with cystic fibrosis. Some evidence has also been put forth regarding exposure to animal fat (18), but little else in the way of specific observational studies has been undertaken.

Several theories have been offered to explain the low incidence of small bowel cancer. The most important ones are: the rapid turnover of the small intestinal mucosal cells; the relative absence of bacteria in normal small bowel; the rapid transit time through the small bowel; a well-developed local IgA-mediated immune system; increase in apoptosis (programmed cell death); and the alkalinity of the contents of the small bowel (2, 19–23).

None of these hypotheses has been very well investigated. Certainly, little research has been invested in exploring these issues in the human small bowel. In particular, although the rapid turnover of small bowel mucosal cells is suggested as a possible reason for the low cancer rate, *i.e.*, that partially transformed cells are shed before full carcinogenesis can occur (24, 25), most experts feel that a high proliferative and turnover rate is directly correlated with carcinogenesis. The higher proliferative rate in the large bowel has been suggested by Lipkin and others (20, 26) as an etiological factor, or at least a marker for risk. Obviously, these two theories are contradictory, and no evidence is currently available to choose between them in the small bowel system.

Another characteristic of the small bowel that distinguishes it from the large bowel is a relative absence of bacteria. Certain carcinogens are known to induce colon cancer in normal animals, but not in those that are bacteria-free (27, 28). Particularly in conjunction with the rapid transit of the small bowel contents, the scarcity of bacteria may minimize exposure to potential bacterial breakdown products that act as carcinogens (2, 28). Certainly rapid transit time has been suggested as a protective mechanism in large bowel cancer, and has been hypothesized as a mechanism by which physical exercise protects against large bowel cancer. Whether the small bowel is fully analogous with regard to the large bowel has not been investigated. It would be satisfying if the same physiological mechanisms were protective in both organs. No studies have

Received 8/29/96; revised 4/15/97; accepted 5/2/97.

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explored the molecular genetic changes associated with rapid transit or with the presence or absence of bacteria. This would be a fertile area for future research.

The small bowel contains certain enzymes that protect it from carcinogenesis. One example is benzopyrene hydrolase. This enzyme converts benzopyrene, a potent carcinogen, to a less active form. It is found in high concentrations in the small bowel. It is possible that there are other enzymes of this type that may be protecting the small bowel against carcinogenesis (29, 30).

One of the major advances in cancer research in the past 10–15 years has been the elucidation of the molecular genetics of colorectal cancer. Elegant studies by Vogelstein and others (31–33) have explored the somatic genetic changes that take place in the course of the adenoma-carcinoma sequence during colorectal carcinogenesis. The result is that we now have a clearer perception of the process of colorectal carcinogenesis on a molecular genetic level than that of any other solid tumor. Clinical benefits have included the identification of germ-line mutations predisposing to colorectal cancer and the identification of new prognostic factors. Research efforts are currently underway to take advantage of these new findings in developing new screening tools for colon cancer (34, 35) and in developing pharmacological agents that capitalize on the new genetic discoveries to treat colorectal cancer (36, 37). On the other hand, very little research has been carried out in the investigation of molecular markers in small bowel cancer; even those few studies that have been done have been limited in size.

Animal Studies

min Mouse System. Animal model and cell culture systems have shed some light on potential molecular biomarkers of small bowel tumors. Of particular importance is the *min* mouse model (38–43). *min* mice carry a dominant mutation in the homologue of the *APC* (*adenomatous polyposis coli*) gene. Genetic linkage analysis has localized the mutation to mouse chromosome 18, in a region known to contain the *APC* gene, the murine homologue of the human *APC* gene (40).

Mutations in the *APC* gene appear to be responsible not only for familial adenomatous polyposis but also for many sporadic cases of gastrointestinal cancer. It has been suggested that *APC* gene modification is a critical event in the initiation of small bowel tumor formation. Mendelian transmission of the mutated gene caused most homozygous mice to die *in utero* before day 8 of gestation. The heterozygous mice developed multiple polyps throughout the intestinal tract, mostly in the small intestine. All adenomas lost the wild-type *APC* allele, whereas the mutant allele remained unchanged. These results indicate that LOH² is followed by formation of adenomas (42, 43).

mom-1. Further analysis of the *min-1* mutation has identified, by quantitative trait loci studies, a locus designated *mom-1* that dramatically modifies the *min*-induced tumor number. This locus maps to the distal region of chromosome 4, in a region syntenic to human chromosome 1p35–36. This region of human chromosome 1 is frequently rearranged or mutated in intestinal tumors. *mom-1* is estimated to account for about 50% of the genetic variation in adenoma number in *min* mice (44). Further analysis of the *mom-1* gene in tumors produced by *min-1* mice should indicate if it is comutated during tumor progression. Recently, MacPhee *et al.* (38) have suggested that the gene for secretory phospholipase A2 is a candidate for the *mom-1* locus,

and that it modifies polyp number by altering the cellular microenvironment within the intestinal crypt.

Strain B10.A. Fijneman and Demant (41) reported that a high percentage of mice of strain B10.A that were treated prenatally with the carcinogen *N*-ethyl-*N*-nitrosourea developed macroscopically visible tumors of the small intestine. These tumors are described as adenocarcinomas containing cells of four histologically different types, each resembling one of the four main differentiated cell types in the mouse small intestine: mucous, enteroendocrine, Paneth, and columnar. Because these four cell types all originate from a common pluripotent stem cell, the crypt-base columnar cell, it is believed that tumors of the small intestine originate from neoplastically affected crypt base columnar cells.

LOH. LOH studies have presented a powerful tool for the study of the development and progression of cases. LOH in human tumors can be difficult to interpret due to the limitations of the number of tumors of a precise type, stage, genetic background, and environmental exposure (45). Transgenic mice would appear to offer an ideal situation to perform genomewide scans for LOH. The overall genomewide rate of LOH of carcinoid tumors in transgenic mice expressing the SV40 Tag was quite low. Chromosomes 9 and 16 showed high rates of allelic loss. The locus on chromosome 9 lies in a region with synteny to human chromosomes 3q, 6q12, 15q24, and 3p21, whereas the locus on chromosome 16 lies in a region corresponding to human chromosomes 3q and 22q. These regions do not encode the two tumor suppressors, *pRB* and *p53*, known to interact with SV40 Tag, suggesting the presence of new genes, the loss of function of which contributes to multi-stage tumorigenesis (45).

SV40 Tag, human *K-ras* and a dominant negative mutant of human *p53* have been expressed singly and in all possible combinations in postmitotic enterocytes of transgenic mice to assess the role of these gene products in the pathogenesis of gut neoplasia. Transgenic mice that produce *K-ras* and/or *p53* did not have any detectable phenotypic abnormalities. *K-ras* cooperates with SV40 Tag to generate marked proliferative and dysplastic changes. Yet, mice that carried one, two, or three of these transgenes did not form adenomas or adenocarcinomas. A modest increase in tumor number was noted in animals that express the *min* mutation and either SV40 Tag alone, SV40 Tag and *K-ras*, or SV40 Tag, *K-ras*, and *p53*. These results demonstrate the remarkable protective effect of a continuously and rapidly renewing epithelium in the small bowel (24).

Other Biomarkers. There is also evidence regarding the production of large quantities of epidermal growth factor and a polypeptide similar to it during experimental carcinogenesis in the small bowel mucosa of rats (46).

We showed that derivatives of the IEC-18 enterocyte cell line, originally isolated from normal rat ileum transformed by an activated human c-*K-ras* oncogene, display increased expression of both *cyclin D1* and *Rb* genes, thus revealing novel effects of these oncogenes. The increased expression of these oncogenes in tumors may be relevant to small bowel carcinogenesis as well (47).

Oncogenes for Human Adenocarcinoma

Activation of the *neu* gene (also called *erbB-2* and *HER-2*) encodes a transmembrane glycoprotein that has tyrosine-specific kinase activity. Cohen *et al.* (48) examined the expression of the *p185neu* protein in normal and malignant digestive tract tissues, including the small intestine. A point mutation in the *neu* gene leading to a single amino acid substitution (valine to glutamine at residue 664) is responsible for the transforming

² The abbreviations used are: LOH, loss of heterozygosity; SV40 Tag, SV40 large tumor antigen.

phenotype (48). In the normal mucosa, there was prominent p185*neu* expression in the villus, with little or no staining in the crypts. Immunoreactivity was consistently greater in adenomatous polyps. These findings suggest that p185*neu* may play a role in the transformation of these cells (48).

Our group examined the frequency of c-K-*ras* in small bowel adenocarcinomas using a PCR-based method by RFLP. c-K-*ras* mutations at codon 12 were observed in five of six cases (49). Recently, we have identified another 6 k-*ras* mutations in an additional 15 small bowel tumors³ for a total of 11 of 21 small bowel tumors.

We also evaluated the level of expression of cyclin D1 protein during the multistage process of human small bowel carcinogenesis (50). Increased expression of cyclin D1 may perturb cell cycle control early in the tumorigenesis process and thereby enhance tumor progression. Cyclin D1 protein abundance was determined by immunostaining samples of normal mucosa ($n = 34$), adenomatous polyps ($n = 24$), and adenocarcinomas ($n = 33$). Cyclin D1 nuclear staining occurred in 33% of adenocarcinomas and 36% of adenomatous polyps but not in normal appearing mucosa.

Genomic instability and replication errors play an important role in the pathogenesis of tumor formation, especially in intestinal tumors, including those of the small bowel (51). Hibi *et al.* (52) observed replication errors in 5 of 11 cases (45%) of small intestinal carcinomas, and Keller *et al.* (53) reported errors in one case of five studied.

Spandidos *et al.* (54) found 46% (6 of 13) of the same group of patients had increased expression of p53. These cases included lymphoma, angiosarcoma, leiomyosarcoma, adenocarcinoma, and two metastases from adenocarcinomas of the large bowel. Our own study of p53⁴ found high levels of p53 expression in small bowel adenocarcinomas with significantly lower expression in small bowel adenomas.

Markers for Carcinoid Tumors

Although most of this review has focused on small bowel adenocarcinomas, small bowel malignant carcinoid tumors are also of interest. They do not appear to have anything, aside from anatomical location, in common with small bowel adenocarcinomas and share no epidemiological characteristics with large bowel tumors. Thus, on some level, they represent a "control" group for contrasting small bowel adenocarcinomas. Biomarkers for the diagnosis of carcinoid tumors are well established. Traditionally, they were based on 5-hydroxy indole-3-acetic acid excretion in the urine and serotonin measurement in blood platelets. Other specific markers of carcinoid tumors include neuropeptide K, substance P, gastrin, histamine, corticotropin-release factor, and growth hormone-releasing factor (55).

The development of a RIA for the analysis of chromogranins in plasma has improved the diagnostic possibilities of early carcinoid. Moreover, changes in chromogranin A and B levels correlate with changes in other markers, and can be used to monitor treatment (55). Funa *et al.* (56) reported on an *in situ* hybridization study of chromogranin A and B mRNA in carcinoid tumors. They claimed that mRNA for chromogranin A and B was a reliable marker for the carcinoid tumors, especially of mid-gut origin. They also found that mRNA expression of chromogranin A after IFN therapy indicated an inhibition at the pre-

translational level. Amplification and increased expression of the *neu* gene was seen on both the mRNA and protein levels in carcinoid tumors. Moreover, quantitation of actual copy number may be an important prognostic determinant.

The tumor markers CA-19-9 and CA-50 are based on monoclonal antibodies to colonic carcinoma cell lines. Immunohistochemical studies have shown that both markers were expressed in 50–60% of patients with small bowel tumors (55). Carcinoembryonic antigen and proliferating cell nuclear antigen production were noted in 8 of 10 cases from Japan (57).

Future Directions

Despite the difference in incidence rates, small bowel adenocarcinomas and large bowel adenocarcinomas share a great many characteristics. In particular, the adenoma-carcinoma sequence appears to operate in as significant a fashion in the small bowel as in the large bowel.

Vogelstein and his coworkers (31–33) have identified many of the molecular genetic changes that occur at various stages in the adenoma-carcinoma sequence. It does not take a great leap in imagination to hypothesize that a similar sequence may be operating in the small bowel. To date, changes in *ras*, *p-53*, and the *APC* gene have been examined to a limited degree. However, a systematic investigation of these and other genetic changes in adenomas and adenocarcinomas needs to be pursued. If these changes are not parallel in the two organs, it would suggest that the resistance of the small bowel to carcinogenesis lies in a mechanism that prevents the occurrence of certain molecular genetic changes. A mechanism for such resistance might be transferable to the large bowel.

Alternatively, if the multistage carcinogenesis process in the small bowel were similar to that in the large bowel, at least at the molecular genetic level, other mechanisms would need to be sought that would explain the low-incidence rate in the small bowel. The rapid turnover rate of the small bowel epithelium, for example, could be used to explain why the molecular genetic changes that appear to occur so commonly in the large bowel do not have an equal opportunity to propagate in the small bowel.

This review article does not provide many answers regarding the mechanisms or molecular genetic changes that play a role in small bowel carcinogenesis. Instead, it raises these issues to encourage others to pursue this line of inquiry. The rarity of small bowel cancer makes its prevention or intensive study unnecessary. Nonetheless, its similarity to the large bowel suggests that lessons learned from its research might prove helpful in our understanding and approach to large bowel cancer and perhaps other cancers as well.

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³ Unpublished data.

⁴ N. Arber, A. Neugut, I. B. Weinstein, and P. Holt, p53 in small bowel malignancies, manuscript in preparation.

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N Arber, A I Neugut, I B Weinstein, et al.

Cancer Epidemiol Biomarkers Prev 1997;6:745-748.

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