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The Role of Infectious Agents in Colorectal Carcinogenesis

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1. Introduction

Infectious agents have been increasingly recognized as bona fide etiologic factors of human malignancies, particularly gastrointestinal cancers. The estimated total of infection-attributed malignancies per year is 1.9 million cases, accounting for 17.8% of the global cancer burden (Parkin, 2006). Given that colorectal cancer (CRC) is the third most common incident cancer worldwide (World health organization, 2003), it seems prudent to explore the role of microbial pathogens in colorectal carcinogenesis. By elucidating the probable mechanisms by which infectious agents contribute to colorectal oncogenesis, the management of CRC may one day parallel what is already in place for cancers such as gastric lymphoma and cervical cancer. Antimicrobial therapy and vaccination against some of these infections may herald a future with a curtailed role for traditional therapies of surgery and chemo-radiotherapy.

Unlike gastric cancer, which is chiefly linked to a single infectious agent, multiple organisms may contribute to the genesis of CRC. Epidemiological and experimental evidence strongly implicate several bacterial and parasitic agents in promotion of colorectal carcinogenesis. Most of these agents incite continual inflammation, which generates a procarcinogenic microenvironment (Parsonnet, 1995; Vennervald & Polman, 2009). Viruses have not attained the same status as other microorganisms as probable causative agents, though merit attention because of their inherent oncogenic properties and the increasing strength of their association with other malignancies (McLaughlin-Drubin & Munger, 2008). Yet, putative viral agents seemingly display an immense geographic variation that has led to much debate regarding the relative importance of one organism versus another. The present review summarizes the data available on the possible relationship of certain micro-organisms and CRC. These include but not limited to *Helicobacter pylori*, *Streptococcus bovis*, *Bacteroides fragilis*, JC virus (JCV), and human papillomavirus (HPV), and intestinal schistosomes. The consistency and nature of these associations are discussed, as are the mechanisms whereby each pathogen participates in the malignant transformation of the colonic mucosa.

2. Bacteria

2.1 *Helicobacter pylori*

H. pylori is a gastric microbiome that colonizes approximately 50% of the population worldwide (EUROGAST study group, 1993). Gastric infection with *H. pylori* fosters chronic inflammation and significantly increases the risk of developing peptic ulcer disease and gastric cancer. Indeed, the bacterium has been designated by the International Agency for Research in Cancer (IARC, 1994), as a class I carcinogen in human causing gastric cancer. Recently, promotion of tumour development by *H. pylori* infection in extragastric target organs, such as the colorectum, has been reported, though causal relationship is presently controversial.

Cancer in human

Numerous comparative and case-control studies have examined the relationship between *H. pylori* IgG seropositivity and colorectal neoplasia risk, but the results have been inconsistent. While some studies demonstrated positive correlations between colorectal neoplastic lesions, especially adenomas, and *H. pylori* seroprevalence (Aydin et al., 1999; Hartwich et al., 2001b; Meucci et al., 1997; Mizuno et al., 2005; Zumkeller et al., 2007), others showed null or inverse associations (Moss et al., 1995; Penman et al., 1994; Fireman et al., 2000; Shmuely et al., 2001; Siddheshwar et al., 2001; Machida-Montani et al., 2007; D'Onghia et al., 2007). Most of these studies were, however, confounded by uncontrolled extraneous variables. Breuer-Katschinski et al. (1999) compared *H. pylori* serostatus between 98 colorectal adenoma patients and age/sex-matched hospitalized and populations-based control groups. The results clearly demonstrated an increase in the risk of colorectal adenoma in association with *H. pylori* infection following adjustment for dietary and lifestyle factors. Importantly, two case-control studies nested in large population-based cohorts failed to establish any association between *H. pylori* seroprevalence and incident CRC, irrespective of adjustment for potential confounders (Thorburn et al., 1998; Limburg et al., 2002). In each study, the presence of *H. pylori* was determined in subjects who developed CRC years after serum donation. The inconclusive findings in these studies have been partially attributed to small sample size, lack of control heterogeneity, and incomplete colonoscopic evaluation (Takeda & Asaka, 2005). Besides, serologic methods may not always reflect real-time *H. pylori* infection and likely yield positive results for infections caused by *Helicobacter* species other than *H. pylori*, which commonly colonize the human colonic mucosa (Keenan et al., 2010).

Other studies have utilized more reliable diagnostic tools for detection of *H. pylori* infection. Lin et al. (2010) conducted a cross-sectional study using biopsy urease test, and demonstrated a significantly increased risk of colorectal adenoma among *H. pylori* infected-patients, particularly those with concomitant metabolic syndrome. Conversely, two case control studies, using 13^{C}-Urea breath test (UBT), did not substantiate any significant associations of *H. pylori* infection with colorectal tumours (Penman et al., 1994; Liou et al., 2006). Fujimori et al. (2005) evaluated 699 patients for *H. pylori* infection using combination of three tests; UBT, rapid urease test, and gastric biopsy histology. Their analysis revealed a significantly higher prevalence of colorectal adenoma and adenocarcinoma among *H. pylori*-positive female patients compared to their *H. pylori*-free counterparts.

Of note, in a metanalysis of 11 case-control studies, the summary odd ratio for the association of *H. pylori* infection with the risk for colorectal carcinoma or adenoma was found to be 1.4 (95% CI, 1.1–1.8). Different testing methods were, nevertheless, combined to

assess the *H. pylori* infection status in these studies (Zumkeller et al., 2006). More recently, a meta-analysis comprising 13 studies and 1709 patients with colorectal neoplasms, arrived at summary odd ration of 1.49 (95% CI 1.17–1.91). Further analysis of studies using serologic response as the sole indicator of infection revealed a higher summary odd ratio of 1.56 (95% CI, 1.14–2.14) (Y. S. Zhao et al., 2008).

Recently, Soylu et al. (2008) have investigated the presence of *H. pylori* in colorectal neoplasms using immunohistochemical methods, which allowed more accurate detection of the non-spiral forms of the bacterium. The prevalence of *H. pylori* was higher in villous type polyps than in tubular type polyps and adenocarcinomas. Contrary to this finding, Jones et al. (2007) demonstrated that villous adenoma had the lowest rate of *H. pylori* positivity compared to other premalignant and malignant colonic lesions. Their results also showed significant associations of *H. pylori* positivity with tubular and tubulovillous adenomas, and adenocarcinomas, but not with villous adenomas.

Likewise, studies employing PCR analysis for detection of *H. pylori* genomic material in the cancerous tissue have yielded conflicting results. A Swedish group detected *H. pylori* DNA in 27% of CRC specimens (Bulajic et al., 2007). In contrast, Grahn et al. (2005) identified *H. pylori* DNA in 1.2% of the malignant tissues and, unexpectedly, in 6% of normal mucosal samples among patients with CRC. Additionally, there was no statistical correlation between *H. pylori* PCR positivity and CRC. This finding was further confirmed in a later study on a separate population (Keenan et al., 2010).

Cancer in experimental animals

Studies have shown that amidated gastrins have no stimulatory effect on colon mucosal growth or progression of colon cancer in different experimental models (Hakanson et al., 1986, 1988). Others demonstrated that non-amidated gastrins, including progastrin and Gly-gastrin, have a mitogenic effect on the colonic mucosa in transgenic mice (T.C. Wang., 1996; Koh et al., 1999). Singh et al. (2000a, 2000b) reported that transgenic mice with elevated plasma progastrin, but not amidated gastrins, exhibit increased aberrant crypt foci, adenomas, and adenocarcinomas after treatment with azoxymethane, whilst no tumours developed in mice exposed to either progastrin or azoxymethane only. These results suggest that non-amidated gastrin is not a carcinogen on its own, but rather promotes oncogenic progression.

Mechanisms/Mechanistic studies

Various pathogenetic mechanisms have been suggested by which *H. pylori* exerts its oncogenic potential. First, persistent *H. pylori* exposure induces hypergastrinemia, which is a putative trophic factor for the human colorectal mucosa, thereby increasing the mutation susceptibility (Renga et al., 1997). Moreover, studies showed that most human colon cancers secrete gastrin, primarily non-amidated gastrins, which likely function in autocrine fashion (Baldwin et al., 1998). Non-amidated gastrin induces proliferation and invasiveness of human tumour cells *in vitro* (Kermorgant & Lehy, 2001). In conjunction with these findings, the overexpression of cyclooxygenase-2 (COX-2) was shown to stimulate the cancer cells to release excessive amount of prostaglandin E_2 (PGE_2), leading to further proliferation (Hartwich et al., 2001b).

Although some reports, including a well-controlled prospective study, provided statistical evidence that high fasting plasma gastrin level is associated with increased risk of colorectal adenoma and carcinoma (Hartwich et al., 2001b; Thorburn et al., 1998; Georgopoulos et al.,

2006), others showed no associations (Penman et al., 1994; Fireman et al., 2000; Machida-Montani et al., 2007; Robertson et al., 2009). In a majority of these studies only amidated gastrin was measured, which may have contributed to the discrepancy in results (Dickinson, 1995). In a recent study, circulating forms of both amidated and non-amidated gastrins were measured. Non-amidated gastrins were significantly higher in patients with colorectal carcinomas, compared with levels in control patients (Ciccotosto et al., 1995).
Second, *H. pylori*-related chronic gastritis might contribute to colorectal carcinogenesis by reducing gastric acid secretion with consequent alteration in the normal gastrointestinal flora (Kanno et al., 2009). Another possibility is that CagA protein (Fig 1.), which is produced by virulent strain of *H. pylori*, may contribute to colorectal carcinogenesis by inducing an enhanced inflammatory response and potentiating gastrin secretion (Peek et al., 1995; J.H. Kim et al., 1999). As for the correlation between colorectal neoplasia and CagA$^+$ *H. pylori* serostatus, three studies indicated positive correlations between CagA$^+$ *H. pylori* seropositivity and colorectal tumours (Hartwich et al., 2001b; Shmuely et al., 2001; Georgopoulos et al., 2006), while two other studies found no such correlation (Zumkeller et al., 2007; Limburg et al., 2002).

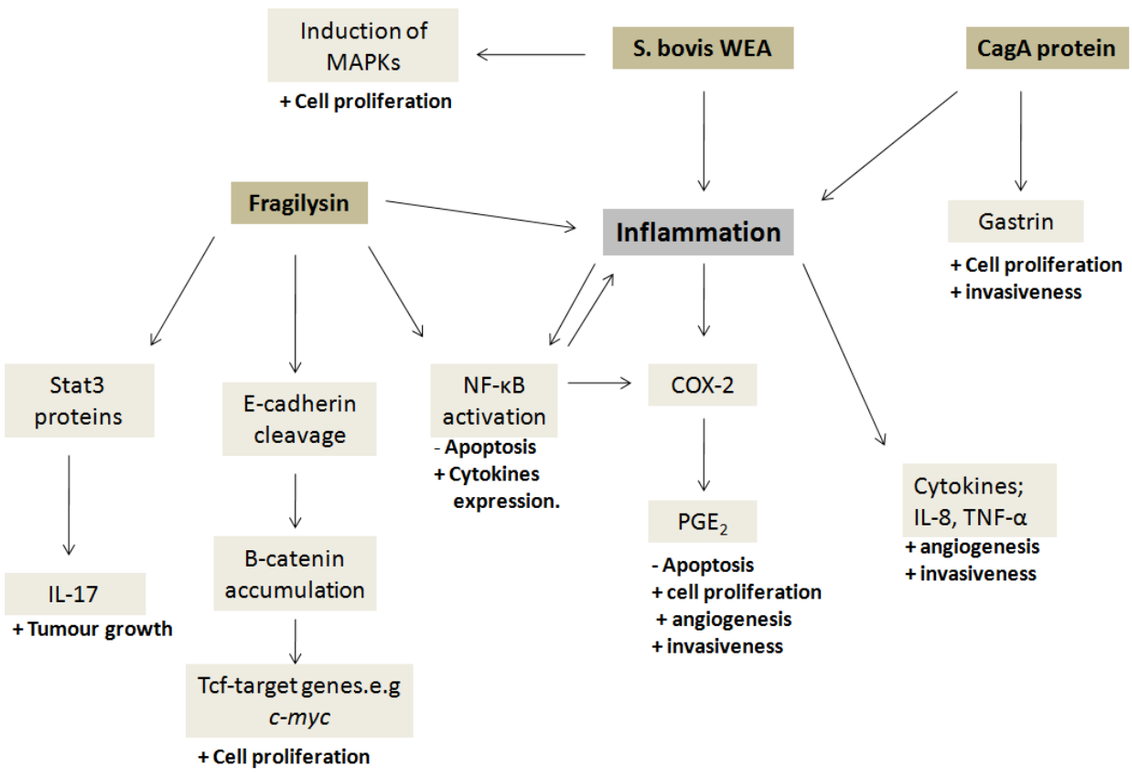

Fig. 1. Illustration of the possible mechanisms of bacterial-toxin-induced carcinogenesis.

2.2 *Streptococcus bovis*

S. bovis, a nonenterococcal lancefield group D *streptococcus*, is a transient colonic commensal with fecal carriage rate of 5 - 13 % in healthy adults (Potter et al., 1998; Dubrow et al., 1991), and accounts for 11-12% of infective endocarditis (Ballet et al., 1995; Kupferwasser et al., 1998). Traditionally, *S. bovis* has been classified into three distinct biotypes; I, II/1, and II/2,

based on phenotypical and genetic characteristics (Coykendall & Gustafson, 1985). Further studies using phylogenetic analysis allowed clear and unambiguous differentiation of human clinical isolates and indicated that all strains of *S. bovis* I and II/2 be identified as *S. gallolyticus* (Schlegel et al., 2003). The latter accounts for most of the human strains isolated from blood or faeces, and is often responsible for endocarditis cases associated with colonic cancer (Schlegel et al., 2003).

Cancer in humans

The association between *S. bovis* endocarditis and colorectal carcinoma was first brought to light by Keusck (1974). Subsequent case studies showed a wide range of prevalence of colorectal neoplasms in patients with *S. bovis* bacteraemia (6 - 67%), depending on the diligence with which the diagnosis was sought (Pigrau et al., 1988; Klein et al, 1979; H.W. Murray & Roberts, 1978; Friedrich et al., 1982a; Reynolds et al., 1983; Zarkin et al., 1990; Gold et al, 2004; Alazmi et al, 2006; Beeching et al., 1985). Additionally, some patients developed new colonic tumours 2 to 4 years following the incidence of *S. bovis* endocarditis, pointing to a possible temporal relationship between the two events (Zarkin et al., 1990; Robbins & Klein, 1983; Muhlemann et al., 1999; Friedrich et al., 1982b). Other studies reported that patients with *S. bovis* endocarditis had significantly higher rates of colorectal neoplasms than those with endocarditis due to other pathogens or non-endocarditis patients (Pergola et al., 2001; Hoen et al., 1994). More particularly, Ruoff et al. (1989) showed that *S. bovis* I bacteraemia was highly correlated with malignant and premalignant colonic lesions, compared to bacteraemia due to other *S. bovis* biotypes. This conclusion was affirmed by several recent analyses, in which the incidence of colonic tumours in patients with *S. bovis* I infection ranged between 27 - 94% (Herrero et al., 2002; Tripodi et al., 2004; Corredoira et al., 2008; Vaska & Faoagali, 2009; Ruoff et al, 1999).

Several investigators have studied the association between the fecal carriage rate of *S. bovis* and both malignant and premalignant colorectal lesions, with the results being contradictory (Klein et al., 1977; Potter et al., 1998; Norfleet & Mitchell, 1993; Burns et al., 1985). Comparing the growth of *S. bovis* from tissue biopsy of adenomas or carcinomas did not show increased frequency compared to normal mucosa from the same patients or non-cancer-patients group (Potter et al., 1998; Norfleet & Mitchell, 1993). In contrast, Abdulamir et al. (2010), using bacteriological studies and molecular techniques to detect *S. gallolyticus* in tissue or faeces, revealed a significantly higher frequency of *S. gallolyticus* isolation from tumorous and non-tumorous tissue in CRC patients than from normal mucosa in control subjects. In parallel, the faecal carriage rate of *S. gallolyticus* was similar in cancer and control groups.

In another aspect, Darjee and Gibb (1993) used immunoblotting and enzyme-linked immunosorbent assay (ELISA) to compare anti-*S. bovis* IgG levels in sera of 16 colonic cancer patients and 16 age-matched controls. Immunoblot assay showed no significant difference in the serologic parameters between patients and controls, whilst ELISA demonstrated higher median *S. bovis* IgG antibody titres in patients with colonic cancer, compared to controls. Using immunocapture mass spectrometry, Tjalsma et al. (2006) showed a higher frequency of anti-*S. bovis* seropositivity in patients with colonic polyps and cancer than age-matched controls. Importantly, recent studies reported that CRC and adenoma were associated with higher levels of serum anti-*S. gallolyticus* IgG antibody in comparison with healthy and tumour-free control subjects (Abdulamir et al., 2009).

It is clear that a strong association does exist between symptomatic *S. bovis* infection and colorectal neoplasia, which has important clinical implications. Patients who have *S. bovis* bacteraemia, with or without endocarditis, require extensive endoscopic evaluation for occult premalignant and malignant colonic cancer (Konda & Duffy, 2008). Further, recent evidence indicates that serum antibodies to *S. bovis* represent a promising potential for early diagnosis and prevention of CRC (Tjalsma et al., 2006).

Cancer in experimental animals

Studies have shown that administration of *S. bovis* or *S. bovis* wall extracted antigens (WEA) to azoxymethane- treated rats resulted in almost two-fold increase in the number of aberrant colonic crypts, compared to azoxymethane-only treated control rats. Fifty percent of the rats receiving WEA developed colonic adenomas, whereas no tumour was detected in the other groups. It is noteworthy to mention that normal rats did not develop hyperplastic colonic crypts upon treatment with *S. bovis* suspension, implying that *S. bovis* proteins are involved in promoting rather than initiating oncogenesis (Ellmerich et al., 2000b). Similar results were obtained by Biarc et al., (2004) who also reported that a purified form of S. bovis WEA (S300 fraction) is even more potent inducer of neoplastic progression than WEA or the intact bacteria.

Mechanisms/Mechanistic studies

Although Klein et al. (1977) originally theorized that *S. bovis* may play a role in producing carcinogens in the large bowel, recent data showed that *S. bovis* wall proteins (Fig. 1.) have proinflammatory potential and procarcinogenic properties (Nguyen et al., 2006). *In vitro* studies indicated that activation of human colonic epithelial cell line Caco-2 by *S. bovis* cell wall proteins, especially S300 fraction, resulted in significant increase in IL-8 production, COX-2 expression, and PGE_2 release (Biarc et al., 2004), whereas binding of *S. bovis* activated human leucocytes cell line to release TNF-α (Ellmerich et al., 2000a). These results are in agreement with those obtained in *in vivo* experiments showing that *S. bovis* as well as cell wall antigens from this bacterium are able to increase the production of IL-8 and PGE_2 in the colonic mucosa of rats (Ellmerich et al., 2000b; Biarc et al., 2004). More recently, human studies have provided evidence for a strong association between *S. gallolyticus* IgG seropositivity and nuclear factor kappa B (NF-κB) and IL-8 expression in tumorous sections of both colorectal adenomas and carcinomas (Abdulamir et al., 2009). Using quantitative PCR analysis to measure bacterial count in cancerous tissue, the same group observed a positive correlation between the levels of expression of IL-1, COX-2, and IL-8 and the *S. gallolyticus* load in tumorous colorectal tissue (Abdulamir et al., 2010). Apart from its inflammatory potential, *S. bovis* cell wall proteins may activate mitogen-activated protein kinases (MAPKs), stimulating a proliferative response in the host cells and increasing the likelihood of cell transformation (Biarc et al., 2004).

Notably, the chemokine 1L-8 is potent angiogenic factor and neutrophil chemoattractant (Li et al., 2001), which as well as other cytokine such as TNF-α, IL-1β, and IL-6, trigger a chronic inflammation with resultant production of highly mutagenic reactive oxygen and nitrogen species (Ohshima & Bartsch., 1994). COX-2, through production of excessive amounts of prostaglandins, inhibits apoptosis, and promotes tumour cell proliferation, angiogenesis, and tumour invasiveness (Hartwich et al., 2001a). In addition, activation of NF-κB pathway induces the expression of downstream mediators such as COX-2, TNF-α, and IL-6, all contributing to inflammation-related tumorigenesis (S. Wang et al., 2009).

2.3 *Bacteroides fragilis*

B. fragilis is a gram-positive, anaerobic colonic microflora in most mammals, and is the leading cause of anaerobic bacteraemia and intraabdominal suppurative infection in human adults (Wexler et al., 2007). The pathogenicity of this bacterium is attributed to several virulence determinants, including a recently identified metalloprotease toxin, called fragilysin. Fragilysin-producing *B. fragilis*, termed enterotoxigenic *B. fragilis* (ETBF), causes acute inflammatory diarrheal disease and asymptomatically colonizes up to 20 -35 % of adults (Sears et al., 2008). As well, it has been recently linked to flare-ups of inflammatory bowel disease (Basset et al., 2004; Prindiville et al., 2000).

Cancer in human

The epidemiological evidence on the association *B. fragilis* infection and colorectal neoplasia is limited. Early studies by Legakis et al. (1981) indicated that the incidence of fecal *B. fragilis* in CRC patients was significantly higher than in healthy subjects, suggesting a possible role for *B. fragilis* in colon carcinogenesis. Moore et al. (1995), however, did not find any significant difference in the frequency of fecal carriage of *B. fragilis* between colorectal adenoma patients and low-risk healthy controls. Similarly, a seroepidemiological study showed lack of associations between *B. fragilis* IgG serostatus and colorectal adenoma and carcinoma (Abdulamir et al., 2009). Using PCR methods, Toprak et al. (2006) recently compared the prevalence of ETBF in stool specimens from 73 patients with CRC with 59 age-matched controls. The frequency of isolation of the organism was significantly higher in the CRC patients (38%) than in the control group (12%). These findings, however, have not been replicated in another population.

Cancer in experimental animals

Studies of murine models have demonstrated that ETBF induced persistent subclinical colonic inflammation and hyperplasia in specific pathogen-free C57BL/6 mice (Rhee et al., 2009). The same group used the adenomatous polyposis coli multiple intestinal neoplasia (*Apc*$^{Min/+}$) mice to model human CRC. ETBF-colonized *Apc*$^{Min/+}$ mice developed inflammatory colitis and unusually early onset microadenomas. In addition, *de novo* colon tumours appeared as early as 4 weeks and distributed predominantly in the distal colon, similar to those found in humans (Wu et al., 2009).

Mechanisms/Mechanistic studies

The current experimental evidence suggests a potential role of fragilysin in the oncogenic transformation of the colonic mucosa (Fig. 1.). *In vitro* studies have shown that fragilysin induces IL-8 expression and NF-κB activation in human colonic epithelial cell lines HT29 and Caco-2 (Sanfiloppo et al., 2000; J.M. Kim et al., 2001). IL-8 is a potent neutrophil chemokine, whereas NF-κB is an essential transcription factor that regulates neutrophils migration and the host epithelial cell chemokine response (J.M. Kim et al., 2002). Additionally, it was demonstrated that fragilysin binds to human colonic epithelial cell line HT29/C1 and stimulates cleavage of the tumour suppressor protein, E-cadherin. The resultant nuclear translocation of the adhesion molecule β-catenin causes increased expression of T-cell factor-target genes, including *c-myc*, with consequent persistent cellular proliferation (Wu et al., 1998, 2003).

Recent showed that all ETBF-induced tumours in *Apc*$^{Min/+}$ mice exhibited intense Stat3 protein activation, which in turn induces dominant colonic IL-17-producing CD4^{+} T-cells infiltrate. Tumour formation was significantly inhibited by administration of blocking

antibodies to IL-17 (Wu et al., 2009). The latter is known to promote tumour growth *in vitro* and *in vivo* through induction of IL-6 synthesis (L. Wang et al., 2009). These results emphasized the contribution of endogenous T cell immune response in ETBF infection-derived colorectal carcinogenesis.

In addition, *B. fragilis* may indirectly promote colon carcinogenesis through production of cytotoxic metabolites such as deoxycholic acid and fecapentaenes. Studies have shown that deoxycholic acid induce proliferation of colonic cells in vitro and promote colonic tumour progression in experimental animals (Peiffer et al., 1997; T. Hori et al., 1998). Several epidemiological studies found a positive association between high faecal deoxycholic acid concentration and colorectal adenoma and carcinoma risk (Little et al., 2002; Reddy & Wynder, 1977), including a prospective study assessing faecal deoxycholic acid levels before the diagnosis of colorectal tumours (Kawano et al., 2010). Fecapentaenes are other fecal mutagens synthesized by *Bacteroides* species, which were shown to be highly genotoxic in both mammalian and bacterial *in vitro* assays (Plummer et al., 1986; Curren et al., 1987). Clinical studies, however, indicated that fecal fecapentaenes levels are not associated with colorectal adenomas and inversely associated with carcinomas (de Kok et al., 1993; Schiffman et al., 1989). It was concluded that if fecapentaenes form a relevant factor in colorectal carcinogenesis, their role is more likely to be related to the transformation of late adenomas into malignant tumors.

2.4 Other bacterial species

There are very few reports on the role of enteric bacterial flora other than *B. fragilis* in colorectal tumorigenesis. Severe distal colitis, rectal dysplasia, and adenocarcinoma were observed in IL-10 knockout mice colonized with *Enterococcus faecalis* (Balish & Warner, 2002; S.C. Kim et al., 2005). *E. faecalis* has been shown to produce reactive oxygen species and induce DNA damage, aneuploidy and tetraploidy in colonic epithelial cells both *in vivo* and *in vitro* (Huycke et al., 2002; X. Wang et al., 2008). Furthermore, it was demonstrated that *E. faecalis* promotes chromosomal instability in mammalian cells, possibly through COX-2 dependent mechanism (X. Wang & Huycke, 2007). Epidemiological studies, however, could not establish any association between colonic colonization of *E. faecalis* and development of CRC (Winters et al., 1998).

Studies showed that mucosa-associated and intramucosal *Escherichia coli* were significantly associated with Crohn's disease, and colorectal adenomas and carcinomas (Swidsinski et al., 1998; Martin et al., 2004). *E. coli* stimulates IL-8 release from the I407 and HT29 cell lines (Martin, 2004), and acts synergistically with *E. faecalis* to induce aggressive pancolitis with reactive atypia in IL-10 deficient mice (S.C. Kim et al., 2007). Recently, Maddocks et al. (2009) reported that enteropathogenic *E. coli* downregulates DNA mismatch repair proteins which increases the susceptibility of colonic epithelial cells to mutations and therefore promotes colonic tumorigenesis.

3. Viruses

3.1 Human papilloma virus

Human papilloma virus is a double stranded DNA virus that is transmitted through direct contact with infected skin or mucous membrane, and causes the most common sexually transmitted disease among sexually active individuals (Koutsky, 1997). While it is well

established that HPV is a necessary cause of cervical cancer, studies suggest HPV may be involved in the malignant transformation of the oropharynx and the anogenital tract (D'Souza et al., 2007; Steenbergen et al., 2005). There are more than 100 subtypes of HPV; some of these subtypes, particularly HPV-16 and HPV-18, are referred to as high risk oncogenic infections (Wiley & Masongsong, 2006; Munoz et al., 2003).

Cancer in human

Early case studies have failed to show any association between HPV infection and colorectal carcinoma in relatively small samples of colorectal carcinoma tissue (Boguszakova et al., 1988; Koulos et al., 1991; Shah et al., 1992; Shroyer et al., 1992). Subsequent studies have employed more stringent methods for HPV detection, including PCR and immunohistochemistry. Despite the variation in the control specimen, all studies confirmed an association between HPV detection rates, specifically subtypes 16 and 18, and CRC with odd ratio ranging between 2.7 (95% CI, 1.1–6.2) and 9.1 (95% CI, 3.7–22.3). (Cheng et al., 1995; Kirgan et al., 1990). Moreover, the strength of association was related to the degree of tumour dysplasia. On the contrary, two of three large prospective cohort studies, with sample sizes ranging between 21,222 and 104,760 cases of cervical cancer, reported no increased risk of subsequent CRC in patients with cervical cancer (Weinberg et al., 1999; Rex, 2000). The other study has shown increased risk of anorectal cancer among patients with cervical cancer, though with lack of clarity over whether it was due to HPV infection or radiation (Chaturvedi et al., 2007).

Mechanism/ mechanistic studies

The oncogenic property of the virus is related to early genes which encode the regulatory proteins E6 an E7. It was hypothesized that these proteins interact and inactivate suppressor genes p53 and pRb, and thus inhibiting apoptosis (Steenbergen et al., 2005). Although about 50% of all colorectal cancer has mutated *p53* (Slattery et al., 2002), Buyru et al. (2003) reported that only 3.6% of HPV-positive colorectal cancers contained mutations in *p53*, suggesting that HPV may have direct oncogenic effects independent of any *p53* mutations.

3.2 John Cunningham virus

JC virus is a widespread neurotropic polyoma virus, with seroprevalence rates of 39-90% among healthy adult population (Kean et al., 2009; Shah, 1996). Primary JCV infection typically occurs during early childhood, probably via fecal-oral route, followed by latency of the virus in the kidney and gastrointestinal tract (Khalili et al., 2003, Ricciardiello et al., 2000). The virus may be reactivated in the presence of severe immunosuppression, and replicates in the central nervous system causing a fatal demyelinating disease, progressive multifocal leukoencephalopathy. Furthermore, there is mounting evidence suggesting that JCV infection may be associated with several human malignancies including brain tumours and upper gastrointestinal cancers (Caldarelli-Stefano et al., 2000; Del Valle et al., 2001, 2005; Shin et al., 2006).

Cancer in human

The potential association between JCV infection and colorectal neoplasia has been examined using nested PCR, Southern blotting and *in situ* hybridization techniques. Ten studies, with sample sizes ranging from 18 to 186, detected JCV genomic sequences in 9-89% of colorectal carcinomas and 5-82% of adenomatous tissue (Laghi et al., 1999; Theodoropoulos et al., 2005;

R. Hori et al., 2005; Casini et al., 2005; Enam et al., 2002; Goel et al., 2006; P. Y. Lin et al., 2008, Niv et al., 2010a; Karpinski et al., 2011; Jung et al., 2008). Comparing neoplastic tissues with normal mucosa, three of these studies showed consistently higher detection rates for JCV in colorectal cancerous tissues and adenomas than in normal tissue (Theodoropoulos et al., 2005; R. Hori et al., 2005; Enam et al., 2002). As well, significantly higher viral copy numbers were observed in colorectal carcinomas and adenomas compared to adjacent normal mucosa (Laghi et al., 1999; Theodoropoulos et al., 2005). Of note, a sequence of the Mad-1 variant of JCV, which lacks 98 nucleotides repeats, has been found preferentially in colon cancers, raising the possibility that certain strains may be selectively activated in colonic epithelial cells (Ricciardello et al., 2001). Other studies have employed real-time PCR, a less sensitive molecular technique, to detect JCV genetic material in colorectal carcinomas, adenomas, normal mucosa, and urine samples from CRC patients and controls. While JCV carrier frequencies in urine were comparable to previously published reports (Agostini et al., 1999), none of the neoplastic tissues and less than 1% of the normal tissues tested positive for JCV DNA (Newcomb et al., 2004; Campello et al., 2010; Militello et al., 2009). The discordant results in previous investigations may be explained by the small sample sizes, variable prevalence of viral infection among the studied populations, inherent lack of uniformity in the sensitivity of the assay used, and possible laboratory contamination particularly in studies where Mad 1 viral sequence was used as a positive template control (Newcomb et al., 2004).

The expression pattern of JCV T-antigen has also been studied in both colorectal neoplastic and normal mucosa. About 35%-94% of CRC tissues and 5-50% of colorectal adenomas were found to host JCV T-antigen, which is often concentrated in the nucleus (Enam et al., 2002; P. Y. Lin et al., 2008; Goel et al., 2006; Link et al., 2009; Nosho et al., 2008, 2009; Ogino et al., 2009; Selgrad et al., 2008; Jung et al., 2008). The expression of JCV T-antigen was significantly higher in colorectal adenomas from liver transplant recipients compared to adenomas in normal controls, pointing to a possible etiologic role for immunosuppression (Selgrad et al., 2008). Interestingly, viral DNA has always been detected more frequently than Tag expression in both colonic adenomas and carcinomas. This suggests that either in some samples, the viral copy number is too low to determine expression of the early gene or, alternatively, that the growing tumour tends to lose viral sequences (Ricciardello et al., 2003). In another aspect, two prospective nested case-control investigated the association between JC seroprevalence and colorectal neoplasms in large groups of patients from whom blood samples were collected months or years before colorectal cancer diagnosis (Rollison et al., 2009; Lundstig et al., 2007). Although there was no association between JC seropositivity and colorectal cancer, one study showed a significantly increased risk of adenomas among seropositive male subjects (Rollison et al., 2009). More recently, Niv et al. (2010b) observed positive correlation between the presence of neoplastic colonic lesion and the titre of JCV antibody in the serum, pointing to JCV infection as an early event for the formation of colorectal adenoma.

Mechanism/ mechanistic studies

The JCV T-antigen is a potent oncogenic protein capable of transforming mammalian cells and is likely involved the early stages of colorectal carcinogenesis though "hit and run" mechanisms. These include disruption of the Wnt signalling pathway and inactivation of tumour suppressor genes such as *pRb* and *p53* (Ludlow, 1993). Both in vitro and in vivo

studies have shown that coexpression of *p53* and JCV T-antigen in CRC cells (Enam et al., 2002; Nosho et al., 2009; Ricciardello et al., 2003). Similarly, colocalization of T-antigen and B-catenin was observed in the nuclei of neoplastic columnar cells (Enam et al., 2002; nosho et al., 2009). Cooperativity between B-catenin and JCV T-antigen increased in vitro transcription of *c-myc*, leading to chromosomal instability (Enam et al., 2002). Ricciardiello et al. (2003) demonstrated that JCV can induce chromosomal instability in vitro using the diploid CRC cell line, which defines loss of heterozygosity (LOH). Subsequent studies reported a significant association between JCV T-antigen expression and CRC with LOH (Nosho et al., 2009; Goel et al., 2006; Ogino et al., 2009). This deletional event probably provides the second hit at the tumour suppressor genes, and eventually leads to clonal expansion. The role of DNA hypermethylation has recently been explored in both colorectal carcinoma and adenoma, nevertheless the results were contradictory (Nosho et al., 2008, 2009; Goel et al., 2006).

3.3 Other viruses

Epstein-Barr virus (EBV) is a DNA virus with strong association with several lymphoreticular malignancies, especially Burkett's lymphoma, as well as certain epithelial tumours such as the nasopharyngeal carcinoma (Parkin, 2006). Additionally, EBV has also been reported with gastric cancer (Koriyama et al., 2001; Takada, 2000), breast (Labrecque et al., 1995; Bonnet et al., 1999; Fina et al., 2001) and lung cancer (Castro et al., 2001; Han et al., 2001; M.P. Wong et al., 1995). For colorectal cancer, although early studies have detected high rates of EBV infection in colorectal carcinoma tissue, using PCR, immunohistochemisrty and fluorescence in situ hybridization (Song et al., 2006; Liu et al., 2002, 2003), only one study reported significant difference in EBV detection rates between colorectal carcinoma tissue and adjacent normal mucosa (Song et al., 2006). Follow-up studies failed to show any evidence that EBV was detected at a significantly higher rate in colorectal carcinoma (Grinstein et al., 2002; Yuen et al., 1994), even in higher risk populations such as patients with ulcerative colitis (N.A. Wong et al., 2003).

In the case of Cytomegalovirus (CMV), early limited studies have detected CMV genome in the colon carcinoma tissue, whereas controls from normal colons and cases of Crohn disease were negative (Huang & Roche, 1978; Hashiro et al., 1979). Further studies then showed that CMV was not detected at a significantly higher rate in carcinoma tissue than normal tissue by multiple detection methods, such as FISH, immunohistochemistry, or DNA hybridization (Hart et al., 1982; Ruger & Fleckenstein, 1985). It was found that patients with colorectal cancer who were treated with chemotherapy had significantly increased CMV IgG titre (Avni et al., 1981). However, this finding appeared to be related to CMV infection or reactivation secondary to immunosuppression by chemotherapy rather than primary infection causing colorectal cancer.

4. Helminths

4.1 *Schistosoma japonicum*

The epidemiologic parallel between schistosomiasis japonica endemicity and the distribution of large bowel cancer has been noted in the eastern provinces of China in the 1970s (E. S. Zhao, 1981). Subsequently, ecological studies in the same endemic areas showed

a strong geographical correlation between the prevalence of schistosomiasis japonica and CRC incidence and mortality (Xu & Su, 1984). Likewise, significant association was observed between the mortality from CRC and from schistosomiasis japonica in rural China, even after adjustment for dietary factors (Chen et al., 1990; Guo et al., 1993). The authors attributed the continuing high incidence of colorectal cancer in endemic regions to persistent large populations of chronically infected individuals. This conclusion was further bolstered by a retrospective cohort study conducted in an endemic area in Japan, where the standardized mortality ratio for colonic cancer was significantly high in females who lived in the area for 50 years or more (Inaba, 1984).

More importantly, a case-control study carried out in the endemic area of Jiangsu Province, China, showed that the risk of rectal cancer was increased among subjects with a previous diagnosis of *S. japonicum* infection with odds ratios of 4.5 and 8.3 (depending on the type of controls used), but the risk of colon cancer was not significantly increased in the same patients group (Xu & Su, 1984). A similar investigation in the same endemic area has confirmed strong associations between colon cancer and early and late-stage *S. japonicum* infection, regardless of the type of control used for comparison. When the results were adjusted to smoking and family history of colon cancer, statistically significant associations were still noted. In addition, the estimated relative risk increased with the duration of exposure to *S. japonicum* infection (Mayer & Fried, 2007). Of interest also is a recent matched case-control study which reported that patients with chronic schistosomiasis japonica have more than three times risk to develop colon cancer than those with no previous exposure to schistosomal infection. Moreover, the authors attributed 24% of colon cancer cases to long-standing schistosomal infestation (Qiu et al., 2005).

The consensus of available pathological data strongly implicates an association between *S. japonicum* infestation and induction of CRC. In a review of the literature between 1898 and 1974, 276 cases of schistosomiasis japonica associated with cancer of the large intestine were analysed. The results showed significant differences between carcinoma with schistosomiasis and ordinary carcinoma in symptoms, age range, sex ratio, and histopathologic findings, indicating that schistosomiasis may induce carcinoma (Shindo, 1976). Ming-Chai et al. (1965) reported similar findings in their study of 90 cases of simultaneous CRC and schistosomiasis, and proposed that *S. japonicum* colitis, in its late phases, is a premalignant condition not infrequently leading to cancer. Supporting their previous results and giving better insight into the pathogenesis of schistosomal colorectal carcinoma, the same group has examined the mucosal changes in the immediate vicinity of the tumours of patients with schistosomiasis, and referred to the close similarity between certain schistosome-induced lesions and those associated with long-standing ulcerative colitis. Pointing to mimicry of cancer evolution in these two clinical entities, they described presence of pseudopolyps, multiple ulcers, and hyperplastic ectopic submucosal glands, with evidence of oviposition and precancerous and cancerous transformation in these lesions (Ming-Chai et al., 1980). It was also demonstrated that the closer to the tumour the area is the more ova tend to be detected (Matsuda et al., 1999). In a following study, Ming-Chai et al. (1981) observed variable degree of colonic epithelial dysplasia in 60% of cases with *S. japonicum* colitis and regarded these changes as the transition on the way towards cancer development in schistosomal colonic disease. A similar conclusion was drawn by Yu et al. (1991) from their studies on different types of schistosomal egg polyps.

Of note, distinct clinico-pathologic characteristics of S. japonicum-related colorectal cancer seem emerge from the existing literature. Bearing in mind the early environmental exposure to schistosomal infection in childhood, schistosomal colorectal cancer was notably shown to occur in younger age group with a maximum age incidence 6 to 16 years earlier than ordinary colorectal cancer (Shindo, 1976**;** Ming-Chai et al., 1965, 1980). Furthermore, the gender ratio of male to female in schistosomal colorectal cancer is consistently higher than in nonschistosomal cancer (Shindo, 1976**;** Ming-Chai et al., 1980). This can be attributed to the fact that men are more prone to schistosomal infection through contact with cercariae-infested waters during agricultural activities.

4.2 *Schistosoma mansoni*

The epidemiological evidence associating *S. mansoni* infection with CRC is lacking, of poor quality, or conflicting. Supporting the absence of such a causal association, Parkin et al. (1986) pointed out that although there is a great disparity in the geographical distribution of *S. mansoni*, CRC occurs in the African continent with clear uniformity. In a recent hospital-based study in Uganda and Zimbabwe, Waku et al. (2005) compared 950 cases of infective gastrointestinal disease, particularly schistosomiasis and amebiasis, with 249 patient controls admitted for various diseases other than GI disease. The cases were thoroughly investigated and further stratified into three groups on the basis of the stage of the disease; cured, acute, and chronic patients group. Colorectal cancer was found in 34 patients; nearly all of them had chronic schistosomiasis or amebiasis, whereas no CRC was detected in the other patients or control groups. It was concluded that large bowel cancer is strongly associated with chronic infectious gastrointestinal diseases. This study, though, was limited by the inability to adjust for potential confounders such as age and gender. Furthermore, the issue of correspondence between the population giving rise to the cases and that sampled for the controls was not addressed. To date, there have been no epidemiological studies conducted at the population level to verify the link between *S. mansoni* infestation and large bowel cancer.

The pathological evidence supporting an association between *S. mansoni* infestation and colorectal carcinoma is rather weak. In 1956, Dimmette et al. (1956) failed to demonstrate any specific pathological changes in patients with simultaneous CRC and *S. mansoni* infestation, and considered the two conditions unrelated. Contrasting to these results, a recent study by Madbouly et al. (2007) has shown that S. mansoni-associated colorectal cancer has distinctive pathological features often similar to those of colitis-induced carcinoma (Fig. 2a,b). These include high percentage of multicentric tumours and mucinous adenocarcinoma, and the tendency of the tumour to present at an advanced stage with high risk of malignant lymph node invasion. Although direct causal inference is limited, this study indicates that *S. mansoni* infestation may exercise some influence on the prognosis of patients with CRC. Other studies have examined the pathological changes in endoscopic biopsies and cadaveric specimens from the colon of patients with *S. mansoni* colitis (Mohamed et al., 1990; Cheever et al., 1987). The gross pathological lesions were akin to those observed in patients with *S. japonicum* colitis. However, histological analysis of the specimens showed no evidence of atypism or carcinomatous changes. This discrepancy in pathologic findings may be explained by the larger number of eggs deposited by *S. japonicum* than *S. mansoni* worms, thus causing more pathological problems (Ishii et al., 1994).

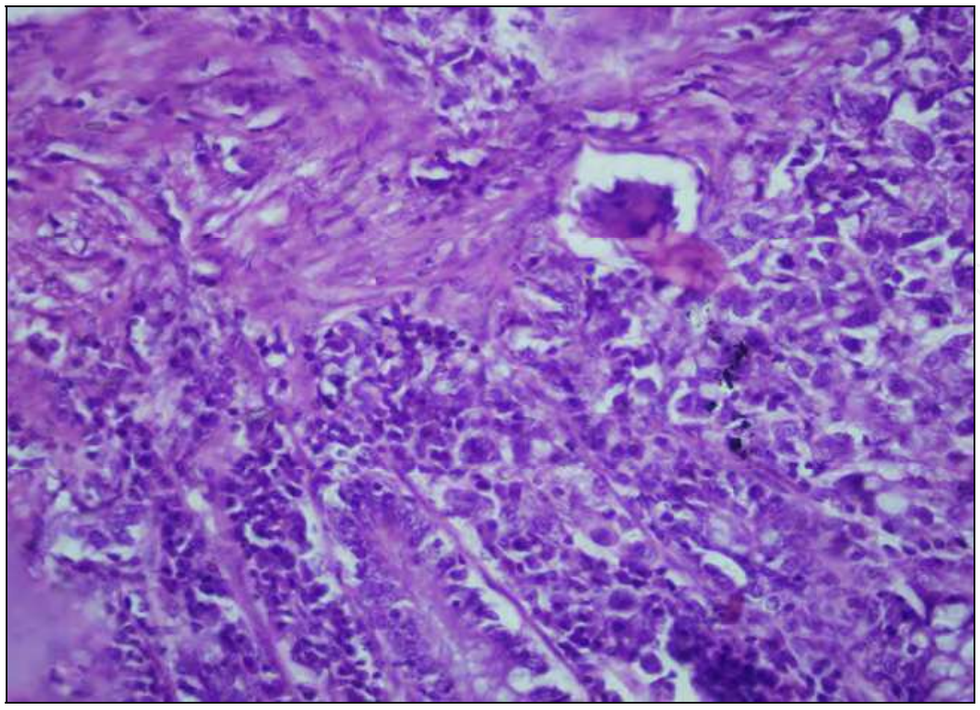

Fig. 2a. Photomicrograph showing S. mansoni egg shell in a background of mucinous adenocarcinoma. H&E × 40

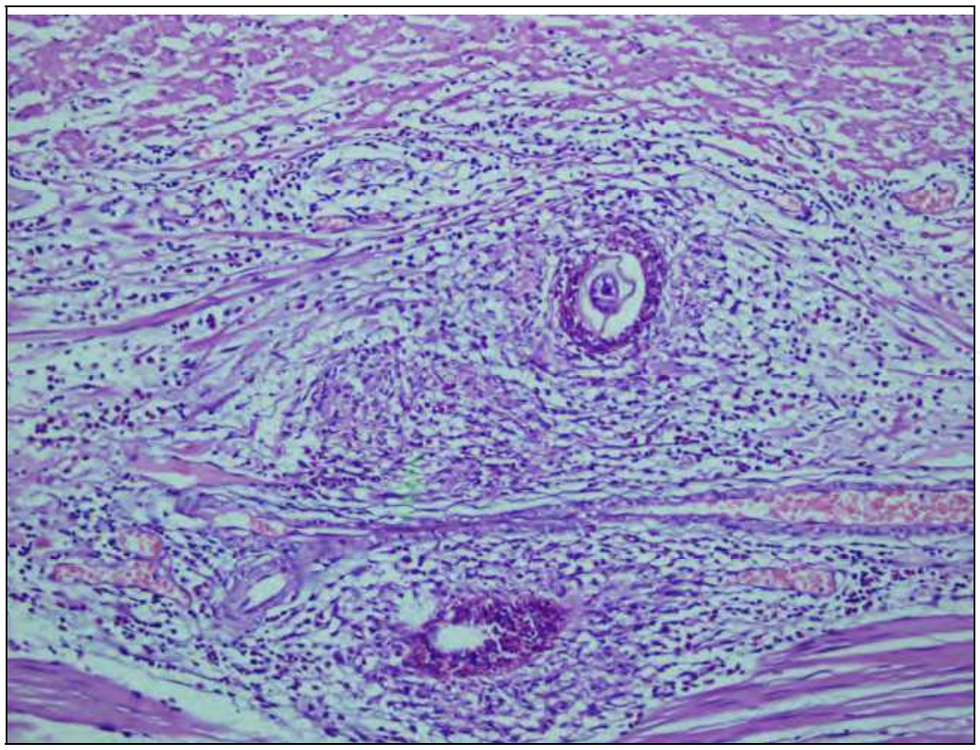

Fig. 2b. Photomicrograph showing calcified and viable S. mansoni ova with granuloma formation in the muscularis propria of the sigmoid colon. H&E × 20

4.3 Mechanisms of tumorigenesis

The exact etiopathogenesis of schistosomal colorectal cancer is enigmatic. Several explanations have been advanced for the possible role of schistosomiasis in colorectal tumorigenesis: the presence of endogenously produced carcinogens (Rosin et al., 1994), chronic immunomodulation resulting in impairment of immunological surveillance (van Riet et al., 2007), symbiotic action of other infective agents (Shindo, 1976), and the presence of schistosomal toxins (Long et al., 2004). While these factors may interact to induce carcinogenesis, chronic inflammation appears to play a central role. In support of this view are data showing that CRC tends to occur mainly in patients who had history of schistosomiasis for 10 years or more and in whom the large bowel is wholly involved (Shindo, 1976; Ming-Chai et al., 1980). Moreover, there is significantly higher rate of synchronous tumours in patients with schistosomal colorectal cancer than in patients with spontaneous colorectal cancer (Ming-Chai et al., 1980; Madbouly et al., 2007). This can be ascribed to the field effect caused by chronic schistosomal inflammation throughout the colon, a phenomenon analogous to that described in the context of colitis-associated cancer.

It has been suggested that chronic inflammatory reaction provoked by schistosome antigens provides the proliferative stimulus necessary to promote cancer growth from potentially malignant foci produced by other carcinogens (Ming-Chai et al., 1980). However, whereas increased epithelial cell proliferation likely contributes to carcinogenesis, it is insufficient to cause cancer. Rather, inflammatory cells generate potentially genotoxic mediators during the course of schistosomal infection such as reactive oxygen and nitrogen species and proinflammatory cytokines, which cause genomic instability and dysregulation of oncogenes and oncosuppresor genes (Herrera et al., 2005; Trakatelli et al., 2005). The accumulation of these molecular disturbances, in turn, drives the progression toward dysplasia and carcinoma. Another factor that may play a major role in colorectal carcinogenesis of schistosomiasis patients is the presence of concomitant enterobacterial infections. In both clinical and experimental studies, various strains of enterobacteriaceae have been described in association with schistosome infection which confers a survival advantage to bacteria by inducing immunosuppression (Chieffi, 1992; Tuazon et al., 1985). Some of these organisms are thought to promote colorectal carcinogenesis through multiple pathways such as production of reactive oxygen intermediates, dysregulation in the T cell response, and alterations in host epithelial carbohydrate expression (Hope et al., 2005).

A further explanation for the carcinogenic process of schistosomal CRC is a possible direct mutagenic effect of the schistosome soluble antigens. Evidence against this hypothesis has come from a study by Ishii et al. (1989), who evaluated the mutagenicity of *S. japonicum* extracts using the Ames *Salmonella/E. coli* test in the presence and absence of rat liver S9 mixture. They did not identify any mutagenic activity for the soluble extracts of both eggs and adult worms. Nevertheless, a weak but significant tumour-promoting activity was noted for the *S. japonicum* soluble egg antigen when tested using cultured viral genome-carrying human lymphoblastoid cells. Osada et al. (2005) tested the adult worm and egg extracts of *S. mansoni* using more reliable genetic toxicology assays, the *Salmonella* Umu test and the hypoxanthine guanine phosphoribosyltransferase (HGPRT) gene mutation assay. They could not demonstrate any mutagenic potential in either parasite extracts of *S. mansoni* before and after addition of S9 mixture.

Recent studies have thrown some light on the molecular events associated with schistosomal colorectal cancer, taking the latter as a separate clinical entity. Zhang et al. (1998) investigated

the mutation pattern in the *p53* gene in S. japonicum-associated rectal carcinomas. They observed a higher proportion of base-pair substitutions at CpG dinucleotides and arginine missense mutations among schistosomal rectal cancer patients than in patients with ordinary CRC, albeit the differences were of marginal significance. Their results also indicated that the majority of mutations in *p53* gene were in exon 7 in schistosomal group compared to exon 5 in non-schistosomal group. Barrowing from the ulcerative colitis example, nitric oxide, an endogenously produced genotoxic agent, is capable of inducing similar transition mutations and activation of *p53* gene in the inflamed colonic mucosa (Goodman et al., 2004). Conceivably therefore, it seems plausible that chronic colonic inflammation induced by schistosomal infection may follow a similar pathway.

For *S. mansoni*-associated colorectal carcinomas, it was demonstrated that parasitism is strongly associated with microsatellite instability, which is a sign of defective DNA repair (Soliman et al., 2001). This genomic instability results in DNA replication errors that preferentially affect target genes such as transforming growth factor (*TGH*)*βRII* and insulin-like growth factor (IGF)2R, and render them incapable of normal colonocytes homeostasis resulting in malignant growth (Itzkowitz & Yio, 2004). In another aspect, Madbouly et al. (2007) evaluated the expression of *p53* in patients with *S. mansoni*-related colorectal cancer, and found that mutant *p53* overexpression was significantly more frequent in schistosomal than in non-schistosomal colorectal cancer. Moreover, *p53* overexpression in schistosomal CRC correlated well with mucinous carcinoma, nodal metastasis, and tumour multicentricity. Zalata et al. (2005) developed a more comprehensive study of the expression pattern of *p53*, *Bcl-2*, and *c-myc* in seventy five CRC cases, 24 of these had pathological evidence of *S. mansoni* infection. Although they did not find a significant association between parasitism and *p53* and *c-myc* expression, their results showed that S. mansoni-associated colorectal tumours characterized by *Bcl-2* overexpression and less apoptotic activity than ordinary colorectal tumours. This supports the contention that evasion of apoptosis through change in the expression of *Bcl-2* may be an alternative molecular pathway through which genotoxic agents can induce carcinogenesis in intestinal schistosomiasis.

5. Concluding remarks

It is clearly evident that a wide array of microbial agents is associated with colorectal cancer. Nonetheless, establishing a causal link between a certain organism and colorectal cancer is a complicated process, considering the long latency of infection during which numerous endogenous and exogenous factors interact to obscure causality. For most of these putative agents, the association has been inconsistent, and may either define subsets of the tumour, or may act to modify phenotype of an established tumour, possibly contributing to some phase of oncogenesis.

Despite the fact that *H. pylori* and *S. bovis* were discovered in colorectal tumours and linked to the malignancy by seroepidemiologic studies and molecular analyses, these pathogens are considered to be at most contributing cofactors. The two reasons for this loss of etiological status were the inconsistency in the epidemiological data regarding *H. pylori* and *S. bovis* infections and risk of colorectal cancer (Gold et al, 2004; Y. S. Zhao et al., 2008), whereas none of these agents produced *de novo* colorectal cancer in animal models (Singh et al., 2000a; Biarc et al., 2004). The relation between gut mictobiota such as *B. fragilis* and *E.*

faecalis and colorectal cancer is far less convincing. Although the oncogenic potential of *B. fragilis* and *E. faecalis* is not disputed, the scarcity of epidemiological evidence renders any association hypothetical.

In case of viral agents, while HPV and JCV have oncogenic properties both in cell culture and experimental animals (Butel, 2000), the detection of viral genomes in tumour tissues is inconsistent, which can be attributed to the fact that PCR technique, used for detection of viral DNA in most studies, is subject to contamination. At this point, this precludes a causative role for these viruses in colorectal cancer, and obtaining more credible results mandates employment of combination of in situ methods for detection of viral genome and its products such as *in situ* cytohybridization and immunohistochemistry (Panago et al., 2004).

In case of *S. japonicum*, the growing epidemiological evidence and the unique clinic-pathological features of schistosome-related colorectal cancer point to a reasonably consistent association. However, *S. japonicum* has been classified by IARC as possible and not as definite carcinogen in human leading to colorectal cancer (IARC, 1994). This perhaps reflects the confounding uncertainties presented by epidemiological studies and the lack of experimental evidence. For *S. mansoni* species, it is still a matter of controversy as to whether or not *S. mansoni* infection is an association factor in colorectal cancer development and progression.

Infection-related colorectal carcinogenesis is a complex multistage process that utilizes several mechanisms. For most bacterial species and helminths associated with colorectal cancer, chronic inflammatory response and immunomodulation induced by secretory or structural proteins are the principal mechanisms of carcinogenesis. These involve release of protumorigenic mediators and dysregulation of multiple cellular transcriptional pathways including NF-κB and β–catenin. Others such as *H. pylori* primarily induce production of growth factor resulting disruption of proliferation-antiproliferation pathways. DNA tumour viruses, such as HPV and JCV, primarily target cellular tumour suppressor proteins, thus modulating cell cycle progression (Butel, 2000).

Together, our observations underpin the necessity of epidemiological studies focusing on specific strains such as CagA$^+$ H. pylori, *S. gallolyticus*, ETBF, and Mad-1 JCV. In addition, the interaction between various infectious agents in relation to carcinogenesis, as illustrated in the additive effect of *B. fragilis* and *E. faecalis* needs further evaluation. Finally it is likely that more agents, both known and unidentified, have yet to be implicated in human colorectal cancer. In the meantime, study of tumorigenic infectious agents will continue to illuminate molecular oncogenic processes.

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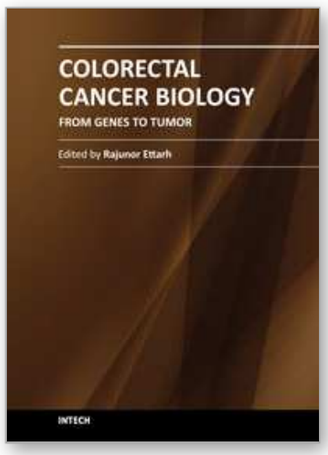

Colorectal Cancer Biology - From Genes to Tumor

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Colorectal cancer is a common disease, affecting millions worldwide and represents a global health problem. Effective therapeutic solutions and control measures for the disease will come from the collective research efforts of clinicians and scientists worldwide. This book presents the current status of the strides being made to understand the fundamental scientific basis of colorectal cancer. It provides contributions from scientists, clinicians and investigators from 20 different countries. The four sections of this volume examine the evidence and data in relation to genes and various polymorphisms, tumor microenvironment and infections associated with colorectal cancer. An increasingly better appreciation of the complex inter-connected basic biology of colorectal cancer will translate into effective measures for management and treatment of the disease. Research scientists and investigators as well as clinicians searching for a good understanding of the disease will find this book useful.

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