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The Role of Viral and Bacterial Pathogens in Gastrointestinal Cancer

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Abstract

The association of *Helicobacter pylori* (*H. pylori*) with gastric cancer is thus far the best understood model to comprehend the causal relationship between a microbial pathogen and cancer in the human gastrointestinal tract. Besides *H. pylori*, a variety of other pathogens are now being recognized as potential carcinogens in different settings of human cancer. In this context, viral causes of human cancers are central to the issue since these account for 10–20% of cancers worldwide. In the case of *H. pylori* and gastric cancer, as well as the human papillomavirus and anal cancer, the causal relationship between the infectious agent and the related cancer in the gastrointestinal tract has been clearly confirmed by epidemiological and experimental studies. Similarly, Epstein–Barr virus and the oncogenic JC virus are being suggested as possible causative agents for cancers in the upper and lower gastrointestinal tract. This review discusses various viral and microbial pathogens and their oncogenic properties in the evolution of gastrointestinal carcinogenesis and summarizes the available experimental data make a convincing agreement favoring the associations between infectious agents and specific human cancers.

Viral and bacterial pathogens have been long proposed to play a role in the development of cancer. For the past 20 years the ongoing research has continuously broadened our knowledge about the role of oncogenic infectious agents. Animal and human studies have widely suggested a carcinogenic role of several pathogens. Viruses in particular have been found to play a major role in the tumorigenic process involving several organs: the human papillomavirus (cervical cancer), the herpes viruses (Kaposi sarcoma), human and simian polyomaviruses (mesothelioma, brain tumors), the Epstein–Barr virus (B-cell lymphomas, nasopharyngeal cancer), the human T-cell leukemia virus-1 (T-cell leukemias), and the hepatitis B and C viruses (hepatocellular carcinoma).

An estimated 17.8% or approximately 1.9 million cases of the worldwide incidence of cancer in the year 2002 can be attributed to bacterial or virus induced infections (Parkin, 2006). This underlines the importance to study these specific pathogens and their pathways leading to cancer.

Cancers of the gastrointestinal tract are a major health problem and represent almost 20% of all cancer related deaths in both men and women (Ferlay et al., 2007). While the incidence of

gastric cancer has slowly declined in developed countries, the disease is still important in Asia, where possible multiple factors are key players for its pathogenesis. Contrary to gastric cancer, the incidence of colorectal and esophageal cancers is still on the rise. In the US, an estimated 112,340 new cases of colon cancers were expected for 2007 with 52,180 deaths among both sexes (Jemal et al., 2007). The picture regarding esophageal cancer is even more critical with 15,560 new cases and 13,940 deaths.

Although various risk factors may influence an individual's predisposition to the development of gastrointestinal cancer, it is clear, at least since the discovery of *Helicobacter pylori* and its role in gastric cancer, that microbial pathogens are critical players in the development of tumors of the gastrointestinal tract. This review focuses on the role of microbial pathogens in the gastrointestinal tract and tries to clarify our understanding on how bacteria and viruses induce cancer in the different segments of the gastrointestinal tract.

The first part of this review introduces the different microbial pathogens and their oncogenic properties, while the second part focuses on the different types of cancers in the gastrointestinal tract and the possible implications of viral and bacterial pathogens in their development.

Oncogenic Viral and Bacterial Pathogens

Epstein–Barr virus (EBV)

EBV is an ubiquitous herpes virus that infects >90% of the world's adult population and infected individuals remain lifelong carriers of the virus with few, if any, symptoms (Henle and Henle, 1980). However, EBV was the first human virus to be directly implicated in carcinogenesis, when the virus was isolated from biopsy tissue samples of the childhood malignancy Burkitt's lymphoma (Burkitt, 1958; Epstein et al., 1964). Subsequently, EBV was found to be strongly associated with other malignancies like nasopharyngeal carcinoma (Pathmanathan et al., 1995), post-transplant lymphoma and gastric carcinoma (Shibata and Weiss, 1992).

The oncogenic properties of EBV are mainly due to the expression of the different types of EBV nuclear antigens (EBNAs) and three latent membrane proteins (LMPs). The main transforming protein of EBV is LMP-1 which behaves like a classical oncogene by transforming fibroblasts and B-cells in vitro (Wang et al., 1985; Kaye et al., 1993). LMP-1 resembles CD40, a member of the tumor necrosis factor receptor (TNFR) family and hence mimics the cellular growth and differentiation signals that normally result from the binding of CD40 ligand (Zimmer-Strobl et al., 1996; Gires et al., 1997). In addition to these effects, LMP-1 can mediate the activation of NF- κ B (Huen et al., 1995) and upregulate bcl-2 and A20b (Fries et al., 1996; Wang et al., 1996), which protects infected cells from p53-mediated apoptosis. On the other hand, the LMP-2 gene of EBV encodes two proteins, LMP-2A and LMP-2B. The structure of these two integral membrane proteins is similar. It is thought that LMP-2 proteins play a role in modifying normal B-cell development and thus prevent activation of the viral replicative cycle to maintain EBV latency. The expression of LMP-2A in many cancers associated with EBV suggests an important function for this protein in carcinogenesis (Tao et al., 2006). A recent work done by Stewart et al. (2004) showed that LMP-2A regulates viral and cellular gene expression by modulating the NF- κ B transcription factor pathway suggesting an important role of LMP-2A in the pathogenesis of EBV-associated tumors.

Moreover, EBV encodes a series of EBV-determined nuclear antigens: EBNA-1, EBNA-2, EBNA-3 (A–C) and EBNA-LP. These products are essential for EBV-induced immortalization of the cell, and also promote EBV infection and transformation. For example, EBNA-LP binds to the tumor suppressors p53 and pRb by forming protein–protein complexes (Szekely et al., 1993). EBNA-A2 upregulates several viral and cellular genes. For example, EBNA-A2

interacts with transcription factors involved in the NOTCH signaling pathway that controls cell fate, proliferation and apoptosis (Henkel et al., 1994; Hsieh et al., 1996). Several studies have confirmed the absolute requirements for EBNA-2 and LMP-1 for cellular transformation. An important role for the transformation process has been suggested for EBNA-1, EBNA-LP, EBNA-3A, and EBNA-3C (Kieff and Rickinson, 2001).

Human papillomavirus (HPV)

Papillomaviruses are small non-enveloped DNA viruses with a virion size of ~55 nm that usually cause sexually transmitted benign tumors. However, HPV infection can sometimes progress to the development of malignant lesions (Bosch et al., 2002; Gillison and Shah, 2003; Cogliano et al., 2005). There are over 80 different HPV subtypes, which have been classified into low-risk and high-risk subtypes. The low-risk HPVs (e.g., types 6, 11, and 33) are associated with the growth of warts and benign lesions. High-risk HPVs (such as 16, 18, and 31) have been recognized as causative agents of several cancers like cervical and anal carcinoma (Ho et al., 1998; Cogliano et al., 2005). The high-risk HPVs 16 and 18 encode for at least three transforming oncoproteins: E5, E6, and E7. These proteins display transforming and growth-stimulating properties by inactivating the tumor suppressor functions of the p53 and retinoblastoma proteins (Werness et al., 1990; Heck et al., 1992; Thomas et al., 1999). Furthermore, it has been reported that the integration of HPV-DNA into host genomic DNA is associated with chromosomal instability (CIN; Ueda et al., 2003). DeFilippis et al. (2003) showed, that integration of E6 and E7 into HeLa cervical carcinoma cells inhibits telomerase activity, increases cyclin-dependent kinase activity and induces expression of c-myc, suggesting that E6 and E7 expressions are required for increased cell proliferation and cell survival.

Helicobacter pylori—*H. pylori* is a gram-negative microaerophilic spiral bacterium, measuring 2–4 µm in length and 0.5–1 µm in width. The bacterium has 2–6 unipolar, sheathed flagella, which confer motility and allow rapid movement in viscous solutions like the mucus layer overlying gastric epithelial cells. The infection with the bacterium remains the main cause of stomach and duodenal diseases. Large epidemiological studies have provided a convincing evidence that *H. pylori* is associated with chronic gastritis, peptic ulcer disease, low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma. The infection is usually acquired during childhood, and when left untreated shows a lifelong persistence in the host (Everhart, 2000). Various mechanisms enable the bacterium to colonize the gastric epithelium and to persist in the mucosa for a very long period: ammonia-mediated metabolism and resistance to acid by using urease; use of bacterial virulence factors; change of the host immune response, and induction of signaling pathways.

The infection rate with *H. pylori* varies among the populations, but remains still high (~40%) in people over 50 years of age in many Western countries. Recent data however demonstrate a lower prevalence (7.1%) in people between 16 and 20 years of age, which most likely will also result in a progressively lower incidence of severe gastroduodenal diseases as future generations age (Malfertheiner et al., 2002, 2004).

JC virus (JCV)

JCV belongs to the polyomavirus family along with the human virus BK (BKV) and the simian virus 40 (SV40). JCV is a 5.13-kb, closed, circular, supercoiled, double-stranded DNA virus that encodes six proteins: Two (alternatively spliced) viral oncoproteins, the T- and t-antigens, three viral capsid proteins—VP1, VP2, and VP3, and the agnoprotein.

JCV infects humans worldwide, and about 90% of the adult population develop antibodies against the virus by age 15 (Major et al., 1992). The initial infection is asymptomatic, but the

virus establishes a lifelong persistent infection. However, in patients with impaired cell-mediated immunity, the neurotropic virus may be reactivated and cause a lytic infection of oligodendrocytes, leading to the lethal demyelinating disease progressive multifocal leukoencephalopathy (PML; Padgett et al., 1971). The oncogenic potential of JCV was discovered when the virus was injected into the brain of Syrian hamsters inducing aneuploid tumors (Walker et al., 1973; Reiss and Khalili, 2003). In a broad range of experiments with several animal models, the oncogenic potential of JCV has been further established (London et al., 1978; Ohsumi et al., 1986). Transgenic mice that express JCV T-antigen (T-Ag) can develop tumors of the pituitary gland and malignant peripheral nerve sheath tumors that resemble rare neoplasms that can occur in patients with neurofibromatosis (Gordon et al., 2000; Shollar et al., 2004). Furthermore, the virus has been found in many human brain tumors, most notably medulloblastomas (Rencic et al., 1996; Krynska et al., 1999; Del et al., 2001; White et al., 2005). JCV is oncogenic because of the expression of the highly transforming protein T-Ag.

T-Ag can transform mammalian cells, in part, by binding and inactivating two key tumor suppressor proteins that regulate cell cycle progression: p53 and pRb (Bollag et al., 1989; Dyson et al., 1990; Krynska et al., 1997). Loss of the tumor suppressor protein p53 is observed in approximately 50% of all human cancers. As a G1/S checkpoint protein, p53 regulates the cell cycle and apoptotic events (Levine, 1997; Vogelstein et al., 2000). As a consequence of the binding and inactivation of p53 by T-Ag, JCV prevents the inhibition of cell cycle or apoptosis that would be expected with the onset of CIN. pRb is another inhibitor of cell cycle progression from G1 to S phase, and acts through its ability to interact with the E2F family of transcription factors (Caracciolo et al., 2006). The inactivation of pRb family members by T-Ag binding leads to the release of E2F, and subsequently the expression of E2F-dependent genes such as c-fos and c-myc, leading to increased cellular proliferation. Thus JCV provides for itself an optimal cellular environment for its replication and packaging during a lytic polyomavirus infection, and also facilitates transformation in non-permissive cells.

JCV T-Ag also induces karyotypic changes when transfected into diploid cells (Ricciardiello et al., 2003). Several studies have reported CIN in T-Ag positive cells (Hunter and Gurney, 1994; Woods et al., 1994; Kappler et al., 1999). The mechanisms underlying the type of genetic instability induced by T-Ag are only partially understood. Trojanek et al. demonstrated that JCV T-Ag inhibits homologous recombination DNA repair, which is a part of the maintenance system insuring genomic stability. This action of JCV T-Ag is mediated through an interaction with the insulin receptor substrate 1 (IRS-1) (Trojanek et al., 2006). Additionally, the receptor for insulin-like growth factor (IGF-1R) plays a major role in mediating both physiological and pathological responses in the cell. The activation of IGF-1R, together with the interaction between JCV T-Ag and IRS-1, triggers cell proliferation, sends anti-apoptotic signals, and inhibits homologous recombination repair, all of which supports the evolution of CIN and the emergence of cancer (Reiss et al., 2006).

Cancers of the Gastrointestinal Tract

Esophageal cancer

Esophageal cancer is the ninth most common malignancy worldwide with an extremely poor prognosis and an overall 5-year survival rate of less than 10% (Pisani et al., 1993, 2002). Incidence rates of this cancer vary worldwide. The highest rates have been found in Asia, southern and eastern Africa and in these high-risk areas the annual mortality exceeds 100 deaths per 100,000 persons (Stoner and Gupta, 2001). Cancers of the esophagus can be divided into two major types: squamous cell carcinoma and adenocarcinoma. In recent years, esophageal adenocarcinoma has risen sharply in the industrialized countries (Blot and McLaughlin, 1999). This is mainly due to Barrett's Esophagus (BE), a metaplastic change of the esophageal

epithelium in the gastro-esophageal junction, which may be induced by chronic gastro-esophageal reflux (van der Woude et al., 2002). BE has been shown to be responsible for 86% of primary esophageal adenocarcinomas (Haggitt et al., 1978). Other risk factors, which mainly account for squamous cell carcinoma, include alcohol, tobacco, smoked food (content of nitrosamines and nitrites), fungal toxins, and thermal injuries (hot drinks and soups; Cheng et al., 1995; Garidou et al., 1996). In addition to these factors, recent findings suggest a role for viral pathogens, in particular of HPV, EBV and JCV in the development of this disease.

HPV and esophageal cancer—Previous studies showed that many HPV subtypes have been found in esophageal cancer specimens (Sur and Cooper, 1998; Matsha et al., 2002). Although several studies failed to detect HPV in esophageal cancer tissues (Gao et al., 2006), many others showed a possible etiological implication for the virus in this disease (Syrjanen, 2002). In particular, the frequent detection of the high-risk HPV-16 and -18 supports the causal role of HPV in esophageal cancer (Togawa et al., 1994). Indirect evidence has been provided by an in vitro experiment in which the genomes of HPV-16 and -18 without the E1 and E2 proteins were transiently transfected into esophageal cancer cells (Togawa and Rustgi, 1995). The HPV E1 and E2 proteins are involved in viral DNA replication and the regulation of the early transcription. In this study the viral genomes replicated without E1 and E2, which suggests that specific host nuclear factors expressed by esophageal squamous epithelial cells may support HPV replication. Further evidence for the involvement of HPV in esophageal carcinogenesis has resulted from animal experiments. In particular, studies in cattle described a persistent papillomatosis and carcinomas in these animals, which was experimentally reproducible with bovine papillomavirus 4 (BPV4; Campo, 1987). It has been shown that up to 96% of the cancer-bearing animals had concomitant papillomas, and the progression from benign papillomas to carcinomas could be clearly identified (Jarrett et al., 1978; Jarrett, 1987). Recently, Shen et al. (2004) were able to demonstrate the transformation toward malignancy of a human fetal esophageal epithelial cell that was immortalized by gene E6/E7 of HPV type 18. Furthermore this infection induced telomere length shortening, altered telomerase activity and aneuploidy, as well as the amplification of several oncogenes including c-myc and ras, and different patterns of p53 expression depending on the stage of transformation. Interestingly, with this study the authors demonstrated that HPV-induced carcinogenesis is a multistage dynamic transformation process, which goes through the initial, immortal, premalignant, and malignant transformation.

In conclusion, these studies provide abundant evidence for a causative role of HPV in esophageal carcinogenesis, but several questions need to be answered and more in vivo experiments need to be carried out before HPV can be more clearly implicated in human esophageal cancers.

Epstein-Barr virus, JC virus, and esophageal cancer—Other viruses like Epstein-Barr virus (EBV) and JC virus (JCV) have also been detected in esophageal cancers. Because of the close anatomical proximity of the esophagus to the nasopharynx and the involvement of EBV into nasopharyngeal cancer, EBV was thought to be involved in the esophageal carcinogenesis. However, subsequent studies revealed either a low prevalence, or no detection of, EBV in esophageal cancer (Lam et al., 1995; Jenkins et al., 1996; Yanai et al., 2003). The explanation for the detection of EBV by PCR in some cases might be due to the detection of the virus from stromal lymphocytes. To date, there is no sufficient evidence that EBV is important in the pathogenesis of this disease.

Recently, Del et al. (2005) detected the neurotropic polyomavirus JCV and its potent transforming protein T-antigen in both esophageal adenocarcinomas and squamous cell carcinomas, and suggested a possible role of JCV in the development of both diseases. This is

thus far the only report of JCV in the esophageal cancer, and further investigation and confirmation of these findings are required.

Gastric cancer

Despite its decreasing incidence, gastric cancer remains the fifth most common cancer, the fourth leading cause of cancer-related death, and is responsible for the death of more than 100,000 people each year in Europe (Ferlay et al., 2007). Histologically, gastric adenocarcinoma is usually classified according to the Lauren's classification into well differentiated/ intestinal and diffuse/signet ring cell types (Lauren, 1965). The intestinal type gastric cancer is associated with atrophy, intestinal metaplasia, and corpus-dominant gastritis. On the other hand, the diffuse type typically occurs with pangastritis without atrophy, or arises even within non-inflamed apparently normal gastric mucosa (Cuello et al., 1979). Depending on its location, gastric cancer is suggested to be the consequence of either *H. pylori* infection or *H. pylori* independent etiologic factors. Most gastric cancers are located in the distal part of the stomach, and evidence for a causal relationship with *H. pylori* infection is strong, however there may also be a relationship with proximal gastric cancer.

***H. pylori* and gastric cancer**—*H. pylori* induces chronic gastric inflammation in all infected individuals that eventually, depending on the individual's susceptibility, may progress to atrophy, metaplasia, dysplasia, and finally to gastric cancer (Peek and Blaser, 2002).

Because of the strong association between *H. pylori*-infection and gastric cancer, the WHO has classified *H. pylori* as a class 1 carcinogen since 1994 (IARC Monographs on the Carcinogenic Risks to Humans, 1994). A malignant complication of *H. pylori* infection other than gastric cancer is mucosal-associated-lymphoid-type (MALT) lymphoma (Hessey et al., 1990; Marwick, 1990; Stolte, 1992; Suerbaum and Michetti, 2002; Vogiatzi et al., 2007). Most infected individuals fortunately remain asymptomatic and the bacterial infection does not lead to gastric cancer, but *H. pylori*-infected patients may have a 2- to 20-fold increase in risk of developing gastric cancer compared to uninfected individuals (Huang et al., 1998; Ekstrom et al., 2001). The fact that *H. pylori* infection leads to gastric cancer in only 0.1–0.5% of the infected subjects underscores the importance of others factors in the development of the cascade leading to cancer. *H. pylori*-induced gastric carcinogenesis depends on at least three different key factors: *H. pylori* and its different virulence determinants, a genetically susceptible host, and permissive environmental factors.

Virulence determinants of *H. pylori*—*H. pylori* strains are extremely diverse and isolates within an individual can change over time, due to DNA rearrangements, recombination events and endogenous mutations (Salama et al., 2000; Cooke et al., 2005). This diversity makes it difficult to identify bacterial virulence factors responsible for the induction of gastric cancer. Among bacterial factors identified, the *cag* pathogenicity island, the vacuolating cytotoxin (VacA), and the outer-membrane protein BabA have been identified to be the most critical ones in the association with malignancy (Peek and Crabtree, 2006). These gene products seem to interact with each other and their expression represents an increased risk for the development of gastric cancer.

The *cag* pathogenicity island (PAI) type IV secretion system (TFSS)—*H. pylori* *cagA*+ strains show an association with higher grades of inflammation and a significantly increased risk of developing gastric cancer (Parsonnet et al., 1997; Enroth et al., 2000). *CagA* + strains contain a 40-kb region of DNA known as the *cag*-PAI. The *cag*-PAI plays an important part in *H. pylori* pathogenesis, and is not present in all strains. The prevalence of *cag*-PAI+ strains varies widely between different geographical regions, with the highest prevalence in Asia and Africa (Suerbaum and Josenhans, 2007). The *cag*-PAI encodes a type IV secretion

system that translocates the *cagA* and other bacterial products (peptidoglycans) into the gastric epithelial cells (Backert et al., 2000; Odenbreit et al., 2000). A recent study by Kwok et al. demonstrated that the *H. pylori* *cagL* protein, a specialized adhesion molecule, binds to and activates the integrin $\alpha_5\beta_1$ receptor on gastric epithelial cells. This interaction triggers *cagA* delivery into target cells as well as activation of focal adhesion kinase and Src (Kwok et al., 2007). Once injected into the host cell, *cagA* becomes tyrosine phosphorylated at its five amino-acid EPIYA repeat region by host Src kinase (Selbach et al., 2002; Stein et al., 2002). After phosphorylation, *cagA* binds specifically to, and activates, the oncogenic tyrosine phosphatase Shp-2, leading to the activation of the mitogenic Ras-mitogen-activated protein kinase (MAPK) pathway, involving the Ras-dependent kinases ERK1 and ERK2 (Higashi et al., 2002; Tsutsumi et al., 2003; Hatakeyama, 2004). The activation of this pathway leads to dephosphorylation of host-cell proteins (Asahi et al., 2000; Odenbreit et al., 2000; Stein et al., 2000) and morphological changes in the epithelial cells (Segal et al., 1999).

Previous data from Brandt et al. (2005) indicated that *cagA* also activates the Ras-Erk pathway in an Shp-2-independent manner. This activation leads to an increased interleukin (IL)-8 release and NF- κ B activation. Interleukin (IL)-8 release leads to the recruitment of neutrophils into the gastric mucosa and NF- κ B activation is essential in inflammation associated cancer (Brandt et al., 2005).

In addition, independent of its phosphorylation status, *cagA* disrupts the apical junctional complex of gastric mucosal cells that maintains the epithelial barrier function and regulates the cell-cell contact (Amieva et al., 2003). Interestingly the *cagA*-Shp-2 complex cannot be detected in the gastric mucosa of patients with intestinal metaplasia or gastric cancer, whereas it is found in chronic atrophic gastritis samples (Yamazaki et al., 2003). These findings suggest that *cagA* expression may represent an early event in *H. pylori*-induced carcinogenesis.

The VacA toxin—VacA is an 88 kDa toxin, which is encoded by all *H. pylori* strains, but there is a considerable genetic diversity among the vac alleles (Atherton et al., 1995, 1997; Cover and Blanke, 2005). Regions of major diversity are localized to the VacA secretion signal sequence (allele types s1 or s2) and the mid-region (m1 and m2). The most extensively studied have been the s1 and m1 vac allele that is strongly correlated with the presence of the *cag* PAI (Covacci et al., 1993; Tummuru et al., 1993), and is associated with enhanced epithelial cell injury (Ghiara et al., 1995; Atherton et al., 1997) and distal gastric cancer (Van Doorn et al., 1999), compared with VacA m2 strains. As a secreted protein, VacA has the ability to induce the formation of cytoplasmic vacuoles and stimulates epithelial cell apoptosis in several gastric cell lines (Leunk et al., 1988; Rudi et al., 1998; Peek et al., 1999; Galmiche et al., 2000; Kuck et al., 2001). Previous studies suggested that VacA acts as a multifunctional protein that modulates epithelial cell and immune-cell function (Cover and Blanke, 2005). Furthermore, VacA efficiently blocks proliferation of T cells by inducing cell cycle arrest in the G1/S phase, which could explain the persistence of *H. pylori* infections (Gebert et al., 2003).

The outer-membrane protein BabA—BabA, encoded by the strain-specific gene *babA2*, is a 78-kDa outer-membrane protein. Depending on the geographic region, 40–95% of *H. pylori* strains express BabA (Prinz et al., 2003). BabA binds the Lewis b blood group antigen and related ABO antigens on gastric epithelial cells which enables maximal adherence of the bacterium to gastric epithelium (Ilver et al., 1998). Patients infected with BabA positive strains have a higher density of bacterial colonization in the gastric mucosa and higher levels of the proinflammatory cytokine IL-8, which leads to enhanced mucosal inflammation (Rad et al., 2002). *H. pylori* strains expressing BabA are associated with an increased incidence of gastric adenocarcinoma. More importantly, the presence of BabA is correlated with the presence of *cagA* and the s1 allele of VacA. It is known that strains possessing all three genes are associated with the highest risk of gastric cancer (Gerhard et al., 1999).

Additional aspects of *H. pylori*-induced gastric carcinogenesis—The *cagPAI+* *H. pylori* strains clearly have an important role in the induction of gastric cancer. However, the very high frequency (nearly 100%) of *cagPAI+* *H. pylori* strains in countries like Korea and Japan indicates the contribution of additional virulence factors for the cancer development in these populations (Covacci et al., 1993; Shimoyama et al., 1997). Previous studies from Suganuma et al. (2005, 2006) identified tumor necrosis factor- α -inducing protein (*Tip α*) released from *H. pylori* as a carcinogenic factor (Kuzuhara et al., 2007). They demonstrated that *Tip α* induced upregulation of TNF- α in gastric cells, mediated through NF- κ B activation, indicating that *Tip α* acts like an inducer of NF- κ B activation. It is well accepted that NF- κ B is essential for promoting inflammation-associated cancer (Brandt et al., 2005) and the authors proposed that the activation of NF- κ B via *Tip α* may play an important role in stomach carcinogenesis, which may provide a new model for gastric cancer development.

Recent work in the ongoing research into *Helicobacter*-induced carcinogenesis has focused on the role of stem cells in cancer. Houghton et al. (2004) showed that chronic infection of C57BL/6 mice with *Helicobacter felis*, a known carcinogen in animal models, led to the repopulation of the stomach with bone marrow-derived cells (BMDCs). In this study the authors indicated that transdifferentiation of BMDCs to gastric epithelial cells would lead to intraepithelial cancer through metaplasia and dysplasia. This work showed that BMDCs might fail to differentiate properly and progress to cancer only in the *Helicobacter*-infected environment. For a more detailed discussion of this topic, we refer to two recent reviews (Starzynska and Malfertheiner, 2006; Correa and Houghton, 2007).

The role of host genetic factors in gastric cancer—Host genetic factors have a significant impact in the clinical outcome and anatomical distribution of *H. pylori* infection. Several functional polymorphisms in the host have been previously described, involving interleukin (IL)-1, tumor necrosis factor alpha (TNF- α), and IL-10. These polymorphisms increase the risk of distal gastric cancer.

H. pylori-infected individuals with the *IL-1B*-31**C* or —511**T* and *IL-1RN2**/*2 are at increased risk of developing hypochlorhydria and gastric atrophy in response to *H. pylori* infection (El-Omar et al., 2000). This is mainly due to IL-1 β , which is the earliest and most important proinflammatory cytokine in the context of *H. pylori* infection, and it is also the most powerful known acid inhibitor. Patients carrying these polymorphisms have a two- to three fold increased risk of developing gastric cancer compared with subjects who have the less proinflammatory genotypes (El-Omar et al., 2003).

TNF- α is another powerful proinflammatory cytokine that is produced in the gastric mucosa in response to *H. pylori* infection (Crabtree et al., 1991). Compared to IL-1 β , TNF- α has also an acid inhibitory effect but at a much weaker level. Polymorphisms in this gene are correlated to an increased risk of gastric cancer (Machado et al., 2003). The polymorphism in the IL-10 gene, in association with down-regulation of the proinflammatory cytokine IL-10, results in elevated levels of IL-1 β , TNF- α , and interferon- γ . Previous studies focusing on the combination of disease-related polymorphisms led to estimates of a 27-fold increased risk of developing gastric cancer in *H. pylori*-infected individuals compared to those who were not infected (El-Omar et al., 2003). In addition, ongoing investigations into other genetic polymorphisms have revealed a broad range of new loci associated with an increased risk of gastric cancer, which are presented in Table 1.

Epstein–Barr virus (EBV), JCV, and gastric cancer—About 6–16% of gastric adenocarcinoma cases worldwide are associated with EBV (Takada, 2000). EBV-positive gastric cancers are more likely to be in male patients (Tokunaga et al., 1993), in the antrum of the stomach (Galetzky et al., 1997) and frequently associated with poorly differentiated tumors

(Adachi et al., 1996; Gulley et al., 1996). The virus is found in almost all tumor cells and the viral DNA shows monoclonality in EBV-positive cancers (Fukayama et al., 2001). It has also been demonstrated that EBV-positive gastric carcinomas are associated with the upregulation of the anti-apoptotic protein bcl-2, and down-regulation of E-cadherin which is an integral component of the cell–cell adhesion (Shiozaki et al., 1996; Kume et al., 1999; Wu et al., 2000). Those findings implicate a delayed apoptosis and abnormal cellular differentiation in EBV-positive gastric carcinomas. This suggests that the virus might play a causative role in the development of a subset of gastric cancers. This conclusion is confounded by the lack of expression of the EBV oncogenes in EBV-positive gastric cancers. Of the different types of EBV EBNA, only EBNA-1 is expressed, and of the three LMPs, only LMP-2A is expressed in some cases (Takada, 2000; Luo et al., 2005).

Kim et al. investigated whether viral microRNAs (miRNAs) were expressed in EBV-associated gastric carcinomas. miRNAs have been proposed to play an important role in the viral cell cycle (Kim et al., 2007). miRNAs may support cell proliferation or suppress apoptosis under certain conditions and might also have a function as tumor suppressors or oncogenes (Bartel, 2004; Cimmino et al., 2005; Esquela-Kerscher and Slack, 2006). In a previous study, Pfeffer et al. (2004) were able to clone five EBV miRNAs, clustered in two genomic regions. One cluster of miRNAs was found in the BHRF gene encoding three miRNAs (miR-BHRF1-1, miR-BHRF1-2, miR-BHRF1-3). The other cluster is located within the BART gene (miR-BART1 and mi-BART2). Kim et al. were able to demonstrate the expression of BART miRNAs in EBV-infected gastric carcinoma cell lines, in an animal model, as well as in human gastric carcinoma tissues. Although they failed to detect the expression of BHRF1 miRNAs, the expression of BART miRNAs might provide new possible insights into EBV-induced epithelial cell transformation.

A recent study by Shin et al. (2006) demonstrated the expression of the oncogenic JCV protein T-Ag in a subset of gastric cancer. These findings were confirmed by Murai et al. (2007) showing a high JCV load in gastric cancer. However, in this study the viral oncoprotein T-Ag was reportedly expressed in only 1 of 23 cancer specimens. Taken together, these studies indicate a possible role for viruses as causative infectious agents for cancers in the proximal stomach.

***H. pylori* and gastric MALT lymphoma**—MALT lymphomas are a unique and distinct form of marginal zone B-cell-non-Hodgkin's lymphoma. MALT lymphomas account for approximately 7–8% of all non-Hodgkin's lymphoma and the gastrointestinal tract is the most common site of the disease (The Non-Hodgkin's Lymphoma Classification Project, 1997). The strongest evidence linking *H. pylori* to this disease is that 62% of patients with low-grade gastric MALT lymphoma have complete remission within 12 months of *H. pylori* eradication (Fischbach et al., 2000, 2004). Furthermore, *H. pylori* is present in the gastric mucosa of 70–90% of patients with gastric MALT lymphoma (Wotherspoon et al., 1991). MALT lymphoma is a good example of the close relationship between chronic inflammation and lymphomagenesis. The hypothesis that MALT lymphoma develops as a consequence of chronic inflammation is supported by the association between low-grade gastric MALT-lymphoma and *H. pylori* induced gastritis (Eidt et al., 1994). Furthermore, several autoimmune diseases (i.e., Sjogren syndrome, Hashimoto's thyroiditis) that are associated with a chronic inflammation show an increased risk of developing MALT lymphomas (Royer et al., 1997; Derringer et al., 2000). In vitro experiments indicate the presence of antigen-driven clonal expansion, showing that B-cells from low-grade MALT lymphomas proliferate in co-culture with *H. pylori*. This stimulation is driven by tumor-infiltrating T-cells activated by *H. pylori* (Hussell et al., 1993, 1996).

H. pylori has been mainly linked to low-grade MALT lymphomas and even though the exact mechanisms underlying the transition of low-grade to aggressive lymphoma remain unclear, several studies have found genetic alterations associated with this histological transformation, including p53 allelic loss and mutation, hypermethylation of p15 and p16, and chromosomal translocations (Du et al., 1995; Martinez-Delgado et al., 1998; Min et al., 2006). The t(11:18) (q21;q21) chromosomal translocation has been described which results in the fusion of the apoptosis inhibitor-2 gene (API2) on chromosome 11 with the MALT1 gene on chromosome 18 (Zucca et al., 2000; Farinha and Gascoyne, 2005). As a result, the fusion protein API2-MALT1 activates the NF- κ B pathway, which plays a central role in the regulation of diverse biological processes, and may promote the survival of B-cell clones via anti-apoptotic effects. The genetic abnormalities, which facilitate the transition of low-grade MALT lymphoma to an aggressive lymphoma have been linked to the presence of *H. pylori* CagA-positive strains. It has been therefore hypothesized that the release of genotoxic free radicals in the *H. pylori*-infected environment might play a role in the development of oncogenic genetic alterations (Peng et al., 1998; Ye et al., 2003).

Colorectal cancer

Colorectal cancer (CRC) is the fourth commonest cancer in Western Countries (Jemal et al., 2005) affecting over one million of new cases globally every year with almost 500,000 deaths (Vainio and Miller, 2003). The molecular pathogenesis of this cancer is incompletely understood, but over the last 20 years it has become clear that CRC evolves through multiple pathways (Jass, 2006, 2007). Three molecular features have been identified in CRC: microsatellite instability (MSI), CIN and the CpG island methylator phenotype (CIMP; Jones, 1996; Jones and Laird, 1999; Goel et al., 2003). In about 15% of all colon cancers, MSI is the mutational signature, and the tumors occur as a consequence of the inactivation of the DNA mismatch repair system (MMR). This is either due to germline mutations in an MMR gene, which occurs in Lynch syndrome (Aaltonen et al., 1993; Ionov et al., 1993), or more often, through hypermethylation of the hMLH1 gene promoter, which occurs as an acquired event in sporadic cancers (Kane et al., 1997). CIN is characterized by aneuploidy and frequent loss of heterozygosity (LOH), which facilitates the sequential inactivation of the adenomatous polyposis coli (APC) and p53 genes, respectively. CIN is present in more than 50% of CRC (Lengauer et al., 1997). Methylation of cytosine residues at CpG-rich sequences (CpG islands), present in the promoter regions of many tumor suppressor genes, is a feature of about 35–40% of colorectal CRC (Baylin et al., 1998; Goel et al., 2003). The causes and the molecular mechanisms underlying CIN and epigenetic alterations, which occur in approximately 80–85% of all CRCs, are still a matter of controversy. An infection with an oncogenic virus might provide some reasonable explanations for many of these findings.

JCV and colorectal cancer—It has been previously reported that JCV DNA sequences are frequently present in the upper and lower gastrointestinal tract and in CRCs, with >10-fold higher viral loads in cancers than in the adjacent normal colon (Laghi et al., 1999; Ricciardiello et al., 2000; Ricciardiello et al., 2001). In this context, Khalili et al. demonstrated that T-Ag is involved in the Wnt signaling pathway. The authors showed that T-Ag forms a complex with b-catenin, a central component of the Wnt pathway, and this is associated with the translocation of β -catenin to the nucleus, with the consequent transcriptional activation of c-myc and cyclin D1 (Enam et al., 2002). The transcription factor c-myc is commonly deregulated in tumorigenesis, and is overexpressed in nearly 70% of CRCs (Erisman et al., 1985). c-myc was one of the first oncogenes recognized to modulate a broad range of biological activities including cell proliferation, growth and transformation. It has been shown that upregulation of c-myc increases apoptosis, genomic instability and angiogenesis (Ponzielli et al., 2005).

Furthermore, Ricciardiello et al. (2003) demonstrated that JCV T-Ag directly induces CIN in human colonic cells and that interaction of JCV T-Ag with β -catenin and p53 causes morphological changes and loss of cell–cell contact. In addition, Goel et al. (2006) demonstrated a significant association between T-Ag expression and CIN in human CRCs. Another important point of this study was that it revealed a strong association between T-Ag expression and the methylator phenotype in CRC. Aberrant methylation in connection to JCV may play a role in early stages of carcinogenesis. Taken together, these results indicate that JCV may be involved in two of the principal molecular mechanisms of carcinogenesis in the colon and rectum: abnormal DNA methylation and CIN.

Anal cancer

Anal cancer is a rare tumor that accounts for 1.5% of cases of the gastrointestinal tract cancers in the USA. In 2007, 4,650 men and women were estimated to develop anal cancer with estimated deaths in 690 individuals (Jemal et al., 2007). Over the last two decades there has been a rising incidence of anal cancer and studies have identified several risk factors for anal cancer: persistent infection with high-risk genotype human papillomaviruses (HPV), cervical dysplasia or cancer, HIV seropositivity, low CD4 count, cigarette smoking, receptive anal intercourse, and immunosuppression after organ transplant (Daling et al., 2004).

HPV, human deficiency virus (HIV), and anal cancer—Several studies analyzing European, Asian and United States populations detected HPV DNA in 70–100% of anal cancer biopsy specimens (Williams et al., 1996; Frisch et al., 1999; Daling et al., 2004). The HPV genotypes detected were mainly the high-risk HPVs 16 and –18 (Frisch et al., 1997; Carter et al., 2001; Munger and Howley, 2002), which implicate this virus as an etiologic agent for the development of squamous cell carcinoma of the anorectal region. The high-risk HPVs 16 and –18 encode the transforming oncoproteins E6 and E7, which inactivate the tumor suppressor functions of p53 and Rb. There is an association between the expression of E6 and an increased risk of high-grade anal neoplasia (Da Costa et al., 2002).

There is a well-documented association between HIV infection, HPV, and cancer. The risk for the development of anal cancer is 37-fold higher in HIV-positive men compared to the general population (Frisch et al., 1997). The risk of anal cancers in HIV-positive women is nearly sevenfold higher over the general population. Furthermore anal cancer occurs almost two decades earlier in both HIV-positive women and men (Frisch et al., 2000). These findings support the hypothesis that HIV infection interacts with HPV, and has a major impact on the etiology of anal cancer. There are several possible mechanisms that may provide a reasonable explanation for these findings: the impact of the immunological changes in the HIV-infected population, direct interactions between HIV and HPV, and direct effects of HIV triggering anal carcinogenesis.

The immune response to HPV plays a critical role in controlling the HPV infection. In general, women become HPV negative after age 30, and only a small proportion of infected healthy individuals develop lesions. Even a smaller percentage acquire high grade dysplasia or cancer (Schiffman, 1992). However, HIV-positive patients have a substantially higher risk of anal cancer and the risk is inversely proportional to the CD4 count (Critchlow et al., 1995; Palefsky et al., 1998).

Several studies have indicated that the local immune response to HPV is altered in HIV-positive individuals (Sobhani et al., 2004). Dendritic Langerhans cells seem to play an important role in the local immune response to HPV infection. Levi et al. (2005) reported that HIV viremia is associated with a decreased number of dendritic cells, suggesting an impaired local immune response to a HPV infection.

Other mechanistic factors contributing to this may be the down-regulation of regulatory cytokines. Kobayashi et al. (2004) demonstrated the down-regulation of regulatory cytokines and a decrease in immune cell densities in cervical intraepithelial neoplasia of HIV-positive women, indicating that both pro- and anti-inflammatory responses are suppressed in HIV-positive women.

Previous in vitro studies have suggested a direct interaction between HIV and HPV at a molecular level. The HIV-1 tat protein transactivates the HPV long control region, and in vitro data suggest that HIV can modulate HPV gene expression (Vernon et al., 1993). However the HIV-1 tat protein has never been found in HPV-infected epithelium in vivo and so it remains speculative if the two viruses interact directly and influence anal carcinogenesis.

Another interesting point of anal carcinogenesis is found in the genetic and epigenetic changes of HIV-positive individuals. Allelic loss is a key feature of CIN, and certain loci are targets in many gastrointestinal cancers. Gervaz et al. (2004) demonstrated that CIN, and specifically allelic losses at 18q (DCC and the SMAD genes), 17p (p53) and 5q (APC) are relatively uncommon in the anal cancers of HIV-positive patients, whereas in HIV-negative patients the allelic losses at these loci were significantly more frequent. Therefore these authors suggested that CIN is part of the mutational signature of anal cancer in HIV-negative patients, but that and that the immunosuppression in the HIV population triggers an alternative pathway of carcinogenesis.

It is possible that MSI plays a role in the putative alternative pathway. In cervical and lung cancers, MSI has been reported to occur more frequently in HIV-positive patients than in the HIV-negative population (Wistuba et al., 1998, 1999). In those two studies, the frequency of microsatellite alterations in the HIV-positive group was six fold greater than in the negative group, suggesting that MSI may be important in HIV-associated tumors. Thus, there is a need for additional investigation to determine the interactions between HIV and HPV in anal cancer, and to define their exact role in anal carcinogenesis.

Conclusion

Research over the last 20 years has shown that viruses and bacterial pathogens are either definitive causative agents or play at least a major role in the etiology of many gastrointestinal cancers (Table 2). Improved abilities to detect and analyze microbial gene products will make it ever more likely to implicate novel microbial pathogens in human cancers in the future. In particular, the era of AIDS and the increased number of organ transplantations will highlight the role of immunosuppression in carcinogenesis, leading to an increasing appreciation of virus related cancers, much in the way Kaposi sarcoma has been elucidated. On the other hand, life style changes and the introduction of new, powerful biological therapeutic agents may relate new viruses and bacteria to human cancers.

The increasing number of studies indicating that viruses might represent a key factor in cancer development and progression open new perspectives on how to tackle each disease and, more importantly, to prevent or treat them. However, the immense challenge for the future research on pathogens and their role in gastrointestinal cancers will be to translate all the in vitro findings into in vivo results. The in vivo proof is critical and will allow us to test new potential drugs or to develop effective vaccines against viral and bacterial pathogens. However, while this has been achieved with the model of *H. pylori* and gastric cancer, it still represents a big challenge for viral-associated gastrointestinal cancers, in particular for the lack of viable animal models. The example of cervical cancer and the effective vaccination against HPV has proven that the incidence of a life threatening cancer can be reduced by tackling a viral pathogen (Koutsky et al., 2002). The fact that *H. pylori* eradication has the potential to reduce the risk of gastric

cancer development, is an indication of how basic research can be translated into medical practice, and this has major implications for the future directions of public health (Roderick et al., 2003; Ford et al., 2005; Malfertheiner et al., 2005; Fry et al., 2007). Thus, the future challenge will be to clearly demonstrate a causative role of viral pathogens in gastrointestinal cancers and eventually to design appropriate vaccines and antiviral agents.

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TABLE 1

Human genetic polymorphisms, associated with an increased of gastric cancer development

Genetic polymorphism	Studied population	Finding	References
Angiotensinogen gene 20 (AGT)	GC (n =135), GU (n =148), DU (n =113)	Carriage of the AGT 20 allele is associated with increased GC risk, especially intestinal type GC	Sugimoto et al. (2007)
Cyclooxygenase-2 (COX-2)	248 GC, 1,523 patients with precancerous lesions	Elevated risk of GC, in association with COX-2 genotypes with high levels of COX-2 expression	Liu et al. (2006)
Human leukocyte antigen (HLA) DQ DR	GC (n =130)	HLA DQ allele is associated with decreased risk of <i>H. pylori</i> infection, HLA DR allele expression is a risk factor for GC	Magnusson et al. (2001)
IL-1 gene cluster	GC (n =366)	IL-1 gene cluster polymorphisms are associated with enhanced IL-1 β production, which leads to an increased risk of both hypochlorhydria and GC	El-Omar et al. (2000)
IL-8	Non-cardia GC (n =212), (GU) (n =153), (DU) (n =130), gastritis (n = 195)	IL-8 polymorphism carrier are at higher risk for GC, GU and progression of gastric atrophy	Ohyauchi et al. (2005)
Matrix metalloproteinase 7 (MMP7)	GC (n =79)	Genotype distribution of MMP-7 is associated with <i>H. pylori</i> and tumor-related survival of patients	Kubben et al. (2006)
NOD-like receptor 2	<i>H. pylori</i> associated low-grade lymphoma (n = 83)	Polymorphism in NOD2 gene increases risk of gastric lymphoma	Rosenstiel et al. (2006)
TNF-alpha	Chronic gastritis (n = 221), GC (n = 287)	Carriers of the TNF-alpha-308* A allele are at increased risk of GC; high-risk genotypes at 3 loci are at increased risk for chronic atrophic gastritis and GC	Machado et al. (2003)
Toll-like receptor 4 (TLR4)	149 relatives of GC patients with premalignant gastric changes, 2 independent Caucasian population (312 non-cardia GC, 184 non-cardia GC, 123 cardia GC)	Carrier of TLR-4 polymorphisms have an increased risk of non-cardia GC and its precursor lesions (no association was observed for cardia GC)	Hold et al. (2007)

GC, gastric cancer; GU, gastric ulcer; DU, duodenal ulcer.

TABLE 2

Viruses and microbes in gastrointestinal cancers

Localization	Microbial pathogen	Evidence	Comment
Esophageal cancer	HPV	(++)	Frequent detection of HPV-16,-18, but lack of in-vivo data
	JCV	(+)	Detection of T-Ag in cancer tissues, but so far only one report
	EBV	(-)	Low or no detection of EBV
Gastric cancer	<i>H. pylori</i>	(+++)	Confirmed evidence by epidemiological, experimental studies and few clinical trials
	EBV	(++)	Strong evidence for a subset of gastric cancer, but no expression of several EBV oncogenes
	JCV	(+)	Detection of T-Ag in cancer tissues with high viral copy numbers, but so far only two reports
Colon cancer	JCV	(++)	T-Ag expression in about 50% of colon cancer specimens
Anal cancer	HPV	(+++)	HPV DNA in 70–100% of anal cancer; mainly HPV-16, -18

— no evidence;

+ weak evidence;

++ strong evidence;

+++ confirmed evidence.