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Mechanisms of Disease: inflammation and the origins of cancer

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SUMMARY

Many common cancers develop as a consequence of years of chronic inflammation. Increasing evidence indicates that the inflammation may result from persistent mucosal or epithelial cell colonization by microorganisms; including hepatitis B virus and hepatitis C virus, which can cause hepatocellular cancer; human papilloma virus subtypes, which cause cervical cancer, and the bacterium *Helicobacter pylori*, which can cause gastric cancer. At present, the cause of other chronic inflammatory conditions associated with increased cancer risk, such as ulcerative colitis, is obscure. Particular microbial characteristics as well as the type of the inflammatory response contribute to clinical outcomes via influence on epithelial cell and immune responses. Persistent inflammation leads to increased cellular turnover, especially in the epithelium, and provides selection pressure that result in the emergence of cells that are at high risk for malignant transformation. Cytokines, chemokines, free radicals, and growth factors modulate microbial populations that colonize the host. Thus, therapeutic opportunities exist to target the causative microbe, the consequent inflammatory mediator, or epithelial cell responses. Such measures could be of value to reduce cancer risk in inflammation-associated malignancies.

KEYWORDS cancer etiology, infectious diseases, inflammation, *Helicobacter pylori*

REVIEW CRITERIA

The data for this review were obtained by searching the MEDLINE database for publications between the period of 1 Jan 1990 to 31 December 2004. The search terms used were "inflammation AND cancer" and "infection AND cancer" restricted to English language publications. The records identified were scrutinized, full articles thought to be potentially relevant were obtained and relevant cross-references were checked. The previous 3 years' conference proceedings of American Gastroenterology Association and American Association for Cancer Research were searched manually.

CME

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

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INTRODUCTION

Nearly 150 years ago, Rudolf Virchow speculated that the chronic inflammatory infiltrates observed in tumors reflected the origins of cancer.[1,2] The chronic inflammatory processes of wound healing and cancer are similar,[3] but less is known about the role of chronic inflammation in malignant transformation. Many of the common cancers are preceded by years of chronic inflammation; examples include cancers of the lung, whereby cigarette smoking usually leads to inflammation; adenocarcinoma of the esophagus, which is usually preceded by years of inflammation caused by gastroesophageal reflux; and colon cancers, which are sometimes associated with chronic inflammatory bowel disease. For many of these inflammation-associated cancers, the initiating influence remains obscure; but for others, infectious etiologies have been identified. Colonization of the stomach by *Helicobacter pylori* (*H. pylori*) may lead to gastric cancer and lymphoma. Likewise, viral colonization by hepatitis B virus (HBV) and hepatitis C virus (HCV) can cause hepatocellular cancer, and particular subtypes of human papilloma virus (HPV) may initiate cervical cancer.[4]

Microbial persistence in or around epithelial cells may lead to a chronic inflammatory state resulting in increased epithelial cell turnover. The combined effects of increased inflammation and epithelial cell turnover can promote the phenotypic and genotypic changes that may ultimately progress to malignant transformation. We will review the molecular and cellular changes associated with this process by examining the role of *H. pylori* in gastric carcinogenesis. Discussion of the relevant mechanisms of inflammation and the role of inflammation in malignancies seen in other organs where inflammation is common may help to improve our understanding of these states and lead to novel cancer prevention and treatment strategies.

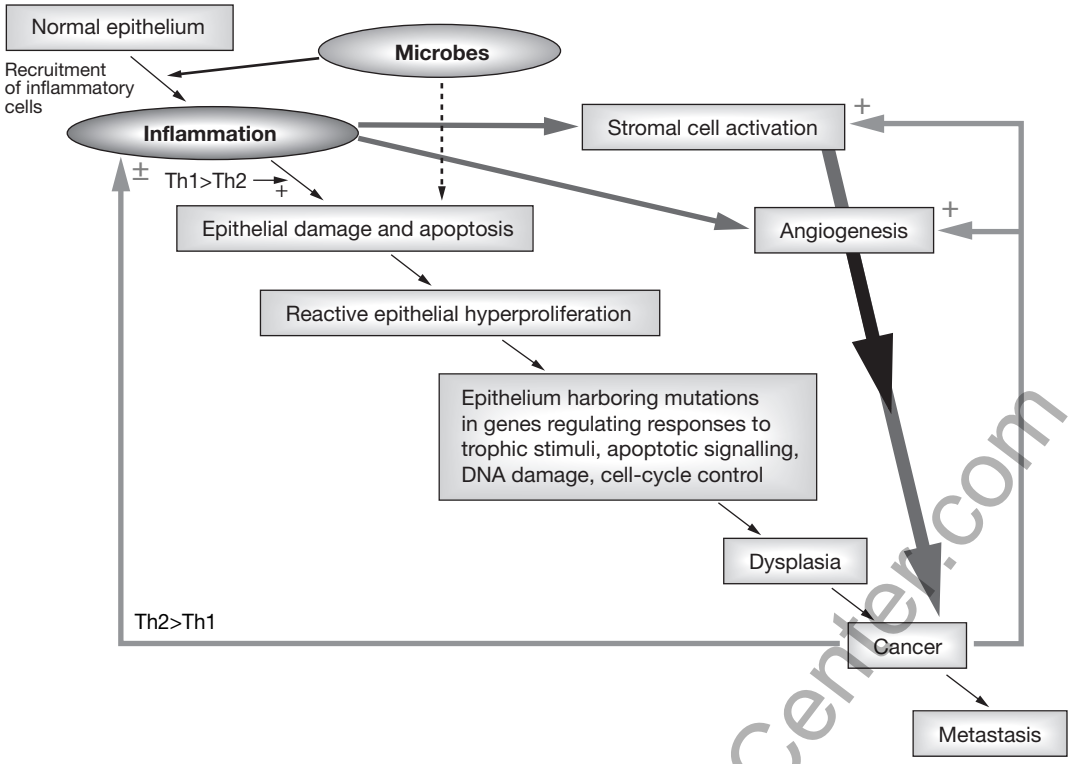

Figure 1 Inflammatory-epithelial interactions in multi-step carcinogenesis. Persistent microbial colonization by viruses, bacteria, nematodes, and other micro-organisms incite chronic inflammation. Numerous feedback and feed-forward loops then contribute to sustained tissue damage and the emergence, under this selection pressure, of populations of epithelial cells bearing survival advantages that ultimately contribute to malignant transformation.

GLOSSARY

CYTOKINES
Intercellular soluble proteins that activate and regulate inflammatory and immune responses through interactions with specific receptors

CHEMOKINES
Cytokines that function to recruit other inflammatory cells by chemo-attraction

FREE RADICALS
Highly reactive oxygen by-products that contain unpaired electrons, created by normal cell metabolism

MOLECULAR MECHANISMS

The specific cellular and molecular pathways that link the inflammatory responses to particular microbes with malignant transformation vary depending on the microbe, target organ, and tumor subtype. In spite of these differentiating factors, several common features exist (Figure 1). Microbial presence in or near epithelia provides a stimulus for recruitment and activation of inflammatory cells from the blood stream. CYTOKINES, CHEMOKINES, and FREE RADICALS initiate and perpetuate inflammatory responses (see glossary and Table 1). Activation of inflammatory cells leads to a respiratory burst that releases free radicals. The free radicals contribute to malignant transformation by peroxidating lipids and inducing genetic mutations, which can alter proteins by chemical and post-translational modifications.[5] Such damage to epithelial cells stimulates apoptotic cell death and reactive epithelial hyperproliferation that promotes further mutation.[6] Accumulation of mutations in key host cell regulatory genes eventually leads to changes in cellular phenotype, at which stage eliminating the initiators of inflammation (e.g. smoking or *H. pylori*), or abolition of the inflammation itself cannot prevent the progression to cancer.[7]

The nature of the inflammatory response is governed initially by the dominant type of T helper (Th) lymphocyte cells recruited to the epithelium in response to inflammation. In this paradigm, the Th1 response is considered pro-inflammatory, driving cell-mediated immune responses, whereas the Th2 response is considered immunoregulatory or even anti-inflammatory, and promotes antibody-mediated immunity.[8] Th1-dominated responses may not kill the causative microbe, but once cancer has developed, the immune response may be skewed to Th2, which reduces the available anti-tumor activity of cytotoxic T cells.[2] Inflammation-related carcinogenesis results from inflammatory cells and mediators that act directly on epithelial cells and indirectly on stromal cells and extracellular matrix components, and by stimulating angiogenesis.[9] Multiple feedback

Table 1 Host inflammatory mediators potentially important in carcinogenesis.

Mediator	Effects
Cytokines	
IFN-γ, IL-6, TNF-α	Pro-inflammatory (Th1)
IL-4, IL-5, IL-10, IL-13	Immunoregulatory (Th2)
IL-1	Pro-inflammatory (Th1) and immunoregulatory (Th2)
TGF-β	Growth inhibitory, pro-inflammatory
Migration inhibition factor	Pro-inflammatory, modulates innate immune responses
Vascular endothelial growth factor	Angiogenesis, increases vascular permeability
Chemokines	
Growth-regulated oncogene α (Gro-α), IL-8	Recruit neutrophils and lymphocytes, can increase tumor growth or curtail tumors but increase free oxygen radicals
Eotaxin	Recruit eosinophils
Free radicals	
Reactive oxygen species	Cell damage
Reactive nitrogen oxide species	Angiogenesis, promotion or protection from cell damage

Gro-α, Growth-regulated oncogene alpha; IFN-γ, interferon-gamma; TGF-β, transforming growth factor-beta; IL-1, interleukin-1; IL-4, interleukin-4; IL-5, interleukin-5; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-13, interleukin-13; Th1, T-helper 1; Th2, T-helper 2; TNF-α, tumor necrosis factor-alpha.

and feed-forward loops add to perpetuation of inflammation;[10] the tumor cells *per se* and tumor-associated macrophages, in particular, modulate inflammation by secreting matrix metalloproteinases, cytokines, chemokines, and growth and angiogenic factors.[2,9]

H. PYLORI AND GASTRIC MALIGNANCIES

Gastric cancer is the second most common fatal malignancy in the world, responsible for approximately 10% of all deaths from cancer.[11] Since gastric cancer usually presents clinically at an advanced stage, there is consequently high mortality highlighted by only 20% 5-year survival.[12] Gastric cancer is usually preceded by decades of chronic inflammation.[13] For the most common 'intestinal' subtype of gastric cancer, a preneoplastic sequence has been defined that manifests from chronic superficial gastritis through atrophic gastritis, intestinal metaplasia, ultimately leading to dysplasia. Progression through these histologic cancer precursors is accompanied by the accumulation of mutations, typical of a multi-step process of carcinogenesis. The 'diffuse' subtype of gastric cancer may also be preceded by years of chronic gastritis, although the molecular pathways and histologic changes involved are less well characterized.[13,14]

A clue to the etiology of chronic inflammation preceding gastric cancer came in 1982 with the first isolation of *H. pylori*.[15] The authors speculated, "If these bacteria are truly associated with antral gastritis…they may have a part to play in other poorly understood, gastritis-associated diseases (i.e. peptic ulcer and gastric cancer)."[15] Epidemiologic, clinicopathologic and animal studies subsequently provided compelling evidence for the importance of persistent *H. pylori* colonization in the etiology of chronic gastritis, and in the genesis of gastric cancer[16–18] Meta-analyses of seroepidemiologic studies estimate that the presence of *H. pylori* increases the risk by 2-fold to 5-fold for development of both histologic gastric cancer subtypes,[19,20] whereas more sensitive and strain-specific assays suggest a 20-fold increased risk.[21] The majority of gastric cancers worldwide are directly attributable to *H. pylori*.[4] Thus, *H. pylori* colonization—an almost universal finding in populations in the developing world[22]—is a more important risk factor for gastric carcinogenesis than other environmental influences, such as diet, socioeconomic status or occupation.[23] For adenocarcinomas of the proximal stomach (cardia), gastroesophageal junction, and distal esophagus, the association with *H. pylori* is inverse, indicative of protection.[17]

H. pylori is usually acquired in early childhood,[22] and despite producing a chronic inflammatory reaction does not cause symptoms in most cases. However, in fewer than 5% of carriers persistent colonization precipitates the development of malignancy 50 years or more later. The genotype of *H. pylori* acquired and particular host polymorphisms govern the inflammatory response that influences cancer risk. *H. pylori* virulence factors associated with increased gastric cancer risk include the following: particular polymorphisms of *vacA*; encoding a multimeric secreted protein that produces endosomal vacuoles in epithelial cells; *babA*, encoding an adhesin that binds to fucosylated Lewis B antigens on epithelial cells; and the *cag* island of genes.[22,24,25] The *cag* gene island comprises approximately 25 open-reading frames, some of which encode a type IV bacterial secretory apparatus that injects bacterial products directly into gastric epithelial cells.[26] Subsequent modulation of epithelial cell signal transduction can result in cytoskeletal alterations and the activation of inflammatory cascades and mitogenic pathways that may contribute to malignant transformation. The immunodominant CagA protein is encoded by *cagA* located at the 3' end of the *cag* island. When CagA is injected into epithelial cells, it undergoes tyrosine phosphorylation by epithelial Src-kinases, and then interacts with SHP-2, leading to anchoring on the plasma membrane and the activation of specific signal transduction pathways.[27] Serum antibodies to CagA are more prevalent in subjects who develop cancer than in those who do not.[21,28,29] The tyrosine phosphorylation motifs of CagA, encoded by the *cagA* gene, may vary in number in isolates from different parts of the stomach;[30] strains with multiple motifs appear more highly associated with cancer.[28]

H. pylori infection results in development of an immune response, characterized by a proinflammatory profile of Th1-dominant cytokines such as interferon-γ, tumor necrosis factor-alpha (TNF-α), and interleukin-12 (IL-12), which continuously recruit leukocytes to the gastric mucosa and activate Th1 lymphocytes[31] (Figure 2). These events are, in part, initiated by *H. pylori* binding to epithelial cells that activate signaling through the nuclear factor-kappa B (NF-κB) transcription factor, with the production of specific chemokines and cytokines, including TNF-α, the interleukins IL-1β, IL-6, IL-8, IL-12, and RANTES c-c motif

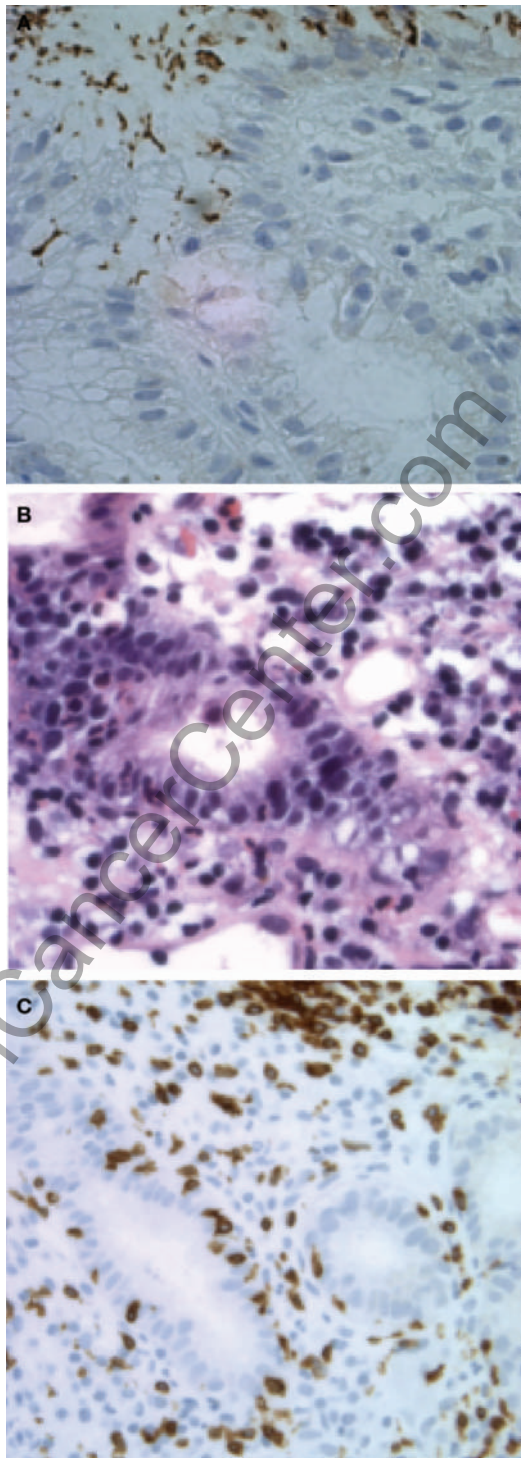

Figure 2 Gastric biopsy from a patient with chronic gastritis due to *H. pylori* persistence. Numerous *H. pylori* organisms identified by immunoperoxidase staining (**A**) induce an intense inflammatory response in the gastric mucosa, with neutrophils, lymphocytes and plasma cells. (**B**) Hematoxylin & eosin staining. (**C**) The many mature T lymphocytes are evident after immunostaining with the antibody CD3. Original magnifications ×200. Photomicrographs courtesy of Murray Resnick, MD, PhD.

ligand 5 (CCL5), growth-regulated oncogene-alpha, macrophage inflammatory protein-1 alpha, and monocyte chemotactic protein-1.[32,33] The upregulation of the integrin CD11b/CD18 and its receptor, intercellular-adhesion molecule-1 (also known as CD54) mediates leukocyte transmigration from the circulation to the gastric mucosa,[34,35] and stimulates gastric epithelial cell expression of the T cell co-stimulatory molecules CD80 and CD86.[36] The cellular infiltration is perpetuated by sustained *H. pylori* presence leading to expression of class II MHC antigens by gastric epithelial cells,[37] allowing continual *H. pylori* antigen presentation to the immune cells populating the gastric mucosa. Persistent *H. pylori* colonization also stimulates B lymphocytes to secrete specific anti-*H. pylori* antibodies, but their functional consequence is not well-defined.

Although the immune response decreases *H. pylori* numbers,[38] it is largely ineffectual in eliminating *H. pylori,* and does not confer protective immunity against reacquisition after antimicrobial therapy.[39] One explanation for the failure of immunity is the ability of *H. pylori* to evade host adaptive and innate responses by frequent antigenic variation, and host antigen mimicry.[24] However, while failing to eliminate *H. pylori*, the immune and inflammatory responses increase cellular damage and turnover, thereby promoting carcinogenesis.[38,40]

The histologic and thus clinical consequences of the host interactions with *H. pylori* are determined partly by single nucleotide polymorphisms in genes encoding inflammatory cytokines involved in the inflammatory response. For example, polymorphisms of IL-1β and its receptor, and TNF-α, which are associated with heightened inflammation, or polymorphisms that cause low activity of the anti-inflammatory IL-10, are associated with more severe inflammation, the development of gastric atrophy, and increased risk of gastric cancer.[41,42,43] Combinatorial analysis of specific *H. pylori* strain differences with specific host cytokine polymorphisms is now being explored as an approach to estimate individual susceptibility to gastric cancer with risk ratios differing up to 90-fold.[43]

Despite these advances in defining host susceptibility and bacterial virulence genes, the precise molecular and cellular events responsible for the promotion of gastric cancer by *H. pylori* and the associated inflammatory response, are not fully defined. Chronic cellular damage from the release of reactive oxygen and nitrogen species,[44,45] increased expression of epithelial cyclooxygenase-2,[46] and activation of the proinflammatory[32] and oncogenic[47] transcription factor NF-κB may all contribute to gastric cancer. Moreover, the modulation of gastric growth factors and peptides,[48] and the ultimate emergence of a state of low acid secretion that encourages the growth of nitrosating non-*H. pylori* bacteria[49] may compound these effects further. A state of increased cell turnover prior to cancer development is both frequent and prolonged, and may contribute to malignant transformation.[6] The increased cell turnover, long recognized in chronic gastritis,[50] is now known to reflect the impact of *H. pylori* colonization.[51] Animal model studies suggest that *H. pylori* can stimulate epithelial apoptosis, and compensatory hyperproliferative responses.[52] Increased cell turnover caused by continual *H. pylori* stimulation, together with the associated inflammatory response, provides selection pressure for the emergence of gastric epithelial cells with altered phenotypes, including resistance to apoptosis,[53] which contributes to malignant transformation.[7] During the cellular coevolution that occurs over the lifetime of the host, selective adaptation occurs not only in gastric epithelial cells, but also in the gastric population of *H. pylori* cells.[24] Considerable experimental evidence indicates that specific *H. pylori* strain characteristics and certain cytokines released by the inflammatory response are important influences of gastric epithelial turnover,[51] but their relative contributions to the gradual dysregulation of apoptosis and continued cellular proliferation that occurs during human gastric carcinogenesis remains unclear. A recent study has provided evidence that the origin of the neoplastic cells in *Helicobacter*-associated gastric cancer may be from recruited bone marrow-derived stem cells that then differentiate into epithelial-like cells in the inflammatory environment of the experimentally-infected mouse.[54] Although the implications of this work are far-reaching, confirmation that the underlying hypothesis is correct is necessary.

THERAPEUTIC IMPLICATIONS

Gastric adenocarcinomas

The fact that specific antibiotic therapy can reverse the histologic changes of chronic gastritis, and the evidence that gastric cancer develops rarely in the absence of *H. pylori*,[18] suggest that gastric cancer may be largely preventable. Definitive answers may emerge from several prospective population-based clinical trials to eradicate

H. pylori from populations at high risk of gastric cancer in Latin America and Asia, but full results are several years away, owing to the slow process of gastric carcinogenesis. Nevertheless, preliminary data in high-risk patients followed for several years indicate that the eradication of *H. pylori* can reduce the rate of progression along the gastric preneoplastic sequence.[55–57] If there is a 'point of no return' in the gastric carcinogenic cascade, it may be the development of intestinal metaplasia. Preliminary analysis of a randomized controlled trial of *H. pylori* eradication in China showed there was a reduction in gastric cancer risk only in those patients whose most advanced lesion at the time of antibiotic therapy was chronic gastritis.[58] Additional chemopreventive therapies may be necessary in those patients who have already progressed to intestinal metaplasia. Rather than an all-or-none 'point of no return', more likely there is a quantifiable risk relationship with the most favorable outcomes in populations reflecting the earliest interventions.

Gastric lymphoma

The eradication of *H. pylori* alone provides apparent 'cure' in most cases of early gastric lymphoma, in contrast to gastric adenocarcinomas. This unusual manifestation of *H. pylori* persistence represents a T cell-driven proliferation of a gastric mucosal B lymphocyte clone. Patients with these lesions who received antibiotic therapy to eradicate *H. pylori* have now been followed for over 10 years. The vast majority of those with early-stage disease (low grade, confined to the gastric mucosa) have had complete clinical remission.[59] However, whether all the patients had malignancies, or whether some had benign monoclonal expansions, remains to be determined. The development of gastric lymphoma occurs in only a few *H. pylori*-positive individuals, and there is considerable geographic variability in incidence. However, because of the dramatic responses observed in patients with gastric lymphoma as a result of *H. pylori* eradication, this has led researchers to speculate that other lymphomas may be bacterially driven, and therefore potentially reversible with antimicrobial therapy.[60]

Hepatocellular carcinoma

Virus-associated cancers may be prevented by elimination of the causative agent. Liver cancer is the third most common cause of cancer-related death worldwide and is usually associated with chronic HBV or HCV infection.[11] Inflammation stimulates liver cell death. Subsequent hepatic regeneration is often associated with the development of dysplastic nodules and ultimately cancer, a sequence characterized by the accumulation of molecular genetic and epigenetic alterations.[61] While HBV causes cellular damage through the induction of inflammatory and immune responses rather than by its direct integration into the genome, the pathophysiology of HCV is less clear. Nevertheless, the chronic inflammation induced may again be the principal pro-oncogenic event. The universal vaccination of newborns against HBV is now common practice in endemic areas and has led to a dramatic reduction in hepatocellular carcinoma incidence.[62] Progress in the prevention of HCV-associated liver cancer has been slower. The causative agent was only identified in 1988 and suitable vaccine candidates and vaccination strategies for clinical use have yet to be defined. Nonetheless, improvements in anti-HCV therapies have been rapid and current combination therapy with pegylated interferon and ribavirin are capable of achieving >50% sustained viral eradication. It is expected that such treatments will greatly reduce the progression to cirrhosis and subsequent cancer risk, but definitive data are not yet available. While there is cause for optimism in the developed world, the relative complexity and costs involved in such treatment for a largely asymptomatic condition pose substantial problems in poorer regions.

Cervical cancer

Despite the widespread use of cytology screening programs, squamous cell carcinoma of the cervix is the second most common cause of fatal cancers in women worldwide.[11] The strong association between cervical cancer and HPV, especially type 16, has spurred considerable interest in the development of HPV vaccines to treat not only the genital infection but also to prevent cervical neoplasia. The development of a vaccine against HPV 16 is proof-of-principle that this prophylactic approach can prevent cervical intraepithelial neoplasia.[63] The development of 'therapeutic vaccines' to boost existing cell-mediated immunity to eliminate the causative virus, and thereby prevent cancer in patients with chronic HPV, is also under investigation.[64] In common with other cancers where the latency between acquisition of infection and malignant transformation can last for decades, large and long-term clinical studies will be necessary to evaluate

the size of the reduction in cancer burden that may be achievable in specific populations.

Other cancers

For other poorly understood chronic inflammatory states associated with increased cancer risk, including long-standing ulcerative colitis (that predisposes to colon cancer), sclerosing cholangitis and other chronic inflammatory conditions of the biliary tract (associated with cholangiocarcinoma), the challenge is to discover whether there are cryptic causative agents, analogous to *H. pylori*, HPV, HBV or HCV that are responsible for the 'idiopathic' chronic inflammation. Regardless of specific causes, long-term anti-inflammatory therapies may be beneficial in reducing the cancer risk, as exemplified by some of the most promising chemopreventive, anti-inflammatory agents currently in clinical investigation to prevent a variety of cancers, such as aspirin, the COX-2 inhibitors, and certain phytochemicals.[65] Therefore, even in the absence of a complete understanding of the underlying etiology, attempts to inhibit exuberant inflammation and angiogenesis may prevent or delay cancer in chronic inflammatory conditions.

CONCLUSION

The increasing recognition of the importance of infection in multi-step carcinogenesis has validated Virchow's speculations about the inflammatory origins of cancer. While chronic inflammation secondary to persistent microbial colonization may have little clinical consequence, the mucosal colonization exerts selection pressure resulting in adaptive responses within the epithelium. The selective replacement of normal epithelial cells with variants adapted for survival caused by inflammatory states may produce cells with abnormal growth patterns and phenotypes that are more malignant. Generally, such deleterious consequences may not be selected against because they occur late in life, after the reproductive years. Because shifts in epithelial cell growth phenotypes are gradual, chemoprevention may benefit when eradication of the microbial cause is not possible. Studying the pathophysiology of chronic infection and host inflammatory responses should contribute to improved understanding of the underlying molecular and cellular pathogenesis of cancer, leading to development of useful therapeutic and chemopreventive agents. Animal models of infection and chronic inflammation, especially cancer-prone mice, may be particularly helpful. The lessons learned from studies of cytokine polymorphisms and *H. pylori* genotypes in relation to gastric carcinogenesis illustrate the potential importance of molecular epidemiological approaches to assessing inflammatory responses in cancer predisposition, especially in populations in which inflammation-associated cancers are prevalent.

References

1 Virchow R (1863) *Cellular Pathology as Based upon Physiological and Pathological Histology*. Philadelphia: JB Lippincott
2 Balkwill F and Mantovani A (2001) Inflammation and cancer: back to Virchow? *Lancet* **357:** 539–545
3 Dvorak HF (1986) Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med* **315:** 1650–1659
4 Pisani P *et al.* (1997) Cancer and infection: estimates of the attributable fraction in 1990. *Cancer Epidemiol Biomarkers Prev* **6:** 387–400
5 Hussain SP *et al.* (2003) Radical causes of cancer. *Nat Rev Cancer* **3:** 276–285
6 Preston-Martin S *et al.* (1990) Increased cell division as a cause of human cancer. *Cancer Res* **50:** 7415–7421
7 Hahn WC and Weinberg RA (2002) Rules for making human tumor cells. *N Engl J Med* **347:** 1593–1603
8 Abbas AK *et al.* (1996) Functional diversity of helper T lymphocytes. *Nature* **383:** 787–793
9 DeClerck YA *et al.* (2004) Proteases, extracellular matrix, and cancer: a workshop of the path B study section. *Am J Pathol* **164:** 1131–1139
10 Coussens LM and Werb Z (2002) Inflammation and cancer. *Nature* **420:** 860–867
11 Parkin DM (2001) Global cancer statistics in the year 2000. *Lancet Oncol* **2:** 533–543
12 Hohenberger P and Gretschel S (2003) Gastric cancer. *Lancet* **362:** 305–315
13 Correa P *et al.* (1975) A model for gastric cancer epidemiology. *Lancet* **2:** 58–60
14 Yuasa Y (2003) Control of gut differentiation and intestinal-type gastric carcinogenesis. *Nat Rev Cancer* **3:** 592–600
15 Warren JR and Marshall B (1983) Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* **1:** 1273–1275
16 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (1994) Schistosomes, liver flukes and *Helicobacter pylori*. *IARC Monogr Eval Carcinog Risks Hum* **61:** 1–241
17 Peek RM and Blaser MJ (2002) *Helicobacter pylori* and gastrointestinal tract adenocarcinomas. *Nat Rev Cancer* **2:** 28–37
18 Uemura N *et al.* (2001) *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* **345:** 784–789
19 Huang J-Q *et al.* (1998) Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. *Gastroenterology* **114:** 1169–1179
20 *Helicobacter* and Cancer Collaborative Group (2001) Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* **49:** 347–353
21 Ekstrom AM *et al.* (2001) *Helicobacter pylori* in gastric cancer established by CagA immunoblot as a marker of past infection. *Gastroenterology* **121:** 784–791
22 Suerbaum S and Michetti P (2002) *Helicobacter pylori* infection. *N Engl J Med* **347:** 1175–1186
23 Neugut AI *et al.* (1996) Epidemiology of gastric cancer. *Semin Oncol* **23:** 281–291
24 Blaser MJ and Atherton JC (2004) *Helicobacter pylori* persistence: biology and disease. *J Clin Invest* **113:** 321–333

25 Aspholm-Hurtig M *et al.* (2004) Functional adaptation of BabA, the H.pylori ABO blood group antigen binding adhesin. *Science* **305:** 519–522
26 Censini S *et al.* (2001) Cellular responses induced after contact with *Helicobacter pylori. Curr Opin Microbiol* **4:** 41–46
27 Higashi H *et al.* (2002) SHP-2 tyrosine phosphatase as an intracellular target of *Helicobacter pylori* CagA protein. *Science* **295:** 683–686
28 Huang JQ *et al.* (2003) Meta-analysis of the relationship between cagA seropositivity and gastric cancer. *Gastroenterology* **125:** 1636–1644
29 Blaser MJ *et al.* (1995) Infection with *Helicobacter pylori* strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach. *Cancer Res* **55:** 2111–2115
30 Aras RA *et al.* (2003) Natural variation in populations of persistently colonizing bacteria affect human host cell phenotype. *J Infect Dis* **188:** 486–496
31 Sommer F *et al.* (1998) Antrum- and corpus mucosa-infiltrating CD4(+) lymphocytes in *Helicobacter pylori* gastritis display a Th1 phenotype. *Infect Immun* **66:** 5543–5546
32 Keates S *et al.* (1997) *Helicobacter pylori* infection activates NF-kappa B in gastric epithelial cells. *Gastroenterology* **113:** 1099–1109
33 Ibraghimov A and Pappo J (2000) The immune response against *Helicobacter pylori*—a direct linkage to the development of gastroduodenal disease. *Microbes Infect* **2:** 1073–1077
34 Crowe SE *et al.* (1995) Expression of interleukin 8 and CD54 by human gastric epithelium after *Helicobacter pylori* infection *in vitro. Gastroenterology* **108:** 65–74
35 Hatz RA *et al.* (1997) Pattern of adhesion molecule expression on vascular endothelium in *Helicobacter pylori*-associated antral gastritis. *Gastroenterology* **112:** 1908–1919
36 Ye G *et al.* (1997) Expression of B7-1 and B7-2 costimulatory molecules by human gastric epithelial cells: potential role in CD4+ T cell activation during *Helicobacter pylori* infection. *J Clin Invest* **99:** 1628–1636
37 Engstrand L *et al.* (1989) Association of *Campylobacter pylori* with induced expression of class II transplantation antigens on gastric epithelial cells. *Infect Immun* **57:** 827–832
38 Mohammadi M *et al.* (1997) Murine CD4 T-cell response to *Helicobacter* infection: TH1 cells enhance gastritis and TH2 cells reduce bacterial load. *Gastroenterology* **113:** 1848–1857
39 Ramirez-Ramos A *et al.* (1997) Rapid recurrence of *Helicobacter pylori* infection in Peruvian patients after successful eradication. Gastrointestinal Physiology Working Group of the Universidad Peruana Cayetano Heredia and The Johns Hopkins University. *Clin Infect Dis* **25:** 1027–1031
40 Fox JG *et al.* (2000) Concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces *helicobacter*-induced gastric atrophy. *Nat Med* **6:** 536–542
41 El-Omar EM *et al.* (2000) Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* **404:** 398–402
42 Machado JC *et al.* (2001) Interleukin 1B and interleukin 1RN polymorphisms are associated with increased risk of gastric carcinoma. *Gastroenterology* **121:** 823–829
43 Figueiredo C *et al.* (2002) *Helicobacter pylori* and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. *J Natl Cancer Inst* **94:** 1680–1687
44 Mannick EE *et al.* (1996) Inducible nitric oxide synthase, nitrotyrosine, and apoptosis in *Helicobacter pylori* gastritis: effect of antibiotics and antioxidants. *Cancer Res* **56:** 3238–3243
45 Smoot DT *et al.* (2000) Influence of *Helicobacter pylori* on reactive oxygen-induced gastric epithelial cell injury. *Carcinogenesis* **21:** 2091–2095
46 Juttner S *et al.* (2003) *Helicobacter pylori* stimulates host cyclooxygenase-2 gene transcription: critical importance of MEK/ERK-dependent activation of USF1/-2 and CREB transcription factors. *Cell Microbiol* **5:** 821–834
47 Greten FR *et al.* (2004) IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell* **118:** 285–296
48 Wang TC *et al.* (2000) Synergistic interaction between hypergastrinemia and *Helicobacter* infection in a mouse model of gastric cancer. *Gastroenterology* **118:** 36–47
49 Houben GM and Stockbrugger RW (1995) Bacteria in the aetio-pathogenesis of gastric cancer: a review. *Scand J Gastroenterol Suppl* **212:** 13–18
50 Lipkin M *et al.* (1963) Cell Proliferation Kinetics in the Gastrointestinal Tract of Man. II: Cell Renewal in Stomach, Ileum, Colon, and Rectum. *Gastroenterology* **45:** 721–729
51 Shirin H *et al.* (2001) Effects of *H. pylori* infection of gastric epithelial cells on cell cycle control. *Front Biosci* **6:** E104–E118
52 Peek Jr, RM *et al.* (2000) *Helicobacter pylori* alters gastric epithelial cell cycle events and gastrin secretion in Mongolian gerbils. *Gastroenterology* **118:** 48–59
53 Shirin H *et al.* (2000) Chronic *Helicobacter pylori* infection induces an apoptosis resistant phenotype associated with decreased expression of $p27^{kip1}$. *Infect Immun* **68:** 5321–5328
54 Houghton JM *et al.* (2004) Gastric cancer originating from bone marrow-derived cells. *Science* **306:** 1568–1571
55 Correa P *et al.* (2000) Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-*Helicobacter pylori* therapy. *J Natl Cancer Inst* **92:** 1881–1888
56 Ley C *et al.* (2004) *Helicobacter pylori* eradication and gastric preneoplastic conditions: a randomized, double-blind, placebo-controlled trial. *Cancer Epidemiol Biomarkers Prev* **13:** 4–10
57 Leung WK *et al.* (2004) Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on *Helicobacter pylori* eradication. *Gut* **53:** 1244–1249
58 Wong BC *et al.* (2004) *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* **291:** 187–194
59 Du MQ and Isaccson PG (2002) Gastric MALT lymphoma: from aetiology to treatment. *Lancet Oncol* **3:** 97–104
60 Lecuit M *et al.* (2004) Immunoproliferative small intestinal disease associated with *Campylobacter jejuni. N Engl J Med* **350:** 239–248
61 Coleman WB (2003) Mechanisms of human hepatocarcinogenesis. *Curr Mol Med* **3:** 573–588
62 Chang MH *et al.* (1997) Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med* **336:** 1855–1859
63 Koutsky LA *et al.* (2002) A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med* **347:** 1645–1651
64 Schreckenberger C and Kaufmann AM (2004) Vaccination strategies for the treatment and prevention of cervical cancer. *Curr Opin Oncol* **16:** 485–491
65 Surh YJ *et al.* (2001) Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF-kappa B activation. *Mutat Res* **480–481:** 243–268

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