Genetics of Inflammation in the Gastrointestinal Tract and How it Can Cause Cancer

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Abstract

Genetic epidemiology is an important discipline that is helping to unravel the aetiology and pathogenesis of complex human diseases. In the context of gastrointestinal malignancy, the paradigm model of host genetic influence on disease outcome is *H. pylori*-associated gastric adenocarcinoma. This cancer represents a classic example of an inflammation-induced malignancy and highlights the importance of host genetics in disease development. This chapter gives an insight into how genetic epidemiology can play an important role in the development of gastric cancer. Increasing our understanding of host genetics in cancer development may allow particularly susceptible individuals to be targeted for screening or treatment to reduce risk of future malignant transformation.

Contents

1 *Helicobacter pylori* and Gastric Cancer 174
2 Role of IL-1β in Gastric Cancer Risk 175
3 Confirmation of the Role of IL-1β in Gastric Cancer Pathogenesis 177
4 Tumour Necrosis Alpha (TNF-α) 177
5 Interleukin-8 177
6 COX-2 and MMP-9 178
7 Role of Innate Immune Response Genes 179
8 Genome-Wide Association Studies and Gastric Cancer 180
9 Overall Contribution of a Host Pro-Inflammatory Genetic Makeup to Pathogenesis of Gastric Cancer 180
10 Conclusion 181
References 181

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Almost 150 years ago, Rudolf Virchow identified leucocytes within neoplastic lesions and hypothesised that malignant change arose within areas of chronic inflammation. This was assumed to be a consequence of the cancer process per se. The last few decades, however, have seen a surge in research interest in the relationship between inflammatory pathways and malignancy (Balkwill and Mantovani 2001; Coussens and Werb 2002; Macarthur et al. 2004). Certainly, the understanding of the mechanisms of inflammatory activity and its role in development of disease has escalated and there can be no doubt that carcinogenesis in a variety of body sites are related to tissue inflammation. Concentrating on the gastrointestinal tract, this is particularly evident in *Helicobacter pylori* (*H. pylori*)-associated gastric cancer, chronic hepatitis C-associated hepatocellular carcinoma and inflammatory bowel disease associated colorectal cancer. This chapter is focussed on discussing the influence of genetic makeup on the process of inflammatory linked cell transformation to cancer.

It must be appreciated that genetic epidemiology is only one part of the jigsaw, a contributing part of the complex web of multifactorial influences determining outcome in human disease processes. A strategy employing population-based genetic epidemiology calculates risk of developing a particular disease in relation to host genotype, and has a particular role in unravelling the complexities of common chronic diseases with strong environmental influences. Specifically, single nucleotide polymorphisms of pro-inflammatory genes in the context of host susceptibility have been extensively studied. SNP's are 'common' mutations, occurring at >1% within the general population, and describes the variation in DNA sequence between the two alleles of a particular gene. Differing genotypes can manipulate phenotypic character and therefore be associated with risk of developing overt pathology, in specific racial groups. Overall, it is estimated that there are over 10 million SNPs within the human genome and this is probably just the tip of the iceberg, with a large number not identified as yet. Luckily, the majority of these will not have functional consequence, occurring either in non-coding sections of DNA or having no influence on the final protein product. However, it is appreciated that carriage of a particular genotype can lead to downstream functional consequences, either silencing or promoting the expression of downstream gene targets that can positively influence pathogenesis of disease.

1 *Helicobacter pylori* and Gastric Cancer

In the context of gastrointestinal malignancy, the paradigm model of host genetic influence on disease outcome is *H. pylori*-associated gastric adenocarcinoma. This cancer represents a classic example of an inflammation-induced malignancy, and highlights the importance of host genetics in disease development. For this reason, this chapter will focus on *H. pylori*-induced gastric cancer to illustrate the role of host genetics in the pathogenesis of disease. Gastric adenocarcinoma remains a major health problem worldwide, with 900,000 new cases diagnosed in 2002, mainly in Eastern Asia and with increasing incidence in the developing world

(Parkin et al. 2005). Eight thousand new cases are diagnosed each year in the UK, and despite advances in treatment, the prognosis remains poor. Clearly, this disease carries significant burden in terms of patient morbidity, mortality and healthcare economics. A major advance in the fight against this malignancy came with the recognition of the role of *H. pylori* infection in its pathogenesis. *H. pylori* is a Gram-negative, urease-positive bacillus, acquired during childhood, probably via the faecal–oral or gastric–oral routes. This infection persists throughout life unless treated with an antibiotic-based eradication regime. The bacteria mainly reside on the surface mucus gel layer, with little invasion of the gastric glands (Amieva and El-Omar 2008). Despite this, the host responds with an impressive humoral and cell-mediated immune response. In most cases, spontaneous clearance is rare leading to chronic carriage of the bacteria. Persistent carriage of the bacteria in itself does not necessarily lead to development of gastric malignancy, at least in the majority of cases. It is now well established that three separate phenotypic outcomes exist. The majority of individuals colonised with *H. pylori* will be asymptomatic and will not develop clinically significant disease. In this group, carriage of the bacteria could be described as commensal. In contrast, chronic carriage can be pathogenic, resulting in one of two significant disease phenotypes. The first of these is antral-predominant gastritis, associated with high gastric acid secretion and duodenal ulceration, the so called 'duodenal ulcer phenotype'. Alternatively, an infected individual may develop corpus predominant chronic inflammation, associated with gastric atrophy and hypochlorhydria, a pre-malignant phenotype, associated ultimately with the development of gastric adenocarcinoma (Amieva and El-Omar 2008).

These diverse clinical outcomes of chronic *H. pylori* infection are mutually exclusive with the development of the 'duodenal ulcer' phenotype protective against subsequent gastric malignancy (Hansson et al. 1996). Therefore, it is clear that infection with *H. pylori* can lead to several diverse disease phenotypes and it is now known that host genetic factors play a key role in determining outcome. Specifically, the course and magnitude of cytokine driven inflammatory response, induced and perpetuated by chronic *H. pylori* colonisation is largely dependent on genetic susceptibility. Overall, genetic variation in important cytokine genes, both pro- and anti-inflammatory, impart an important influence on the final outcome.

2 Role of IL-1β in Gastric Cancer Risk

The pro-inflammatory cytokine IL-1β is recognised as an important candidate in the development of gastric malignancy, reflecting profound pro-inflammatory action, up-regulation in response to *H. pylori* infection, and potent gastric acid suppression (El-Omar et al. 2001). The IL-1 gene cluster lying within a 430 kb region on chromosome 2q contains three related genes, namely, *IL-1A, IL-1B* and *IL-1RN*, which encode for pro-inflammatory cytokines IL-1α and IL-1β as well as their endogenous receptor antagonist IL-1ra, respectively. Three diallelic polymorphisms at the *IL-1B* loci have been reported, all representing C–T or T–C transitions, at positions −511, −31, and +3,954 bp from the transcriptional start

site (Bidwell et al. 2001). The *IL-1RN* gene has a penta-allelic 86 bp tandem repeat (VNTR) in intron 2.

In a Caucasian population of gastric cancer relatives, polymorphisms in the *IL-1* gene cluster were found to be associated with increased risk of developing pre-malignant gastric changes of gastric atrophy and hypochlorhydria, in response to *H. pylori* infection (El-Omar et al. 2000). Specifically, carriage of the *IL-1B*-31*C or -511*T and *IL-1RN**2/*2 genotypes were associated with these pre-malignant gastric changes. This association also extends into the development of overt non-cardia gastric adenocarcinoma, with an estimated odds ratio of 1.6 (95% CI, 1.2–2.2) and 2.9 (95% CI, 1.9–4.4) for carriage of IL-1β-31*C/-511*T and IL-1RN*2/*2, respectively (El-Omar et al. 2000). In terms of other upper gastrointestinal tract malignancies, this pro-inflammatory genotype was not associated with gastric cancer of the cardia, or oesophageal malignancy of either glandular or squamous origin (El-Omar et al. 2003). This is in keeping with the underlying physiological consequence of enhanced IL-1β signalling and particularly, reflects its potent acid inhibitory action. These findings have been confirmed independently in both Caucasian (Figueiredo et al. 2002; Machado et al. 2001) and other ethnic groups, specifically Asian (Furuta et al. 2002; Zeng et al. 2003) and Hispanic (Garza-Gonzalez et al. 2005) populations. Machado et al. were the first to confirm the association between *IL-1* gene markers and gastric cancer in Caucasians and reported similar results to those reported by the initial study. They then later investigated the combined influence of pro-inflammatory *IL-1* genotypes and *H. pylori* bacterial virulence factors (*cagA* positive, *VacA s1* and *VacA m1*), highlighting a potentially important interaction between host and bacterium in the pathogenesis of gastric cancer. Specifically, combination of high-risk bacterial/host genotype conferred the greatest risk of developing gastric malignancy (Figueiredo et al. 2002).

Not all studies, however, have confirmed the association between genetic variability of the *IL-1* loci and gastric cancer. There are a number of reasons why this may be the case. Firstly, the reported discrepancies may reflect issues with study design, such as use of inappropriate controls or an underpowered study population. Overall, within the last few years, meta-analyses of *IL-1B* genotype as a risk factor for gastric cancer have been published (Wang et al. 2007; Camargo et al. 2006; Kamangar et al. 2006) and these suggest that genetic variation in the pro-inflammatory gene, *IL-1*β, is a risk factor for developing gastric malignancy. However, it is likely that there are other influences. Positive associations between genotype and disease appear to be demonstrated more readily in low incidence compared with high incidence areas, suggesting that background prevalence of gastric cancer in a population is an important factor when carrying out these studies. The haplotype context is also an important consideration for genetic risk associations. This describes the relationship between haplotype structure and gene regulation. Specifically, the question of whether individual SNPs within a gene promoter region (*IL-1*β in this case) might affect promoter function was raised. It has also recently been recognised that potential synergy between two or more genetic markers may influence phenotypic outcome. For example, association between carriage of *IL-1B*-31C allele and gastric cancer was identified but only in individuals with *GTF2A1* GG genotype (Lee et al. 2007).

3 Confirmation of the Role of IL-1β in Gastric Cancer Pathogenesis

A crucial piece of evidence that confirmed the apparent role of IL-1β in *H. pylori*-induced gastric carcinogenesis came from a transgenic mouse model in which IL-1β overproduction was targeted to the stomach by the H +/K + ATPase beta promoter (Tu et al. 2008). With overexpression of IL-1β confined to the stomach, these transgenic mice had a thickened gastric mucosa, produced lower amounts of gastric acid and developed severe gastritis followed by atrophy, intestinal metaplasia, dysplasia and adenocarcinoma. Crucially, these IL-1β transgenic mice proceeded through a multistage process that mimicked human gastric neoplasia. These changes occurred even in the absence of *H. pylori* infection, which when introduced led to an acceleration of these abnormalities. Most interestingly, the pathological changes including the progression to gastric cancer were prevented by infusion of interleukin-1 receptor antagonist, proving beyond doubt that IL-1β is responsible for the pathological effects (Tu et al. 2008).

From these initial studies, interest in the role of host genetics in the pathogenesis of gastric cancer escalated to include other key inflammatory genes. The target candidate genes under investigation mirror the cytokine response evoked by *H. pylori* infection and included potent pro-inflammatory cytokines, such as TNFα, IL-8 and IL-6 and also genes encoding for key inflammatory mediators such as COX-2 and MMP-9. There have been many other studies. The list of genes investigated is extensive and we have chosen to expand on a few of these to illustrate the expanding knowledge base in this field.

4 Tumour Necrosis Alpha (TNF-α)

TNF was recognised as a potentially important cytokine in the development of gastric malignancy, due to its powerful pro-inflammatory action and acid-inhibitory effect, albeit weaker than that of IL-1β. The G > A polymorphism at position −308 within the TNF-α gene was identified as significant, with carriage of the pro-inflammatory A allele associated with a 2-fold increase in malignant phenotype (El-Omar et al. 2003). This finding was subsequently reproduced in a population of similar ethnicity (Machado et al. 2003), and a recent meta-analysis confirmed the role of *TNF-A* polymorphisms in gastric cancer risk (Gorouhi et al. 2008).

5 Interleukin-8

Interleukin-8 (IL-8) is a potent pro-inflammatory cytokine, involved not only in recruitment of neutrophils and macrophages at the site of inflammatory activity, but also exerting a multitude of additional functional capabilities, many central to

tumour biology. IL-8 is mitogenic and angiogenic, through linked expression of MMP's, namely MMP-2 and 9, influences tumour cell motility so that tumour invasion is enhanced. IL-8 has been found to be increased in a number of cancers, including those of the GI tract (Xie 2001). There is a well defined promoter T > A polymorphism on the IL-8 gene at position −251. Functionally, carriage of the A allele results in enhanced IL-8 expression within the gastric mucosa of *H. pylori* infected individuals. The association of this genotype to overt gastric malignancy however, remains under debate, with both positive and negative associations reported across different ethnic groups (Ohyauchi et al. 2005; Savage et al. 2006; Taguchi et al. 2005) .

6 COX-2 and MMP-9

Cyclo-oxygenase (COX) is the key rate limiting enzyme in arachidonic acid metabolism, resulting in the production of many active prostaglandins, prostacyclins and thromboxanes. There are two recognised isoforms. COX-1 is constitutively expressed in normal cellular homeostasis. In contrast, COX-2 is inducible and expressed in response to mainly inflammatory stimuli, growth factors and mitogens. It is now widely recognised that COX-2 activity is implicated in a wide range of cell processes that are central to cell function and life cycle, such as angiogenesis, cell proliferation, inflammatory response and apoptosis (Wang and DuBois 2006). Clearly, this could play an important role in the development of malignancy. COX-2 is known to be up-regulated in gastric carcinoma. Sitarz et al. (2008) found a positive association between gastric cancer and carriage of the G allele at position −765 of the COX-2 gene in a Dutch population. Overall, a systematic review published recently, assessing the role of 17 SNP's within the *COX-2* gene on gastrointestinal malignancy, concluded that the polymorphisms found at positions −1329A, −899C and *429TT were associated with up to a 3-fold increased risk of gastric cancer (Pereira et al. 2010).

MMP-9 is a key inflammatory mediator released from neutrophils and macrophages within areas of inflammatory activity and has been implicated in carcinogenesis at a number of body sites, mainly due to breakdown of collagen matrix, supporting tumour cell invasion and exerting a positive influence on angiogenesis. MMP-9 has been associated with pathobiological behaviour of gastric malignancy, including tumour size, invasion and lymphatic metastasis (Zheng et al. 2006). Recently, a study on a Chinese population identified a 3-fold increase risk of developing lymph node metastasis from primary gastric cancer with carriage of 2 SNP's within the *MMP-9* gene (Tang et al. 2008).

When concurrent carriage of pro-inflammatory alleles in up to four genes (*IL-1B*, *IL-1-RN*, *TNF-A and IL-10*) was assessed in relation to risk of gastric cancer, the risk progressively increased along with an increasing pro-inflammatory genotype, such that, when three or four of the pro-inflammatory alleles were present, risk increased to 27-fold (El-Omar et al. 2003).

7 Role of Innate Immune Response Genes

Overall, in considering the pathogenesis of this disease and the role of genetic variation within this process, researchers have investigated both bacterial variability within microbial virulence factors as well as the host cytokine response to persistent infection. In addition, the investigative focus has included the initial contact between bacterium and host, and it is now clear that genetic variation within the adaptive immune response involved in this initial interaction is an important consideration. Lipopolysaccharide (LPS) is found in the cell membrane of Gram-negative bacteria, including *H. pylori*, and binds to trans-membranous pattern-recognition receptor, *TLR*-4, expressed on immune cells of the adaptive immune system, namely macrophages. Binding to this receptor activates a signalling cascade involving MyD88, IL-1 receptor associated kinase and TRAF6, to activate NFkB and mitogen-activated protein kinase pathways, which results in a plethora of cytokines and pro-inflammatory mediators being released into the environment. There are functionally relevant polymorphisms in the *TLR*-4 gene that profoundly alters host response to bacterial challenge. In particular, an A–G transition at position +896 on exon 4 leads to change in protein sequence, specifically replacement of aspartic acid to glycine at position 299. This ultimately alters the extracellular domain of the receptor and its overall function, renders the cell hyporesponsive to an LPS challenge through inhibition of ligand binding, inhibition of protein binding and by altering transport of the receptor to the cell membrane, reducing capacity of the cell to deal with pathogenic challenges. Initially, the immune response is jaded. However, overall, due to a reduction in IL-10 secreting regulatory cells, the immune response that is able to be activated through alternative signalling mechanisms becomes overwhelming and exaggerated in magnitude. Not surprisingly, it was hypothesised that defective signalling through TLR-4/*H. pylori* interaction associated with carriage of genetic variation could lead to an exaggerated immune response to this organism and contribute to the development of gastric malignancy. Indeed, it has been found that carriage of *TLR-4* +896G confers an 8-fold increase for pre-malignant change in 3 Caucasian populations, with profound corporeal inflammation and gastric atrophy. In terms of malignancy per se, carriage of the variant allele conveys a doubling of risk (Hold et al. 2007).

Santini et al. (2008) showed that another *TLR4* polymorphism increases risk of intestinal-type gastric cancer. Thus, the *TLR4* Thr399Ile was associated with an increased hazard ratio of 5·38, 95% CI 1·652–8·145, $p = 0{\cdot}006$. More work is required on elucidating the full impact of polymorphisms within the toll-like receptors and their associated pathways.

There are other reports of innate immune response gene polymorphisms being associated with increased risk of gastric cancer. Mannose binding lectin is an antigen-recognition molecule involved in systemic and mucosal innate immunity. It is able to bind to a range of microbes and subsequently kill them by activating the complement system and promoting complement-independent opsonophagocytosis.

Baccarelli et al. (2006) showed that polymorphisms in the mannose binding lectin-2 gene (*MBL2*) were associated with increased risk of gastric cancer. In haplotype analysis, the HYD haplotype was associated with increased risk of stomach cancer when compared with HYA, the most common haplotype (OR = 1.9, 95% CI 1.1–3.2; $p = 0.02$). Further analyses to examine the joint effect of *MBL2* and *IL-1B* polymorphisms indicated that the combination of at-risk *IL-1B* genotypes (CT or TT at location −511) and HYD *MBL2* haplotype was associated with a 3.5-fold risk (OR = 3.5, 95% CI 1.6–7.6; $p = 0.001$). The findings suggest that the codon 52 D *MBL2* variant causing a cysteine > arginine replacement is specifically associated with gastric cancer risk.

8 Genome-Wide Association Studies and Gastric Cancer

Genotyping technology has advanced dramatically in the past 5 years and it is now possible to study hundreds and thousands of SNP's simultaneously. This approach, termed genome-wide association studies, was recently used by Sakamoto et al. (2008) to study gastric cancer in the Japanese population. Employing a two-stage genome-wide association study (stage 1: 85,576 SNPs on 188 cases and 752 references; stage 2: 2,753 SNPs on 749 cases and 750 controls) identified a significant association between an intronic SNP (rs2976392) in PSCA (prostate stem cell antigen) and diffuse-type gastric cancer (allele-specific OR = 1.62, 95% CI = 1.38–1.89, $P = 1.11 \times 10^{-9}$). Interestingly, the association was far less significant in intestinal-type gastric cancer. The PSCA gene is possibly involved in regulating gastric epithelial-cell proliferation and it will be very interesting to find out how it influences susceptibility to diffuse-type gastric cancer.

9 Overall Contribution of a Host Pro-Inflammatory Genetic Makeup to Pathogenesis of Gastric Cancer

It appears that subjects with a pro-inflammatory genetic makeup based on a combination of markers from cytokine/chemokine genes (e.g. *IL-1B*, *TNF-A*, *IL-10*, *IL-8*) and the innate immune response (e.g. *TLR4*, *MBL2*), respond to *H. pylori* infection by creating a gastric environment that is chronically inflamed and with reduced acidity. The damage is exacerbated if the infecting organisms are particularly virulent, and particularly if CagA positive. This bacterial protein has recently been shown to act as an oncoprotein and there is no doubt that its presence heightens the inflammatory process further (Ohnishi et al. 2008). This environment is conducive to the growth of other non-*H. pylori* bacteria within the gastric milieu, leading to sustained inflammation and oxidative/genotoxic/oncogenic stress. Subjects with the same pro-inflammatory polymorphisms may respond in the same exaggerated manner to these non-*H. pylori* bacteria, thus maintaining the pro-neoplastic drive. This may explain why *H. pylori* is not required in the later stages of gastric carcinogenesis and why it is often absent from gastric tumor tissue.

10 Conclusion

Overall, this chapter has given a brief insight into how host genetics can play an important role in the development of malignancy. Clearly, this is only part of the story, yet an important strand of the complex web of disease pathogenesis. Increasing our understanding of host genetics in cancer development may allow particularly susceptible individuals to be targeted for screening or treatment to reduce risk of future malignant transformation, for example, targeting those people who may benefit from *H. pylori* eradication therapy in an attempt to reduce gastric cancer prevalence. However, this benefit may be theoretical as the outcome in altering the natural progression of this disease is unknown. In addition, the currently recognised genetic risk markers are very common and do not carry the necessary degree of specificity required for a screening test. As the genetic revolution continues and technology advances, it will be possible to define a much more robust genetic profile that could be used for screening. This would certainly be a worthwhile achievement.

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