Hum Genet (2009) 126:615–628
DOI 10.1007/s00439-009-0722-x

REVIEW PAPER

Nature meets nurture: molecular genetics of gastric cancer

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Received: 19 June 2009 / Accepted: 16 July 2009 / Published online: 6 August 2009

Abstract The immensity of genes and molecules implicated in gastric carcinogenesis is overwhelming and the relevant importance of some of these molecules is too often unclear. This review serves to bring us up-to-date with the latest findings as well as to look at the larger picture in terms of how to tackle the problem of solving this multi-piece puzzle. In this review, the environmental nurturing of intestinal cancer is discussed, beginning with epidemiology (known causative factors for inducing molecular change), an update of *H. pylori* research, including the role of inflammation and stem cells in premalignant lesions. The role of E-cadherin in the nature (genotype) of diffuse gastric cancer is highlighted, and finally the ever growing discipline of SNP analysis (including *IL1B*) is discussed.

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Introduction

Gastric cancer (GC) is a worldwide health burden (Jemal et al. 2007) with little hopeful progress. Even after a curative resection alone or after adjuvant therapy, nearly 60% of those patients affected succumb to GC (Macdonald et al. 2001; Bonenkamp et al. 1999; de Maat et al. 2007). Despite tremendous advances in the past few decades, there are still no tools to address the inherent molecular heterogeneity of GC that expresses itself in divergent clinical biology. The age-old debate of whether diseases are inherited ("nature") or occur as a result of environmental influences ("nurture") has been resolved to a certain extent, and we now acknowledge that environment and genetics have a delicate interplay which varies between sexes, individuals and ethnic backgrounds, providing in each individual a unique environment for cancer growth or suppression. The relative importance of nature versus nurture can however vary with tumour type, and it is long known that the impact of environmental triggers can be seen at gene level. With this knowledge and the age of personalized medicine, the importance of the crucial relationship between nature and nurture is ever increasing.

Gastric cancer is thought to result from a combination of environmental factors and the accumulation of generalized and specific genetic alterations, and consequently affects mainly older patients often after a long period of atrophic gastritis. The commonest cause of gastritis is infection by *H. pylori*, which is the single most common cause of gastric cancer (Forman et al. 1991; Parsonnet et al. 1991) and has been classified by the WHO as a class I carcinogen since 1994 (IARC monographs 1994; Suerbaum and Michetti 2002) and the causal role has been extensively studied in animal models (Watanabe et al. 1998).

The risk of infection varies with age, geographical location and ethnicity, but overall 15–20% of infected patients

develop gastric or duodenal ulcer disease and less than 1% will develop gastric adenocarcinoma (Suerbaum and Michetti 2002).

The pattern of gastritis has also been shown to correlate strongly with the risk of gastric adenocarcinoma. The presence of antral-predominant gastritis, the most common form, confers a higher risk of developing peptic ulcers; whereas, corpus predominant gastritis and multifocal atrophic gastritis leads to a higher risk of developing gastric ulcers and subsequent gastric cancer (Watanabe et al. 1998; Craanen et al. 1992). The response to *H. pylori* infection and the subsequent pattern of gastritis depends on the genotype of the patients and in particular a polymorphism in interleukin 1 beta, an inflammatory mediator triggered by *H. pylori* infection, is known to be of importance as will be discussed (El-Omar et al. 2000).

The most commonly used classifications of GC are the World Health Organization (WHO) (Hamilton and Aaltonen 2000) and the Laurén classifications which describes two main histological types, diffuse and intestinal (Lauren 1965), which have different clinicopathological characteristics. Diffuse cancer occurs more commonly in young patients, can be multifocal, is not often accompanied by intestinal metaplasia and can be hereditary, as will be discussed in detail below (Matley et al. 1988; Kokkola and Sipponen 2001; Lim et al. 2003; Furukawa et al. 1989; Carneiro et al. 2004). Intestinal type is more frequently observed in older patients and follows multifocal atrophic gastritis. This is usually accompanied by intestinal metaplasia and leads to cancer via dysplasia, and thus intestinal metaplasia is considered a dependable morphological marker for gastric cancer risk. Unlike intestinal gastric cancer, the diffuse type typically develops following chronic inflammation without passing through the intermediate steps of atrophic gastritis or intestinal metaplasia. Intestinal adenocarcinoma predominates in the high-risk areas whereas the diffuse adenocarcinoma is more common in low-risk areas (Hamilton and Aaltonen 2000). These clinicopathological factors suggest that the "nurture" component of intestinal GC is greater than that of diffuse GC and conversely that the "nature" aspect of diffuse GC may be stronger than that of intestinal-type GC.

Previous reviews have given us an overview of the general state of GC research (Milne et al. 2007), and this current review serves to bring us up-to-date with the latest findings. Gastric carcinogenesis can be considered a multistep process involving generalized and specific genetic alterations that drive the progressive transformation of cells into cancer. In fact some have even tried to quantify the number of steps needed for various cancers, with GC averaging at 4.18 genomic alterations necessary (Nishimura 2008). Hanahan and Weinberg describe how virtually all mammalian cells carry a similar molecular machinery regulating their proliferation, differentiation, and death and suggest that there are six essential alterations in cell physiology that collectively dictate malignant growth (Hanahan and Weinberg 2000) and this framework can be applied to GC, as described previously (Milne et al. 2007). Despite the breadth of molecules, genes and indeed pathways implicated in GC, there are a few that stand out and deserve mention. In this review, the environmental "nurturing" of intestinal cancer is discussed, beginning with epidemiology (known causative factors for inducing molecular change), an update of *H. pylori* research, including the role of inflammation and stem cells in premalignant lesions. The role of E-cadherin in the "nature" (genotype) of diffuse gastric cancer is highlighted, and finally the ever growing discipline of SNP analysis (including IL1B), which can account for individual inherited cancer risk, is discussed.

The "Nurture" component

Epidemiology

Cigarette smoking and *H. pylori* infection are classically associated with GC(Shikata et al. 2008), and diet is a known etiological factor, especially for intestinal-type adenocarcinoma whereby an adequate intake of fruit and vegetables appears to lower the risk with ascorbic acid, carotenoids, folates and tocopherols acting as antioxidants (Hamilton and Aaltonen 2000; Jenab et al. 2006a). It is possible that cereal fibre intake may reduce the risk of adenocarcinoma, particularly diffuse type (Mendez et al. 2007), and the interplay of diet on genomic stability has been recognized (Young 2007), by showing that substances such as green tea can affect methylation status of genes (Yuasa et al. 2009). It is said by some that salt intake strongly associates with the risk of gastric carcinoma and its precursor lesions (Pelucchi et al. 2009; Kato et al. 2006), and this risk is increased in certain genetically predisposed individuals (Chen et al. 2004), yet others refute the importance of salt as a risk factor (Sjodahl et al. 2008). Other foods associated with high risk in some populations include smoked or cured meats and fish, pickled vegetables and chilli peppers (Hamilton and Aaltonen 2000). Alcohol and occupational exposure to nitrosamines and inorganic dusts have been studied in several populations, but the results have been inconsistent (Hamilton and Aaltonen 2000) and the possible role of vitamin C remains under scrutiny (Jenab et al. 2006b).

The incidence of gastric adenocarcinoma is declining worldwide, mainly due to decline of the intestinal type. There has also been a change in the anatomical distribution of this malignancy, with a fall in the incidence of mid and distal GC and a progressive increase in cardia cancer. This fall in incidence may be explained by the decline in

H. pylori infection and associated atrophic gastritis. Interestingly, *H. pylori* infection is a strong risk factor for non-cardia GC, but is inversely associated with the risk of gastric cardia cancer (Kamangar et al. 2006). Relatively high rates of cancer in the central/distal portions of the stomach among North American Indians and Alaska Natives in some geographic regions may indicate a disproportional burden of *H. pylori*-associated disease (Wiggins et al. 2008). There is a male predominance of GC which may be related to hormonal factors (Chandanos and Lagergren 2008), and this male predominance mainly relates to the intestinal type (Derakhshan et al. 2009).

In addition, a further decrease of at least 24% in the incidence of gastric corpus cancer in the coming decade may be anticipated in Western countries without specific intervention (de Vries et al. 2007). On the other hand, because the risk of gastric cardia adenocarcinoma increases with higher BMI, growing obesity may explain the rising incidence of oesophageal and gastric cardia adenocarcinoma in the Western world (Merry et al. 2007). Long-term pharmacological gastric acid suppression is yet another marker of increased risk of oesophageal and gastric non-cardia adenocarcinoma (Garcia Rodriguez et al. 2006). These associations may be explained by the underlying treatment indication being a risk factor for the cancer rather than an independent harmful effect of these agents per se although this is a subject of debate (Langman and Logan 2007; McColl 2006).

Inflammation and *H. pylori*

One of the triumphs of 19th century biology was the understanding that neoplastic processes were different and distinguishable from infectious or inflammatory processes (Rather 1978). From late in the 20th century, it has become increasingly clear that these processes are not as distinct as the histopathology had suggested. There are a variety of chronic inflammatory conditions (where no causal agents have been identified), e.g. Barrett oesophagus, chronic ulcerative colitis, as well as a variety of infectious conditions, such as chronic gastric infection with *H. pylori* and chronic viral hepatitis, that markedly elevate the risk of cancer. Chronic inflammation induces increased tissue turnover, which is thought to predispose to an excessive rate of proliferation, and in many cases results in more frequent mitotic errors and an increased rate of mutagenesis. Notably, Matsumoto et al. recently reported that *H. pylori* infection of the gastric epithelium induced the expression of the activation-induced cytidine deaminase (*AID*) gene (Matsumoto et al. 2007), a gene originally linked to immunoglobulin class switching and B lymphocyte hypermutation, but aberrantly expressed in cancer, where it may predispose to point mutations of the *p53* tumour suppressor gene. Recent studies have also highlighted important roles for specific immune cell populations (e.g., macrophages, T cells) and proinflammatory cytokines [e.g., interleukin (IL)-1B, IL-6, tumour necrosis factor] in the pathogenesis of cancer (Fox and Wang 2007; Lin and Karin 2007).

Although infection with *H. pylori* significantly increases the risk of developing GC, the exact mechanism underlying the malignant transformation needs to be clarified, but it is believed that the combination of a virulent organism, a permissive environment and a genetically susceptible host is necessary (Figueiredo et al. 2002; Machado et al. 2003; Amieva and El-Omar 2008; Egan et al. 2007). Molecular and cell biology approaches aimed at understanding the interaction between *H. pylori* and the transforming epithelial cell are the subject of intense research (Ferreira et al. 2008; Chiba et al. 2008), including new insights into the mechanisms by which *H. pylori* disrupts gastric barrier function via urease-mediated myosin II activation (Wroblewski et al. 2009). In addition, persistent inflammation is known to cause genetic instability through the generation of mutagenic substances such as reactive oxygen species (Baik et al. 1996; Farinati et al. 2008) and reactive nitrogen species (Fu et al. 1999) which may act to directly damage the host cell nuclear and mitochondrial DNA(Machado et al. 2009) and limit the mucosal defence by decreasing the antioxidant properties of the gastric mucosa (Sobala et al. 1993). Such a direct gastric mutagenic effect through oxidative DNA damage in *H. pylori* infection has been shown in transgenic mouse models (Touati et al. 2003). Nitric oxide can also directly influence mitochondrial pathways of apoptosis (Mannick et al. 1999) and also potentially plays a role in multiple levels of cell signal transduction during *H. pylori* infection. Furthermore, bacterial factors may also directly induce apoptosis (Galmiche et al. 2000).

The ultimate effectors of apoptosis include an array of intracellular proteases termed caspases. Caspases are important in the life and death of immune cells and therefore influence immune surveillance of malignancies. Two "gatekeeper" caspases, caspase-8 and -9, are activated by death receptors such as FAS or by the cytochrome C released from mitochondria, respectively, and the Fas antigen pathway of apoptosis is recognized as the leading cause of tissue destruction during *H. pylori* infection (Cai et al. 2005). In fact, a six-nucleotide deletion (-652 6N del) variant in the *CASP8* promoter has been found to be associated with decreased risk of lung cancer.(Sun et al. 2007) Further case–control analyses in a Chinese population showed that this genetic variant is associated with reduced susceptibility to multiple cancers, including lung, oesophageal, gastric, colorectal, cervical and breast cancers (Sun et al. 2007), supporting the hypothesis that genetic variants influencing immune status modify cancer susceptibility, and strengthening the argument that both nature and nurture are needed for carcinogenesis.

Different strains of *H. pylori* vary in their carcinogenic potential, with those containing the virulence factor CagA inducing a greater degree of inflammation. CagA is delivered into gastric epithelial cells through a bacterial type IV secretion system, and interacts with several major growth-regulating signal transduction pathways including the Ras/MEK/ERK pathway (Mimuro et al. 2002) and the Src family of protein kinases (Tsutsumi et al. 2003). In addition, forms of *cagA* encoding multiple type C EPIYA segments (which increase phosphorylation-dependent CagA activity) have been shown and the number of *cagA* EPIYA-C segments relate to cancer risk amongst Western strains (Basso et al. 2008). Loss of cell polarity and tissue architecture is a hallmark of carcinomas that arise from epithelial cells. Studies on Drosophila tumour suppressors have provided evidence that epithelial polarity and cell proliferation are functionally coupled, suggesting a function for polarity defects in the development of carcinomas. It has been discovered that CagA specifically binds and inhibits PAR1/MARK polarity-regulating kinase, thereby causing junctional and polarity defects in epithelial cells (Hatakeyama 2008). Thus, the bacterial oncoprotein simultaneously targets the polarity-regulating system and growth-regulatory system.

H. pylori can also produce the vacuolating cytotoxin VacA responsible for epithelial damage which contributes to gastric carcinogenesis. A new type i1 "intermediate region" polymorphism, in *vacA* (which confers toxicity) has recently been described (Rhead et al. 2007; Ogiwara et al. 2008), and it appears that this it is the intermediate region type of *vacA* confers peptic ulcer risk (Basso et al. 2008). Bacterial factors (motility, adhesion, urease, cag pathogenicity), components of the host immune response (toll-like receptors, adaptive immunity, *IL1B* polymorphisms, MHCII), gastrin hormonal responses and decreased acid secretion are all thought to play a role in malignant transformation of the gastric mucosa (Stoicov et al. 2004). Gastrin, whose main role is acid secretion, is a diverse transcriptional activator, mediating gene expression that is associated with cell division, invasion, angiogenesis and anti-apoptotic activity, which are all pivotal in the gain of malignant potential. However, it is still unclear whether gastrin is a central player or a secondary phenomenon in the development of gastric adenocarcinoma, as has been previously discussed (Watson et al. 2006). There is a long-standing association of gastrin with malignant progression in transgenic mouse models, yet clinical conditions associated with hypergastrinaemia in humans, such as the Zollinger–Ellison syndrome, result in the development of hyperplasia of enterochromaffin-like (ECL) cells and carcinoid tumours, not GC, suggesting that the role of gastrin is not critical in gastric carcinogenesis. Despite this observation, *H. pylori* infection in the insulin–gastrin transgenic mouse produces an early increase in acid secretion and over time progresses to atrophy, achlorhydria, hyperplasia of mucous cell compartment, metaplasia, dysplasia and invasive GC by 8 months of age (Wang et al. 2000). Conversely, gastrin deficiency has also been reported to cause gastric adenocarcinoma (Zavros et al. 2005). Interestingly, expression profiles of gastrin knock-out mice revealed activation of immune defence genes, interferon-regulated response genes, and intestinal metaplasia of the gastric mucosa. Over time, the changes accumulated, became irreversible, and progressed into metaplasia and polyp development (Friis-Hansen et al. 2006).

The intricacy of our defence systems are constantly being refined, and bacterial interactions with the human immune system play a crucial role in triggering inflammation and ultimately cancer. Chochi et al. have highlighted that *H. pylori* augments the growth of GC via the lipopolysaccharide toll-like receptor 4 pathway, whereas its lipopolysaccharide attenuates antitumour activities of human mononuclear cells (Chochi et al. 2008). In addition, antitumour T lymphocytes play a pivotal role in immunosurveillance of malignancy, with the CTL antigen 4 (CTLA-4) being a vital negative regulator of T-cell activation and proliferation. This polymorphism is associated with increased susceptibility to multiple cancers, including lung, breast, oesophagus, and gastric cardia cancers, as demonstrated by genotyping in 5,832 individuals with cancer and 5,831 control subjects in northern and southern Chinese populations (Sun et al. 2008). It has also been reported that CCL17 and CCL22 chemokines within the tumour microenvironment are associated with the accumulation of regulatory T cells (Tregs) in GC (Mizukami et al. 2008). Furthermore, the density of tumour infiltrating lymphocytes was found to be independently predictive of regional lymph node metastasis and patient survival (Lee et al. 2008), highlighting the importance of the individual immune defences. Individual genetic variation may also explain the probable dual role of eosinophils in chronic gastritis, whereby elevated eosinophil density in the low-risk area, representing a T helper 2-biased response down-regulate the effects of proinflammatory cytokines preventing cancer development, whereas eosinophils in the high-risk area promote a T helper 1-type response leading to progression of precancerous lesions (Piazuelo et al. 2008). An in-depth understanding of the mechanism by which inflammation can lead to carcinogenesis may also enable the development of drugs targeted at signal transduction systems that are involved in the progression from inflammation to carcinogenesis, providing a powerful tool for preventing cancer development (Maeda and Omata 2008; Levidou et al. 2007).

COX-2 has long been known to play a role in GC, although there are numerous debates on the relative value of the COX-2 polymorphism (Sitarz et al. 2008a). In a

surveillance/screening study of 2,813 subjects in China (Liu et al. 2006), investigators found a greater than twofold higher risk for progressing to GC among those with the 1195AA COX-2 genotype and report that this risk of progression was largely accounted for by those with the −1195AA COX-2 genotype that were also infected with *H. pylori* or were smokers (Liu et al. 2006). COX-2, is frequently upregulated in gastric adenocarcinomas (Ristimaki et al. 1997) and its expression, which can be induced by *H. pylori* (Fu et al. 1999; Sung et al. 2000) is thought to be a relatively early event in gastric carcinogenesis (van Rees et al. 2002). It is predominantly expressed in intestinal-type gastric carcinomas and its precursor lesions (van Rees et al. 2002; Saukkonen et al. 2001; Milne et al. 2006). Recently, the molecule C/EBP-β, a transcription factor for COX-2 (Caivano et al. 2001) has been shown to play a role in GC (Milne et al. 2006; Sankpal et al. 2006; Regalo et al. 2006). Patients with COX-2 methylated tumours have been shown to have a significantly longer time to recurrence and improved overall survival (de Maat et al. 2007) and COX-2 expression has been suggested as a prognostic indicator (Park et al. 2009; Mrena et al. 2005). Studies have highlighted the reduced risk of GC in non-steroidal anti-inflammatory drug users (Hu et al. 2004; Langman et al. 2000; Akre et al. 2001), in particular non-cardia gastric adenocarcinoma (Abnet et al. 2009) and recent reports have suggested that a COX-2 inhibitor may be useful for prophylaxis of lymph node metastasis by reducing macrophage-mediated tumour lymphangiogenesis (Iwata et al. 2007). Worthy of mention is that growth factors of the epidermal growth factor (EGF) family and their respective receptors including c-erbB2 oncogene are also preferentially overexpressed in intestinal gastric cancers (Park et al. 1989; Yokota et al. 1988) and with the advent of anti-Her-2 antibody based treatment, more may heard on this subject in the future (Marx et al. 2009; Gravalos and Jimeno 2008).

Interestingly, despite the importance of *H. pylori* as an initiating factor in gastric carcinogenesis, the molecular pathology of *H. pylori* and non-*H. pylori* cancers cannot be easily separated, and it has been reported that *H. pylori* -related and non-related GCs do not differ with respect to chromosomal aberrations (van Grieken et al. 2000). Also, although it may seem intuitively obvious that removing the offending organism would negate the cancer risk, this approach is not straightforward. Most patients are infected in childhood, and present with varying degrees of mucosal damage before any therapy (Correa and Houghton 2007). Prophylactic eradication of *H. pylori* after endoscopic resection of early GC should be used to prevent the development of metachronous GC say researchers (Fukase et al. 2008). However, the causal association seems somewhat enigmatic in some Asian countries where high prevalence of *H. pylori* infection does not translate into high GC incidence (Sharma 2008). *H. pylori* infection is more common and contracted earlier in India, Pakistan, Bangladesh, and Thailand, where seroprevalence of *H. pylori* infection in adults varies from 55 to 92% compared with about 50% in China and Japan. However, the frequency of GC is low in these so-called Asian enigma countries compared with that in Japan and China. The increased understanding of the relationship between inflammation and GC still leaves many questions unanswered regarding recommendations for prevention and treatment (Fox and Wang 2007; Buckley and O'Morain 1995).

Premalignant lesions

Intestinal-type GC typically arises in the setting of chronic gastritis and develops through intermediate stages of atrophic gastritis, intestinal metaplasia, dysplasia, and finally GC. This lengthy process, known commonly as the Correa pathway, is dependent on continued chronic inflammation (Correa and Houghton 2007; Correa 1995; Correa and Piazuelo 2008). Genetic changes can already be detected in intestinal metaplasia, with p16 methylation being significantly associated with *H. pylori* infection in precancerous lesions (Dong et al. 2009). Studies have also shown decreased E-cadherin expression in the gastric mucosa of *H. pylori* infected individuals (Terres et al. 1998) and the interaction of CagA with E-cadherin, which causes cytoplasmic and nuclear accumulation of beta-catenin has been documented and implicated in the development of intestinal metaplasia (Murata-Kamiya et al. 2007). Metaplasia is a particularly interesting feature because it is a permanent alteration that suggests a marked change in the genetic and epigenetic program of the gastric stem or progenitor cells. Some argue that biologic detection of genomic instability in intestinal metaplasia may be a surrogate marker for GC risk and for clinical evaluation of malignant potential (Zaky et al. 2008). Intestinal metaplasia occurs in a variety of settings, including induction by bile reflux, where it is also associated with induced *COX-2*, via the sequential transcriptional induction of *SHP* and *CDX1* in precancerous lesions (Park et al. 2008).

It is known that loss of Sonic hedgehog (Shh), an essential regulator of patterning processes throughout development, and CDX2, a regulator for intestinal development and differentiation, have a role in early premalignant change (Watson et al. 2006) and they seem to be interdependently linked with cellular differentiation through different signal cascades (Shiotani et al. 2008). *H. pylori* downregulates Shh expression, resulting in the loss of morphogenic differentiation, the disruption of glandular structure and the gain of a more intestinal phenotype by upregulation of intestine-related genes, such as *CDX2*, *MUC2* and villin (Zavros et al. 2005). Notably, ectopi-

cally-expressed Cdx2 was found to induce gastric intestinal metaplasia in two separate mouse models (Mutoh et al. 2002; Silberg et al. 2002). Furthermore, in the insulin–gastrin (InsGas) hypergastrinaemic mouse +/− *Helicobacter felis (H. felis)* infection, Sonic hedgehog gene and protein expression was reduced in pre-metaplastic lesions from non-infected mice compared to normal mucosa, and was reactivated in gastric metaplasia of *H. felis*-infected mice (El-Zaatari et al. 2007). A study by Wang et al. found that SHH was completely absent in the upper part of normal gastric epithelia (gastric pit cells), and no significant differences were observed among the lower parts of normal epithelia, chronic gastritis, and intestinal metaplasia. However, Shh expression was significantly elevated in neoplastic lesions, such as carcinoma and high- and low-grade dysplasia, compared to non-neoplastic lesions. In carcinomas, Shh expression was associated with clinical stage, direct tumour invasion, and differentiation of tumour cells (Wang et al. 2006). These results suggest that the increased and constitutive Shh expression is implicated in gastric carcinogenesis.

Stem cells in gastric cancer

Given the current hypothesis that cancer arises from cancer stem cells (CSCs), the mechanism by which chronic inflammation leads to the emergence of CSCs needs to be addressed. It has been presumed that the gastric stem or progenitor cell is located in the isthmus of the gastric glands in the corpus, and gives rise to differentiated daughter cells via bidirectional migration patterns. In the gastric antrum, the stem or progenitor cells are located at the bottom of the glands, and descendents migrate toward the surface unidirectionally (Takaishi et al. 2008). Bjerknes et al. provided the evidence for the existence of multipotent stem cells in the adult mouse gastric epithelium using chemical mutagenesis to label random epithelial cells by loss of transgene function in transgenic mice (Bjerknes and Cheng 2002). This work revealed that many gastric glands showed a loss of transgene function in all major epithelial cell types, consistent with clonal expansion of a single mutation, therefore indicating the existence of multipotent gastric stem cells.

For many years, resident tissue stem cells have been viewed as the best candidate for CSCs, because the simplest model is one in which a tumour arises from stem or progenitor cells at the existing site. In the intestine, mutations in long-lived (Lgr5+) stem cells located at the crypt bottoms are believed to be the precursor to intestinal cancer (Barker et al. 2009). Barker et al. reported that the G-protein coupled receptor Lgr5 was expressed in the bottom of gastric glands, and ongoing lineage tracing experiments implied that the entire gastric gland derived from Lgr5+ cells.(Barker et al. 2007) Possible gastric progenitor cells are recently shown to give rise to multiple gastric cell lineages in the gland (Qiao et al. 2007). McDonald et al. have investigated the clonality of the gastric unit and have shown how mutations expand in normal mucosa and in intestinal metaplasia, using mitochondrial DNA (mtDNA) mutations as a marker of clonal expansion. They showed that mtDNA mutations establish themselves in stem cells within normal human gastric body units, and are passed on to all their differentiated progeny, thereby providing evidence for clonal conversion to a new stem cell-derived unit–monoclonal conversion, encompassing all gastric epithelial lineages. The presence of partially mutated units indicates that more than one stem cell is present in each unit. Mutated units can divide by fission to form patches, with each unit sharing an identical, mutant mtDNA genotype. They also showed that intestinal metaplastic crypts are clonal, possess multiple stem cells, and that fission is a mechanism by which intestinal metaplasia spreads (McDonald et al. 2008). Interestingly, methylation of promoter CpG islands in intestinal metaplasia, which is known to be deeply involved in the progression to cancers, occurs independently in multiple genes in multiple glands, each of which has its own stem cell (Mihara et al. 2006).

Although gastric stem or progenitor cells might seem to be good candidates for gastric CSCs, another possible source is the bone marrow-derived cell (BMDC) identified during the course of studies employing mouse models of *H. pylori*-induced GC (Houghton et al. 2004). Bone marrow-derived stem cells tend to migrate through peripheral organs as a result of inflammation and tissue injury and the differentiation pattern and growth regulation of these cells may depend largely on local environmental signals and cues (Krause et al. 2001; Okamoto et al. 2002). Studies have demonstrated that cancer-associated fibroblasts can be partly derived from BMDCs (Iwano et al. 2002; Direkze et al. 2004) and it has also been reported that bone marrow-derived human mesenchymal stem cells, when mixed with otherwise weakly metastatic human breast carcinoma cells, cause the cancer cells to increase their metastatic potency greatly, through stimulation of de novo secretion of the chemokine CCL5 (Karnoub et al. 2007). In view of the remarkable plasticity of BMDC, it has been suggested that BMDCs might contribute directly or indirectly to epithelial cancers, particularly those associated with chronic inflammation (Takaishi et al. 2008).

Dysregulation of the stem cell signalling network due to the accumulation of germline mutation, SNP, *H. pylori* infection, epigenetic change and genetic alteration has been suggested to give rise to GC (Katoh 2007). *H. pylori* may adapt to and influence stem cell biology, thus contributing to gastric tumourigenesis (Giannakis et al. 2008).

The "Nature" component

The role of CDH1, encoding E-cadherin

The existence of a familial form of GC has been known since the 1800s when multiple cases of GC were noted in the Napoleon Bonaparte family (Sokoloff 1938). Approximately 1–3% of GCs arise as a result of inherited GC predisposition syndromes, such as hereditary diffuse GC (HDGC), caused by a germline mutation in the *CDH1* gene, encoding E-cadherin, a molecule central in the processes of development, cell differentiation, and maintenance of epithelial architecture (Grunwald 1993). GC in its hereditary form can also be caused by germline mutations of the *TP53* tumour suppressor gene which occurs in the Li–Fraumeni syndrome (Olivier et al. 2003) and new germ line mutations in this gene continue to be discovered (Yamada et al. 2007). BRCA2 gene mutations are associated with familial aggregations of not only breast but also of gastric, ovarian, pancreatic, and prostate cancers (The Breast Cancer Linkage Consortium 1999; Jakubowska et al. 2002). A proportion of hereditary nonpolyposis colorectal cancer (HNPCC) kindreds (the so-called Lynch II families) are associated with a high frequency of extracolonic carcinomas, most commonly affecting the endometrium and stomach (Lynch et al. 1996) and these are known to harbour microsatellite instability (Aaltonen et al. 1994).

Approximately 30–40% of all HDGC families carry *CDH1* germline mutations (Oliveira et al. 2006). The remaining 60–70% are genetically unexplained and may be caused by alterations in other genes. Mutations in *CDH1* were initially identified in 1998 in three Maori families from New Zealand that were predisposed to diffuse GC (Guilford et al. 1998). Since then, similar mutations have been described in more than 151 HDGC families of diverse ethnic backgrounds Carneiro et al. (2008a). Recurrent CDH1 mutations in families with hereditary diffuse GC are due to both independent mutational events and common ancestry and findings support the presence of a founder mutation from Newfoundland (Kaurah et al. 2007). Preliminary data from these families suggest that the penetrance of *CDH1* gene mutations is high, ranging between 70 and 80% (Pharoah et al. 2001). Management options for unaffected mutation carriers include prophylactic total gastrectomy (Lynch et al. 2008; Cisco and Norton 2008; Rogers et al. 2008). There also appears to be an increased frequency of cancers occurring at other sites such as the breast, colorectum, and prostate in these mutation carriers (Pharoah et al. 2001). However, inclusion of associated cancers into the definition of HDGC is not yet recommended (Caldas et al. 1999) although updated recommendations from the International Gastric Cancer Linkage Consortium (IGCLC) are expected to be published later in 2009.

The gastric mucosa in *CDH1* germline mutation carriers is normal until the second *CDH1* allele is inactivated. It is postulated that this downregulation occurs in multiple cells in the gastric mucosa, accounting for the multifocal tumour lesions which develop and (Carneiro et al. 2004) environmental and physiological factors such as diet, carcinogen exposure, ulceration and gastritis are suggested to promote this downregulation event. The tumour then expands slowly until additional genetic events, probably in combination with an altered microenvironment, lead to clonal expansion and tumour progression. Interestingly, because the second hit only rarely involves somatic, irreversible, mutation of the second *CDH1* allele, but rather more frequently occurs via methylation (Grady et al. 2000; Oliveira et al. 2009a; Barber et al. 2008), it is plausible that the early stage lesions may be reversible. Identification of patients with germline *CDH1* mutations paves the way for studies to increase our understanding of the mechanisms by which these mutations ultimately lead to sporadic cancer as well as HDGC.

Analysis of all reported genetic abnormalities in *CDH1* found in HDGC reveals that the majority are inactivating mutations (splice site, frameshift, and nonsense) rather than missense mutations. Furthermore, *CDH1* germline mutations are evenly distributed along the E-cadherin gene, in contrast with the clustering in exons 7–9 observed in sporadic diffuse GC (Berx et al. 1998). Frequent deletions of *CDH1* in HDGC families have recently been recognized (Oliveira et al. 2009b). Loss of heterozygosity as the "second hit" does not appear to be frequent in HDGC. Instead, hypermethylation of the *CDH1* promoter is likely to be a common cause of down-regulation or inactivation of the second *CDH1* allele in HDGC tumours (Grady et al. 2000). A remarkably high percentage (approximately 80%) of *CDH1* mutations in HDGC patients and carriers generate premature termination codons (PTCs). It is possible to examine whether *CDH1* transcripts harbouring PTCs are downregulated by nonsense-mediated decay (NMD), an RNA surveillance pathway that degrades PTC-bearing transcripts. Analysis of HDGC patients harbouring *CDH1* alleles with PTCs at a wide variety of different positions indicates an association of their predicted ability to induce NMD and an earlier age of onset of GC (Karam et al. 2008). Interestingly, regulators of E-cadherin-mediated cell adhesion, such as the Rho GTPases are implicated in the carcinogenic process by deregulated expression of the family members itself or of upstream modulators or downstream effectors (Walch et al. 2008). As well as E-cadherin dysregulation, overexpression of epidermal growth factor receptor (EGFR) is among the most frequent genetic alterations associated with diffuse-type gastric carcinoma. Accumulating evidence suggests a functional relationship between E-cadherin and EGFR that regulates both proteins (Bremm et al. 2008).

There are various models for the development of HDGC on both the histopathological and molecular level (Carneiro et al. 2004, 2008a; Humar and Guilford 2008). The earliest indications of cancer in the stomachs of *CDH1* mutation carriers are microscopic *foci* of in situ carcinoma, pagetoid spread of signet ring cells and intramucosal signet ring cell carcinoma (SRCC; designated "eHDGC"), as seen in Fig. 1. In a study investigating wild-type (wt) and cdh1(+/−) mice induced with *N*-methyl-*N*-nitrosourea (MNU), intramucosal SRCC developed with an 11 times higher incidence compared with wt mice (Humar et al. 2009). The murine SRCC resembled the human eHDGCs in that they were hypoproliferative, lacked nuclear beta-catenin accumulation, and had reduced membrane localization of E-cadherin and its interacting junctional proteins. The down-regulation of E-cadherin in the murine SRCCs confirmed the importance of the second *CDH1* hit to the initiation of diffuse GC, and promoter hypermethylation of the *CDH1* gene was found to be the second hit in 50% of foci. These findings provide compelling evidence for a deficiency in cell-to-cell adhesion being sufficient to initiate diffuse GC in the absence of hyperproliferation and beta-catenin activation (Humar et al. 2009).

A verdict has not yet been reached concerning the possible carcinogenic role of coexistent infection with *H. pylori* on a *CDH1* mutated background, and it remains possible that *H. pylori* infection as well as dietary and other environmental influences may modify the disease risk in these susceptible individuals (McColl and El-Omar 2002). In addition, the role of genetic polymorphisms of the *CDH1* gene in increasing the risk of sporadic GC is under investigation (Zhang et al. 2008a; Wang et al. 2008). In one case–control study (cases = 245/controls = 950) nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) none of the eight *CDH1* polymorphisms or haplotypes analysed were associated with GC risk and no differences of effect were observed by *H. pylori* infection status. However, three *CDH1* polymorphisms in the same haplotype block, including the *CDH1*–160C/A, interacted with smoking to increase GC risk in smokers, again highlighting the importance of environmental interaction on genotype (Jenab et al. 2008).

Microsatellite instability

Genetic instability at the level of microsatellite instability (MSI) occurs in many sporadic human tumours and the relation between microsatellite instability and gastric carcinoma has received considerable attention. This is due to the discovery that MSI may be found in sporadic carcinomas that are characteristic of hereditary nonpolyposis colorectal cancer (HNPCC) (Peltomaki et al. 1993), a syndrome where germline mutations of the mismatch repair genes are present. The levels of MSI found in gastric carcinomas from both Western and Eastern populations is probably in the region of up to 15–20% (Hayden et al. 1998; Carneiro et al. 2008b). Several authors demonstrated that the subset of sporadic GC with high-frequency MSI (MSI-H) showed a distinct clinicopathologic and genetic profile from those with a low frequency (MSI-L) or microsatellite stable (MSS) genotype (Wu et al. 2000; Falchetti et al. 2008; dos Santos et al. 1996). For example, frameshift mutations in the Wnt pathway genes *AXIN2* and *TCF7L2* have been found in GCs with high microsatellite instability (Kim et al. 2009) and alternative lengthening of telomeres frequently occurs in mismatch repair system-deficient gastric carcinoma (Omori et al. 2009). Genome-wide expression profiles of sporadic GCs with and without microsatellite instability reveal that the immune and apoptotic gene networks efficiently discriminated these two cancer types (D'Errico et al. 2009). However, whereas the role of microsatellite instability and DNA mismatch repair gene defects in HNPCC is unquestionable and well established, the relevance of this phenomenon in GC is far from clear and currently has limited clinical value (Hayden et al. 1998). Somatic mutations of mismatch repair (MMR) genes such as *hMLH1* or *hMSH2* are extremely rare in sporadic GCs, with only one mutation found, in *hMSH2* and two cases of a germline frameshift mutation in *hMLH1* (Wu et al. 1997; Bacani et al. 2005). More recently, 29 sporadic GCs with

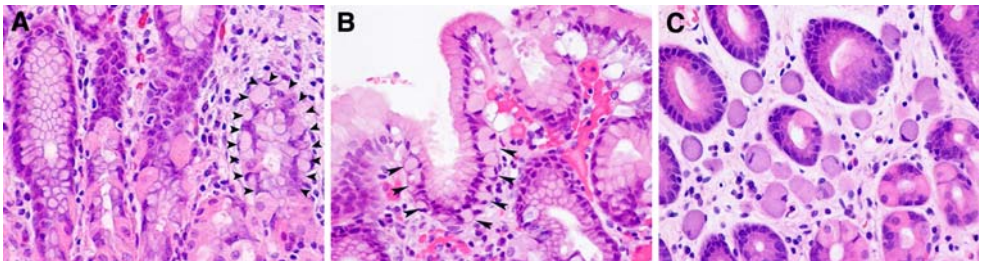

Fig. 1 In situ carcinoma, pagetoid spread of signet ring cells and early invasive signet ring carcinoma. **a** In situ signet ring cell carcinoma: gland with intact basement membrane lined by signet ring cells (*arrow heads*) (H&E, original magnification ×400); **b** pagetoid spread of signet ring cells below the preserved epithelium of one foveolae (*arrow heads*) (H&E, original magnification ×400); **c** early invasive signet ring cell carcinoma (eHDGC) (HE, original magnification ×400)

high level of MSI were screened for somatic mutations in *MLH1*, *MSH2*, *MSH6*, *MLH3*, and *MBD4*, and only five truncating mutations (3 in *MSH6*, 1 in *MLH3,* and 1 in *MBD4*) and one missense mutation (*MLH1*) were identified. All truncating mutations were found in the coding poly-A tracts, thus suggesting that they result from the MSI phenotype rather than causing it (Pinto et al. 2008). However, MSI positive tumours can still lack *hMLH1* protein expression and many studies suggest that hypermethylation of the *hMLH1* promoter region may be the principal mechanism of gene inactivation in sporadic gastric carcinomas with a high frequency of MSI (Fleisher et al. 1999; Leung et al. 1999).

Polymorphisms, including IL1B

Countless research articles focus on the role of polymorphism as a risk factor or protective factor for gastric carcinogenesis. Continuing advances in genotyping technologies and the inclusion of DNA collection in observational studies have resulted in an increasing number of genetic association studies. Polymorphisms in genes from diverse molecular pathways have been significantly associated with GC, such as *MTHFR* C677T, involved in folate metabolism Dong et al. (2008a) prostate stem cell antigen (PSCA), the function of which is not well understood (Sakamoto et al. 2008), and the DNA repair genes *XPA, XPC, ERCC2* Dong et al. (2008b; Capella et al. 2008) which play an important role in repairing DNA damage related to *H. pylori*-induced inflammatory process (Li et al. 2009). The role of the activation and detoxification of polycyclic aromatic hydrocarbons, by genes such as *GSTT1, SULT1A1*, *NAT2* and the *EPHX1* gene (Boccia et al. 2007) highlight how environmental carcinogens are crucially triggered by a particular genetic profile (Agudo et al. 2006). Pathways with a largely unknown role in GC, such as oestrogen and androgen metabolizing genes, have also been found to be associated with GC (Freedman et al. 2009).

Polymorphisms in some genes have been highlighted more than other, such as the *IL1B* gene, which appears pivotal in determining a patient's inflammatory response to a *H. pylori* infection. Interleukin-1beta (IL-1β) is a key pro-inflammatory cytokine, which regulates the expression of several genes involved in inflammation. It is an endogenous inhibitor of gastric acid secretion and is important in initiating and enhancing the inflammatory response to *H. pylori* infection (Noach et al. 1994). Although the production of IL-1β depends on several factors, there is increasing evidence that the genetic background plays a major role. Several single nucleotide polymorphisms in *IL1B* gene have been studied, and two biallelic polymorphisms at positions -31 and -511 in the promoter region of *IL1B*, are in positive linkage disequilibrium and associated with GC risk. It has been reported that carriers of the *IL1B*-31C allele, showed higher plasmatic concentrations of IL-1β than subjects with wild-type *IL1B* genotype (Hall et al. 2004) and the IL-1B-31C/-511T alleles are associated with increased risk of gastric cancer (El-Omar et al. 2000; El-Omar et al. 2003).

However, there are also studies which do not support these results (Sitarz et al. 2008b; Murphy et al. 2009), including findings from a relatively extensive Swedish and Spanish study, which did not lend support to the hypothesis that human genetic polymorphisms related to the production of IL-1β are associated with the risk of GC (Persson et al. 2009; Garcia-Gonzalez et al. 2007), which may be explained by population-specific cancer risks. Further findings which support the importance of *IL1B* includes human IL-1β in transgenic mice, where spontaneous gastric inflammation and cancer was observed, that correlated with early recruitment of myeloid-derived suppressor cells (MDSCs) to the stomach (Tu et al. 2008). Here, IL-1β activated MDSCs in vitro and in vivo through an IL-1RI/NF-kappaB pathway and *IL1B* transgenic mice deficient in T and B lymphocytes developed gastric dysplasia accompanied by a marked increase in MDSCs in the stomach. These results demonstrated that the pathologic elevation of a single proinflammatory cytokine can be sufficient to induce neoplasia in experimental mice (Tu et al. 2008).

Polymorphisms in other crucial inflammatory molecules have also been implicated in GC. The toll-like receptors (TLRs), again important members of the host's innate immune response have been found to be polymorphic (El-Omar et al. 2008). Genetic variation allows for a more intricate repertoire that enables the host to withstand microbial challenges. While this may be advantageous on a population level, there may be less favourable outcomes for individuals that harbour certain genotypes associated with excessive immune activation and inflammatory drive. There is a role for innate immune responses and TLRs specifically in promoting gastrointestinal malignancies (Fukata and Abreu 2008) and a functional polymorphism of toll-like receptor 4 has been found to be associated with non-cardia cancer (Hold et al. 2007). Candidate pathways linking TLRs to gastrointestinal malignancies include activation of cyclooxygenase-2, and of nuclear factor-kappaB (NFκB), a crucial inflammatory transcription factor.

TNF alpha, a crucial inflammatory mediator upstream of NFκB has also been implicated in the development of GC (Zhang et al. 2008b) and interestingly, it has been shown by meta-analysis that this effect appears to be restricted to western populations (Gorouhi et al. 2008). Chemokines have also been shown to modulate tumour behaviour, and the sex-specific effect of the chemokine polymorphisms on the host susceptibility to several diseases has been reported (Liou et al. 2008). In addition, variant alleles of *TGFB1* and *TGFBR2*, which occupy a central position in the signalling

networks that control cell growth and differentiation, are associated with a decreased risk of GC (Jin et al. 2007).

Numerous other polymorphisms have been implicated, only some of which can be mentioned within the scope of this article. Host genetic factors are emerging as key determinants of disease risk for many cancers, and the interaction of numerous polymorphisms on a countless genes products, combined with environmental triggers may provide crucial clues explaining diverse risks in various populations. The study of these using SNP chips or studies where the whole genome are sequenced, may enable us to assess the strength of the "nature" component in many gastric cancers, assuming we have the accurate bioinformatic expertises available to cope with such vast amounts of data.

Summary

The immensity of genes and molecules implicated in gastric carcinogenesis is overwhelming and the relevant importance of some of these molecules is too often unclear. Multiple genetic and epigenetic alterations in oncogenes, tumour-suppressor genes, cell cycle regulators, cell-adhesion molecules, DNA repair genes and genetic instability as well as telomerase activation are implicated.(Milne et al. 2007) However, particular combinations of these alterations differ in the two histological types of GC.(Wu et al. 2002; Hou et al. 2008) The diffuse phenotype in GC (hereditary and sporadic) is related to reduced E-cadherin expression(Machado et al. 1999) and loss of E-cadherin is probably the fundamental defect in diffuse-type gastric carcinoma, providing an explanation for the observed morphological phenotype of discohesive cells with loss of polarity and gland architecture. However, despite the differences in diffuse and intestinal cancers in terms of the balance of nature and nurture, there remains a correlation between diffuse GC and *H. pylori* infection (Eslick et al. 1999). Human genetic variation in countless signalling pathway and aspects of human immune function, along with an individual's specific environmental triggers together with genetic variation and temporal variation in gene expression in *H. pylori* are determinants of GC. Identifying one discriminating biomarker (e.g. COX-2 or p53) has not led to a new clinical algorithm and has as yet not impacted patient care as a single biomarker is likely insufficient for making such clinical decisions or providing information. Cancer cells employ multiple and diverse survival pathways (Hahn and Weinberg 2002) and it is necessary to define a battery of biomarkers (complex signatures that define multiple outcomes). Such signatures might more appropriately represent the breadth of molecular diversity inherent in cancers in general, and pave the way to understanding the impact of both nature and nurture on the molecular genetics of gastric carcinogenesis.

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