The Pathogenesis of Gastric Carcinoma

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ABSTRACT
Gastric cancer is one of the leading causes of cancer mortality in the world. Gastric adenocarcinomas account for more than 95% of gastric tumours, and these epithelial tumours result from the accumulation of multiple genetic defects which leads to uncontrolled growth. The most plausible pathway for gastric carcinoma indicates that the underlying mechanisms may be different for the diffuse and intestinal types of tumour. The distinct subtypes - proximal, diffuse and distal gastric cancer that are different from a histological and epidemiological standpoint, can also distinguished by gene expression data. The disease classification of the epithelial tumours may lead to different treatment paradigms for individual gastric cancer subtypes. The changes present can be classified as consisting of abnormalities in DNA content, the karyotype (including allele loss), oncogene and tumour suppressant gene expression (or deletion), cell cycle regulation and DNA repair genes. This article reviewed the biological/molecular differences of the gastric carcinoma subtypes, the risk factors and precursors of gastric carcinoma and the implications on early diagnosis and response to adjuvant treatment. Despite the heterogeneity of multiple somatic alterations in the neoplastic lesion, the implication of a molecular classification is its exploitation to identify prognostic and predictive biomarkers and to identify targets for therapy.

Key words: gastric carcinoma, pathogenesis, molecular, epidemiology

INTRODUCTION
Gastric cancer is the third most common malignancy worldwide with 974,000 new cases in the year 2000, although in recent decades a decline has been observed in its incidence and mortality (1-3). It is the second most common cause of cancer-related mortality worldwide with 700,349 deaths annually (1). The incidence of gastric cancer was 24,590 cases and 10,720 deaths in the USA in 2015 (4) with the case fatality rate of 75% (5). It is the leading cause of cancer death in Japan (50,562 in 2004), although the incidence of advanced gastric cancer and mortality have decreased in the last decade in Japan because of endoscopic screening and early diagnosis (6, 7). The most dramatic fall in the incidence of distal gastric cancer, by 8-fold in the last 50 years, occurred in the affluent Western countries, predominantly Caucasian population, and low population density regions, such as USA, Canada, Australia, and New Zealand. There was a less dramatic decline in Western Europe, however (8-10). Pathologically, gastric adenocarcinoma may be distinguished according to the

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Lauren’s classification into intestinal, diffuse, or mixed subtype (11). Epidemiologically, intestinal gastric cancer, particularly of the antrum, is strongly associated with chronic inflammation (i.e. atrophic gastritis) (12, 13) which is often a consequence of chronic infection with *Helicobacter pylori* (*H. Pylori*) (14, 15). Conversely, inflammation is characteristically absent in the development of Lauren’s diffuse type gastric cancer, particularly when the latter is a result of a germ line mutation in CDH1 (16). Anatomically, proximal gastric cancer may be classified as a third type of gastric cancer, as tumours of the gastric cardia/gastro-oesophageal junction (GOJ), for which inflammation of a different type (i.e. chronic gastric acid/bile reflux) may be the driving force for carcinogenesis (17, 18). Proximal/GOJ tumours are also usually not diffuse in histology and similar to distal non-diffuse gastric cancer. Obesity and gastric reflux are risk factors.

**MOLECULAR EPIDEMIOLOGY**

Gastric adenocarcinoma is a tumour derived from the lining mucosa which usually presents late in its natural history. The most widely accepted histological classification of gastric carcinoma is the one created by Lauren, who divided the tumours into two main types. Those which formed glandular structures were known as intestinal (53%) whereas those without any structure and secreting mucin were known as diffuse type carcinomas (33%). The remaining 14% had a mixed appearance with elements from both types and were regarded as unclassified (11). The classification of gastric carcinoma has proved most useful epidemiologically as the two types may represent different diseases and as a result have different aetiological factors. The intestinal type of gastric cancer has presents substantial interest from an epidemiological standpoint. The intestinal type which is thought to arise from intestinal metaplasia (IM) in the stomach is more prevalent in the older age group. This contrasts with the diffuse type which has an equal sex incidence and occurs at a younger age. The intestinal type is more common in areas of high incidence whereas the diffuse type occurs equally irrespective of incidence rates. Furthermore, the excess incidence of intestinal type is associated with the high mortality seen in areas of high incidence (18). Conversely the reduction in mortality in areas of decreasing incidence is associated with a reduction in incidence of the intestinal type (19). Moreover, this reduction is associated with the decrease in incidence in the distal stomach suggesting that the intestinal type is a disease of the gastric antrum. This subtype, which remains endemic in the Far East, parts of South America, and Eastern Europe, is principally a disease of the distal stomach associated with chronic gastritis, intestinal metaplasia, and mucosal atrophy. The high incidence rates in these regions is thought to be due to continuing high rates of *Helicobacter pylori* infection, adverse dietary factors (nitrosamines), and genetic predisposition (12, 21-23). The increasingly occurring subtype found in Western countries is commonly found near the gastro-oesophageal junction (GOJ) and is associated with significant gastritis (19, 20, 24, 25). Over the last 30 years, the marked increase in incidence of GOJ was associated with the downward migration of oesophageal tumours and proximal shift of gastric tumours (6, 7). The epidemiological profile suggests a similar aetiology and is consistent with the two cancers having a similar phenotype and p53 gene mutation (6). GOJ cancer is the fastest increasing solid malignancy of adult life in the West, with an increasing incidence of 3% – 4% per annum (2-4). This suggests that it is certain dietary or environmental factors which are important in the development of the intestinal lesion. On the other hand, the diffuse type, whose incidence tends to decrease, is often related to hereditary factors. Because the much lower incidence of gastric cancer in the United States and other Western countries does not justify screening, endoscopic surveillance has been proposed and advocated for populations at risk, including African-Americans, native Americans, and immigrants from high-risk regions (22). The disease thus presents late in its natural history in these countries.

**PATHOGENESIS OF GASTRIC CANCER**

The pathogenesis of gastric cancer is complex and multifactorial. Environmental factors are required to effect multistage progression to malignant transformation according to the Correa hypothesis (9, 26, 27).

**Risk factors**

The risk factors for gastric cancer include low socioeconomic status, diet (nitrosamines- dye, cured meat, fish, alcohol, tobacco), blood group A, obesity (2-fold increase risk of gastric cancer), genetic predisposition [E-Cadherin mutations, hereditary diffuse gastric cancer (HDCG); associated with lobular breast cancer] (9, 28). Most adenocarcinomas are sporadic and associated with consumption of heavily salted and preserved foods (e.g. nitrates in pickled or salted foods such as bacon), low intake of fruits and vegetables and use of tobacco and alcohol. Dietary salt enhances the conversion of nitrates to carcinogenic nitrosamines in the stomach.
Salt and nitrates (NO3) converted to nitrites (NO2) are caustic to the stomach, delay gastric emptying, and cause chronic atrophic gastritis (9).

Precursors

Chronic atrophic gastritis

The development of gastric adenocarcinoma of the intestinal type is thought to progress sequentially through four stages: non-atrophic gastritis, multifocal atrophic gastritis, IM, and dysplasia. Correa et al have proposed that there is a progression from normal gastric mucosa to carcinoma in high risk populations (29). The initial change is early onset superficial gastritis which, although reversible, is triggered by a variety of agents. *H. pylori*, chemical irritants (reflux/ ingested), autoimmune disease (pernicious anaemia) all cause inflammatory damage to the gastric mucosa, resulting in atrophic gastritis and intestinal metaplasia (30, 31). The progress to chronic gastritis may be associated with varying degrees of atrophy. Atrophic gastritis predisposes a high gastric pH, bacterial overgrowth and conversion of nitrates to nitrites. The resulting increase in nitrosamines damages the deoxyribonucleic acid (DNA) of mucosal cells, further promoting metaplasia and neoplasia. Alongside nitrogen compounds found in food and drugs bile acids degrade these nitrosamines to nitric oxide mutagens, which initiate small intestine metaplasia or promote dysplasia from colonic metaplasia. Duodenal reflux may contribute to intestinal metaplasia as it contains caustic bile salts that destroy the mucosal barrier which normally protects the stomach. While IM may occur in all areas of gastric atrophy, it occurs particularly in areas where metaplasia is similar to large bowel epithelium where dysplasia and hence carcinoma of the intestinal type may supervene (32-33). In high risk areas both IM and chronic gastritis are found in association with intestinal type cancer. Other evidence comes from studies of chronic gastritis associated with autoimmune pernicious anaemia. Patients with chronic atrophic gastritis (CAG) associated with autoimmune pernicious anaemia are at risk from gastric cancer. Moreover, the gastric mucosa the early stage of the disease has similar features of intestinal metaplasia. IM incidence in patients with the diffuse type of cancer is no different from the general population (34, 35). Intestinal metaplasia (IM) of the stomach has been shown to increase the relative risk of gastric cancer by a factor of 4.58 when compared to type 1 (36). Both precursor lesions are common in areas of high incidence. Endoscopic surveillance has been proposed and advocated for populations at risk.

*Helicobacter Pylori*

*H. pylori* is a micro-aerophilic, Gram negative, spiral micro-organism, classed by WHO as Group 1 carcinogen. A 100% infection results in 6-fold increase in incidence of gastric cancer (14, 37). The *H. pylori* that carry the Cag A gene product cytotoxin associated vacuolating antigen A (Vac A) also causes gastric B-cell mucosa-associated lymphoid tissue (MALT) lymphoma (38). Despite the fact that the stomach does not normally have any lymphoid tissue like the terminal ileal Peyer’s patches from which lymphoid malignancy could arise, recent studies have demonstrated that up to 90% of the gastric MALT type lymphoma were associated with *H. pylori* infection. This has suggested that the bacterial antigens may not only initiate gastritis but also perpetuate the immunological drive from which the lymphomatous process develops (39, 40). The sub-sequent development of monoclonal lymphocytosis requires accumulation of genetic abnormalities (41). It is important to note that regression of primary low grade B-cell gastric lymphoma of MALT type occurs after eradication of Helicobacter pylori but the results of similar trials on gastric carcinoma are awaited (42). *H. pylori* infection causes cell loss due to urease, ammonia, acetaldehyde activity, resulting from chemotactic effect on inflammatory cells releasing oxygen metabolites. The resulting loss of fundic glands leads to hypochlorhydria and proliferation of *H. pylori*. Chronic *H. pylori* infection induces chronic inflammation in the gastric mucosa, which may progress to atrophy and IM. The latter is a precursor to gastric adenocarcinoma (14, 43). IM initially appears at the antrum-gastric body junction, especially at the gastric incisura angularis. As atrophy and metaplastic changes advance, they tend to extend to the antrum and gastric body, and dysplastic foci may eventually appear.

Gastric remnant

Following previous gastrectomy, there is a 2% increase in the risk of gastric cancer, usually found at the stomal site (35, 44). Those who are at most risk are patients who have undergone surgery before the age of 40 and who have had a post surgery interval of 15-20 years (45, 46). Although alkalinity may play a role, the risk of developing this type of cancer is increased in countries with a high intrinsic rate of gastric cancer but apparently not in those with a lower rate (47-50). In addition, cases of lymphoma of the stomach are now being described in the gastric stump (51). Nonetheless, those patients who had undergone surgery for gastric malignancy would have exhibited precancerous lesions such as atrophic gastritis and IM, and the possibility of
anastomotic recurrence is higher than for the patients who had undergone benign gastric surgery (38, 49, 52). At present, there are no other recognized good markers of gastric dysplasia or cancer and residual premalignant (type III) IM may be the only marker for anastomotic recurrence of gastric cancer (38, 53-55). Micro RNAs are currently being evaluated as a specific diagnostic and prognostic marker (55).

**Gastric polyps**

Gastric polyps are found with increasing incidence in the elderly, and in some series they are present in up to 7% of patients over 80 years old (56). The classification is important as it indicates whether or not they are premalignant or are just incidental and sometimes associated with tumours (57, 58). Gastric mucosal polyps fall into three main groups; the hyperplastic polyps, fundic gland polyps or neoplastic polyps (adenomas). The hyperplastic subtype represents 80-85% of all gastric polyps, and is more common in the antrum rather than the gastric body. It generally consists of usually multiple polyps, less than 1 cm in diameter and has no increased risk of cancer (59). Hyperproliferative hamartomas occur in fundic glands but with no increased risk of cancer (60). Gastric polyps may be associated with familial adenomatous polyposis (FAP) but they are more commonly sporadic. Malignant change may occur in 40% of those neoplastic adenomas greater than 2 cm (61) The gastroduodenal polyps associated with FAP have an increased risk of malignant transformation to duodenal and peri-ampullary carcinoma (61,62)

**Gastric epithelial dysplasia**

Dysplasia may occur in an epithelium which shows intestinal metaplasia and may be flat, depressed or polypoid (38, 62). The natural history (mild/moderate/severe dysplasia is not a relentless march to carcinoma. There is a regression to normal in 60-70% of mild to moderate cases, but regression is less common in severe cases with 50-60% progressing to invasive carcinoma in this category (63). It is important to note that low grade dysplasia can be confused with inflammatory atypia, which can regress with acid suppression. The possibility of malignant transformation of gastric ulcers is controversial. Only 1-3% of gastric ulcers with an atrophic gastritis are associated with dysplasia (64). There are several problems associated with histological interpretation which include distinguishing regenerative atypia from true dysplasia, the ability to differentiate high-grade dysplasia from intramucosal carcinoma, a lack of experience due to the rarity of dysplasia (especially in low incidence areas) and the problem of sampling identical areas in the gastric mucosa on follow-up endoscopy. The natural history of dysplasia also compounds the potential ‘premalignant’ problem of regression. A diagnosis of severe dysplasia is a frequent marker of co-existent cancer, with 50% of the tumours being diagnosed within 3 months of the initial finding of dysplasia on biopsy. This is accompanied by a gross endoscopic lesion by erosion ulcer or polyp (64). The epidemiological evidence would suggest that ulcers do not have a significant role in gastric carcinogenesis. It is thought that less than 1% of chronic peptic ulcers will have undergone malignant transformation. Few long-term studies of peptic ulcers are available and these have shown a relative risk of developing cancer no more than twice that of the normal population (65).

**Menetrier’s disease**

*(Hypertrophic gastropathy)*

This is a rare cause of hypertrophic rugal gastropathy characterised by hyperplasia of the surface cells, hypochlorhydria and a protein-losing enteropathy. Approximately 10% are associated with gastric cancer, diagnosed either simultaneously or within 12 months. However, follow-up in a total of 16 cases shows the risk of malignancy to be low or negligible (66). A few cases have been associated with gastric dysplasia.

**Molecular aspects of gastric cancer**

Epithelial tumours result from the accumulation of multiple genetic defects which leads to uncontrolled growth. Modification of the tumour growth occurs as a result of the local effects of cytokines, growth factors and the interaction with the stromal components. A stepwise progression has been suggested, from the possible precursor lesions to cancer. Nevertheless, the initiating agents are unknown. The most plausible pathway for gastric cancer indicates that the underlying mechanisms may be different for the diffuse and intestinal types of tumour, respectively. There has been a steep rise in the knowledge of the genetic abnormalities in both gastric and oesophageal cancers (67-72). The changes which occur in these malignancies can be classified as consisting of abnormalities in DNA content, in the karyotype (including allele loss), oncogene and tumour suppressant gene expression (or deletion), of cell cycle regulation and finally of DNA repair genes. Loss of heterozygosity (LOH) studies have shown several chromosomal loci with significant allelic loss, thus indicating the possibility of harbouring a tumor suppressor gene which plays an important role in gastric tumorgenesis. Microsatellite instability (MIS) and associated alteration of the TGF-bIIIR,
IGFRII, BAX, E2F-4, hMSH3, and hMSH6 genes are also found in a subset of gastric carcinomas (73).

**Genetic pathway**

The heterogeneity of tumours is not only expressed in the morphological structure, but also in its DNA content as up to 30% of tumours show a mixed diploid and aneuploidy pattern. There are significant differences in the DNA content of tumours. For instance, tumours of the cardia display aneuploidy and have a poor prognosis (74). Despite this, diffuse cancers with their generally poor prognosis, tend to be less associated with aneuploidy than the intestinal type malignancies. The tumour suppressor gene p53, which is found on the short arm of chromosome 17, is thought to play a pivotal role in cell regulation and tumorigenesis. Its normal function is to put a brake on DNA replication and to act as a trigger for apoptosis, in response to significant DNA damage. Thus the p53 protein has roles in the repair of DNA and the induction of programmed cell death. Point mutations are the most frequent abnormality in this type of malignancy. Overall, genetic defects are noted in up to 60% of gastric tumours (75). Abnormalities of the proto-oncogenes are now being described, (75) which suggests they occur as early events in carcinogenesis. Comparative genomic hybridization analyses have identified several amplifications and losses of DNA copy numbers in gastric cancers. Loss of heterozygosity (LOH) in the proto-oncogene C-met continues to be present in up to 30% of intestinal cancers and correlates with peritoneal dissemination (70). Although their abundance only accounts for <10% of all cellular kinases, many PTKs have been shown to be oncogenic once they lose their biological regulation either by gene amplification, somatic mutation, or viral activation.

**Growth factors**

K-sam is a member of the fibroblastic growth factor receptor family, which is amplified in both diffuse and scirrhoues carcinomas but not in other types of tumours (66). In some tumours overexpression of c-erB-2 has been associated with more rapid metastases to the liver. Nevertheless, in other reports over expression had the reverse effect with patients experiencing longer survivals (72). Amplification and overexpression of the oncogene c-myc is found in both intestinal metaplasia and some cases of dysplasia as well as advanced gastric cancer, but not in early gastric cancer. The growth factors - tumour growth factor-α, (TGFα), epithelial growth factor (EGF), amphiregulin and interleukin 1α, which modulate interactions between tumour cells and stroma, are overexpressed in tumours. A new onco-gene cripto, a member of the EGF family is associated both with intestinal metaplasia and carcinoma and so far there is good correlation between the tumour stage and prognosis when the oncogene is expressed. Deletions of the crypto gene occur both in intestinal metaplasia and well-differentiated adenocarcinoma although over expression has been reported (73).

**Mismatch repair genes**

Abnormalities of the mismatch repair genes (74, 75) have been found in significant numbers of diffuse (64%) type of adenocarcinomas, whereas only 7% of the intestinal type malignancies have similar defects. At present it is unclear whether this abnormality causes the accumulation of the genetic changes, of oncogenes or tumour suppressor genes in the same cancer (76). Gastric cancer has been observed to be part of the spectrum of neoplasms associated with germline mismatch repair gene (MMR) alterations that give rise to the hereditary non-polyposis colorectal cancer (HNPPC) entity. Comparative genomic hybridization analyses have identified several amplifications and losses of DNA copy numbers in gastric cancers (69).

**Metastasis-related gene**

The metastasis- related gene CD44 (77) is a linking protein the extracellular matrix and the cell surface. In cancers, this protein is defective and shows a significant difference in expression between intestinal and diffuse
cancers. Another is nM23 which is thought to be a suppressor gene for metastasis and encodes the nucleotide diphosphate kinase and the c-myc transcription factor. Overexpression of this gene in a primary tumour is found to be related to the reduced risk of developing metastasis.

**Intestinal type**

Genetic instability of the normal cell leads to intestinal metaplasia in the well differentiated type (intestinal). *Cryptothyphleum* overexpression, p53, adenomatous polyposis gene (APC, which is central to ordered cell motility), as well as K-ras mutations are thought to represent earlier events. K-ras on chromosome 12 induces cell growth by activating growth factor signal transduction. P53, APCLOH, c-met 6.0Kb and bcl-2 gene loss occur as later events in the conversion to early gastric cancer. The change in the TGFβ receptor and CD44 abnormal transcripts would lead to advanced gastric cancer. C-Erb-B2 amplification and reduction in nM23 also lead to metastasis (71, 73).

**Diffuse-type**

Diffuse gastric cancer is a poorly differentiated type of cancer which accounts for about 30% of all gastric carcinomas. Somatic mutations in E-cadherin (CDH1 gene), an adhesion molecule and a tumor suppressor protein, were found in more than 50% of these cases (78, 79). The genetic instability of the normal cell leads to the mutation of the tumor suppressor gene p53 and allele loss with loss of heterozygosity in the proto-oncogene C-met which leads to early gastric cancer. Cell adhesion molecule abnormalities such as those involving E-cadherin (CDH1) loss, TGFβ over expression and CD44 abnormal transcripts would lead to advanced diffuse-type gastric cancer. The amplification of K-sam and reduction of C-met reduction in nM23 also lead to metastasis (71, 73). Inactivating CDH1 mutations were also described in the germ line of families with hereditary diffuse gastric cancer (HDGC), an autosomal-dominant disease characterized by clustering of early onset documented diffuse gastric cancer (80, 81).

**Hereditary diffuse gastric cancer** (HDGC) is a rare cause of early onset gastric cancer occurring in a younger age group. It is characterized by E-cadherin (CDH1) mutation, multi-centricity and linked to lobular breast cancer. HDGC families carry CDH1 heterozygous germ line mutations. Their tumours acquire complete CDH1 inactivation through “2nd-hit” mechanisms. The 2nd hit in CDH1 frequently occurs via epigenetic changes in HDGC primary tumours and loss of heterozygosity (LOH) in metastases. This occurs most frequently via promoter hypermethylation (epigenetic modification) (81). The oncogenes/tumour suppressor genes p53 (Li-Fraumeni syndrome), BRCA2, Peutz-Jeghers and hereditary non-polyposis colorectal cancer (HNPCC) mutations increase risk. HDGC should therefore be managed by prophylactic gastrectomy.

**The new paradigm**

It is suggested that ‘proximal non-diffuse’, ‘diffuse’ and ‘distal non-diffuse’ gastric cancers may be distinguished at the genomic level (82). The clinical indications to support this hypothesis include the suggestions that (a) proximal gastric tumours have a worse prognosis stage for stage when compared to distal tumours (84), (b) Lauren’s diffuse gastric cancers appear to have a different pattern of spread and behaviour than intestinal gastric adenocarcinoma (85), and (c) Her-2 over expression incidence is different between intestinal and diffuse types of gastric cancer. Her2 amplification is most prevalent in proximal or GOJ gastric cancer (30% Her-2 positivity rate) and least prevalent in diffuse type gastric cancer (5% Her2 positivity rate) (86). The RAS pathway seems to be down regulated in proximal non-diffuse gastric cancer when compared with diffuse gastric cancer (87, 88). The glycolysis pathway is upregulated in proximal and distal non-diffuse gastric cancers and diffuse gastric cancers are commonly FDG non-avid for PET scanning (89, 90). Although three pathways were dysregulated in >70% of gastric cancer; (i) proliferation /stem cell, (ii) NF-kB and (iii) Wnt/Beta catenin, combinations of several pathways may provide greater predictive value for patient outcomes than individual pathways (87, 88). The clinical relevance of this new molecular classification would potentially be represented by its capability to identify prognostic and predictive biomarkers, alongside new targets for therapy (90).

**CONCLUSIONS**

Although multiple somatic alterations have been described in gastric carcinomas at the molecular level, the therapeutic significance remains to be established in most instances. The lack of progress in identifying new drug targets in gastric adenocarcinoma is compounded by the concomitance and heterogeneity of alterations in the neoplastic lesions, and the plasticity of hypermethylated promoters during tumour initiation and progression. In addition, failure to appreciate the biological/molecular differences of the gastric carcinoma subtypes may affect response to adjuvant treatment. The increasing concentration of the disease at the gastro-
oesophageal junction strongly implicates reflux gastritis as an important factor but knowing which patients are at high risk and require careful assessment and review remains to be established. The role of *H. pylori* as an indicator of early diagnosis remains to be evaluated and the ability of the novel biomarkers in determining early gastric cancer should translate into improving cure rate.

**Ethical policies**

Compliance with Ethical Standards.

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**Conflict of interest**

The author declare that has no conflict of interest.

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