

Mitochondrial DNA alterations in the progression of gastric carcinomas: Unexplored issues and future research needs

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pathways of carcinogenesis. Somatic mitochondrial DNA (mtDNA) mutations and variable mtDNA copy number are involved in gastric tumorigenesis. The aim of this article is to review the growing literature on the mtDNA changes in gastric carcinomas and in their precancerous conditions. Furthermore, the authors describe which research questions remain unexplored, and suggest future research directions.

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Abstract

Gastric cancer is the second most frequent cause of cancer death worldwide. Patients infected with *Helicobacter pylori* (*H. pylori*) are at increased risk of gastric cancer. *H. pylori* induces genomic instability in both nuclear and mitochondrial (mt) DNA of gastric epithelial cells. Changes in mtDNA represent an early event during gastric tumorigenesis, and thus may serve as potential biomarkers for early detection and prognosis in gastric carcinoma. This review article summarizes the mtDNA mutations that have been reported in gastric carcinomas and their precancerous conditions. Unexplored research topics, such as the role of mtDNA alterations in an alternative pathway of gastric carcinogenesis, are identified and directions for future research are suggested.

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Key words: Gastric carcinoma; Precancerous lesions; Histopathology; mtDNA; Molecular biology

Core tip: Gastric cancer is a heterogeneous disease with multiple environmental etiologies and alternative

INTRODUCTION

Mitochondria are cytoplasmic organelles that play an essential role in numerous biological processes such as ATP production, iron and calcium homeostasis, production of reactive oxygen species, autophagic cell death and apoptosis^[1]. Mitochondrial (mt) DNA was initially considered to be naked, unprotected, and vulnerable to injuries. However, recently several works have shown that mtDNA is protein-coated and packaged into aggregates called nucleoids^[2-3]. Nucleoids are also important for the biogenesis of mtDNA, as they contain proteins that mediate DNA replication, repair, and recombination^[4-5]. Human mtDNA is a 16.6-kb double-stranded closed-circular DNA molecule, and a few hundreds to several thousand copies of mtDNA are present in each cell^[6-7]. It contains 37 genes, including the structural genes for 13 polypeptides of the electron transport chain involved in oxidative phosphorylation, two ribosomal RNAs, and a complete set of 22 tRNAs that are required for translation of the mtDNA-encoded mRNAs^[8]. In addition, mtDNA contains a non-coding region: the displacement loop (D-

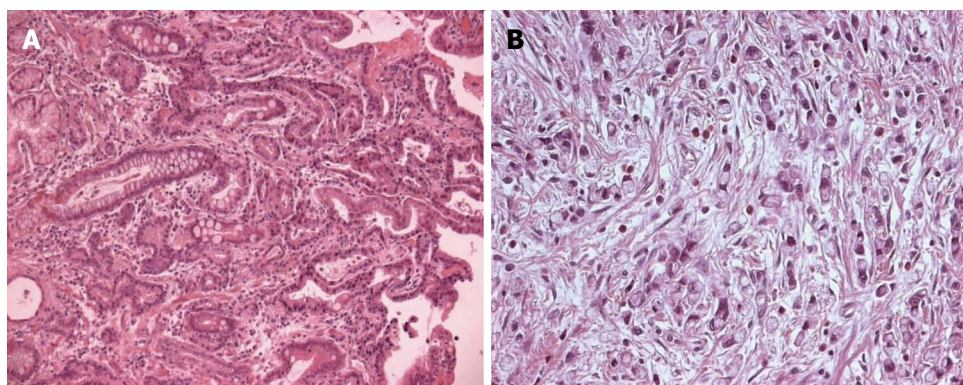


Figure 1 Intestinal-type adenocarcinoma. Intestinal metaplastic epithelium is adjacent to the carcinoma (A), diffuse-type carcinoma composed of signet-ring cells showing foamy cytoplasm and an eccentrically located nucleus (B).

loop) that controls both replication and transcription^[9]. Generally, each human cell contains several hundred to 1000 mitochondria, and each mitochondrion has 2-10 copies of mtDNA. Somatic mtDNA mutations occur randomly, both in the non-coding D-loop region and the coding genes, increase with age, and can affect all mtDNA copies within a cell (homoplasmy) or only some (heteroplasmy)^[10,11]. Homoplasmy or a high degree of heteroplasmy are needed so that a mutation results in an observable mutated cellular phenotype^[10]. How mtDNA regulates the tumorigenesis process has not been clearly defined, but current evidence suggests that mutation, reduction, or deletion of mtDNA lead to defective oxidative phosphorylation, increased reactive oxygen species production, induction of the glycolytic pathway, and increased expression of prosurvival proteins, which ultimately results in cancer proliferation and tumorigenesis^[12]. Therefore, modulation of mtDNA content in cancer is important for understanding the disease process.

Gastric cancer is the second leading cause of cancer death and the fourth most common malignant tumour in the world. The reason for fatality of gastric cancer is mainly due to late diagnosis and lack of programs for early detection; thus, identification of early events in gastric carcinomas is a challenging task^[13,14]. Gastric carcinoma is a heterogeneous disease with several epidemiological and histopathological characteristics. This tumour is classified anatomically as proximal (also known as cardia) and distal (also known as noncardia). This classification seems to distinguish two clinicopathologic entities^[15-17]. The risk factors positively associated with cardiac adenocarcinoma include obesity, hiatal hernia and reflux gastroesophagitis, whereas *Helicobacter pylori* (*H. pylori*) infection appears to be the main causative agent for distal gastric adenocarcinomas^[15,18,19]. Pathologically, distal gastric carcinoma may be distinguished according to the Lauren classification^[20] as intestinal or diffuse subtypes. Recently, a gastric-type differentiation has been demonstrated in some cases of intestinal-type adenocarcinomas^[21-24], but the introduction of these new terms may be a source of semantic confusion, particularly with clinicians.

This review article discusses controversies regarding histogenesis and classification of distal gastric cancer. In

addition, it summarizes the mtDNA changes that have been reported in gastric carcinomas and their precancerous conditions. Future research directions on the role of mtDNA in gastric carcinogenesis are suggested.

CLASSIFICATION AND PATHOLOGY OF DISTAL GASTRIC ADENOCARCINOMAS

Based on histopathological features, several classification systems of gastric cancer have been proposed. The two most commonly used classifications are the Lauren's^[20] and the World Health Organization (WHO) systems^[25]. The WHO classification distinguishes five major types of gastric carcinoma. This is based on the predominant morphologic component of the tumour and includes: papillary, tubular, mucinous, poorly cohesive (including signet-ring cells and other variants) and mixed carcinomas. In Lauren's classification, gastric adenocarcinomas are divided into two main types: intestinal (Figure 1A) and diffuse (Figure 1B). Intestinal adenocarcinomas usually arise in an older population with an increased incidence in men (male/female ratio of 2:1)^[15]. These tumours have the gross appearance of an exophytic mass, and histologically show a glandular structure resembling the glandular pattern of the intestine, although some solid or papillary areas are often present. Diffuse-type carcinomas do not show gender predominance, tend to develop in younger subjects, and have a poorer prognosis than intestinal-type tumours. Grossly, these tumours appear as ulcerative lesions or involve the entire thickness of the stomach wall, causing the thickening and increased firmness that has been called "linitis plastica". Histologically, they are made up either of separated single cells with or without signet ring cell configuration or small aggregates of malignant cells with little or no gland formation^[15,26]. It is thought that diffuse-type gastric carcinomas develop through the loss of function of E-cadherin, as germline mutations of the CDH1 gene (encoding E-cadherin) have been found in 30%-40% of hereditary diffuse gastric cancer cases. Furthermore, CDH1 is also frequently inactivated in sporadic diffuse-type gastric cancers through genetic and epigenetic alterations^[27-33]. A neoplastic precursor lesion associated

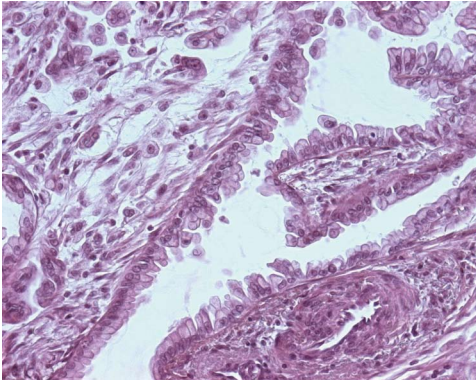


Figure 2 Gastric-type adenocarcinoma showing a papillary growth pattern admixed with a poorly differentiated component. Neoplastic glands are lined by cuboidal to tall columnar cells showing clear mucinous cytoplasm and basally oriented enlarged nuclei.

with the development of diffuse-type gastric cancer, and familial gastric cancer related to E-cadherin mutations, is usually referred to as “tubule neck dysplasia” and consists of signet ring cells that line the deep foveolar pits in a pagetoid fashion without mucosal involvement^[34-36]. However, this lesion is rarely found and is not readily recognizable. Distinctive clinicopathological features of intestinal and diffuse type of gastric carcinoma are shown in Table 1.

Recently, a new classification of gastric carcinomas based on mucin expression has been proposed^[21-24]. Intestinal gastric carcinomas were reclassified as gastric or intestinal phenotype on the basis of mucin expression by surface mucous cells, glandular mucous cells, and intestinal columnar and goblet cells^[21-24,37]. Histologically, gastric-type adenocarcinoma shows a papillary growth pattern in the upper portion and irregular branching/fusion in the deeper portion. Papillary projections are lined by columnar cells with clear mucinous cytoplasm and basally oriented enlarged vesicular nuclei with prominent nucleoli (Figure 2). Tajima *et al.*^[22] showed that gastric-type adenocarcinomas were significantly associated with a high risk of peritoneal recurrence and a poorer outcome after surgical resection compared with those with intestinal phenotype adenocarcinoma. Immunohistochemically, gastric type adenocarcinoma is positive for MUC5AC, and negative for CD10 and MUC2. Instead, intestinal-type adenocarcinoma is positive for CD10 and MUC2 and negative for MUC5AC^[23,24]. Diffuse-type carcinoma shows a variable positivity for MUC1, MUC2, MUC5AC and MUC6^[26].

The main clinicopathologic features of gastric-type adenocarcinoma compared to intestinal and diffuse type carcinomas are shown in Table 1.

H. PYLORI, MTDNA COPY NUMBER AND GASTRIC CARCINOGENESIS

Several studies show that both intestinal and diffuse types of gastric cancer are equally associated with *H. pylori* infection^[15]: a Gram-negative bacterium classified as a

Class I carcinogen by the WHO^[38]. However, only a subset, 1%-2% of infected individuals develop gastric malignancies^[15]. Clinical outcome of *H. pylori* infection may be correlated with specific virulence-associated bacterial genotypes such as *cagA* and *VacA* s1/m1. This genetic variability of *H. pylori* has been extensively studied in numerous laboratories and results have been summarized in previous publications^[39-41].

Experimental studies investigating the role of *H. pylori* on the mitochondrial genome of gastric epithelial cells have recently been reviewed by Strickertsson *et al.*^[42]. *H. pylori* infection has been associated with an increase of mtDNA mutations both in the mitochondrial D-loop region and in several genes encoding subunits of the electron transport chain^[43,44]. Deletion/insertion mutations have been described in the D-loop region^[43,45,46]. The increase in the number of mutations was mainly attributed to a rise of transitions, possibly a consequence of oxidative damage, and was correlated with bacterial virulence-associated *cagA* and *vacA* s1/m1 genotypes^[43]. mtDNA D-loop mutations may provoke a decrease in the copy number of the mitochondrial genome and alteration in gene expression. mtDNA depletion is a common event in gastric cancers^[47,48]. Over 55% of gastric cancers have a lower mtDNA copy number than their corresponding non-tumoural gastric mucosa^[47,48]. These results suggest that the mtDNA mutations in the D-loop region, due to *H. pylori* infection, contribute to the decrease in the mtDNA copy number in gastric cancer. Recently, Zhang *et al.*^[49] demonstrated that variable mtDNA content (either decreased or increased mtDNA content) markedly increased the risk of lymph node metastasis and high mortality in patients with advanced gastric carcinomas. These observations suggest that copy number variations of mtDNA may be involved in gastric cancer progression. However, the disparity of these findings in the alteration of mtDNA copy number among gastric carcinomas needs further study.

GASTRITIS CLASSIFICATION

The most widely used grading system for gastritis is the Update Sydney System^[50]. The system classifies chronic gastritis on the basis of topography, morphology, and, when possible, etiology. Topographic information provides further opportunities for assessing the risk of *H. pylori* gastritis. These are: (1) the predominance or restriction of *H. pylori*-related gastritis in the antrum strongly correlates with an increased risk of peptic ulcer disease, and of duodenal ulcer in particular; and (2) the occurrence of corpus-predominant or pangastritis is associated with a high risk of gastric cancer^[30]. In particular, patients with pangastritis are at high risk of diffuse-type gastric cancer, whereas those with corpus-predominant gastritis are at high risk of intestinal type gastric cancer (Table 1)^[51].

An international group of gastroenterologists and pathologists [the Operative Link for Gastritis Assessment (OLGA)] has proposed a system for reporting gastritis in terms of stage (the OLGA Staging System)^[52]. The

Table 1 Clinicopathologic features of intestinal, gastric and diffuse types of distal gastric adenocarcinomas

	Intestinal-type adenocarcinoma	Gastric-type adenocarcinoma	Diffuse-type carcinoma
Age	Old age	Old age	Young age
Sex (Male: Female)	2:1	Unknown data	1:1
Precancerous condition	Corpus-predominant gastritis with intestinal metaplasia	Corpus-predominant Gastritis with pseudopyloric metaplasia	Pangastritis
Precancerous lesion	Intestinal-type adenoma	Pyloric-gland adenoma	Tubular-neck dysplasia: signet-ring cell <i>in situ</i>
Gross feature	Exophytic lesion	Exophytic lesion	Ulcerative lesion and linitis plastica
Microscopy	Tubulopapillary glands lined by columnar cells with eosinophilic cytoplasm	Tubulopapillary glands lined by columnar cells with clear mucinous cytoplasm	Discohesive cells or signet ring cells
Immunohistochemistry	CD10 and MUC2 immunoreactivity	MUC5AC immunoreactivity	Variable positivity for MUC1, MUC2, MUC5AC, MUC6
Liver metastasis	Frequent	Rare	Rare
Peritoneal spread	Rare	Frequent	Frequent
Malignant potential	Low	High	High

OLGA system considers gastric atrophy as the lesion that indicates disease progression. Atrophy is distinguished in a non-metaplastic (shrinkage or complete disappearance of glandular units, replaced by expanded (fibrotic) lamina propria) and a metaplastic form including intestinal metaplasia and pseudopyloric metaplasia also known as spasmolytic polypeptide-expressing metaplasia. The OLGA staging system ranks gastric cancer risk according to the extent and severity of gastric atrophy and includes 5 stages: 0, I, and II, or low-grade atrophy associated with a low risk of gastric cancer, and III and IV, or high-grade atrophy associated with a high risk of gastric cancer^[52]. The histopathological diagnosis of pseudopyloric metaplasia requires the endoscopist to communicate a correct identification of the location of the biopsy specimen in the body mucosa otherwise the pathologist considers antral-like mucosa as non-metaplastic^[53]. As atrophic gastritis and pseudopyloric metaplasia remain difficult histopathologic diagnoses with low interobserver agreement, a gastritis staging system has recently been proposed as an alternative to the OLGA (OLGIM system)^[54]. In the OLGIM system only intestinal metaplasia is considered as the key lesion to score for staging purposes^[54]. Although replacement of atrophic gastritis by intestinal metaplasia in the staging of gastritis considerably increases interobserver agreement, the OLGIM system disregards pseudopyloric metaplasia that is now recognized as an important step in the tumorigenesis of gastric-type adenocarcinoma. By focusing on intestinal metaplasia only, the OLGIM system might be less sensitive in identifying patients with high-risk gastritis^[55].

HISTOGENETIC PATHWAY OF INTESTINAL-TYPE GASTRIC CARCINOMA

According to the Correa model, histogenesis of intestinal

type gastric cancer follows a pathway of chronic active gastritis due to *H. pylori* infection leading to multifocal atrophy, intestinal metaplasia, followed by gastric dysplasia and finally invasive adenocarcinoma^[15]. Previous studies^[56-58] showed a sequential accumulation of mitochondrial microsatellite instability (MSI) in the histological progression from chronic gastritis to cancer via intestinal metaplasia and dysplasia. These findings suggested an important role of mtMSI in the progression of gastric carcinogenesis. Recent studies^[59] using mtDNA mutations as a marker of clonal expansion demonstrated that intestinal metaplastic epithelium shares a common mtDNA mutation and spreads by fission: a process characterized by a bud arising from the isthmus/neck region that continues until a new gland and foveolus is formed. Furthermore, they showed that dysplasia can arise from a single clone of mutated intestinal metaplastic glands and expand to form the entire dysplastic lesion^[60]. These morphologic and mtDNA findings strongly support Correa's hypothesis of intestinal-type gastric carcinogenesis^[15].

ALTERNATIVE PATHWAYS OF GASTRIC CARCINOGENESIS

However, recent studies based on minute EGC less than 3 mm in diameter have not confirmed the association between intestinal metaplasia and intestinal type gastric cancer^[61]. Some authors consider intestinal metaplasia a paracancerous lesion rather than a precancerous condition, a withered branch in the histogenetic evolution of gastric carcinoma^[62,63]. Detailed mapping studies of resected stomachs from patients with intestinal-type gastric cancer have shown that atrophic gastritis, but not intestinal metaplasia, is present in every case^[64,65]. Gastric atrophy therefore appears to be a better indicator of gastric cancer risk than intestinal metaplasia. Atrophy is generally present as either a multifocal or a diffuse pattern in gastric

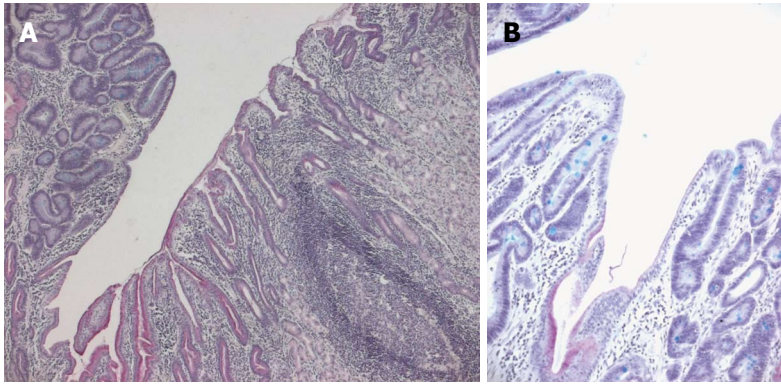


Figure 3 Gastric adenoma of intestinal type (A), dysplastic epithelium shows mild architectural changes with little branching or irregularity (left, note prominent lymphoid follicle in the adjacent non-neoplastic mucosa (right), alcian bleu- periodic acid Schiff; A few small goblet cells are scattered among columnar cells showing elongated nuclei (B) (Alcian blue- periodic acid Schiff).

tissue and is, by definition, associated with the presence of pseudopyloric metaplasia^[66,67]. This type of metaplasia may be a consequence not only of *H. pylori* corpus-dominant gastritis, but also of autoimmune gastritis, where disruption of oxyntic glands is due to lymphocytes. Pseudopyloric metaplasia is more strongly associated with gastric cancer than intestinal metaplasia and might be the precursor to the cancerous lesion^[64,66]. In some mouse models of gastric cancer, classic intestinal metaplasia seen in humans is not observed, whereas pseudopyloric metaplasia clearly precedes and gives rise to gastric cancer^[68]. The precancerous condition of pseudopyloric metaplasia has also been confirmed in patients who developed remnant carcinomas 16-20 years after a previous gastrectomy^[69]. In experimental models, where chronic inflammation is absent, pseudopyloric metaplasia does not progress to dysplasia or neoplasia, suggesting that pseudopyloric metaplasia *per se* may not be precancerous in the absence of inflammation. To our knowledge, there are no biomolecular studies regarding the role of mtDNA mutation in pseudopyloric metaplasia.

GASTRIC ADENOMA: RECLASSIFICATION BASED ON CLINICAL, MORPHOLOGIC AND MTDNA FINDINGS

To elucidate the role of mtDNA mutations in gastric carcinogenesis, we analyzed mutations in the D-loop region of mtDNA in 24 paraffin-embedded gastric adenomas from a high gastric cancer risk area in northern Italy^[46]. *H. pylori* infection was assessed by histological examination (Giemsa staining). The gastric adenomas were divided into two groups by their association with *H. pylori* gastritis. Group A with lesions arising on a background of *H. pylori*-positive gastritis contained 7 patients, and group B with lesions associated with *H. pylori*-negative gastritis contained 17 patients. Group A had a larger proportion of high-grade lesions than group B and showed a foveolar phenotype. Group B had a larger proportion of cases with mtDNA

D-loop mutations than group A and exhibited an intestinal phenotype. Our data provide evidence for the morphologic and mtDNA biomolecular heterogeneity of gastric adenomas^[46]. Further studies confirmed clinical and morphologic heterogeneity in gastric adenomas^[37,70-76]. Phenotypically, the majority of gastric adenomas belong to the intestinal type (containing goblet cells, absorptive cells, Paneth cells, and/or columnar cells with various degrees of differentiation) (Figure 3). Gastric-type adenomas are predominantly composed of pyloric gland mucous cells (pyloric gland adenomas) or foveolar-like cells (foveolar-type adenomas)^[37,70-75]. Pyloric gland adenomas occur predominantly in old women; they tend to arise in the corpus mucosa of the stomach, showing close association with pseudopyloric metaplasia of fundic glands^[70-75]. Histologically, pyloric gland adenomas are composed of pyloric glands-type tubules that are not fused and are lined by a monolayer of cuboidal to low columnar epithelial cells containing clear cytoplasm or pale eosinophilic cytoplasm (showing a ground glass appearance) without an apical mucin cap^[69-70,73-74]. The nuclei tend to be round and usually lack prominent nucleoli. Immunohistochemically, pyloric gland adenomas are positive for MUC6 (pyloric gland marker) with variable MUC5AC (foveolar cell marker) stain. MUC2 and CD10 are generally negative^[74]. Taken together, these studies confirm that intestinal-type adenomas may represent a step towards malignant transformation of intestinal-type adenocarcinoma, according to Correa's cascade, but suggest that gastric-type adenomas represent a distinct evolutionary pathway of gastric carcinogenesis. Thus, it is plausible that each metaplasia gives rise to a distinct type of differentiated gastric adenocarcinoma; *e.g.*, classic intestinal metaplasia could evolve into intestinal-type gastric adenocarcinoma, according to Correa's hypothesis, whereas it is possible to suggest a histogenetic sequence: *pseudopyloric metaplasia-gastric-type adenoma-gastric-type adenocarcinoma*.

CONCLUSION

Gastric adenocarcinoma is a heterogeneous disease with

alternative pathways of carcinogenesis. This review article reveals that most research efforts regarding mtDNA alterations focus on gastric carcinogenesis according to the Correa model. Further studies are needed to define with greater clarity the possible role of mtDNA mutations in alternative pathways of gastric carcinogenesis, such as pseudopyloric metaplasia-gastric type adenocarcinoma.

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