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

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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.

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[6]. 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 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-
Diffuse-type gastric carcinomas develop through the histogenesis and classification of distal gastric cancer. In semantic confusion, particularly with clinicians, the introduction of these new terms may be a source of some cases of intestinal-type adenocarcinomas a gastric-type differentiation has been demonstrated in classification carcinoma may be distinguished according to the Laurèn adenocarcinomas appears to be the main causative agent for distal gastric esophagitis, whereas Helicobacter pylori infection as intestinal or diffuse subtypes. Recently, a gastric-type differentiation has been demonstrated in some cases of intestinal-type adenocarcinomas, 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 and the World Health Organization (WHO) systems. 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). 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 plastic”. 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. 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. A neoplastic precursor lesion associated

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).
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]. Inestinal 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[21-24,35]. 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 nucleoli (Figure 2). Tajima et al[30] 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[22,34]. 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[13]: 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[13]. 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 Strickertson 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[46]. 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[51]. 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)[52].
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   | Corpus-predominant gastritis with pseudopyloric metaplasia | Pangangitis           |
| Precancerous lesion    | Intestinal-type adenoma        | Pyloric-gland adenoma      | Tubular-neck dysplasia: signet-ring cell in situ |
| Gross feature          | Exophytic lesion               | Exophytic lesion           | Ulcerative lesion and linitis plastic |
| 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      | Low                             | Frequent                   | Frequent              |
| Malignant potential    |                                |                            | 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 spasmyotic 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, II, III, and IV, 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[25]. 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[25]. 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)[34]. In the OLGIM system only intestinal metaplasia is considered as the key lesion to score for staging purposes[34]. 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[34].

**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[35]. Previous studies[36-38] 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 supported an important role of mtMSI in the progression of gastric carcinogenesis. Recent studies[39] 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[40]. These morphologic and mtDNA findings strongly support Correa’s hypothesis of intestinal-type gastric carcinogenesis[38].

**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[41]. Some authors consider intestinal metaplasia a paracancerous lesion rather than a precancerous condition, a withered branch in the histogenetic evolution of gastric carcinoma[42,43]. 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[44-46]. 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
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alternative pathways of carcinogenesis. This review article reveals that most research efforts regarding mtDNA alterations focus on genetic 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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