TOPIC HIGHLIGHT

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Somatic alterations in mitochondrial DNA and mitochondrial dysfunction in gastric cancer progression

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Abstract

Energy metabolism reprogramming was recently identified as one of the cancer hallmarks. One of the underlying mechanisms of energy metabolism reprogramming is mitochondrial dysfunction caused by mutations in nuclear genes or mitochondrial DNA (mtDNA). In the past decades, several types of somatic mtDNA alterations have been identified in gastric cancer. However, the role of these mtDNA alterations in gastric cancer progression remains unclear. In this review, we summarize recently identified somatic mtDNA alterations in gastric cancers as well as the relationship between these alterations and the clinicopathological features of gastric cancer. The causative factors and potential roles of the somatic mtDNA alterations in cancer progression are also discussed. We suggest that point mutations and mtDNA copy number decreases are the two most common mtDNA alterations that result in mitochondrial dysfunction in gastric cancers. The two primary mutation types (transition mutations and mononucleotide or dinucleotide repeat instability) imply potential causative factors. Mitochondrial dysfunction-generated reactive oxygen species may be involved in the malignant changes of gastric cancer. The search for strategies to prevent mtDNA alterations and inhibit the mitochondrial retrograde signaling will benefit the development of novel treatments for gastric cancer and other malignancies.

Core tip: In this review, we summarize recent somatic mitochondrial DNA (mtDNA) alterations identified in gastric cancer, and the relationship between these alterations and the clinicopathological features of gastric cancer. We suggest that point mutations and mtDNA copy number decreases are the two most common mtDNA alterations that potentially result in mitochondrial dysfunction in gastric cancer. Mitochondrial dysfunction-generated reactive oxygen species may be involved in the malignant changes of gastric cancer. The search for strategies to prevent the mtDNA alterations and inhibit the mitochondrial retrograde signaling will benefit the development of novel treatments for gastric cancer and other malignancies.

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INTRODUCTION

Gastric cancer is one of the most common causes of death in cancer patients throughout the world. Surgical resection with radical lymph nodes dissection is the primary therapy for gastric cancer[1]. Chemotherapy is an alternative treatment for unresectable gastric cancer or tumor recurrence after surgical resection. However, the response to chemotherapy remains unsatisfactory. Thus, it is important to identify novel drug targets and develop effective treatments for gastric cancer.

Based on the conceptual progress of the past decades, energy metabolism reprogramming was recently included as one of the cancer hallmarks[2]. Warburg[3,4] first proposed that tumor cells, unlike normal cells, exhibit increased glycolytic activity and reduced mitochondrial respiration even in the presence of oxygen. This phenomenon is known as the "Warburg effect". Increasing lines of evidence suggest that various molecular mechanisms generate the Warburg effect[5,6]. One of these mechanisms is mitochondrial dysfunction resulting from mutations in nuclear genes or mitochondrial DNA (mtDNA)[5-9].

Mitochondria are intracellular organelles in eukaryotic cells that participate in bioenergetics metabolism and cellular homeostasis, including the generation of ATP through respiration and oxidative phosphorylation (OXPHOS), the production of reactive oxygen species (ROS), and the initiation and execution of apoptosis[10]. Mitochondria contain multiple copies of mitochondrial DNA (mtDNA). Human mtDNA is a 16.6-kB double-stranded, circular DNA molecule that encodes 13 respiratory enzyme complex polypeptides, 22 transfer RNAs and 2 ribosomal RNAs required for mitochondrial protein synthesis[10]. Because mtDNA is essential for the maintenance of functionally competent organelles, the accumulation of mtDNA mutations or decreased mtDNA copy number is expected to affect energy production as well as enhance ROS generation and cell survival, and these processes may be involved in aging, mitochondrial diseases or cancer[9-12].

In the past decade, somatic mtDNA alterations have been identified in several types of cancer[8,9], including gastric cancer[13-15]. However, the role of these mtDNA alterations in tumorigenesis and cancer progression remains unclear. In this article, we review recent findings on somatic mtDNA alterations in gastric cancer. In addition, we discuss the potential factors that may lead to mtDNA mutations and propose a role of mtDNA alterations and mitochondrial dysfunction in the progression of gastric cancer.

SOMATIC MITOCHONDRIAL DNA ALTERATIONS IN GASTRIC CANCER

Several studies have identified various types of mtDNA alterations in gastric cancer[13-15], including point mutations, large-scale deletions, insertions, and copy number changes.

In one of our studies[15], 65% of the examined gastric cancer patients carried at least one mtDNA somatic point mutation. Among the identified point mutations, 69% occur in the D-loop region of mtDNA, 27% are found in the protein-coding region, and 4% are located in *tRNA* genes. Compared with other cancers, these mutations are similar in their incidence and distribution (Table 1)[15-38]. The D-loop region of mtDNA is the most frequent site of somatic mutation in cancers. Because the D-loop region contains the major regulatory sites for mtDNA replication and transcription, mutations near these sites might affect mtDNA copy number in cancers.

Given that the mtDNA D-loop region is a hot spot for somatic mutations in gastric cancer as well as other cancers, numerous studies focus on somatic mutations in this region[13,39-43]. The incidence of somatic mtDNA point mutations in the D-loop of gastric cancer patients ranges from 4% to 48%. The most common mutations in this region are mononucleotide repeat variants of the poly-cytosine (poly-C) sequence at nucleotide positions (np) 303-309 (D310) in mtDNA[8]. The variants were also identified in normal subjects[44] and patients with neurodegenerative diseases[45]. The effect of these variants is not clearly defined.

Moreover, several somatic point mutations identified in the mtDNA protein-coding region and tRNA genes in gastric cancer patients are potentially harmful[15]. These mutations include missense mutations (*e.g.*, G3697A and G4996A) that cause amino acid substitutions at the highly evolutionarily conserved amino acid residues, frameshift mutations (*e.g.*, 12418insA) that result in truncated polypeptides, and tRNA mutations (*e.g.*, 7472insC) that potentially alter tRNA structure. Moreover, studies have demonstrated that these mutations are pathogenic and associated with mitochondrial diseases[15]. tRNA gene mutations as well as missense and frame-shift mutations in the mitochondrial genome may promote mitochondrial dysfunction in gastric cancer cells.

A common 4977-bp mtDNA deletion occur less frequently in gastric cancers compared with the corresponding noncancerous stomach tissues[13,46,47], though large-scale mtDNA deletions are the most common mutation in the somatic tissues of aged human subjects[9]. This finding is consistent with observations in other types of cancer[8,9]. The low accumulation of large-scale mtDNA deletions in cancer could result because an increased frequency of these mutations may cause severe mitochondrial dysfunction and sensitize the cells to apoptosis. Any cells harboring high levels of large-scale mtDNA deletions could be eliminated during tumorigenesis[9].

Unlike large-scale deletions, a 50-bp deletion flanked

Table 1 The distribution of somatic mitochondrial DNA mutations in human cancers *n* (%)

Cancer	Cases	No. of cancers with mutation	No. of mutations	D-loop	rRNA	tRNA	mRNA	Ref.
Adult leukemia	24	9 (37.5)	9	2 (22.2)	1 (11.1)	0	6 (66.7)	[16]
Bladder cancer	14	9 (64.3)	20	6 (30.0)	3 (15.0)	0	11 (55.0)	[17]
Breast cancer	18	11 (61.1)	12	7 (58.3)	0	0	5 (41.7)	[18]
	19	14 (73.7)	27	22 (81.5)	1 (3.7)	0	4 (14.8)	[19]
	15	14 (93.3)	45	17 (37.8)	3 (6.7)	2 (4.4)	23 (51.1)	[20]
	58	27 (46.6)	40	21 (52.5)	2 (5.0)	2 (5.0)	15 (37.5)	[21]
Esophageal cancer	20	11 (55.0)	14	9 (64.3)	1 (7.1)	0	4 (28.6)	[22]
Follicular thyroid cancer	3	3 (100.0)	4	2 (50.0)	2 (50.0)	0	0	[23]
Gastric cancer	31	20 (64.5)	26	18 (69.2)	0	1 (3.8)	7 (26.9)	[15]
Head-and-neck cancer	13	6 (46.2)	9	6 (66.7)	1 (11.1)	0	2 (22.2)	[17]
Hepatocellular cancer	10	5 (50.0)	24	23 (95.8)	0	0	1 (4.2)	[24]
	44	23 (52.3)	34	21 (61.8)	1 (2.9)	2 (5.9)	10 (29.4)	[25]
Lung cancer	14	6 (47.1)	10	7 (70.0)	1 (10.0)	2 (20.0)	0	[17]
	55	33 (60.0)	56	18 (32.1)	1 (1.8)	3 (5.4)	34 (60.7)	[26]
Medulloblastoma	15	6 (40.0)	18	11 (61.1)	0	3 (16.7)	4 (22.2)	[27]
Oncocytic head-and-neck tumor	25	16 (64.0)	18	0	0	0	18 (100.0)	[28]
Oncocytic pituitary adenoma	25	18 (72.0)	20	3 (15.0)	0	2 (10.0)	15 (75.0)	[28]
Oncocytic thyroid tumor	45	26 (57.8)	30	0	0	0	30 (100.0)	[29]
Oral cancer	18	14 (77.8)	26	20 (76.9)	0	0	6 (23.1)	[30]
	300	240 (80.0)	645	355 (55.0)	36 (5.6)	21 (3.3)	233 (36.1)	[31]
Ovarian cancer	10	6 (60.0)	15	11 (73.3)	3 (20.0)	0	1 (6.7)	[32]
Pancreatic cancer	5	4 (80.0)	4	0	1 (25.0)	1 (25.0)	2 (50.0)	[33]
Papillary thyroid cancer	7	3 (42.9)	4	0	0	0	4 (100.0)	[23]
Parathyroid adenoma	30	15 (50.0)	27	6 (22.2)	1 (3.3)	1 (3.3)	19 (70.4)	[34]
Renal cell cancer	8	5 (62.5)	6	1 (16.7)	2 (33.3)	0	3 (50.0)	[35]
	9	7 (77.8)	9	4 (44.4)	1 (11.1)	1 (11.1)	3 (33.3)	[36]
	15	7 (46.7)	14	4 (28.6)	4 (28.6)	1 (7.1)	5 (35.7)	[37]
Renal oncocytomas	9	9 (100.0)	14	1 (7.1)	0	0	13 (92.9)	[38]
Total	859	567 (66.0)	1180	595 (50.5)	65 (5.5)	42 (3.6)	478 (40.4)	

by a 9-bp direct repeat at nps 298-306 and 348-356 of the mtDNA D-loop region was reportedly found at high levels in four gastric cancers[48]. This deletion is associated with decreased mtDNA copy number in cancer[49].

A 260-bp tandem duplication/triplication mtDNA mutation in the D-loop region was identified in approximately 13% of the examined gastric cancers[14]. The duplicate/triplicate insertion of an 260-bp fragment is flanked by two poly-C sequences at nps 303-309 and 568-573[13,14,44]. The insertion was also detected in other types of cancer[14]. However, the occurrence of this mutation does not appear to be specific to cancer cells[14,44,50-52].

Decreased mtDNA copy number was frequently detected in gastric cancer patient tissues compared with corresponding noncancerous stomach tissue[13,53]. Alterations in mtDNA copy number change (increase or decrease) appear to be tissue specific[7,8,54]. A decreased mtDNA copy number is also found in the majority of hepatocellular carcinomas[49] and breast cancers[55].

These findings reveal that somatic point mutations and a decreased mtDNA copy number are two common mtDNA alterations in gastric cancer. The increased rate of somatic mtDNA alterations in gastric cancer is also observed in other cancers, suggesting that these two types of somatic mtDNA alterations are common events in human cancer progression. These mtDNA alterations may result from similar factor(s) and/or play a consistent role in the tumorigenesis of gastric cancer and other malignancies.

SEVERAL POTENTIAL FACTORS MAY CAUSE TO SOMATIC mtDNA ALTERATIONS IN GASTRIC CANCER

The mutation type could provide clues regarding factors that potentially contributing to somatic mtDNA alterations in gastric cancer. Among the mtDNA mutations identified in gastric cancer, 46% of the somatic point mutations are transition mutations (*e.g.*, T-to-C or G-to-A), and another 46% result from mononucleotide or dinucleotide repeat instability (*e.g.*, poly-C or poly-A)[15]. Compared with other types of cancer, 60% of the mutations are transition mutations, 31% are mononucleotide or dinucleotide repeat instability, and 4% are transversion mutations (*e.g.*, T-to-A or G-to-C) (Table 2)[15-38]. These findings indicate that transition mutations and mononucleotide or dinucleotide repeat instability are two major types of somatic mtDNA mutations in cancers.

Given that the mitochondrial electron transport chain is a major site for intracellular ROS formation, oxidative mtDNA damage is predicted to be an important factor promoting mtDNA mutations and genome instability in cancers. However, whether steady-state levels of oxidative mtDNA damage are increased in gastric cancer compared with corresponding noncancerous stomach tissue remains unknown.

The main pyrimidine and purine product of oxidative DNA base damage is thymine glycol and 7,8-dihydro-

Table 2 The types of somatic mitochondrial DNA mutations in human cancers *n* (%)

Cancer	Cases	No. of cancers with mutation (%)	No. of mutations	Transitions	Transversions	Mono-/di-nucleotide repeat instability	Others	Ref.
Adult leukemia	24	9 (37.5)	9	9 (100.0)	0	0	0	[16]
Bladder cancer	14	9 (64.3)	20	14 (70.0)	3 (15.0)	1 (5.0)	2 (10.0)	[17]
Breast cancer	18	11 (61.1)	12	6 (50.0)	1 (8.3)	5 (41.7)	0	[18]
	19	14 (73.7)	27	22 (81.5)	1 (3.7)	4 (14.8)	0	[19]
	15	14 (93.3)	45	33 (73.3)	7 (15.6)	5 (11.1)	0	[20]
	58	27 (46.6)	40	20 (50.0)	2 (5.0)	17 (27.5)	1 (2.5)	[21]
Esophageal cancer	20	11 (55.0)	14	3 (21.4)	1 (7.1)	9 (64.3)	1 (7.1)	[22]
Follicular thyroid cancer	3	3 (100.0)	4	3 (75.0)	0	1 (25.0)	0	[23]
Gastric cancer	31	20 (64.5)	26	12 (46.2)	0	12 (46.2)	2 (7.7)	[15]
Head-and-neck cancer	13	6 (46.2)	9	7 (77.8)	0	2 (22.2)	0	[17]
Hepatocellular cancer	10	5 (50.0)	24	15 (62.5)	0	9 (37.5)	0	[24]
	44	23 (52.3)	34	19 (55.9)	0	13 (38.2)	2 (5.9)	[25]
Lung cancer	14	6 (47.1)	10	8 (80.0)	1 (10.0)	1 (10.0)	0	[17]
	55	33 (60.0)	56	47 (83.9)	1 (1.8)	8 (14.3)	0	[26]
Medulloblastoma	15	6 (40.0)	18	13 (72.2)	0	5 (27.8)	0	[27]
Oncocytic head-and-neck tumor	25	16 (64.0)	18	13 (72.2)	1 (5.6)	1 (5.6)	3 (16.7)	[28]
Oncocytic pituitary adenoma	25	18 (72.0)	20	10 (50.0)	0	9 (45.0)	1 (5.0)	[28]
Oncocytic thyroid tumor	45	26 (57.8)	30	22 (73.3)	1 (3.3)	5 (15.2)	2 (6.7)	[29]
Oral cancer	18	14 (77.8)	26	12 (46.2)	4 (15.4)	8 (30.8)	2 (14.3)	[30]
	300	240 (80.0)	645	356 (55.2)	20 (3.1)	237 (36.7)	32 (5.0)	[31]
Ovarian cancer	10	6 (60.0)	15	10 (66.7)	0	4 (26.7)	1 (6.7)	[32]
Pancreatic cancer	5	4 (80.0)	4	3 (75.0)	1 (25.0)	0	0	[33]
Papillary thyroid cancer	7	3 (42.9)	4	4 (100.0)	0	0	0	[23]
Parathyroid adenoma	30	15 (50.0)	27	18 (66.7)	1 (3.7)	6 (22.2)	2 (7.4)	[34]
Renal cell cancer	8	5 (62.5)	6	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)	[35]
	9	7 (77.8)	9	6 (66.7)	0	3 (33.3)	0	[36]
	15	7 (46.7)	14	13 (92.9)	1 (7.1)	0	0	[37]
Renal oncocytomas	9	9 (100.0)	14	7 (50.0)	2 (14.3)	4 (28.6)	1 (7.1)	[38]
Total	859	567 (66.0)	1180	707 (59.9)	49 (4.2)	370 (31.4)	54 (4.6)	

8-oxo-2'-deoxyguanosine (8-oxodG), respectively[56-59]. Thymine glycol is poorly mutagenic, but 8-oxodG can result in G-to-T transversion mutations during replication because unrepaired 8-oxodG can pair with adenine[60]. However, the most common mtDNA mutations in cancer are transition mutations rather than the mutational consequences specific to 8-oxodG (G-to-T transversion). Therefore, DNA lesions other than 8-oxodG could be primarily responsible for mtDNA transition mutations in cancer. Some studies indicated that oxidative lesion 8-oxodG can be efficiently repaired in mtDNA[61]. In addition, oxidative DNA damage can produce a range of base lesions, and the mutagenic potential of these lesions has not been fully elucidated[62]. In fact, some of these lesions may be responsible for ROS-mediated mtDNA mutagenesis. Moreover, reactive nitrogen species (RNS) can deaminate adenine to hypoxanthine, cytosine to uracil, and guanine to xanthine, thereby causing transition mutations[63,64]. Thus, it is possible that mtDNA transition mutations in cancer could result from the deamination of adenine, cytosine, or guanine by RNS. Alternatively, factors other than oxidative damage are primarily responsible for the formation of mtDNA mutations, such as defects in mtDNA polymerase or repair systems[61,65].

Oxidative damage could also contribute to mononucleotide or dinucleotide repeat instability in mtDNA[63]. The mononucleotide repeat in the D310 poly-C sequence of the D-loop region, the most common site of somatic mtDNA mutations in cancer, is the site most susceptible oxidative damage in mtDNA[66]. Moreover, extensive oxidative damage to the mononucleotide repeats may result in slippage and/or misincorporation of nucleotides during mtDNA replication or repair by mtDNA polymerase (POLG). Importantly, it has been reported that POLG is a target of oxidative damage[67] and frequently harbors mutations in cancerous tissues[68]. Specifically, mutations were identified in all three domains of the POLG protein, including the exonuclease domain, the linker region and the polymerase domain[63]. In addition, increased mtDNA mutations are observed in *Polg*[exo-/-] and *Polg*[exo+/-] mice[69,70]. Therefore, defects in the polymerase and repair activities of POLG might enhance the generation of mtDNA mutations and genome instability in cancer. However, whether a general defect in POLG *per se* leads to increased mutations or genome instability in the D-loop region compared with other region in the mitochondrial genome and the mechanisms governing this action remains unknown.

Some studies indicated that *Helicobacter pylori* (*H. pylori*) infection can affect mitochondrial function and impair DNA repair mechanisms, thereby inducing genetic instability of nuclear and mitochondrial DNA in gastric cells[71-73]. Therefore, *H. pylori* infection may promote mtDNA instability and contribute to gastric carcinogenesis in infected individuals.

Decreased mtDNA copy number could result from

mutations in the D-loop region. Because this region is the control site for mtDNA replication and transcription, mutations in the region could repress the rates of primer synthesis and mtDNA replication. This hypothesis is supported by the observation that decreased mtDNA copy number is associated with the mutations in the D-loop region[49].

In addition, decreased mtDNA copy number in cancer could be attributed to defects in mitochondrial biogenesis or other proteins localized to the mitochondria (*e.g.*, p53 or SIRT3). Defects or decreased expression in several factors involved in mtDNA replication and maintenance as well as mitochondrial biogenesis, such as POLG[68], peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1)[74], mitochondrial single-strand DNA binding protein (mtSSB)[74], and mitochondrial transcription factor A (mtTFA)[74], have been observed in cancer. Decreased mtDNA copy number correlates with reduced expression of PGC-1 in HCC[74] and mtTFA in colorectal cancer[75]. These findings suggest that reduced mitochondrial biogenesis may lead to decreased mtDNA copy number in cancers. Moreover, the tumor suppressor p53 can localize to mitochondria, and contribute to the maintenance of mtDNA stability through interactions with POLG[76]. Thus, the loss of p53 in cancer may lead to decreased mtDNA copy number. In addition, the mitochondrial deacetylase SIRT3 is down-regulated and acts as a tumor suppressor in several cancers, including gastric cancer[77-79]. The loss of SIRT3 expression is an independent prognostic marker for reduced disease-free survival and overall survival in gastric cancer[78,79]. The loss of SIRT3 is correlated with decreased mtDNA integrity and mtDNA copy number[77].

Therefore, enhanced mtDNA damages and/or reduced efficiency in the mtDNA replication and repair activities as well as the loss of mitochondrial-localized proteins may contribute to mtDNA somatic mutations and decreased copy number in gastric cancer.

CLINICAL CORRELATIONS OF SOMATIC mtDNA ALTERATIONS IN GASTRIC CANCERS

To understand the roles of somatic mtDNA alterations in gastric cancer progression, the analysis of the clinicopathological features of cancers harboring these mutations may provide insight.

We analyzed the relationships between each somatic mtDNA mutation and the clinicopathological features of gastric cancer. However, no significant correlation was observed between the clinicopathological features of gastric cancer and somatic point mutations in the D-loop[13,43] or the mitochondrial genome[15], the 4977-bp deletion[13], or the tandem duplication/triplication of mtDNA[14].

For mutations of a specific mononucleotide repeat (D310) of mtDNA, the mutations are not associated with nuclear microsatellite instability in gastric cancer[80],

and are more frequent in gastric cancer patients with *H. pylori*-associated chronic gastritis compared with cancer-free patients[81]. These findings suggest that mtDNA mononucleotide instability may be involved in the early stages of gastric carcinogenesis.

A significant association between decreased mtDNA copy number and ill-defined gastric cancers, including the ill-defined ulcerative and infiltrating (Borrmann's type Ⅲ) and diffusely infiltrating (Borrmann's type Ⅳ) types, was observed[13]. A recent report further confirmed that mtDNA copy number is significantly decreased in gastric cancer, particularly in ill-defined stage Ⅲ and Ⅳ cases, and suggested that alterations in mtDNA copy number may correlate with DNA methylation[53]. Because most patients with Borrmann's type Ⅲ and Ⅳ gastric cancer have a poorer prognosis and reduced 5-year survival rate after gastrectomy, these findings suggest that decreased mtDNA copy number may modify gastric cancer progression.

THE POTENTIAL ROLES OF mtDNA MUTATIONS AND MITOCHONDRIAL DYSFUNCTION IN GASTRIC CANCER PROGRESSION

In gastric cancer, somatic point mutations in the mitochondrial coding region are potentially harmful mutations that may cause mitochondrial dysfunction. These harmful mtDNA mutations along with decreased mtDNA copy number contribute to mitochondrial dysfunction. In addition, decreased mitochondrial aconitase (ACO2) expression, decreased respiratory capacity, and mitochondrial complex Ⅰ deficiency were observed in gastric cancer[82,83]. These findings have been suggested as a mechanism to explain the Warburg effect. However, the role of mtDNA mutations and mitochondrial dysfunction in tumorigenesis and cancer progression remains unclear in gastric cancer.

Among the mtDNA mutations identified in gastric cancers, the role of the 12418insA mutation in tumorigenesis has been examined using a cybrid cell model (though not in gastric cancer cells)[84]. The 12418insA mutation is an "A" nucleotide insertion in the mononucleotide repeat of a poly-adenosine (poly-A) sequence at np 12418-12425 in mtDNA. The mutation causes a frameshift and premature termination of the ND5 gene, thereby resulting in a truncated ND5 subunit protein. In addition to gastric cancer[15], this mutation was also reported in the rotenone-resistant VA2B cell line[85], colorectal cancer[86], HCC[25], and breast cancer specimens[21]. A study revealed that the heteroplasmic 12418insA mutation contributes to reduced oxidative phosphorylation and increased ROS production in human cancer cells and promotes tumorigenesis in nude mice[84]. The report provided evidence suggesting that mtDNA mutation and mitochondrial dysfunction contribute to tumorigenesis.

Additional evidence was obtained from an approach

using mitochondrial specific inhibitors to suggest that mitochondrial dysfunction enhances chemo-resistance and cell migration in human gastric cancer cells[15,87]. Oligomycin-induced mitochondrial dysfunction promotes cisplatin resistance and enhances cell migration in a human gastric cancer cell line[15]. Moreover, mitochondrial inhibitors (antimycin A and oligomycin) increased intracellular ROS levels, and the antioxidant N-acetyl-cysteine preventes the enhanced cell migration mediated by the mitochondrial inhibitors. These results suggest that ROS generated by defective mitochondria may be involved in the mechanism[15,87]. In addition, the mitochondrial inhibitors increase the expression of the cell adhesion molecule alpha5-integrin *via* ROS induction[87]. Alpha5-integrin on the cell surface is required for mitochondrial dysfunction-enhanced cell migration[87]. These findings suggest that ROS-mediated increased alpha5-integrin expression might serve as the molecular basis by which mitochondrial dysfunction promotes gastric cancer cell migration.

An addition approach employed a method to select the subpopulation of cancer cells demonstrating enhanced migration. This study indicated that highly migratory gastric cancer cells display reduced oxygen consumption rates, increased intracellular ROS content and increased alpha5-integrin expression compared with the parental cells[87]. Importantly, the evidence from clinicopathological studies with gastric cancer specimens suggest that alpha5-integrin expression is highly correlated with gastric cancer invasion[87]. These results further support the association between mitochondrial dysfunction and cell migration in gastric cancer.

Although most of the studies were not focused on gastric cancer, data from several lines of research have substantiated the pathological role of mtDNA mutation or mitochondrial dysfunction in cancer. Using cybrid cell models, pathogenic mtDNA mutation (*e.g.*, the T8993G transversion) have been shown to promote tumor growth in nude mice by preventing apoptosis[88-90]. Moreover, it was reported that the mtDNA mutation-mediated mitochondrial dysfunction contributes to metastatic cancer phenotypes, and ROS induction is mechanistically involved[88,91]. Mitochondrial inhibitors or mtDNA depletion can induce chemo-resistance or enhance the invasive phenotypes of various cancers[92-96]. "Retrograde signaling," signaling from mitochondria to the nucleus[97,98], has been proposed to be mechanistically involved. However, the common biomolecules involved in retrograde signaling remain undefined. The detailed mechanisms by which mtDNA mutation and mitochondrial dysfunction affect gastric cancer progression require further investigations.

CONCLUSION

Several types of somatic mtDNA alterations have been identified in human gastric cancers. The point mutation and decreased mtDNA copy number are the two most common mtDNA alterations, and these alterations might result in mitochondrial dysfunction in gastric cancers. These findings provide a molecular basis for the meta-

bolic reprogramming or the "Warburg effect" in gastric cancers. Clinical correlative analyses reveal that decreased mtDNA copy number is associated with the ill-defined ulcerated and infiltrating types as well as the diffusely infiltrating types of gastric cancer, which might correlate with poorer patient prognosis[13]. However, the presence of somatic mtDNA point mutations in gastric cancers does not correlate with tumor size and grade, or patient survival[15]. This finding might be attributed to the possibility that these mtDNA point mutations do not always affect mitochondrial function nor contribute to gastric cancer progression. In addition, different heteroplasmic levels of the same mtDNA mutation might produce varying results for tumorigenesis and cancer progression. The results are consistent with *in vitro* studies using mitochondrial inhibitors, suggesting that mitochondrial dysfunction might induce chemo-resistance and enhance cell migration in part in gastric cancer cells[15,84]. Thus, the role of specific mtDNA point mutation in mitochondrial function and gastric cancer progression warrants further study.

Among the somatic mtDNA mutations identified in gastric cancer, transition mutations and mononucleotide or dinucleotide repeat instability, not transversion mutations, are the two most common types of mutation. Transition mutations may not result from oxidative DNA damage; rather, these mutations may result from specific types of DNA damage and/or reduced efficiency in mtDNA replication and repair activities as well as other undefined mechanisms.

Increasing lines of evidence have important implications in the pathological role of mtDNA mutation or mitochondrial dysfunction in gastric cancer. Increased ROS production induced by mitochondrial dysfunction may be involved in the malignant changes of gastric cancer. However, the detailed mechanism by which mtDNA mutation and mitochondrial dysfunction affect gastric cancer progression remains unclear. Elucidation of the factors causing mtDNA mutations and activating retrograde signaling pathways in gastric cancer will be important for understanding the role of mitochondria and mtDNA in gastric cancer. The search for strategies to prevent mtDNA alterations and inhibit these pathways will aid in the development of novel treatments for gastric cancers.

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