Potential role of mitochondria in gastric cancer detection: Fission and glycolysis (Review)

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Abstract. Gastric cancer (GC) is characterized by high morbidity and mortality rates worldwide. *Helicobacter pylori* infection, high salt intake, smoking, alcohol, low fiber intake, family history of GC, obesity and precancerous lesions, including chronic atrophic gastritis and intestinal metaplasia, are considered general risk factors for GC. Image enhancement endoscopy methods, which improve the visualization of mucosal structures and vascularity, may be used for the early diagnosis of GC, such as narrow band imaging, which can reveal fine details of subtle superficial abnormalities of early gastric cancer (EGC). Mitochondria are well-known for their role in producing ATP via the tricarboxylic acid cycle. In cancer cells, the energetic metabolism can be reprogrammed as anaerobic glycolysis for energy production and anabolic growth. In addition to their dominant metabolic functions, mitochondria participate in several central signaling pathways, such as the apoptotic pathway and NLRP3 inflammasome activation. Conversely, mitochondrial dynamics, including fission/fusion and mitophagy, can also contribute to the pathogenesis of cancer. The dysfunction and dysregulation of mitochondria have been associated with several ageing and degenerative diseases, as well as cancer. The present review focuses on energy metabolism and mitochondrial dynamics, and summarizes the changes in gastric carcinogenesis, the diagnosis of EGC and indicates potential targeted treatments.

Contents

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1. Introduction

Chronic atrophic gastritis (CAG) is considered a common risk factor for the development of gastric cancer (GC). Endoscopic imaging and biopsy are crucial for early detection and diagnosis of GC (1). Image-enhanced endoscopy combined with biopsy, according to the Sydney protocol and regular endoscopic surveillance, are recommended for patients with extensive CAG or intestinal metaplasia (2). A visible lesion may be treated by endoscopic mucosal resection or endoscopic submucosal dissection. However, when a lesion is invisible, regular endoscopic surveillance is required for high-risk patients. The interval between *Helicobacter pylori* eradication and cancer occurrence may vary from several months to >10 years (3). Surveillance endoscopy is one of the methods enabling the early diagnosis of GC (4). Once an existing lesion is identified, it can be treated in a timely manner. Interval cancer can occur due to missed lesions or to a newly developed lesion during surveillance (5). Thus, it is essential to identify a molecular biological marker for the detection of invisible lesions at the organelle level.

Recently, diverse pathophysiological functions of mitochondria have been reported, including mitochondrial dynamics (6), metabolic reprogramming (7), mitochondria-released damage-associated molecular patterns and NLRP3 inflammasome activation (8), mitochondrial DNA (mtDNA), autophagy and mitophagy (9), mitochondrial outer membrane permeabilization (10) and mitochondrial aging (11). In addition, mitochondrial (mt)DNA mutations, deletions and impaired DNA replication are the most common causes of mitochondrial dysfunction (12). mtDNA sensing via STING signaling participates in inflammation and cancer (12,13). The effects of mitochondrial dynamics on carcinogenesis and cancer progression have also been reported, highlighting the potential use of mitochondrial biomarkers in cancer detection and prognosis, as well as the potential targeting of mitochondrial dynamics for treating cancer (14). However, there is still a paucity of research associated with GC.

The present review summarizes the role of mitochondrial dynamics and energy metabolism reprogramming in GC to identify potential indicators for biologically complemented endoscopy and further promote translating discoveries of molecular biology. Thus, fission and glycolysis from mitochondria may be useful in detecting GC. If an electron microscope can be installed on the endoscopy system, the mitochondrial dynamics may be observable during the early stages of GC. Furthermore, when fission is increased and fusion is decreased, further precision biopsy of the targeted tissue should be performed to detect metabolic activity. The combination of both approaches may enable early diagnosis and provide a novel treatment strategy. However, further investigation is required.

2. Mitochondrial dynamics: Fission and fusion

Mitochondria are responsible for energy supply and are involved in several biological processes, including cell death and proliferation (6). Mitochondria constantly maintain a dynamic shape, which may change in response to cellular bioenergetic demands, such as nutrient status, which is defined as mitochondrial dynamics (12). The mitochondrial morphology is a result of the interplay between rapid fusion and fission events (15). The key components mediating these processes belong to the dynamin family of GTPases that utilize GTP hydrolysis to drive mechanical work on biological membranes (16). Mitofusin proteins, Mfn1 and Mfn2, are involved in the fusion of the outer mitochondrial membrane, while GTPase optic atrophy 1 mediates the fusion of the inner mitochondrial membrane (17). Mitochondrial fission is mediated by the GTPase dynamin-related protein 1 (Drp1) following its recruitment by the membrane-anchored proteins, namely mitochondrial fission factor and fission protein 1 (Fis1) (18). Commonly, the mitochondrial fission/fusion machinery is involved in generating new mitochondria, and eliminating old, damaged and non-repairable mitochondria (6). Mitochondrial fission plays an important role in mitochondrial proliferation, mitochondrial distribution during cell division and the removal of damaged mitochondria via mitophagy (19). Unopposed mitochondrial fission causes mitochondrial fragmentation, which is generally associated with metabolic dysfunction and several diseases, such as degenerative diseases and cancer (20). It has been reported that impaired mitochondrial fission is associated with mitochondrial elongation (21). In addition, unopposed fusion results in a hyperfused network and serves to counteract metabolic insults, preserve cellular integrity and protect against autophagy (20). It was previously reported that impaired mitochondrial fusion may promote fission-induced mitochondrial fragmentation (21). Thus, the maintenance of mitochondrial fission/fusion balance plays a key role in cell cycle progression (6). The dynamics is critical for the effects of fission/fusion on morphology regulation, content exchange, and the maintenance of mtDNA and mitochondrial oxidative phosphorylation (OXPHOS) activity (22,23).

3. Fission, mitophagy and GC

Fission isolates depolarized mitochondria, while it coordinates the downregulation of fusion mediators to prevent network reintegration, thereby facilitating mitophagy, mainly via interactions between Parkin, Bcl-2/adenovirus E1B 19 kDa protein interacting protein 3 (BNIP3) and Drp1 (24). Increasing Drp1 results in excessive mitochondrial fragmentation and deficiencies, decreases mitochondrial motility and shortens mitochondrial length (25), which may be further enhanced in hypoxia (26). Fission can also be triggered by stress stimuli, such as nutrient deprivation, DNA damage, inflammation and mitochondrial membrane depolarization (27). Given that mitochondria-associated membranes related to the endoplasmic reticulum at specific regions can facilitate calcium (Ca^{2+}) flux into the mitochondria and further control the homeostasis and metabolism of Ca^{2+}, close coupling of these organelles increases mitochondrial Ca^{2+} levels, thus initiating apoptosis (28). It has also been reported that enhanced fission attenuates adherence to inhibit Ca^{2+} overload in mitochondria and apoptosis (29). In terms of mitophagy, this process maintains cellular health by selectively enclosing damaged and depolarized mitochondria in autophagic vacuoles for lysosome-mediated elimination (30). Mitophagy degrades dysfunctional mitochondria and further attenuates reactive oxygen species (ROS) generation, which in turn promotes cell survival and protects against cell death (31). Increasing evidence suggest that several modulators of mitophagy are deregulated in human cancer, including Parkinson protein 2 E3 ubiquitin protein ligase, FUN14 domain containing 1, BNIP3 and BNIP3L (32,33). In addition, a study revealed that impaired mitophagy can enhance the aggressiveness in GC cells under hypoxia by activating the mtROS/hypoxia-inducible factor (HIF)-1α interplay (34). Mitophagy may also be enhanced by overexpression of Opa-interacting protein 5, thus plays an important role in cell survival and death in docetaxel-treated GC cells (35). Another study demonstrated that Drp1 expression is upregulated, and the expression levels of the mitophagy-related regulators, PTEN-induced putative kinase 1 and Parkin, are downregulated in patients with GC (36). Given that mitophagy can clear the damaged part of mitochondria and mtDNA, it protects healthy cells from malignant transformation and tumor cells from apoptosis (31). It has been suggested that, in the early stages of GC, mitophagy is associated with tumor suppression, whereby it can promote tumor growth at the advanced stages of GC. For example, mitophagy was increased in advanced-stage GC to sustain the viability and migration of GC cells (37), since mitophagy in solids tumor may be activated by two common factors, namely hypoxia and low nutrient supply (38) (Fig. 1).

4. Fusion and GC

Mitochondrial fusion results in a more interconnected mitochondrial network and enhances the communication with the endoplasmic reticulum (39). Fusion allows the diffusion of matrix content among mitochondria, diluting the accumulated mtDNA mutations and oxidized proteins (40). Fusion is commonly enhanced by starvation by triggering the protein kinase A-mediated phosphorylation of Drp1 (at Ser637) to blunt fission (41). In addition, mitochondrial fusion is required for mtDNA maintenance (22). Thus, impaired mitochondrial fusion is often accompanied by bioenergetic defects due to loss of mtDNA (42). Furthermore, mitochondrial fusion is also associated with increased OXPHOS and ATP generation

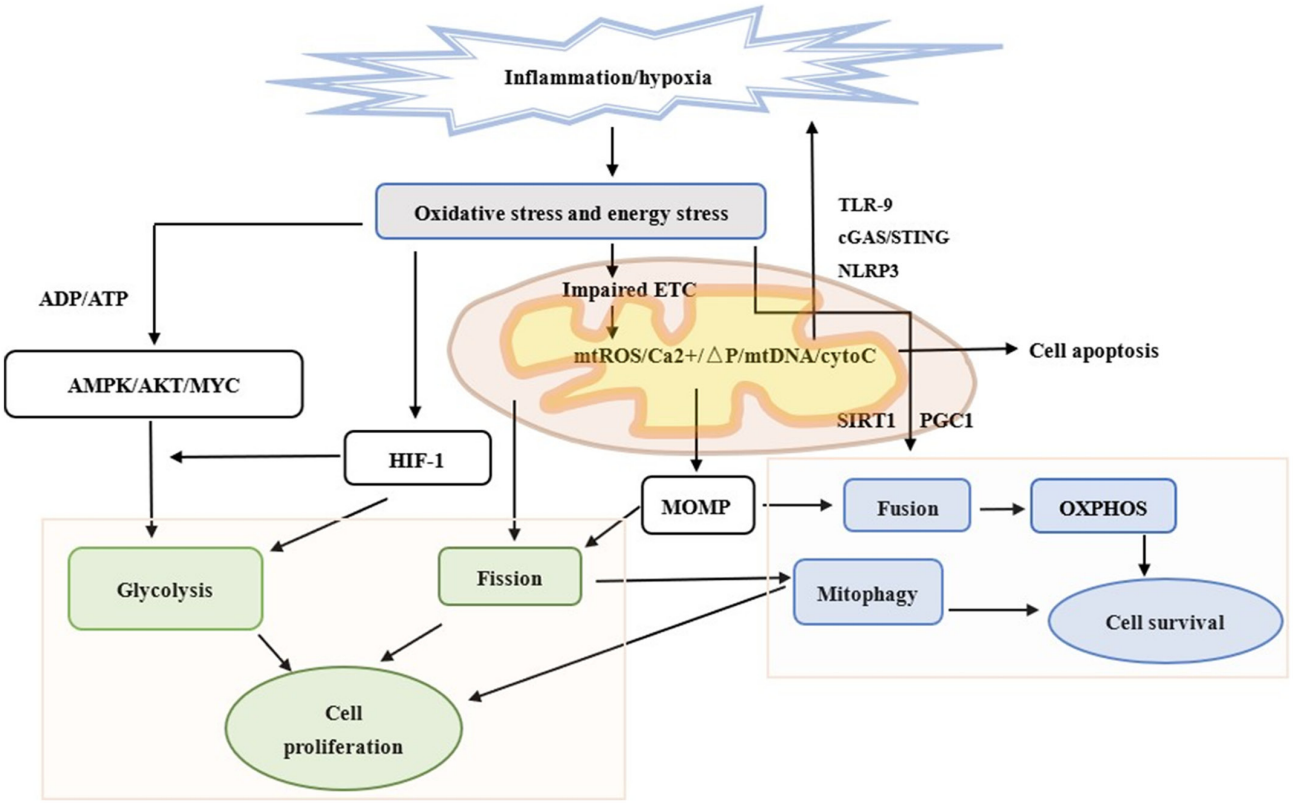

Figure 1. Different mitochondrial dynamics and energy metabolism in an epithelial cell subjected to chronic inflammation. Chronic inflammation causes the injury of epithelial cells. Mitochondria is involved in further innate immune responses, including cGAS-STING signaling, TLR-9 and NLRP3 inflammasome formation following the release of mtDNA. Mitochondria is also associated with apoptosis. When atrophic epithelial cells preserve their programed cell death ability and surrounding inflammation is sufficiently severe, cells undergo apoptosis instead of necrosis. Chronic inflammation can also damage mitochondria and lead to changes in mitochondrial metabolism and dynamics via HIF-1, AMPK and MOMP. Fission and glycolysis promote cell proliferation and invasion. Fusion and OXPHOS are compatible with cell survival. Mitophagy protects both normal and cancer cells by selectively eliminating damaged mitochondria. Green outline represents proliferation, blue outline represents survival and the text without boxes represent apoptosis. cGAS, cyclic GMP–AMP synthase; STING, stimulator of interferon genes; TLR-9, Toll-like receptor-9; NLRP3, NOD-like receptor family pyrin domain-containing 3; mtDNA, mitochondrial DNA; HIF-1, hypoxia-inducible factor-1; AMPK, AMP-activated protein kinase; MOMP, mitochondrial outer membrane permeabilization; OXPHOS, oxidative phosphorylation; ETC, electron transport chain; mtROS, mitochondrial ROS; ΔP, increased potential; cytoC, cytochrome c; PGC1, proliferator-activated receptor-γ coactivator.

via remodeling of the cristae (43,44), and downregulation of OPA1, which is responsible for fusion, resulted in mitochondrial dysfunction and mtDNA stress (45). The number of mitochondria is regulated by mitochondrial biogenesis to meet the energy demands of the cells and compensate for their damage (46). A study demonstrated that peroxisome proliferator-activated receptor gamma coactivator (PGC-1) and the protein deacetylase sirtuin 1 (SIRT1) can regulate fusion and OXPHOS (14). Thus, activation of PGC-1α by SIRT1 induces mitochondrial biogenesis and confers metabolic advantages (14). Another study revealed that PGC-1β can induce mitochondrial fusion by upregulating Mfn2 expression via estrogen-related receptor α coactivation (47). Mfn2 expression is downregulated in GC tissues compared with normal gastric mucosal tissues, and is negatively associated with tumor size, indicating an antitumor role of Mfn2 (48). *In vitro* experiments have demonstrated that overexpression of Mfn2 can suppress gastric cancer cell proliferation and colony formation (48). SIRT1 is an enzyme that mediates NAD^+-dependent deacetylation of target substrates (49). Given that the cellular redox balance of NAD^+ and NADH is highly associated with catabolic fluxes, SIRT1 can act as a sensor, directly connecting metabolic perturbations with transcriptional output (49). SIRT1 expression is significantly downregulated in GC tissues, which is associated with poor prognosis (50). It has also been reported that SIRT1 exerts inhibitory effects on chemoresistance and cancer stem cell properties via Forkhead box O3 and AMP-activated protein kinase (AMPK) (51). AMPK, another key energy metabolic sensor, plays a key role in maintaining cellular energy homeostasis and is activated upon alterations in the cellular AMP/ATP ratio (52). Previous studies have demonstrated that, upon energy deficiency, AMPK activation may result in increased PGC-1α expression and phosphorylation to modulate the expression of several key players in mitochondrial biogenesis and OXPHOS of fatty acids (53,54) (Fig. 1).

5. Reprogrammed energy metabolism and GC

Energy metabolism is essential for maintaining cellular homeostasis and biological functions, and includes ATP production in the cytosol (glycolysis) and mitochondria (OXPHOS) (55), which can be reprogrammed during carcinogenesis (56). Cancer cells undergo metabolic reprogramming, including enhanced glycolysis, mutations in genes encoding tricarboxylic acid (TCA) cycle enzymes, upregulation of de novo lipid synthesis and glutaminolysis (57). Glycolysis is characterized by an increased rate of glucose uptake and its glycolytic conversion to lactate, even under oxygen-rich conditions (55). There

are several pathways and transcriptional regulators involved in the regulation of metabolic reprogramming, such as PI3K/AKT pathway and HIF-1 (58,59). The PI3K/AKT pathway can regulate several aspects of this metabolic program (58). A previous study demonstrated that AKT activation was sufficient to induce glycolysis by promoting glucose transporter 1 and phosphorylating pyruvate dehydrogenase kinase to inhibit pyruvate dehydrogenase and favor lactate dehydrogenase (LDH) activity (60). It has been reported that HIF-1 is overexpressed in human cancers as a result of intratumoral hypoxia, as well as genetic alterations, such as gain-of-function mutations in oncogenes and loss-of-function mutations in tumor suppressor genes (61). HIF-1 may also be triggered by the accumulation of TCA substrates (62), while its degradation is regulated by O_2-dependent prolyl hydroxylation (PHs) (61). HIF-1α maintains its stability by avoiding the hydroxylation of PHs in cancer cells, since PHs can be inhibited by the increased levels of cytosolic pyruvate, lactate, succinate, fumarate and ROS (59). Most genes encoding glycolytic enzymes and transporters are the targets of HIF-1α, and its overexpression in cancer cells is associated with increased levels of glycolytic proteins (63). A study revealed that HIF-1α levels were high in certain tumors, even under oxygen-rich conditions, indicating that hormones or growth factors can cause the stabilization of HIF-1α expression, which may serve important roles in carcinogenesis (64). A previous study suggested that HIF-1α can act as a negative regulator of mitochondrial biogenesis and oxidative phosphorylation to inhibit the conversion of pyruvate to acetyl-CoA and mitochondrial respiration and to promote LDH expression (65). HIF-1α activation can also inhibit MYC transcription to further downregulate PGC-1α and PGC-1β expression, which in turn regulates mitochondrial biogenesis and OXPHOS (54). In GC, inhibiting HIF-1α signaling attenuates the migratory and invasive abilities of GC cells, and epithelial-to-mesenchymal transition (66), whereas activation of HIF-1α signaling promotes cell metastasis and glucose metabolism (67).

The tumor microenvironment favors the growth and expansion of cancer and inflammatory cells, which in turn directly or indirectly promotes gastric tumorigenesis by secreting soluble factors or modulating immune responses (68). It has been reported that NF-κB is activated in chronic inflammation, thus promoting the further activation of tumor-promoting genes, such as IL-6 and cyclooxygenase (COX)-2 (69). NF-κB and HIF-1 can link inflammatory signaling to hypoxia and coordinate the activation of both COX-2 and IL-6, and the Janus kinase/STAT3 pathway (70). It has been reported that STAT3 cooperates with NF-κB and HIF-1 in the regulation of both genes (71). NF-κB can be strongly induced by hypoxia and chronic inflammation, and is involved in the reprogramming of tumor glycolysis by interacting with HIF-1α (70). Given that inflammation can induce cells lacking oxygen and upregulate HIF-1α, glycolysis gradually becomes the main energy source instead of OXPHOS (55) (Fig. 1)

6. Association between mitochondrial dynamics and energy metabolism: Fission and glycolysis

Mitochondrial morphological changes are a type of primary signal to shape metabolic reprogramming during cellular quiescence or activation (14,72). Recent studies have demonstrated that increased mitochondrial fission promotes a pro-tumorigenic phenotype (12,73,74). Several studies have been performed in different cell types that alter their mitochondrial morphology to meet their energy demands, functions and behaviors. Conversely, certain cells, such as T cells and stem cells, have higher energy demands to perform their metabolic and cell-specific functions (75,76). When T cells recognize major histocompatibility complexes presented by antigen-presenting cells in response to infection or tumors, they proliferate and differentiate into different T-cell subsets (23). Effector T cells display looser cristae remodeling via fission with reduced electron transport chain (ETC) complexes, thus attenuating ETC efficiency and promoting aerobic glycolysis (23). Conversely, in memory T cells, tight cristae remodeling via fusion with enhanced ETC complex activity is observed, thus enhancing ETC efficiency and OXPHOS (23). Endothelial progenitor cells (EPCs) accelerate glycolysis to produce lactate during angiogenesis by upregulating the expression levels of HIF□1α and vascular endothelial growth factor (77). In human EPCs, downregulation of Fis1 expression is associated with mitochondrial dysfunction and may contribute to the impaired activity of EPCs during the senescence process (73). However, upregulation of Fis1 expression in senescent EPCs restores the younger phenotype (73). Another study investigated the function of mitochondrial fission genes in embryonic stem cells (ESCs). Transmission electron microscopy revealed a significant increase in the cytoplasm-to-nucleus ratio and mitochondrial elongation in dynamin-1-like protein (-/-) ESCs caused by incomplete fission. In addition, increased OXPHOS and intracellular ATP concentration and reduced glycolysis was observed, which were associated with mitochondrial elongation (78). The proliferation and invasion of tumor cells also require faster and increased energy supply (79). Thus, Drp1 expression is upregulated in several types of cancer cells, including liver (80), breast (81) and lung cancers (82), and may be considered as a biomarker for predicting poor survival in patients with these types of cancer. A study on ovarian cancer demonstrated that glycolysis is promoted by activating PI3K/AKT/HIF-1α signaling, while mitochondrial fission is enhanced by phosphorylation of Drp1 at Ser616 (83). As a member of the AMPK family, salt-inducible kinase 2 was demonstrated to be involved in both pathways (83). In addition, Drp1 expression was significantly upregulated in pancreatic cancer (PC) cells and tissues via downregulation of microRNA-29a expression (74). High Drp1 expression was associated with poor survival of patients with PC, while Drp1 promoted both the proliferation and metastasis of PC cells, mainly through facilitating aerobic glycolysis (74). Another study revealed that Drp1 may promote KRAS-driven tumor growth by supporting both glycolysis and mitochondrial function (84). Taken together, these findings suggest a mutual association between Drp1 and glycolysis, and the promoting effect of Drp1 and glycolysis on cancer cell proliferation and invasion.

7. Conclusions

GC is the fifth most common type of cancer and the third most common cause of cancer-associated mortality, with 784,000 mortalities reported in 2018 worldwide (85). Early detection and treatment can improve the outcome of patients with GC. Innovative endoscopic techniques may be more accurate in achieving cytological or even biological diagnosis. Mitochondria

are strongly associated with carcinogenesis. The present review summarized the role of mitochondria dynamics, reprogramming of energy metabolism and their changes in GC. Based on current literature, it can be concluded that mitochondria in GC are characterized by fission and enhanced glycolysis to meet the increased energy requirements of cancer cells, and decrease necrosis via mitophagy. Upregulated expression levels of Drp1 and HIF-1α are associated with fission and glycolysis, respectively. The balance of mitochondrial fission and fusion and the ratio of glycolysis to OXPHOS are positively associated with different stages of carcinogenesis. When increased fission and glycolysis and decreased apoptosis and fusion are detected in high-risk patients, they may indicate that cells are in the process of malignant transformation. Thus, treatment is required to inhibit this process, which may be a promising approach to the detection of early gastric cancer via organelle- and molecular-level endoscopy in the future.

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Authors' contributions

HY designed the present review and drafted the initial manuscript. BH contributed to designing and reviewing the manuscript. HY, YL and BH contributed to revising the manuscript for important intellectual content. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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