PI3K/AKT/mTOR and MAPK Pathways in Gastric Cancer

Subjects: Oncology

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Gastric cancer (GC) is the fourth leading cause of death worldwide, with more than 1 million cases diagnosed every year. *Helicobacter pylori* represents the main risk factor, being responsible for 78% of the cases. Increased amounts of salt, pickled food, red meat, alcohol, smoked food, and refined sugars negatively affect the stomach wall, contributing to GC development.

gastric cancer PI3K/AKT/mTOR MAPK gene mutations

1. Introduction

1.1. Gastric Cancer Incidence

Gastric cancer (GC) is a multifunctional disease that is the fourth leading cause of death worldwide [1][2][3][4][5], without any symptoms in early stages [6]. Even though the incidence of GC has decreased since the 1970s due to medical progress, it still represents a major health problem, particularly in Eastern Asian countries, where over 1 million cases were reported in 2020 [7]. GC is considered an aggressive malignancy characterized by uncontrolled cell proliferation and metastasis [8]. Globally, every year, more than 1 million people are diagnosed with GC [9][10].

This malignant pathology is more often found in men, being approximately twice as common compared with women, and usually occurs after 60 years of age [11]. The lower risk of women developing GC is due to estrogen, an effect that lasts until menopause [12]. Moreover, GC is often found in the tropics [13]. GC incidence and mortality vary, with increased rates being observed in Eastern and Western Asia, while in North America, Northern Europe, and most African regions, decreased incidence is reported [14]. The southern region of India has an increased incidence of gastric adenocarcinoma, while South Asia presents decreased incidence [15]. Usually, 90% of GC involves sporadic cases, and 10% present familial aggregation [16]. Australia also has a decreased rate of GC [17]. These variations may be explained by differences in *Helicobacter pylori* (*H. pylori*) genotypes *cagA* and *vacA*; in areas with elevated GC incidence, type *cagA* is predominant [18]. Worldwide, the GC overall 5-year survival rate is about 20%. In China, GC represents the second leading cause of death among women and the third leading cause in men [19]. Japan has reported a survival rate of more than 70% for GC diagnosed in stages I and II. This elevated survival rate may be due to the mass screening programs adopted [20], where endoscopy is the gold standard

method [21]. In the last five decades, the US has reported a decreased incidence of GC, while a subtype of GC, non-cardia, is increasing among adults younger than 50 years of age [22].

1.2. Gastric Cancer Classification

The Cancer Genome Atlas (TCGA) classifies GC into four subtypes [23]. Anatomic gastric adenocarcinoma is classified into two subtypes: cardia, which includes the upper stomach adjoining the esophagus, and non-cardia, which involves the mid and distal stomach [24]. Histologically, gastric adenocarcinomas represent 90% of GC and have been subdivided into two main types: the intestinal type, or well-differentiated, and the diffuse type, or undifferentiated [25]. The cardia subtype represents one-quarter of cases, while non-cardia represents three-quarters of the incidence worldwide [26]. According to the Laurean classification, the majority of GC cases are represented by adenocarcinoma (90%), and 10% are lymphoma or gastrointestinal stromal tumors [27]. The intestinal type accounts for 50% of cases, the diffuse type 33%, and 17% of cases are mixed or unclassified [27].

The World Health Organization (WHO) classifies GC into four subtypes: papillary, tubular, mucinous, and poorly cohesive [28]. Moreover, Epstein–Barr virus (EBV)-associated GC is another GC subtype, with definitive clinical and molecular characteristics [29], together with human epithelial growth receptor 2 (HER2), which is overexpressed in 6–30% of GC cases [30]. Infection with EBV contributes to 9% of all GC [31]. HER2 is also overexpressed in other malignant pathologies, including breast cancer [32]. The TCGA analyzed 295 primary gastric adenocarcinomas and further proposed a new classification of GC into four subtypes, including EBV-positive, microsatellite instability (MSI), genomic stability (GS), and chromosomal instability (CIN). The Asian Cancer Research Group (ACRG) also provides another classification of the four mentioned GC subtypes, as follows: (i) MSI, (ii) epithelial-to-mesenchymal transition (EMT)/GC, (iii) microsatellite stable with intact *TP53* activity (MSS/*TP53*+), and (iv) microsatellite stable GC with loss of *TP53* activity (MSS/*TP53*−) [33][34]. Moreover, GC intestinal histology is often found in Caucasians.

The cardia subtype is less detected in Africa and Latin America [35]. With the lack of significant symptoms in the early stages, most GC cases are diagnosed in middle or late stages, leading to a decreased survival rate [36][37]. In the early stages, a small number of patients manifest nausea, vomiting, or symptoms similar to ulcers. In advanced GC stages, patients usually report pain and weight loss as the most common symptoms [38]. Unfortunately, the 5-year survival rate is about 20–30% for advanced GC cases [39].

2. PI3K/AKT/mTOR and MAPK Pathways in Gastric Cancer

PI3K/AKT/mTOR signaling pathway dysregulation is found in various pathologies, including cancer progression such as in GC. This pathway is involved in various cancer-vital processes, such as apoptosis, autophagy, cell growth, survival, and proliferation [40][41][42][43][44]. This signaling pathway is one of the main regulators of the cell cycle, growth, proliferation, metastasis, apoptosis, and autophagy [45]. In GC, PI3K/AKT/mTOR inhibits apoptosis and induces the chemo-resistance phenotype, metastasis, angiogenesis, and EMT [46].

Besides the catalytic subunit of Class IA PI3K, other compounds such as the Class IA p85α-regulatory subunit, AKT, mTOR, and eukaryotic translation initiation factor 4E (eIF4E) possess oncogenic potential [47]. The downstream effectors of the PI3K/AKT/mTOR signaling pathway are usually dysregulated in the majority of solid tumors [48]. Moreover, PI3K/AKT/mTOR also controls cancer metabolism and genomic instability [49], having immunomodulatory potential as well [50].

In a sufficient supply of nutrients and energy, activated AKT will phosphorylate mTOR, further promoting tumor cell growth [51]. A very important component of this pathway, mTOR, is upregulated in malignancies, suppressing autophagy [52]. AKT was overexpressed in various neoplastic pathologies, such as pancreatic and ovarian cancer, as well as in gastric carcinoma, where the first isoform of AKT was found to be overexpressed [53]. GC-PI3K/AKT activation is induced by aberrant epigenetic regulations, necessary for GC development [54]. It is considered that *PIK3CA* is the second most common mutated gene in GC, responsible for 4–25% of cases, and also found in 85% of EBV GC cases [55]. Iranpour and his research group analyzed 100 patients with GC who underwent surgical resection and detected mutations in exon 20 of the *PI3KCA* gene in 11% of GC patients [56].

In gastric malignant tumors, p-AKT had elevated levels in 74% to 78%, being associated with GC angiogenesis and lymph nodes, leading to tumor invasion [57][58]. Overexpression of p-AKT is significantly correlated with HER2 overexpression and not with *PIK3CA* mutations. Moreover, the loss of *PTEN* is associated with GC initiation and development [57].

GC-EMT implies that the gastric cells lose their identity and acquire a mesenchymal phenotype with upregulation of N-cadherin, MMPs, and vimentin and downregulation of E-cadherin. PI3K/AKT/mTOR plays a pivotal role in EMT, leading to apoptosis resistance, invasion, and metastasis [59]. p-AKT induces dysregulation of the cell cycle, apoptosis suppression, and finally activation of angiogenesis. p-AKT will induce the phosphorylation of other proteins, including GSK-3β, BAD, caspase-9, and FoxOs [58].

Infection of gastric-epithelial cells with *H. pylori* will activate PI3K/AKT/mTOR and MAPK cascades, inducing the transformation of epithelial cells into neoplastic cells through changes including apoptosis, proliferation, and differentiation. The increased release of proinflammatory cytokines implies a higher production of free radicals, inducing DNA methylation [60].

RTK/MAPK pathway alteration, together with *TP53* mutations, was detected in GC subtypes. A cell motility gene, *CDH1*, is usually mutated in GC subtypes and induces the activation of the RTK/MAPK cascade [61]. The *PIK3CA* gene mutation rate was increased in GC, compared with *AKT1*, *AKT2*, and *AKT3*-mutations genes. Moreover, A*KT2* was significantly increased in EBV-positive GC as compared to EBV-negative GC. *AKT2* mutation was correlated with a poor survival rate in EBV-positive GC [62]. HER2 is frequently overexpressed in GC, leading to PI3K/AKT/mTOR and MAPK signaling pathway activation via RTK receptors and to increased cell proliferation, invasion, and metastasis [63].

Raf-1 rs3729931, *HRAS* rs45604736, *MAPK1* rs2283792, and *MAPK1* rs9610417 genes are correlated with GC development [64]. Ras and Raf family member mutations induce the activation of RAF/MEK/ERK in GC [65]. GC-HER2 overexpression induces PI3K/AKT/mTOR and MAPK activation, promoting tumor-cell survival, proliferation, adhesion, and migration [66]. Lian et al. reported that IL-8 secretion via the ROS/NF-κB and ROS/MAPK (Erk1/2, p38)/AP-1 axis stimulates endothelial cell proliferation and angiogenesis in the GC tumor microenvironment [67]. Although ROS have a negative impact, they can also have positive roles, because they can be produced even by anti-cancer drugs to induce autophagy and apoptosis of malignant cells [68]. The PI3K/AKT/mTOR and Ras/Raf/MEK/ERK signaling pathways can be activated by common targets, such as Ras, and present some compensatory signaling properties; when one pathway is inhibited, the other is activated. Therefore, if mTOR is inhibited, PI3K will activate MAPK via Ras. These two cascades are also coactivated in various tumors, such as found in melanoma, prostate, and colorectal cancer [69]. Casein kinase II (CSNK2A1) is a serine/threonine kinase that is able to phosphorylate multiple substrates involved in cell cycle regulation, DNA repair and replication, transcription, apoptosis, and carcinogenesis. This kinase may be implicated in the processes of cancer invasion and migration via EMT transition and NF-kB signaling pathways. Regarding GC pathogenesis, CSNK2A1 is overexpressed, inducing the activation of AKT and mTOR, being involved in migration, invasion, and proliferation of GC cells [70].

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