
MINI-REVIEW

Gastric Carcinoma: Recent Trends in Diagnostic Biomarkers and Molecular Targeted Therapies

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Abstract

Gastric cancer is generally associated with poor survival rates and accounts for a remarkable proportion of global cancer mortality. The prevalence of gastric carcinoma varies in different regions of world and across the various ethnic groups. On the basis of pathological assessment, gastric cancer can be categorized as intestinal and diffuse carcinomas. The etiology is diverse, including chemical carcinogen exposure, and high salt intake. *Helicobacter pylori* also plays a vital role in the pathogenesis of certain gastric carcinomas. The development of gastric cancer involves various alterations in mRNAs, genes (GOLPH3, MTA2) and proteins (Coronins). miRNAs, Hsa-mir-135b, MiR-21, miR-106b, miR-17, miR-18a, MiR-21, miR-106b, miR-17, miR-18a and MiRNA-375, miRNA-195-5p are the latest diagnostic biomarkers which can facilitate the early diagnosis of gastric carcinomas. Recent development in the treatment strategies for gastric carcinoma include the introduction of monoclonal antibodies, TKI inhibitors, inhibitors of PDGFR β , VEGFR-1, VEGFR-2, Anti-EGFR and anti-HER2 agents which can be applied along with conventional therapies.

Keywords: miRNAs - GOLPH3 - MTA2 - MiRNA-375 - PDGFR β - VEGFR-1 & 2 - anti-HER2

Asian Pac J Cancer Prev, 17 (7), 3053-3060

Introduction

Gastric carcinoma is a destructive disease that has a daunting impact on health globally. The main etiology of all types of cancers worldwide is the mutation in nuclear genes in all cells of the body (Majeed et al., 2014). Gastric cancer is the second major cause of mortality from malignancies. The prognosis for stomach cancer particularly in Asian countries is very poor because in most of the cases it is diagnosed at advanced stages. However, new screening methodologies are required for early detection of gastric cancer (Tsunehiro et al., 2013). According to the American Cancer Society, cancerous cells are formed when the DNA of a cell is damaged and this damaged DNA is responsible for the formation of other cells with the same damaged DNA which are called as cancerous cells. These cancerous cells are then transported towards the other tissues of the body and can cause metastasis.

Currently, the use of neoadjuvant and adjuvant therapies along with surgery is getting more importance for the treatment of advanced gastric tumors. However, literature has shown that neoadjuvant therapies are more important in the prognosis of gastric carcinoma in comparison to adjuvant therapies (Rebekka et al., 2015).

Etiology of Gastric Cancer

Gastric cancer is the fourth most common cancer. Etiology of gastric cancer involves both genetic and environmental factors. Evidences from several molecular studies revealed that along with environmental factors and genetic variations, epigenetic alterations also play a vital role in the tumor genesis and cellular immortalization (Resende et al., 2011).

Gastric cancer is a multifactorial disease resulting from interaction between environmental factors and host genetic susceptibility. The most important environmental factors involved in gastric cancer are *Helicobacter pylori* infection and diet. *H. pylori* colonizes the gastric mucosa and results in a complex inflammatory reaction and immune response which in turn generate ROS. Levels of nitric oxide synthase also increased in *H. pylori* infection which can cause activation of oncogenes and inactivation of oncosuppressor genes and this can ultimately lead to the development of gastric carcinoma. High intake of salted fish, refined grains, processed meat, saturated fat and total carbohydrates are major contributors in the prognosis of gastric cancer. A positive family history of gastric cancer also increases the risk by three-folds. Research studies

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have demonstrated that *H. pylori* should be eradicated in childhood or early teen age because eradication after the irreversible gastric mucosal lesions does not help in prevention of carcinogenesis (Compare et al., 2010).

Gastric cancer can occur both in the distal and proximal region. Distal gastric cancers prevail in developing countries, more common in blacks, and in people with lower socio-economic status. Proximal gastric cancers are predominant in developed countries, common in whites, and in people with higher socio-economic status (Nagini, 2012).

Among all malignant gastric tumors 95 percent are adenocarcinomas and the remaining 5 percent are stromal tumors, lymphomas and other rare tumors. Gastric colonization by *H. pylori*, possible familial or genetic syndrome and conditions like gastric dysplasia has been reported as definite risk factors for the development of gastric cancer. Smoking, *H. pylori* infection, chronic atrophic gastritis, heavy alcohol use, and several dietary aspects have been associated to the increased risk of gastric carcinoma. The majority of stomach cancers are sporadic. Environmental components are predominant in sporadic cancer while genetic components are predominant in familial type of gastric cancer. Small percentage of gastric cancers have familial component and it shows an autosomal pattern of inheritance (Lastraioli et al., 2012; Carcas, 2014).

Global Distribution of Gastric Cancer

Incidence of gastric cancer is approximately two times greater in men as compared to women and this incidence also increases with age. Within above mentioned global regions distribution of gastric cancer may also varies among population. In the same geographic region the incidence of gastric carcinoma is more for some ethnic groups in comparison to other ones. Distribution of gastric cancer also varies with location in the stomach with a distinction between distal (noncardia) and proximal (Cardia) regions of stomach due to difference in their etiology (Lauren, 2014). However the burden of gastric cancer disease is more in less developed countries particularly in Asian countries in comparison to developed countries. Prevalence of *H. pylori* associated gastric carcinoma is more in areas with lower socioeconomic status and unsanitary conditions.

Types of Gastric Cancer

Lauren histologically classified gastric cancer into diffuse gastric cancer or intestinal type gastric cancer. The diffuse type is characterized by multifocal signet ring cell infiltrates and usually occurs in younger patient whereas the intestinal type occurs as a result of pathology associated with environmental factors and advanced age (Robin et al., 2008). CDH1 is the most important GC susceptible gene and it accounts for 1-3% of gastric carcinomas. Diffuse gastric cancer often referred to as signet cell carcinoma because in this type poorly cohesive signet cells are present. In intestinal type tubular or glandular components with various degrees of

differentiation are present. The major cause of hereditary diffuse gastric cancer is the germline mutations in CDH1 gene (Vogelaar et al., 2012).

The diffuse type gastric carcinomas are more common in endemic areas, mostly found in women. It is due to genetic susceptibility linked with blood group A. The intestinal gastric cancers are common in older people mostly occur in men. It develops from precancerous lesions such as intestinal metaplasia and gastric atrophy. Intestinal gastric cancer is influenced by dietary factors; environmental factors such infection with *H. pylori* and obesity (Nagini, 2012).

Numbers of molecular abnormalities such as gene silencing and gene overexpression have been recognized in GC. Several genes either through oncogenic activation (CD133, CDH17, P-Cadherin, DSC2, GSK3 β , CD44 and CD168) or through tumor suppressor gene inactivation mechanisms (PDX1, TFF1, and BCL2L10, GRIK2, XRCC, HAI-2, psiTPTE-HERV and RUNX3) have been associated with gastric cancer (Resende et al., 2011).

Evidences from research studies have now revealed that chronic inflammation of the gastric epithelium plays a vital role in the pathogenesis of gastric cancer. *H. pylori* cause infiltration of the gastric mucosa by macrophages, polymorphonuclear cells, B and T lymphocytes. As a result of inflammatory response to *H. pylori* infection epithelial cell proliferation and cell death by apoptosis increases. Other inflammatory mediators such as interferon- γ and tumor necrosis factor also trigger cell death by apoptosis. Activated T-cells can also directly kill gastric epithelial cells. B cells also contribute to mucosal epithelial cell damage as they produce auto-reactive antibodies that bind to gastric epithelial cells; antigen-antibody complex formed, complement becomes activated. This suggests that inflammation and epithelial cell damage is due to immune-complex formation (Lauren, 2014).

Genetic Basis of Gastric Cancer

It is of utmost importance to recognize the pathogenesis of gastric carcinoma in order to find new and improved ways for its amelioration. In the current review, we are limiting our focus on role of novel and mostly unexplored MRNAs, genes and proteins, which may have a likely effect in the tumorigenesis and spread of gastric cancer.

GOLPH3 (Golgi Phosphoprotein 3) and Akt/mTOR pathway

GOLPH3 gene is a member of the Golgi matrix protein family, which is responsible for Golgi trafficking and maintenance of Golgi structure (Dippold et al., 2009).

The carcinogenic role of GOLPH3 was first discussed by Scott et al, by revelation of its role in differentiation and proliferating activity and its presence in many solid cancers (Scott et al., 2009). In their research, Peng et al. (2014) identify a possible role of GOLPH3 in gastric carcinomas. They state that although GOLPH3 is expressed in gastric cancer tissue, normal tissue and adjacent tissue to the cancerous cells, expression in the cancerous tissue was significantly higher (75.00%) as compared to that in normal tissue (12.50%). Furthermore,

it was found that expression of aforementioned gene was also related to distant as well as lymph node metastasis, histological grading and depth on invasion (Peng et al., 2014). This was also corroborated by others (Wang et al., 2012; Zhou et al., 2012; Ma et al., 2014).

Latest advancements have shown the involvement of a large number of signal transduction pathways in metastasis and tumor projection. Of these the Akt/mTOR (Mammalian target of rapamycin) pathway is one of the most reported to be frequently activated in various carcinomas including breast, melanoma, hepatocellular carcinoma, ovarian cancer and urothelial carcinoma, new studies are also linking it to gastric cancer, showing that increased expression levels of p-Akt/mTOR pathway were significantly associated with depth of invasion, distant metastasis, lymph node metastasis and grading based on histology. This suggests that the Akt/mTOR pathway is activated in gastric carcinomas and may have an emerging role in cancer tumorigenesis, metastasis and invasion. (Slomovitz and Coleman, 2012; Peng et al., 2014).

TLR 2 (toll like receptor-2)

TLRs have already been shown to play an eminent role in the spread of gastric cancer (Pimentel et al., 2011). However our review sheds light in specific on TLR-2, which has recently been implicated to be involved in carcinogenesis of gastric cancers. (Pimentel et al., 2011).

In their study, Yang et al, looked at the possible role of increased invasiveness by SGR-7901 gastric carcinoma cells with the help of TLR2. Their findings showed increase of interleukin-6 in TLR2 activated cancer cells, interleukins being pivotal in regulating cytological behaviors of tumor cells. They also saw significant correlation of TLR2 in SG-7901 cell lines with relation to distant and lymph node metastasis as well as depth of invasion, however no correlation was found with ages or genders of the patients. (Yang et al., 2014).

Similarly, (Vaisanen et al., 2010) have all indicate links of TLR2 to increased apoptosis and tumorigenesis of gastric cancer cell lines .

MTA2 (Metastasis Associated 1 Family Member 2)

MTA2 is a gene which inhibits transcription of E-cadherin and also forms part of the Twist complex (Luo et al., 2008).

Various studies have now reported that aberrant and irregular expression of MTA2 in gastric carcinomas participate in the movement and invasion of cells. This might be due to a possible overexpression of Sp1 (Luo et al., 2008; Hall, 2009; Fu et al., 2011).

Coronins

These are proteins responsible for regulation of the actin cytoskeleton (Hall, 2009). Recent studies have shown that coronins (1A, 1 B and 3) play a role in the metastasis of various malignancies like primary effusion lymphoma and more prominently hepatocellular carcinoma (Thal et al., 2008).

The mechanism for cancer spread by coronins appears to be upregulation of MMP9 and cathepsin K expression

and down regulation of TIMP2 expression. (Thal et al., 2008; Ren et al., 2012).

Diagnostic Biomarkers in Gastric Cancer - miRNAs

Despite the advances in healthcare, pharmacology and genetics over the past decade, gastric cancer continues to be the third most common and lethal type of cancer worldwide (Siegel et al., 2015). A major issue related to gastric cancer treatment and prognosis is late diagnosis and lack of a proper noninvasive technique for prognosis as well as detection. (Jian et al., 2016).

To date, the gold standard of gastric cancer detection continues to be endoscopically guided biopsy which not only is invasive but by itself may incur damage to the mucosal tissues. There is need for developing novel cost effective approaches of both diagnosis and management of these cancers.

MicroRNAs are a type of noncoding RNAs functioning in the post transcriptional regulation of genes, each miRNA has been show to target up to 200 mRNAs hence contributing to an array of cellular biological processes such as differentiation, apoptosis, migration, development and carcinogenesis. Variety of studies are indicating that the non-coding RNA serum profiles differ in healthy individuals and in those with gastric carcinoma. Hence, a probable role of these miRNAs is quite likely in early diagnosis. (Shiotani et al., 2013; Takahashi et al., 2013; Dong et al., 2015).

Our review intends to highlight the significance of miRNAs in detection and prognosis of gastric carcinomas. We have chosen eight different mi RNAs based on literature reviews and feasibility/cost effectivity. We aim to direct miRNA studies towards new horizon for gastric carcinoma patients.

Favorable factors of microRNAs as biomarkers include stability at room temperature even after 24 hours of incubation. They can even resist up to 8 cycles of freeze thawing meaning that they can be used repeatedly, hence meriting some cost effectiveness. Overall they are stable molecules with tensile strength which is easily testable (22bp), therefore warranting more research on their scope as good biomarkers for gastric cancers (Song et al., 2012).

Hsa-mir-135b

Hsa-mir-135b is a miRNA already of prognostic value in cancers of colon (Darnet et al., 2015), lung and breast (Gomes et al., 2014). Wand et al. investigated its specific role in gastric cancers and discovered that hsa-mir-135b is down regulated in normal tissue and intestinal type gastric adenocarcinoma but up regulated in intestinal metaplasia. It has two validated target genes, these genes are downregulated in gastric carcinoma KLF4 and APC (Ribeiro et al., 2010). Ribero et al. (2010) further corroborate these results by explaining that has-miR-135b has very good discriminatory accuracy between normal tissue and gastric lesions which are very likely to be precursors of gastric carcinoma and hence they will prove to be novel biomarkers of early diagnosis if further investigations are performed.

As studied Wang et al, miR-21, miR-106a, miR-17, miR-18a were consistently upregulated in at least 4 or profiling studies, making them significant. To further validate their acceptancy as biomarkers, these miRNAs were compared by real time PCR in 32 cases of gastric cancer (Wang et al., 2013).

We have reviewed several different studies corroborating the same results (Xiao et al., 2009). It was found that miRNA 21 also has significant relationship with tumor size (more upregulation in larger tumor size), poor differentiation and metastasis. Hence making it a very important prognostic biomarker, similarly miRNA -106b, miRNA-17 and 18a were all shown to be significantly higher expressed in gastric cancer tissues which showed greater levels of dysplasia and poorer differentiation (Kim et al., 2013). Aforementioned, biomarkers are all upregulated in gastric cancer, and may prove to be novel markers in early detection. Moreover, detection in serum warrants further study, as this will be a non-invasive, convenient and rapid procedure.

miRN-199a-3p is another miRNA which can be of value as a circulatory biomarker. Li et al., (2013) investigated the expression of miRNA-199a-3p between postoperative and preoperative plasma of healthy controls and early gastric cancer patients by using real time PCR. The expression of miRNA-199a-3p in plasma of early gastric cancer patients was found to be significantly increased as compared to levels of expression in the healthy population. Additionally plasma miRNA-199-3p expression was significantly less in patients of the post-operative group (Li et al., 2013).

Numerous studies have shown that miRNA-375 is downregulated in gastric carcinoma (Wang et al., 2013; Xiao et al., 2009). miRNA 375 was shown to be significantly downregulated in both tissue and serum samples of distal gastric carcinoma. It was shown to have a specificity of 80% and sensitivity of 85%, in discrimination of distal gastric adenocarcinoma from control tissues (Wang et al., 2013). Similarly, studies have indicated that miRNA-195-5p is also downregulated in gastric carcinomas giving the possibility of its role as a novel tumor suppressor miRNA marker for prognostic use (Gorur et al., 2013).

In the search to find easier, faster and non-invasive ways to detect gastric carcinomas, microRNAs have become a research hotspot in this field. Offering ease of detection by qRT-PCR, microRNAs promise a new and rapid detection and prognosis in gastric cancers. Overall, miRNAs open new avenues in gastric carcinoma detection and prognosis and definitely warrant further investigation.

Therapies for Gastric Cancer

Anti-VEGFR agents

One of the main and important mechanisms involved in development and progression of cancer is angiogenesis.

A critical role is played by vascular endothelial growth factor A (VEGF-A) in the development of most of the primary tumors and consequent progression of metastasis (Ychou et al., 2011). The VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and PGF (Placental growth factor). Several VEGF receptors (VEGFR) are responsible to mediate the activities of these VEGFs. Two tyrosine kinase receptors (VEGFR-1 and VEGFR-2) can bind the VEGF-A (Vita et al., 2014). It is considered that VEGFR-2 is the main receptor to drive angiogenesis, hence, plays a crucial role in physiology and pathology of angiogenesis. In gastric cancer (GC) of intestinal type, the stage of disease and the vessel count are found to be correlated with the expression of VEGFR-2. Moreover, it is concluded that a major role is played by VEGFR-2 in the proliferation and regulation of GC cells.

Many agents have been developed which are anti-VEGF; among these, monoclonal antibodies and multi-target tyrosine kinase inhibitors (TKIs) have found more clinical applications (Vita et al., 2014).

Bevacizumab

It is a monoclonal antibody that exhibited its activity in various solid tumors including ovarian, breast, non-small cell lung and colorectal cancer by targeting the VEGF-A. It prevents the interaction of VEGFR-1 and VEGFR-2 with VEGF on endothelial cell surface as it binds to VEGF. In this way, it interferes with the tumor angiogenesis and hence, prevents the growth of tumor (Vita et al., 2012).

Ramucirumab (IMC-1121B)

It is also a monoclonal antibody (human IgG 1) that specifically blocks the extracellular domain (VEGF-binding domain) of the VEGFR-2 and interferes with the blood supply to tumor as it inhibits the downstream signaling responsible for the synthesis and maintenance of abnormal blood vessels (Krupitskaya and Wakelee, 2009). Its dose is administered intravenously every 1st, 2nd or 3rd week with MTD (maximum tolerated dose) as 13 mg/kg/week (Spratlin et al., 2010).

Sorafenib

It is TKI inhibitor that is multi target and administered orally. Its anti-tumor effect is exhibited by two mechanisms. Firstly, it directly blocks the RAF/MEK/ERK mediated cell signaling to inhibit the proliferation of tumor. Secondly, it blocks the VEGFR and PDGFR for the indirect inhibition of angiogenesis (Wilhelm et al., 2008).

Sunitinib

It is a TKI inhibitor given orally. It targets colony stimulating factor receptor 1 (CSFR-1), PDGFR α , PDGFR β , VEGFR-1, VEGFR-2 and VEGFR-3. It is used in second line setting where it exhibited a low activity as a single agent in advanced cancer (Chow and Eckhardt, 2007).

Cediranib (AZD2171)

It is a powerful inhibitor of PDGFR β , VEGFR-1 and VEGFR-2 (Lindsay et al., 2009). It has a good tolerability profile. Its toxicities observed most commonly include

fatigue, nausea and anorexia (Satoh et al., 2012).

Apatinib

It is a TKI inhibitor which specifically targets VEGFR-2 (Tian et al., 2011). Hand foot syndrome and hypertension are its most common adverse effects. Its recommended dose is 425 mg per os once a day (Vita et al., 2014).

Telatinib

It inhibits specifically PDGFR, VEGFR and tyrosine kinases. It shows no toxicity at high doses and tolerated well (Vita et al., 2014).

Anti-EGFR agents

Epidermal growth factor receptor (EGFR) is a transmembrane receptor. It consists of three portions; an extracellular ligand binding domain, a transmembrane portion and inside the cell a cytoplasmic domain having tyrosine kinase (Ciardiello and Tortora, 2008). Specific ligands including EGF, betacellulin, heparin-binding EGF, transforming growth factor- α , neuregulin-2- α , amphiregulin and epiregulin activate this receptor. This ligand mediated activation of EGFR leads to homo or heterodimerization of receptor which results in phosphorylation and activation of tyrosine kinase. This process results in activation of various intracellular signaling mechanisms including the Akt/mTOR pathway or Ras/Raf/MAPK pathway which determine the cell growth and proliferation, inhibition of apoptosis, activation of metastatic growth and tumor induced angiogenesis. EGFR have been associated in pathogenesis of various malignancies, so in recent past the monoclonal antibodies and molecule inhibitors have become the therapeutic tools for several types of malignancies (Alanazi and Khan, 2016).

Gefitinib and erlotinib

Gefitinib is an EGFR quinazoline tyrosine kinase inhibitor. It is administered orally. Erlotinib hydrochloride is also an EGFR tyrosine kinase inhibitor given orally and it reversibly blocks ATP binding site of the receptor (Vita et al., 2014).

Cetuximab, panitumumab

Cetuximab (mouse/human IgG1) and panitumumab (fully human IgG2) are monoclonal antibodies which are anti-EGFR. They block extracellular ligand binding region of the EGFR and interferes with downstream activity of tyrosine kinase. It leads to the internalization and ultimately degradation of the receptor. It is considered that another mode of action is exhibited by cell mediated cytotoxic activity which is antibody dependent and exerts an indirect anticancerous effect (Ciardiello and Tortora, 2008; Vita et al., 2011).

Matuzumab and nimotuzumab

Metuzumab (human IgG1) monoclonal antibody is anti-EGFR. It exhibited very limited immunogenic activity because it has about 10 % murine origin. It can induce cytotoxicity which is antibody dependent.

Nimotuzumab (human IgG1) is also a monoclonal antibody and it targets EFGR. It shows its efficacy in gliomas and neck and head squamous cancer cells (Brade et al., 2007).

Anti-HER2 agents

A transmembrane receptor called HER2 belongs to epidermal growth factor receptor family containing; HER1, HER2, HER3 and HER4. Structurally HER2 consist of a short hydrophobic transmembrane region, an extracellular ligand binding domain and an intracellular domain with tyrosine kinase activity except for HER3. Recent studies have showed role of HER2 in the development of GEJ cancer and GC. In 10-30% samples of GC tumor, HER2 overexpression has been observed, with higher prevalence in intestinal type and GEJ tumors than in diffuse type and GC (Grabsch et al., 2010). In 382 patients of metastatic GC and GEJ adenocarcinoma, prognostic significance of HER2 was evaluated with a finding that approximately 20% of patients were HER2 positive, but it was not an independent prognostic factor (Janjigian et al., 2012). Lapatinib, transtuzumab and pertuzumab are anti HER2 drugs (Vita et al., 2010).

Lapatinib

It is an oral TKI inhibiting both HER2 and EGFR kinases that can be employed in subjects with trastuzumab-resistant tumors (Vita et al., 2014).

Transtuzumab

Transtuzumab is a monoclonal antibody (humanized recombinant) that selectively binds to extracellular domain of HER2 to block its downstream signaling, activation of apoptotic signals of tumor cells and down modulation of HER2 protein. Another known mechanism is an antitumor effect of by antibody dependent cell mediated cytotoxic activity. Association of transtuzumab with other chemotherapeutic agents like capecitabine, cisplatin, irinotecan, taxanes and doxorubicin has been shown to enhance its therapeutic effect. Currently in clinical trials is a drug called T-DMI (Transtuzumab emtansine) which is an antibody drug conjugate, developed by combining humanized antibody transtuzumab and potent cytotoxic antimicrotubule DM1. A proportion of receptors are thought to internalize when T-DMI binds to HER2, as a consequence intracellular release of active form of DM1 occurs causing cell death (Lewis et al., 2008).

Pertuzumab

An humanized anti HER2 antibody called pertuzumab exerts its antitumor activity by binding to HER2 domain II, region of dimer formation, preventing ligand dependant HER2 signaling and inhibiting dimerization of HER2 with other HER family protein. Working under different mode of actions for HER2 inhibition, pertuzumab and transtuzumab combination might provide better antitumor activity than either single agent for HER2 positive tumors including GC. In HER2 positive human GC xenograft models, combination of both pertuzumab and transtuzumab exhibited increase antitumor activity (Yamashita et al., 2011).

PI3K-AKT-MTOR targeted therapy

An intracellular signaling mechanism called PI3K/AKT pathway transduce signals from receptors of cell membrane including IGF, VEGF and HER2 to the cell cytoplasm and plays a key role in proliferation of cell. This mechanism acts on cell cycle and antiapoptosis via angiogenesis and mTOR (Shitara et al., 2012). Activation of PI3K/AKT/mTOR was seen in almost 30-60% of cancers including GC because of PIK3CA gene amplification and mutation and amplification of AKT gene (Markman et al., 2010).

Everolimus (RAD001)

This drug is administered orally and it inhibits mammalian target of rapamycin serine kinase by blocking the PI3K/Akt/mTOR pathway. This drug showed its efficacy in phase I/II studies and preclinical patients of GC (Cidon et al., 2013).

HGF-C-MET pathway targeted therapy

A cell surface receptor for HGF (hepatocyte growth factor) called c-Met (receptor tyrosine kinase mesenchymal-epithelial transition factor) results in the stimulation of various signaling mechanisms which are involved in the regulation of cell motility, proliferation, angiogenesis, invasion and tumor cell metastasis (Appleman, 2011; Sierra and Tsao, 2011).

Crizotinib

It is MET inhibitor and binds to MET kinase at ATP binding domain. Hence, it is a potential drug for GC patients having amplification of MET. This drug was approved recently for treating the patients with non small cell lung cancer (Okamoto et al., 2012).

Rilotumumab

Rilotumumab (human IgG2) targets HGF that inhibits the MET binding with HGF, hence, leads to the blocking of MET signaling pathway as observed in preclinical trials (Gao et al., 2009).

Fibroblast growth factor receptor targeting agents

FGFR (fibroblast growth factor receptor) belongs to largest family of growth factor ligands, to bind FGF (fibroblast growth factor). Each receptor consists of cellular ligand domain, consisting of a single transmembrane helix domain, three immunoglobulin like domains and an intracellular domain having tyrosine kinase activity. FGFR1, FGFR2, FGFR3 and FGFR4 are tyrosine kinase receptors present in FGFR family (Itoh and Ornitz, 2011). Recently another receptor has been discovered which acts by decoy receptor that binds to FGF ligand, lacking tyrosine kinase domain as a result it cannot signal by transautophosphorylation like other FGFRs (Trueb, 2011). Formation of various complexes leads to signal transduction where receptor binds to different FGFRs ligands (Tiong et al., 2013; Turner and Grose, 2010). Vital role is played by FGFRs in physiological processes like cellular proliferation, differentiation, development, transforming activities, wound repair, regulation of

angiogenesis and motility, however it also plays leading role in various neoplasms because of gene amplification or mutation induced aberrant FGFR activation leading to carcinogenesis. Chromosomal translocation of FGFR1 in 8p11 myeloproliferative syndrome, in glioblastoma gain of functional mutation of FGFR1kinase domain, in lung cancer, about 10% breast cancer and oral squamous cell carcinoma gene amplification of FGFR1, are the most known FGFR mutations (Matsumoto et al., 2012).

FGFR2 is found to be a promising therapeutic target in GC. In preclinical trials small molecules like, PD173074, cediranib (AZD2171), KI23057, dovitinib (TKI258), ponatinib (AP24534) and SU5402 has been found that inhibit cell growth and FGFR2 phosphorylation in FGFR2 amplified GC cell lines. (Deng et al., 2012). Dovitinib is a potent multitarget tyrosine kinase inhibitor and ponatinib (AP24534) is an oral multitarget tyrosine kinase inhibitor with pan-FGFR activity, resulting in potent inhibition of cell growth due to genomic amplification(Gozgit et al., 2012).

Novel therapy targeting CD9

CD9 belongs to tetraspanins family which consists of 33 different members including CD151, CD82, CD81, CD63, CD53, CD37 and CD9. It is considered as an inhibitor of cancer spread. It has four putative domains which are transmembrane including two extracellular loops, a small intracellular loop and a cytoplasmic domain containing short C- and N- terminals. It is expressed on the surface of numerous types of cells including normal endothelial, epithelial and hematopoietic cells as well as several malignant tumor cells (Murayama et al., 2015).

Galectins in gastric cancer

Galectins are involved in several pathological progressions. Galectin-7 is a potential regulator in several types of cancers through neogenesis and apoptosis. Literature have shown that Galectin-7 is involved in suppression of expression, proliferation and tumor invasions in gastric carcinoma (Kaur et al., 2016).

Conclusions

The studies and reviews we have cited demonstrated that microRNAs can give higher specificity and sensitivity as compared to other tissue biomarkers. Interestingly, most groups in the past have suggested that combinations of miRNAs reached higher specificity and sensitivity in comparison to single miRNA. Our review echoes their statements to be correct, but also demonstrates that if we establish standardized protocols of sample collection and treatment and have favorable controls, we may be able to identify and utilize single miRNAs as cancer detectors in clinical practice. For the prevention of gastric carcinoma recent studies have demonstrated the development of various drugs that particularly target the various genes and signaling pathways. Our review summarizes the recent molecular targeted therapies in advanced stages of gastric cancer.

References

- Alanazi, IO, and Khan Z (2016). Understanding EGFR signaling in breast cancer and breast cancer stem cells: overexpression and therapeutic implications. *Asian Pac J Cancer Prev*, **17**, 445-53.
- Appleman LJ (2011). MET signaling pathway: a rational target for cancer therapy. *J Clin Oncol*, **29**, 4837-8.
- Brade AM, Magalhaes J, Siu L, et al (2007). A single agent, phase I pharmacodynamic study of nimotuzumab (TheraCIM-h-R3) in patients with advanced refractory solid tumors. ASCO annual meeting proceedings Part I. *J Clin Oncol*, **25**, 14030.
- Carcas LP (2014). Gastric cancer review. *J Carcinog*, **13**, 14.
- Chow LQ, Eckhardt SG (2007). Sunitinib: from rational design to clinical efficacy. *J Clin Oncol*, **25**, 884-96.
- Ciardello F, Tortora G (2008). EGFR antagonists in cancer treatment. *N Engl J Med*, **358**, 1160-74.
- Cidon EU, Ellis SG, Inam Y, et al (2013). Molecular targeted agents for gastric cancer: a step forward towards personalized therapy. *Cancers (Basel)*, **5**, 64-91.
- Compare D, Rocco A, Nardone G (2010). Risk factors in gastric cancer. *Eur Rev Med Pharmacol Sci*, **14**, 302-8.
- Darnet S, Moreira FC, Hamoy IG, et al (2015). High-Throughput Sequencing of miRNAs Reveals a Tissue Signature in Gastric Cancer and Suggests Novel Potential Biomarkers. *Bioinform Biolo Insights*, **9**, 1-8.
- Deng N, Goh LK, Wang H, et al (2012). A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets. *Gut*, **61**, 673-84.
- Dippold HC, Ng MM, Farber-Katz SE, et al (2009). GOLPH3 bridges phosphatidylinositol-4-phosphate and actomyosin to stretch and shape the Golgi to promote budding. *Cell*, **139**, 337-51.
- Dong L, Qi P, Xu MD, et al (2015). Circulating CUDR, LSINCT-5 and PTENP1 long noncoding RNAs in sera distinguish patients with gastric cancer from healthy controls. *Int J Cancer*, **137**, 1128-35.
- Fu J, Qin L, He T, et al (2011). The TWIST/Mi2/NuRD protein complex and its essential role in cancer metastasis. *Cell Res*, **21**, 275-89.
- Gao CF, Xie Q, Zhang YW, et al (2009). Therapeutic potential of hepatocyte growth factor/scatter factor neutralizing antibodies: inhibition of tumor growth in both autocrine and paracrine hepatocyte growth factor/scatter factor: c-Met-driven models of leiomyosarcoma. *Mol Cancer Ther*, **8**, 2803-10.
- Gorur A, Fidanci SB, Unal ND, et al (2013). Determination of plasma microRNA for early detection of gastric cancer. *Mol Biol Reports*, **40**, 2091-6.
- Gomes LL, Moreira FC, Hamoy IG, et al (2014). Identification of miRNAs expression profile in gastric cancer using self-organizing maps (SOM). *Bioinformatics*, **10**, 246-50.
- Gozgit JM, Wong MJ, Moran L, et al (2012). Ponatinib (AP24534), a multitargeted pan- FGFR inhibitor with activity in multiple FGFR-amplified or mutated cancer models. *Mol Cancer Ther*, **11**, 690-9.
- Grabsch H, Sivakumar S, Gray S, Gabbert HE, Müller W (2010). HER2 expression in gastric cancer: Rare, heterogeneous and of no prognostic value - conclusions from 924 cases of two independent series. *Cell Oncol*, **32**, 57-65.
- Itoh N, Ornitz DM (2011). Fibroblast growth factors: from molecular evolution to roles in development, metabolism and disease. *J Biochem*, **149**, 121-30.
- Janjigian YY, Werner D, Pauligk C, et al (2012). Prognosis of metastatic gastric and gastroesophageal junction cancer by HER2 status: a European and USA International collaborative analysis. *Ann oncol*, **23**, 2656-62.
- Jian-Hui C, Er-Tao Z, Si-Le C, et al (2016). CD44, Sonic Hedgehog, and Gli1 expression are prognostic biomarkers in gastric cancer patients after radical resection. *Gastroenterolo Res Pract*, **2016**, 1-8.
- Kaur M, Kaur T, Kamboj SS, Singh J (2016). Roles of Galectin-7 in Cancer. *Asian Pac J Cancer Prev*, **17**, 455-61.
- Kim BH, Hong SW, Kim A, Choi SH, Yoon SO (2013). Prognostic implications for high expression of oncogenic microRNAs in advanced gastric carcinoma. *J Surg Oncolo*, **107**, 505-10.
- Krupitskaya Y, Wakelee HA (2009). Ramucirumab, a fully human mAb to the transmembrane signaling tyrosine kinase VEGFR- 2 for the potential treatment of cancer. *Curr Opin Investig Drugs*, **10**, 597-05.
- Lastraioli E, Raffaella Romoli M, Arcangeli A (2012). Immunohistochemical biomarkers in gastric cancer research and management. *Int J Surg Oncol*, **1**, 1-9.
- Li C, Li JF, Cai Q, et al (2013). MiRNA-199a-3p: A potential circulating diagnostic biomarker for early gastric cancer. *J Surg Oncolo*, **108**, 89-2.
- Lindsay CR, MacPherson IR, Cassidy J (2009). Current status of cediranib: the rapid development of a novel anti-angiogenic therapy. *Future Oncol*, **5**, 421-32.
- Luo GQ, Li JH, Wen JF, et al (2008). Effect and mechanism of the Twist gene on invasion and metastasis of gastric carcinoma cells. *World J Gastroenterol*, **14**, 2487-93.
- Ma Y, Ren Y, Zhang X, et al (2014). High GOLPH3 expression is associated with a more aggressive behavior of epithelial ovarian carcinoma. *Virchows Arch*, **464**, 443-52.
- Majeed W, Aslam B, Javed I, et al (2014). Breast cancer: major risk factors and recent developments in treatment. *Asian Pac J Cancer Prev*, **15**, 3353-8.
- Markman B, Atzori F, Perez-García J, Tabernero J, Baselga J (2010). Status of PI3K inhibition and biomarker development in cancer therapeutics. *Ann Oncol*, **21**, 683-1.
- Matsumoto K, Arai T, Hamaguchi T, et al (2012). FGFR2 gene amplification and clinicopathological features in gastric cancer. *Br J Cancer*, **106**, 727-2.
- Murayama Y, Oritani K, Tsutsui S (2015). Novel CD9-targeted therapies in gastric cancer. *World J Gastroenterol*, **21**, 3206-13.
- Nagini S (2012). Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. *World J Gastrointest Oncol*, **4**, 156-69.
- Okamoto W, Okamoto I, Arai T, et al (2012). Antitumor action of the MET tyrosine kinase inhibitor crizotinib (PF-02341066) in gastric cancer positive for MET amplification. *Mol Cancer Ther*, **11**, 1557-4.
- Peng J, Fang Y, Tao Y, et al (2014). Mechanisms of GOLPH3 associated with the progression of gastric cancer: a preliminary study. *PLoS one*, **9**, 107362
- Lewis GDL, Li G, Dugger DL, et al (2008). Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. *Cancer Res*, **68**, 9280-90.
- Pimentel-Nunes P, Afonso L, Lopes P, et al (2011). Increased expression of toll-like receptors (TLR) 2, 4 and 5 in gastric dysplasia. *Pathol Oncol Res*, **17**, 677-3.
- Rebekka S, Daniel R, Alexander R (2015). Adjuvant and/or neoadjuvant therapy for gastric cancer? A perspective review. *Ther Adv Med Oncol*, **7**, 39-8.
- Ren G, Tian Q, An Y, et al (2016). Coronin 3 promotes gastric cancer metastasis via the up-regulation of MMP-9 and cathepsin K. *Mol Cancer*, **11**, 1.
- Resende C, Thiel A, Machado JC, Ristimäki A (2011). Gastric cancer: basic aspects. *Helicobacter*, **16**, 38-4.

- Ribeiro-dos-Santos A, Khayat AS, Silva A, et al (2010). Ultra-deep sequencing reveals the microRNA expression pattern of the human stomach. *PLoS One*, **5**, 1320-5.
- Satoh T, Yamada Y, Muro K, et al (2012). Phase I study of cediranib in combination with cisplatin plus fluoropyrimidine (S-1 or capecitabine) in Japanese patients with previously untreated advanced gastric cancer. *Cancer Chemother Pharmacol*, **69**, 439-46.
- Scott KL, Kabbarah O, Liang MC, et al (2009). GOLPH3 modulates mTOR signalling and rapamycin sensitivity in cancer. *Nature*, **459**, 1085-90.
- Shiotani A, Murao T, Kimura Y, et al (2013). Identification of serum miRNAs as novel non-invasive biomarkers for detection of high risk for early gastric cancer. *Br J Cancer*, **109**, 2323-30.
- Shitara K, Doi T, Ohtsu A (2012). Molecular targeting therapy and biomarker for advanced gastric cancer. *J Phys Chem Biophys*, **2**, 1-6.
- Siegel RL, Miller KD, Jemal A (2015). Cancer statistics. *CA Cancer J Clin*, **6**, 5-29.
- Sierra JR, Tsao MS (2011). c-MET as a potential therapeutic target and biomarker in cancer. *Ther Adv Med Oncol*, **3**, 21-35.
- Slomovitz BM, Coleman RL (2012). The PI3K/AKT/mTOR pathway as a therapeutic target in endometrial cancer. *Clin Cancer Res*, **18**, 5856-64.
- Song MY, Pan KF, Su HJ, et al (2012). Identification of serum microRNAs as novel non-invasive biomarkers for early detection of gastric cancer. *PLoS one*, **7**, 33608.
- Spratlin JL, Cohen RB, Eadens M, et al (2010). Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol*, **28**, 780-7.
- Takahashi T, Saikawa Y, Kitagawa Y (2013). Gastric cancer: current status of diagnosis and treatment. *Cancers*, **5**, 48-63.
- Thal DR, Xavier CP, Rosentreter A, et al (2008). Expression of coronin-3 (coronin-1C) in diffuse gliomas is related to malignancy. *J Pathol*, **214**, 415-24.
- Tian S, Quan H, Xie C, et al (2011). YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity *in vitro* and *in vivo*. *Cancer Sci*, **102**, 1374-80.
- Tiong KH, Mah LY, Leong CO (2013). Functional roles of fibroblast growth factor receptors (FGFRs) signaling in human cancers. *Apoptosis*, **18**, 1447-68.
- Trueb B (2011). Biology of FGFR1, the fifth fibroblast growth factor receptor. *Cell Mol Life Sci*, **68**, 951-64.
- Turner N, Grose R (2010). Fibroblast growth factor signalling: from development to cancer. *Nat Rev Cancer*, **10**, 116-29.
- Vaisanen MR, Vaisanen T, Jukkola-Vuorinen A, et al (2010). Expression of toll-like receptor-9 is increased in poorly differentiated prostate tumors. *Prostate*, **70**, 817-24.
- Vita F, Giuliani F, Silvestris N, et al (2010). Human epidermal growth factor receptor 2 (HER2) in gastric cancer: a new therapeutic target. *Cancer Treat Rev*, **3**, 11-5.
- Vita F, Giuliani F, Silvestris N, et al (2012). Current status of targeted therapies in advanced gastric cancer. *Expert Opin Ther Targets*, **16**, S29-4.
- Vita F, Orditura M, Martinelli E, et al (2011). A multicenter phase II study of induction chemotherapy with FOLFOX-4 and cetuximab followed by radiation and cetuximab in locally advanced oesophageal cancer. *Br J Cancer*, **104**, 427-32.
- Vita F, Di Martino N, Fabozzi A, et al (2014). Clinical management of advanced gastric cancer: The role of new molecular drugs. *World J Gastroenterol*, **20**, 14537-58.
- Vogelaar IP, van der Post RS, Bisseling TM, et al (2012). Familial gastric cancer: detection of a hereditary cause helps to understand its etiology. *Hered Cancer Clin Pract*, **10**, 18.
- Wang JH, Chen XT, Wen ZS, et al (2012). High expression of GOLPH3 in esophageal squamous cell carcinoma correlates with poor prognosis. *PLoS One*, **7**, 45622.
- Wang JL, Hu Y, Kong X, et al (2013). Candidate microRNA biomarkers in human gastric cancer: a systematic review and validation study. *PLoS One*, **8**, 73683.
- Wilhelm SM, Adnane L, Newell P, et al (2008). Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. *Mol Cancer Ther*, **7**, 3129-40.
- Xiao F, Zuo Z, Cai G, et al (2009). miRecords: an integrated resource for microRNA-target interactions. *Nucleic Acids Res*, **37**, 105-10.
- Yamashita Y, Iijima S, Yorozu K, et al (2011). Pertuzumab in combination with trastuzumab shows significantly enhanced antitumor activity in HER2-positive human gastric cancer xenograft models. *Clin Cancer Res*, **17**, 5060-70.
- Yang H, Wang B, Yan J, et al (2014). Toll-like receptor 2 promotes invasion by SGC-7901 human gastric carcinoma cells and is associated with gastric carcinoma metastasis. *Ann Clin Lab Sci*, **44**, 158-66.
- Ychou M, Boige V, Pignon JP, et al (2011). Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol*, **29**, 1715-21.
- Zhou J, Xu T, Qin R, et al (2012). Overexpression of Golgi phosphoprotein-3 (GOLPH3) in glioblastoma multiforme is associated with worse prognosis. *J Neurooncol*, **110**, 195-3.