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MOLECULAR INSIGHTS INTO GASTRIC CANCER

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ABSTRACT

Gastric cancer (GC) is the fourth most common cancer and the second leading course of cancer-related deaths worldwide (after cancers of lung, breast and colon/rectum), with an estimated 989,600 new cases and 738,000 deaths in 2008. It is the second-most common cancer among men and third-most among females in Asia and worldwide. Incidence rates can be attributed to many factors but refer particularly to differences in dietary habits, and infection with *Helicobacter pylori*. A report of a joint World Health Organization (WHO)/Food and Agriculture Organization (FAO) Expert Consultation concluded that salt-preserved food and salt "probably" increase the risk of gastric cancer, whereas fruit and vegetables "probably" decrease the risk. Telomerase activity was initially assayed in gastric carcinoma tissues, matched adjacent normal tissues and digestive ulcer lesions. Carcinoembryonic antigen (CEA), CA19-9 and CA72-4 are the most commonly used biomarkers of GC. With increasing knowledge about the function of miRNAs, their possible therapeutic associations have attracted attention. The association between MUC1 polymorphism rs4072037 and the risk of GC has been also described. Mechanism of metastasis in gastric cancer is still under investigation. Development of molecular biomarkers, molecular and functional imaging techniques will be of great help in GC. The core of individualized treatment is to use the appropriate strategy on the right patient.

KEY WORDS: Gastric cancer, genes, biomarkers, miRNA, treatment.

INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer and the second leading course of cancer-related deaths worldwide (after cancers of lung, breast and colon/rectum), with an estimated 989,600 new cases and 738,000 deaths in 2008.[1] It is the second-most common cancer among men and third-most among females in Asia and worldwide.[2] The symptoms and sign of the stomach cancer are often reported late when the disease is already in advanced stages and 5-year survival is less than 30% in developed countries and around 20% in developing countries.[3] About 8.6% of all cancers that occurred in 2002 were GC. The GC rates shows marked geographical variation, with high-risk areas in Japan, China, Eastern Europe and certain countries in Latin America. Low-risk population is seen among whites in North America, India, Philippines, most countries in Africa, some Western European countries and Australia.[3] In the United States[4] and Europe[5], GC used to be one of the most common cancers; however, mortality rates have fallen dramatically over the last 50 years in all Western countries without any specific intervention taken, and GC is now rare.

In India, the number of new stomach cancer cases in 2001 was estimated to be approximately 35,675 (*n*=23,785 in men; 11,890 in women).[6] These differences in incidence rates can be attributed to many factors but refer particularly to differences in dietary habits, and infection with *Helicobacter pylori.* The prevalence of *H. pylori* varies from 56 to 89% among GC cases. A study from North India reported the prevalence of *H. pylori* infection to be 56.5% in GC patients.[7]

In 2012, an estimated 1 million new cases of GC have occurred, with half of the world total occurring in Eastern Asia.[8] The age-standardized incidence rates are about three times as high in men as in women; 35.4 for 100000 men and 13.8 for 100000 women in the world. The highest mortality rates are observed in Eastern Asia, occurring at 24.0 per 100000 men and 9.8 per 100000 women. A recent report of a joint World Health Organization (WHO)/Food and Agriculture Organization (FAO) Expert Consultation concluded that salt-preserved food and salt “probably” increase the risk of gastric cancer, whereas fruit and vegetables “probably” decrease the risk.[9] Other established non-dietary factors include cigarette smoking[10] in addition, there is some evidence that the intake of green tea and vitamin C is associated with the risk of GC.

TYPES OF STOMACH CANCERS[11]

1. Adenocarcinoma

It is the most common malignancy of the stomach, comprising more than 90% of all gastric cancers. Early symptoms resemble those of chronic gastritis, including dyspepsia, dysphasia and nausea. As a result, in low-incidence regions such as the United States, the cancer is often at advanced stages when clinical manifestation such as weight loss, anorexia, altered bowel habits, anemia and hemorrhage trigger diagnostic evaluation.

2. Lymphoma

Lymphomas can arise in virtually any tissue; they do so most commonly in the gastrointestinal tract, particularly the stomach. Nearly 5% of all gastric malignancies are primary lymphomas, the most common of which are indolent extranodal marginal zone B cell lymphoma. The second most common primary lymphoma of the gut, diffuse large B cell lymphoma.

3. Carcinoid tumor

Carcinoid tumors arise from neuroendocrine organs and neuroendocrine differentiated gastrointestinal epithelia. A majority is found in the gastrointestinal tract, and more than 40% occur in the small intestine. The tracheobronchial tree and lungs are the next most commonly involved site. Gastric carcinoid may be associated with endocrine cell hyperplasia, chronic atrophic gastritis and Zollinger-Ellison syndrome. These tumors were called "carcinoid" because they are slower growing than carcinomas.

4. Gastrointestinal stromal tumor

A wide variety of mesenchymal neoplasms may arise in the stomach. Many are named according to the cell type they most resemble; for example, smooth muscle tumors are called leiomyomas or leiomyosarcomas, nerve sheath tumors are termed schwannomas, and those resembling glomus bodies in the nail beds and at other sites are termed glomus tumors.

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the abdomen, and more than half of these tumors occur in the stomach.

5. Other cancers

Other types of cancer, such as squamous cell carcinoma, small cell carcinoma and leiomyosarcomas, can also start in the stomach, but these cancers are very rare.[12]

DIET AND LIFESTYLE

Diet plays a major role in gastric carcinogenesis. Globally, literature suggests that none or low-starch vegetable including green yellow vegetables, cruciferous and allium vegetables (garlic and onion) and fruits are considered to be probable protective factors. Limited evidence suggests that pulses (including soy) and selenium are also protective in nature.[13,14] Recent decline in the incident of stomach cancer in many countries may be in part explained not only by higher consumption of fruit but also due to highly reduced intake of salt, preserved foods as well as the availability of refrigeration.

Salt-preserved food and salt

Salt intake is a risk factor for gastric carcinoma as it damages the gastric mucosa, which results in gastritis and increased cell proliferation.[15] Salted tea, a peculiar beverage, is commonly consumed by a majority of population in Kashmir valley was observed to be a risk factor.[16] Indian studies have not observed salt intake as a separate factor but salted and processed products were taken into consideration. Soda, which is an additive commonly added in the foods, was found to be associated with increased risk (OR=2.9). A protective effect of leafy vegetables and fruits was observed in these studies. Tea consumption was shown to have protective effects in one study. Reheated foods, reheated oils and refrigeration were not observed to be associated with risk of gastric cancer.[17]

The studies on diet and stomach cancer could provide breakthrough in understanding role of diet because of heterogeneous food consumption throughout India. Although the inter-individual variation might be high, the intra-individual variation is usually low. Unlike western countries where animal foods are the major part of diet and being a vegetarian is voluntary, in India the effect of lifelong vegetarianism on risk of gastric cancer could be explored.

In experimental studies in rats, ingestion of salt is known to cause gastritis and, on co-administration, to enhance the carcinogenic effects of known gastric carcinogens such as N-methyl-N-nitro-N-nitrosoguanidine (MNNG).[18,19] A high salt concentrations in the stomach destroys the mucosal barrier and leads to inflammation and damage such as diffuse erosion and degeneration. Further, the induced proliferative change may act to promote the effect of food-derived carcinogens. It is therefore biologically plausible that high salt intake increases the risk of gastric cancer in humans.

In an evaluation performed by the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) in 1997, 16 case-control studies reported an association between salt or salted food and the risk of GC.[20] Eight of these estimated overall dietary salt or sodium intake; four showed strong statistically significant increases in risk OR = 2.1–5.0 for the highest intake level], whereas the remaining four showed no substantial association. Six of sixteen studies specifically examined the use of table salt, with three reporting statistically significant increased risks (OR = 1.6–6.2 for highest intakes) and two nonsignificant or several recent case-control studies have also revealed an association between salted food and the risk of gastric cancer.[21–24]

An alternative explanation for the strong association between highly salted food and gastric cancer might involve the presence of chemical carcinogens such as N-nitroso compounds, which are formed by the reacting nitrate or nitrite during the process of preservation and during digestion in the stomach.

Salt, salted food intake and *Helicobacter pylori* infection

Infection with *H. pylori* is an established risk factor of, but not a sufficient cause for, the development of gastric cancer.[25, 26] It is important to elucidate the role salt and salted food play in the causal link between *H. pylori* infection and gastric cancer. Mucosal damage induced by salt and salted food may increase the possibility of persistent infection with *H. pylori*.[19]

Fruits and vegetables

Fruits and vegetables are rich sources of carotenoids, vitamin C, folate, and phytochemicals, which may have a protective role in the carcinogenesis process. It is likely that modulation of xenobiotic metabolizing enzymes, in particular phase II enzymes, contributes to this putative preventive mechanism. The mechanisms of antioxidant activity may be also possible. In 1997, an expert panel assembled by the WCRF and AICR concluded that diets high in fruit and vegetables "convincingly" protect against gastric cancer.[9] The joint WHO/FAO Expert Consultation in 2003 concluded that fruit and vegetables "probably," but not "convincingly," decrease the risk of gastric cancer.[27] A subsequent report by the International Agency for Research on Cancer (IARC) determined that higher intake of fruit "probably" and higher intake of vegetables "possibly" reduce the risk of gastric cancer.[28]

Vitamin C (ascorbic acid)

Fruits and vegetables are rich sources of vitamin C. Vitamin C acts as an antioxidant and can quench reactive oxygen species produced in the gastric environment[29]; it is also known to inhibit production of carcinogenic N-nitroso compound in the stomach.[30] A possible relation between *H. pylori* infection and ascorbic acid is under investigation, as some research has indicated that high-dose vitamin C is effective in inhibiting *H. pylori* infection.[31,19] The WCRF/AICR report[32] concluded that high dietary vitamin C intake probably decreases the risk of gastric cancer.

Telomerase

Peritoneal dissemination of gastric carcinoma is one of the main factors affecting the prognosis of these patients, and it leads to recurrence rates of 50 – 60% following resection.[33,34] At present, the cytological examination of ascites or peritoneal washings is the most reliable method for detection of peritoneal metastasis,[35] although the enzyme telomerase is attracting interest as another promising candidate tumour marker. Telomerase activity was initially assayed in gastric carcinoma tissues, matched adjacent normal tissues and digestive ulcer lesions. Furthermore, to elucidate whether it would be possible to detect cancer cells in peritoneal washings; telomerase activity was assayed in the lysate of exfoliated cells obtained from peritoneal washings. A conventional cytological examination and an enzyme immunoassay for cancer antigen 125 (CA125) were routinely performed at the same time. A high expression of telomerase was demonstrated in gastric cancer.[36] The survival time of patients with detectable telomerase activity in their tumours has been shown to be significantly shorter than those without telomerase activity.[37] Molecular approaches using the highly sensitive PCR technique have been developed which allow the detection of micrometastasis by screening for tumour associated and/or epithelial cell-specific mRNA expression in the circulation, bone marrow and lymph nodes.[38] It has been reported that carcinoembryonic antigen (CEA) and E-cadherin are potential target genes and they have been shown to be specific and highly sensitive.[39,40] Many limiting factors were, however, described in these studies, such as the limited correlation between CEA and gastric carcinoma or the reduced expression of E-cadherin in poorly differentiated adenocarcinoma. Continued research into a more reliable marker for the early detection of peritoneal dissemination is warranted.

In one study, the majority (85%) of gastric cancers had telomerase activity. In 38 advanced staged tumors (stage II, III, and IV), 36 (95%) showed telomerase activity, whereas telomerase activity was undetectable in 8 (29%) of 28 early stage (stage I) gastric cancers *(P = 0.012).* Tumors with telomerase activity were generally of large size and with a high frequency of lymph node metastasis. The survival rate of the patients with telomerase activity was significantly shorter than those patients without telomerase activity ($P < 0.05$). These results suggest that telomerase-positive gastric cancers have more malignant potential than do those without telomerase activity. Telomerase is not always activated in gastric cancer, especially in early stage cancers. In gastric cancer, telomerase may occur as a late event of cancer progression as we demonstrated previously in non-small-cell lung cancer.[41] However, because 20 of 28 (71%) stage I gastric tumors had telomerase activity; telomerase activation is not necessarily a late event in gastric cancer cell progression. Once cancer cells acquire telomerase activity, their TRF lengths could be stabilized at any length, as observed in immortal cell lines with telomerase activity.[42]

The aneuploid pattern of gastric cancer cells correlates with a poor prognosis.[43] All aneuploid gastric cancers have telomerase activity, although many tumors that retain a diploid karyotype also express telomerase activity. A critical shortening of telomeres may cause chromosomal instability, leading to cellular senescence. The cells overcoming this critical phase acquire immortalization concomitant with telomerase activation and telomere stabilization, enabling the cells to continue to proliferate. [44, 45]

In conclusion, telomerase activity could be a useful ancillary tool for the diagnosis of gastric carcinoma. There is a close correlation between telomerase activity and gastric carcinoma. It is suggested that the detection of telomerase activity in peritoneal washings by the TRAP–ELISA method could be used to diagnose early peritoneal dissemination and, as it might be a potential predictor of peritoneal dissemination in patients with gastric carcinoma, it is worthy of further investigation. Future development of drugs aimed at telomerase inhibition may potentially provide a therapy with relatively limited side effects.

miRNA

Carcinoembryonic antigen (CEA), CA19-9 and CA72-4 are the most commonly used biomarkers of GC. Although widely used, they are not ideal markers. miRNAs are small single stranded non-coding RNAs of about 22 nucleotides that post-transcriptionaly regulate gene expression via either translational repression or mRNA degradation.[46] Since two

miRNAs (lin-4 and let-7) were first discovered, an increasing number of miRNAs have been successively identified.[47,48] In human epithelial malignancies, miRNA expression profiles have shown that distinct tumor specific miRNA signatures can classify different cancer types,[49] identify their subtypes [50,51] and distinguish the tissue origin of tumors.[52]

There is emerging interest in the investigation of miRNAs as non-invasive biomarkers for GC patients in circulating blood. Endogenous circulating miRNAs are present in a remarkably stable form that is protected from endogenous RNAse activity.[53] miRNAs exist stably as free miRNAs, exosomal miRNAs, or most predominantly as Argonaute2 (Ago2) protein bound miRNA in blood.[54]

miRNAs as prognostic markers: These are summarized in Table 1.

Table 1: miRNAs as prognostic markers

First author (reference)	Sample	Method	Prognostic miRNA (up or down in tumor)	Effect on Prognosis	Outcome
Katada[55]	42 pairs (tissue)	qRT-PCR	miR-20b, miR-150(up)	unfavorable	OS
Bandres[56]	45 (tissue)	qRT-PCR	miR-451 (down)	unfavorable	OS, DFS
Li[57]	50 (training set) 0 (testing set) 0 (validation set)	qRT-PCR	let-7a, miR-10b, miR-21, iR-30a-5p, miR-126, iR-223, miR-338	et-7a, miR-30a-5p, miR-126 (high expression correlate with longer survival); iR-10b, miR-21, miR-223, iR-338 (high expression correlate with shorter survival)	S, RFS
Ueda[58]	353 (tissue)	Microarray, RT-PCR	et-7b(down), let-7g(down), iR-19a (down), iR-214(up), iR-433(down), iR-495(high)	et-7g, miR-214, miR-433 (unfavorable factor of OS); et-7b, let-7g, miR-19a, iR-495 (unfavorable factor of DFS)	S, DFS
Motoyama[59]	49 (tissue)	qRT-PCR	miR-21(up)	unfavorable	Tumor size, depth
Tchernitsa[60]	6 (testing set)	qRT-PCR	miR-21(up), miR-	-	Lymph node

	0 (validation set)		103(up), iR-106b(up), miR-145(up), iR-146a (down), iR-148a(down)		metastasis
Nishida[61]	87 (tissue)	qRT-PCR	miR-125a-5p (down)	unfavorable	Tumor size, tumor invasion, metastasis, OS
Zhang[62]	65 (tissue)	Microarray, RT-PCR	miR-142-5p, miR-375	miR-375^{high}/miR-142-p^{low} (unfavorable)	Recurrence, survival
Kogo[63]	90 pairs (tissue)	qRT-PCR	miR-146a (down)	unfavorable	Venous invasion, lymph node metastasis, OS
Valladares-Ayerbes[64]	38 (tissue)	qRT-PCR	miR-17, miR-20a(up)	unfavorable	OS, PFS
Jiang[65]	55 pairs (tissue)	qRT-PCR	miR-21, miR-181b(up)	unfavorable	OS
Wu[66]	30 (testing set) 2 (validation set)	qRT-PCR	miR-195, miR-212 (down)	unfavorable	Lymph node metastasis
Brenner[67]	45 (tissue)	Microarray, RT-PCR	iR-195, miR-199a-3p, iR-451	high expression correlate with poor prognosis	Recurrence, survival
Hashiguichi[68]	70 pairs (tissue)	qRT-PCR	miR-125a-3p (down)	unfavorable	Tumor size, invasion, metastasis, stage, OS
Wang[69]	87 (plasma)	qRT-PCR	miR-17-5p, miR-20a	high expression correlate with poor prognosis	Differentiation status, stage, progression, OS
Inoue[70]	161 pairs (tissue)	TaqMan microRNA assays	miR-107(up)	unfavorable	Stage, depth of tumor invasion, lymph node metastasis, OS, DFS
Tsai[71]	72 pairs (tissue) 0 (serum)	qRT-PCR	miR-196a(up)	unfavorable	Relapse
Chen[72]	158 pairs (tissue)	qRT-PCR	miR-93(up)	unfavorable	Stage, deep invasion, nodal metastasis, OS, DFS
Liu[73]	92 pairs (tissue)	qRT-PCR	miR-221(up)	unfavorable	Stage, local invasion, lymphatic metastasis, OS

*qRT-PCR: quantitative real time polymerase chain reaction.

*PFS: progression free survival, *DFS: di eases free survival, *OS: overall survival.

miRNAs as predictive markers of therapeutic response

With increasing knowledge about the function of miRNAs, their possible therapeutic associations have attracted attention. The current literature describing the impact of miRNAs on prediction and modification sensitivity to anticancer treatment is summarized in Table 2.[56,61,69,74–79] Several studies demonstrated that miR-15b, miR-16, miR-181b, miR-200bc/429, and miR-497 could modulate multidrug resistance (MDR) in GC cells via targeting Bcl-2[74,76,78,79] In addition, several miRNAs were shown to influence sensitivity to chemo- or radiotherapy: miR-200c reversed drug resistance by regulating apoptosis through E-cadherin in GC cells, miR-125a-5p enhanced antitumor efficacy in combination with trastuzumab via targeting ERBB2, and up-regulation of miR-451 increased sensitivity to radiotherapy by down-regulating macrophage migration inhibitory factor (MIF).[56,61,77] Activation of miR-512-5p by epigenetic treatment induced suppression of Mcl-1, resulting in apoptosis of GC cell.[75] Wang et al.[69] established a mouse tumor model and conducted chemotherapy *in vivo*. The circulating miR-17-5p/20a levels in plasma may be a promising non-invasive molecular marker for monitoring of chemotherapeutic effects for GC. Wu et al.[80] explored miRNA expression profiling in hydroxycamptothecin (HCPT)-resistant and HCPT-sensitive cell lines. MiR-224 and miR-338-3p were only expressed in HCPT-resistant cells, and miR-141, miR-200a, miR-200b, miR-372, andmiR-373were only expressed in HCPT-sensitive cells. A chemoresistance miRNA expression signature (miR-363*, miR-518f*, miR-519e*, miR-520a*, and miR-520d*) was identified for resistance to cisplatin and fluorouracil (CF) therapy.[81] As shown in Fig. 1, a total of 18 miRNAs were identified as diagnostic markers for GC, 36 miRNAs were identified as prognostic markers for GC and 12 miRNAs were identified as predictive markers of therapeutic response. Several miRNAs (let-7a, miR-17, miR-21, miR-106b, and miR-221) are associated with both diagnosis and prognosis of GC. MiR-125a-5p and miR-181b were identified not only as prognostic indicator but also as predictive markers of therapeutic response in GC. Meanwhile, some miRNAs (miR-17-5p, miR-20a, and miR-451) appeared repeatedly among three groups.

Table 2: miRNAs as predictive markers of therapeutic response

Year	First author (reference)	Sample	MiRNA	Target	Function
2008	Xia[74]	Cell lines	miR-15b, miR-16	Bcl-2	Modulate MDR
2009	Bandres[56]	Tissues and cell lines	miR-451	MIF	Enhance radiosensitivity
2009	Saito[75]	Cell lines	miR-512-5p	Mcl-1	Epigenetic treatment

2010	Zhu[76]	Cell lines	miR-181b	Bcl-2	Modulate MDR
2010	Chen[77]	Cell lines	miR-200c	E-cadherin	Reverse drug resistance
2011	Nishida[61]	Tissues and cell lines	miR-125a-5p	ERBB2	Enhance antitumor efficacy in combination with trastuzumab
2012	Zhu[78]	Cell lines	miR-497	Bcl-2	Modulate MDR
2012	Zhu[79]	Cell lines	miR-200bc/ 429 cluster	Bcl-2, XIAP	Modulate MDR
2012	Wang[69]	Plasma and mouse model	miR-17-5p, miR-20a	-	Modulate chemotherapeutic effects

*MDR: multidrug resistance.

*MIF: macrophage migration inhibitory factor.

*XIAP: X-linked inhibitor of apoptosis protein.

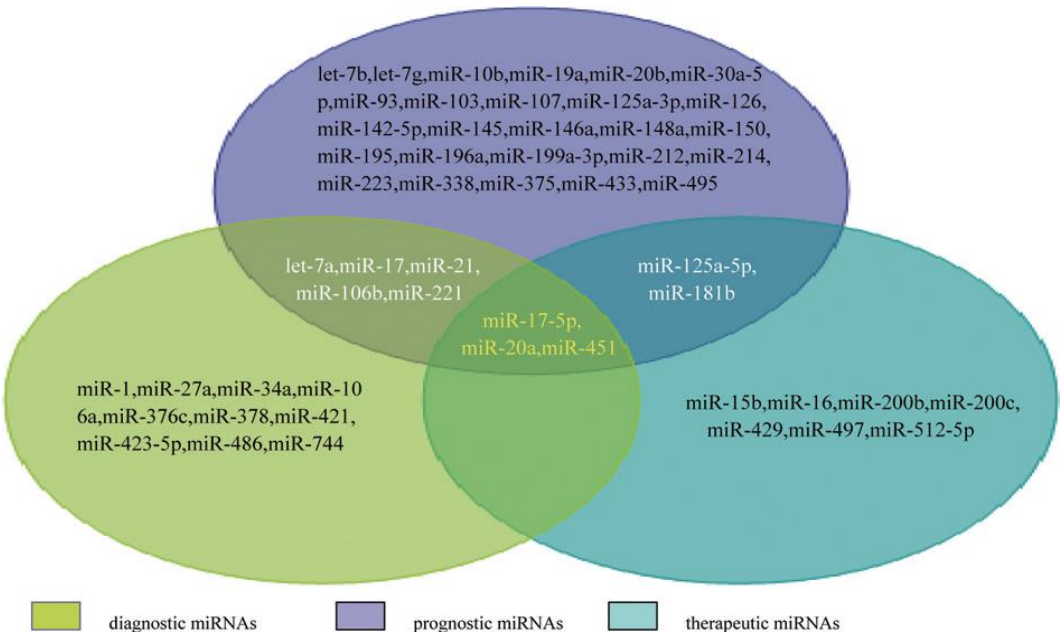

Fig.1: Diagnostic, prognostic and therapeutic miRNAs in gastric cancer

SNPs at miRNA loci and its target as well as methylation may act as low-penetrance 'modifiers' of GC susceptibility. There are many challenges in the research field of tumor related miRNAs. Firstly, it is difficult to identify a consistent miRNA signature for diagnosis and prognosis. The expression of miRNAs can be influenced by various factors such as pathology, hypoxia, infection and cytoxic treatment.[82] As a result; more stringent protocols for collecting and analyzing samples are needed. This approach will lead to reductions in inter-study discrepancies and production of highly reproducible results. Secondly, there is not yet enough data available on circulating miRNA profiles to be used as potential biomarkers for diagnosis and prognosis of GC. Thirdly, more robust platforms as well as more

appropriate bio-computational and statistical analyses are needed to identify candidate miRNA signatures for predicting outcome. Furthermore, studies of miRNAs as prognostic predictors have involved small sample sets. Thus, these candidate miRNA signatures must be validated using large independent cohorts in order to confirm the existence of a predictive signature. Fourthly, existing literature provides only a very small insight into the role of miRNAs in modulation of anticancer treatment. The data point out the immense prospect of using miRNAs in combination with existing therapeutic strategies to maximize the effect of cancer treatment and to improve survival of GC patients. So, the utilization of miRNAs themselves as therapeutic molecules or therapeutic targets is expected to be investigated in further extensive research. Last but not least, more attention should be paid on specific miRNAs (miR-17-5p, miR-20a, and miR-451) associated with diagnosis, prognosis and therapeutic effect in GC. This further highlights the complexity of miRNA function in the interacted gene regulation network.

Polymorphisms and susceptibility

The association between MUC1 polymorphism rs4072037 and the risk of GC has been described in previous studies[83,84] with a candidate gene approach. Recently, a genome-wide association study (GWAS)[85] performed in Chinese population identified the same suspicious locus in the scanning phase but not in the second phase. The identification of genetic variants capable of modulating cancer development could be helpful for the early detection and design of targeted treatment and prevention strategies. Subgroup analyses also revealed that G allele at rs4072037 was associated with GC risk in Asian rather than Caucasian. Interestingly, we notice that the allele frequencies of G allele were more than 0.5 in both the Caucasian studies, while G was the minor allele in all the Asian studies. This remarkable difference in the frequency of the G allele might be due to distinct genetic backgrounds of different ethnicities and this might attribute to the different susceptibility of G allele to gastric cancer.

MUC1 is a highly polymorphic transmembrane glycoprotein expressed on the surface of many epithelia, including gastric mucosa. It acts as a barrier against exogenous insults in normal epithelial cells. In contrast, once the cells lose cell polarity, MUC1 protein interacts freely with other molecules including membrane receptor involved in cell growth and, consequently, promote cell growth cell growth and, consequently, promote cell growth and acts for tumorigenesis.[86] Interestingly, SNP rs4072037, located in exon 2 of MUC1 gene, controls alternative splicing of the 5'-exon 2 region, resulting in both full-length transcripts

and those lacking the polymorphic tandem repeat domain.[87] The different protein products encoded by the two splice variants differ in the protective function of gastric mucosa,[88] which ultimately results in the difference in GC susceptibility. Presence of the G allele contributes to protection against GC in Asian, regardless of anatomic location and pathological subtype.

Inflammation is an essential component of the carcinogenic process in GC.[89] IL-10 is an anti-inflammatory cytokine involved in down regulating cell-mediated and cytotoxic inflammatory responses.[90] It is well known that single-nucleotide polymorphisms are the most common sources of human genetic variation, which may contribute to an individual's susceptibility to cancer. Multiple studies have demonstrated an association between the IL-10 gene -592C>A polymorphism and GC. However, the results are inconsistent.

The mechanism the interaction between the -592C>A polymorphism and GC risk remains unclear. Previous studies have found that IL-10 is highly expressed in patients with GC.[91,92] The haplotype alleles formed in the promoter region of the IL-10 gene at positions 1082, 819, and 592 (GCC) are related to the ability to produce high levels of IL-10.[93,94] The GCC haplotype stimulated peripheral blood mononuclear cells, increased expression of mRNA, and elevated serum levels of IL-10, which is linked to the susceptibility and severity of GC. In addition, tobacco use has been shown to affect the immune system and influence the production of IL-10.[95] Smokers have impaired T lymphocyte suppressor cell function and decreased natural killer cell activity compared with non-smokers.

Molecular aspects of local invasion and metastasis

Mechanisms of metastasis in GC are still under investigation. Metastasis-associated tumor gene family (MTA) has three members, MTA1, MTA2 and MTA3. MTA1 overexpression was observed in some solid tumors, including breast, esophageal, pancreatic, hepatocellular carcinoma,[96] and correlated with cancer cell invasion and metastasis.[97,98] Currently, its biological function in GC is still unclear.

Transcription factor Sp1 plays an important role in physiological process and also in human cancer progression by regulating transcription of diverse downstream genes.[99,100] Concomitant expression of MTA2 and Sp1, and high GC-content sequence in proximal region of human MTA2 promoter, the potential Sp1 binding region,[101] indicated that MTA2 might also be a downstream gene of Sp1 in GC.

Molecular aspects of response to chemotherapy and radiotherapy, and upcoming treatment modalities

Different types of GC may respond differentially to chemotherapy or radiotherapy. For example , hepatoid adenocarcinoma, a rare form of GC, responds poorly to chemotherapy and the best strategy is to operate as early as possible.[102] However, several different histological classification of GC currently exist and include the Lauren classification, Japanese Gastric Cancer Association classification, and World Health Organization (WHO) classification.[103,104]

Tumors of the mesenchymal subtype contained cells with features of cancer stem cells, and cell lines of this subtype were particularly sensitive to phosphatidylinositol 3-kinase- AKT-mTOR inhibitors *in vitro*. This study has been touted by some experts in the field as a new direction for personalized therapy of gastric adenocarcinoma and they are finding ways to apply this information to identify tumor subsets and develop molecularly tailored, individualized therapies.[105] Although many other studies have been conducted, there is still no consensus on the molecular subtypes of GC.[106-109] Recently, several studies have focused on predicting the efficacy of chemotherapy using genome-guided chemotherapy. Molecular biomarkers including VEGFR-1 and ERCC1/TS mRNA levels[110] were reported in the 2013 International Gastric Cancer Congress.[111] While there is still a long way before these studies can be translated into clinical practice, clinical trials may provide some clues for the choice of treatment regimen in the postoperative setting.

A meta-analysis from Janunger et al[112] also found that there was a significant difference in the effect of chemotherapy on AGCs between Asian and European patients. This study has raised the issue about whether there are ethnic differences between GC patients in the East and West.

Perioperative targeted therapy

Recent advances in molecular therapies have developed a new weapon against AGCs through the use of antihuman epidermal growth factor 2 (HER2) therapies. Trastuzumab, a HER2 monoclonal antibody, was the first drug in the metastatic setting that showed a benefit in overall survival when combined with 5-FU chemotherapy. Assaying the HER2 status of a tumor is imperative to achieve the utmost treatment efficacy. Only HER2 positive (immunohistochemistry [IHC] +++ or fluorescence *in situ* hybridization +/IHC ++) GC is eligible for trastuzumab treatment. HER2 treatment is a good example for targeted therapy as

well as personalized medicine. Although there are not any trials reporting results on the role of trastuzumab in the preoperative setting, a number of case reports with trastuzumab-containing preoperative chemotherapy regimens have been published with promising outcomes, and complete remission has been observed occasionally in these cases.[113,114] The value of perioperative-targeted therapy in clinical practice still needs to be thoroughly evaluated, in addition to the rapid development of molecular oncology.

CONCLUSION

GC is a multifactorial condition with varied molecular profiles and clinical expressions. Different therapies including preoperative and postoperative chemotherapy and radiochemotherapy are applied in clinical practice and new concepts of perioperative-targeted therapies are starting to play a role in this field. The core of individualized treatment is to use the appropriate strategy on the right patient. Development of molecular biomarkers, molecular and functional imaging techniques will be of great help.

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