Review

Review of recent molecular landscape knowledge of gastric cancer

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Summary. Gastric cancer (GC) is one of the most frequently diagnosed cancers worldwide and its prognosis remains dismal. One reason for poor outcomes of GC patients is that most are diagnosed when the cancer has already advanced. Novel biomarkers with high sensitivity and specificity are needed to diagnose GC in the early stage. In addition, to improve the outcome of patients with GC, patient stratification according to prognostic factors and sensitivity to chemo(radio)therapy are necessary. Appropriate follow-up criteria and individualized treatment will contribute to improvement in prognosis. Over the past decades, development of microarray and sequencing technology have coalesced to increase reports regarding epigenetic alterations that affect the character of malignancies including GC. These advances help our understanding of gastric carcinogenesis and have the possibility of improving the prognosis of GC by contributing to the optimization of therapeutic strategies. Further development of biomarkers for diagnosis and prognosis are desperately needed. Here, we enumerate and describe some GC-related molecules reported over the past few years that may be useful biomarkers.

Key words: Gastric cancer, Biomarker, Prognosis, Expression

Introduction

Gastric cancer (GC) is the third most frequent cause of cancer-related deaths worldwide. Because of high recurrence rates after curative resection, 5-year survival rates of patients with advanced GC are only 25-30% (Allemani et al., 2015; Ferlay et al., 2015). Most GC patients are currently diagnosed in an advanced stage; therefore, early diagnosis and early therapeutic intervention are necessary to improve the prognosis of GC patients. Available biomarkers for GC diagnosis, such as carcinoembryonic antigen and carbohydrate antigen 19-9 measured in serum, are not sufficient because of their deficient sensitivity and specificity (Duraes et al., 2014; Yin et al., 2015). Development of noninvasive diagnostic methods such as liquid biopsies with high sensitivity should make it possible to diagnose GC earlier and improve outcome. Likewise, there are matters of concern to stratify patients after curative resection and choose appropriate individualized treatment strategies according to their prognostic factors. Several clinicopathological prognostic factors such as older age, macroscopic type (Borrmann type 4), poor differentiation, infiltrative growth pattern c (INFc), lymphatic invasion, vessel invasion, and perioperative blood transfusion have been reported (Baba et al., 1989; Haraguchi et al., 1991; Moriguchi et al., 1992; Kanda et al., 2016a,f). In addition, the representative clinical factor influencing GC patient outcomes is TNM classification. Perioperative therapies performed in Japan, South Korea, The United States, and the United Kingdom with a high evidence level are all based on TNM classification (Macdonald et al., 2001; Cunningham et al., 2006; Sakuramoto et al., 2007; Bang

et al., 2012). However, stratification of GC patients according to only TNM classification cannot reflect the complicated biology and diversity of GC. Novel biomarkers for the stratification of GC patients should be developed. Similarly, identification of new therapeutic molecular targets is of importance, since we have only two molecularly targeted drugs, trastuzumab and ramucirumab, for GC treatment (Bang et al., 2010; Fuchs et al., 2014).

From a molecular biology point of view, improvement in array technology has contributed to the identification of genetic and epigenetic prognostic factors in various cancers in recent decades (Inaoka et al., 2015). Upregulated genes in cancer tissues have the possibility of becoming not only prognostic biomarkers but also therapeutic targets, making the study of these molecules very appealing. Though downregulated genes in cancer tissues rarely become the therapeutic target, their low expression levels and DNA methylation, which suppresses transcription through an epigenetic mechanism, make them potentially useful as biomarkers. Additionally, novel therapeutic strategies could be determined by investigating suppression mechanisms and downstream pathways of downregulated molecules. Recently, the appearance of next-generation sequencing has accelerated the development of cancer-related molecules. Furthermore, the epigenetic effects of non-coding RNAs have been as important as those of protein-coding RNAs. In this article, we review GC-related molecules reported in the literature over the past few years as well as our own recent work.

Upregulated genes in GC

Many upregulated genes in GC patients have been reported. The Cancer Genome Atlas (TCGA) Research Network also shows that ERBB2, PIK3CA, KRAS/NRAS, JAK2, and EGFR are amplified in GC (Comprehensive molecular characterization of gastric adenocarcinoma, 2014). Generally, upregulated genes act as oncogenes and their high expression levels correlate with poor prognosis or malignant GC phenotypes. These genes function to resist apoptosis, drive cell cycle progression, and inhibit tumor suppressor gene (TSG) expression or activity, enabling enhanced proliferation, migration, and invasive ability of cancer cells. Though a small number of upregulated genes have been applied clinically (Bang et al., 2010; Fuchs et al., 2014), it is reasonable to expect that they are more likely to become treatment targets. Investigating these genes should lead to the development of companion diagnostics and tailor-made medications. If proteins coded by these upregulated genes are overexpressed in the serum, they could be useful tumor markers. We have listed the upregulated genes in GC that have been reported recently in Table 1, and below we discuss current findings (Kanda et al., 2014b, 2016b,c,g,h,i; Bargiela-Iparraguirre et al., 2016; Cao et al., 2016a; Chang et al., 2016; Dou et al., 2016; Hou et al., 2016b; Huang et al., 2016; Kim et al., 2016; Kubo et al., 2016; Kwon et al., 2016; Li et al., 2016b,c; Lin et al., 2016; Peng et al., 2016; Subhash et al., 2016; Wang et al., 2016c; Wei et al., 2016; Xia et al., 2016; Xu et al., 2016; Yuan et al., 2016a; Zhang et al., 2016b,c; Companioni Napoles et al., 2017; Fang et al., 2017).

Schlafen 5 (SLFN5)

Companioni et al. reported that SLFN5 expression in gastric mucosa correlated with the progression of intestinal metaplasia to GC (Companioni Napoles et al., 2017). Intestinal metaplasia is one of the preceding steps leading to carcinogenesis (Correa, 1992). Immuno-histochemical (IHC) staining showed that SLFN5 was expressed at a significantly higher level in intestinal metaplasia that progressed to GC than in intestinal metaplasia that did not. Receiver operating characteristic (ROC) curves revealed that the area under the curve (AUC) value of intestinal metaplasia with high SLFN5 expression was 0.953 for the detection of patients who progressed to GC. They concluded that IHC scores for SLFN5 derived from endoscopic biopsies might provide clues to the likelihood of progression to GC. Early detection of GC is therefore enabled by careful follow-up of patients with intestinal metaplasia and high SLFN5 expression.

CDGSH iron sulfur domain 2 (CISD2)

The CISD2 gene, whose cytogenetic location is 4q24, encodes a protein that binds an iron/sulfur cluster and participates in calcium homeostasis (Amr et al., 2007). CISD2 was reported to participate in the progression of breast cancer (Holt et al., 2016), cervical cancer (Liu et al., 2014), hepatocellular carcinomas (Chen et al., 2015), and laryngeal squamous cell carcinomas (Yang et al., 2016a). In GC, overexpression of CISD2 in GC tissues contributed to shorter overall survival (OS) and was an independent prognostic factor for poorer OS (Wang et al., 2016c). Wang et al. also showed that high CISD2 expression was significantly associated with TNM stage, depth of invasion, lymph node metastasis, distant metastasis, and venous and lymphatic invasion. Additionally, silencing of CISD2 expression inhibited proliferation and tumorigenicity *in vivo*, and overexpression of CISD2 promoted GC cell proliferation via activation of the AKT signaling pathway and downregulation of p21 and p27. This study demonstrates that CISD2 may be a novel prognostic biomarker for OS in GC.

Homeobox A1 (HOXA1)

The Hox gene family encodes transcription factors that play an important role in embryonic development and participate in proliferation, differentiation, and apoptosis (Garcia-Fernandez, 2005). Although HOXA1 is a member of this family and the HOXA1 protein is

Table 1. Upregulated genes in gastric cancer.

Symbol (location)	Biological function	Specimen	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo*	Ref.
Early detection										
SLFN5 (17q12)	thymocyte development and T cell activation	tissue	qPCR, IHC	173	-	progression to GC	-	-	-	Companioni Napoles et al., 2017
Prediction of survival										
KRT8 (12q13.13)	keratins heteropoly-merize to form intermediate-sized filaments in the cytoplasm of epithelial cells	tissue	qPCR	-	OS	stage	Proliferation, Migration	Integrin β1, FAK, p-smad2/3, TGFβ	-	Jian et al., 2016
ADAR (1q21.3)	enzyme responsible for RNA editing by site-specific	Tissue	qPCR, IHC	143	OS	T, N, stage	Proliferation, Migration, Tumorigenicity, metastasis	mTOR, p70S kinase, S6 ribosomal protein	Yes	Dou et al., 2016
CAPNS1 (19q13.12)	calcium-dependent cysteine proteinases	tissue	qPCR, IHC, WB	174	OS	v, N, stage	-	-	-	Peng et al., 2016
NRAGE (Xp11.22)	family member of tumor specific antigen	tissue	qPCR, IHC	179	OS, RFS	T, Tumor size, N, CY, stage	Proliferation, Migration, Invasion	AATF	-	Kanda et al., 2016i
MMP16 (8q21.3)	breakdown of extracellular matrix	Tissue	qPCR, WB	67	OS, DFS	-	Clone formation, Invasion	-	-	Cao et al., 2016a
CYR61 (1p22.3)	growth factor-inducible and promotes the adhe-sion of endothelial cells	Tissue	IHC, WB	214	OS	stage	Migration, Invasion	-	-	Wei et al., 2016
AGR2 (7p21.1)	p52 suppressor inhibitor	Tissue	IHC	436	OS	Tumor location, Tumor size, T, stage, v, N, M, Lauren's classification, Differentiation	-	CTSD	-	Zhang et al., 2016b
PSMB8 (6p21.32)	processing of class I MHC peptides	Tissue	qPCR, IHC, WB	48	OS	Tumor size, Gross type, stage, T, P, ly, N	Migration, Invasion	-	-	Kwon et al., 2016
PSEN1 (14q24.2)	regulate amyloid precursor protein processing	Tissue	WB, IHC	340	OS	N	Migration, Invasion, Metastasis	E-Cad	Yes	Li et al., 2016c
HOXA1 (7p15.2)	transcription factors	Tissue	qPCR, WB, IHC	48	OS, DFS	T, N, Differentiation, stage	Proliferation, Migration, Invasion, Cell cycle	Cyclin D1	Yes	Yuan et al., 2016a
CISD2 (4q24)	calcium homeostasis	Tissue	qPCR, IHC, WB	210	OS	T, N, M, stage v, ly	Proliferation, Cell cycle, Colony formation	AKT, P21, P27	Yes	Wang et al., 2016c
ATAD2 (8q24.13)	Mediator of protein complexes	tissue	qPCR, IHC	166	OS	stage, T, N, M	-	-	-	Zhang et al., 2016c
PTTG1 (5q33.3)	stimulation of basic fibroblast growth factor	tissue	qPCR, IHC	78	OS, DSS	-	-	-	-	Xu et al., 2016
DPYSL3 (5q32)	Cell-adhesion factor	Tissue	qPCR, IHC	238	OS, RFS	Differentiation, T, N, CY, stage	-	VEGF, FAK, EZR	-	Kanda et al., 2014b
ANOS1 (Xp22.31)	neural cell adhesion and axonal migration	tissue, serum	qPCR, IHC, ELISA	237	OS	Sex, CA19-9, Tumor size, T, Differentiation, ly, v, Infiltrative growth type, N, CY, stage	Proliferation, Migration, Invasion	ITGAV, FOXC2, NODAL, TFPI2	-	Kanda et al., 2016h
MAGED2 (Xp11.2)	family member of tumor specific antigen	tissue, serum	qPCR, IHC, ELISA	225	OS, RFS	N, Stage	-	-	-	Kanda et al., 2016g
PRMT5 (14q11.2)	methyltransferase	tissue	qPCR	179	OS	CY	Proliferation, Migration, Invasion	GEMIN2, TGFβ3, STAT3	-	Kanda et al., 2016c
IL13RA2 (Xq23)	internalization of IL13	Tissue	IHC	507	OS	T, N, stage	-	-	-	Lin et al., 2016
USP42 (7p22.1)	deubiquitinating enzymes	Tissue	qPCR, WB	90	OS	Tumor size, stage, N	Proliferation, Invasion, Cell cycle	-	Yes	Hou et al., 2016b

usually regulated and expressed during embryogenesis, it has been reported that aberrant HOXA1 expression causes carcinogenesis in several neoplasms (Shah and Sukumar, 2010). Yuan et al. investigated the expression and clinical significance of HOXA1 in GC (Yuan et al., 2016a). HOXA1 was overexpressed in GC tissues and inhibition of HOXA1 expression reduced proliferation, migration, and invasive ability *in vitro*, and inhibited tumor formation *in vivo*. Moreover, they showed that HOXA1 contributed to driving the cell cycle and correlated positively with cyclin D1 expression. GC patients with high HOXA1 and cyclin D1 expression showed significantly worse prognosis. The combination of HOXA1 and cyclin D1 expression was an independent prognostic factor for OS and disease-free survival (DFS) in multivariate analysis. Their results suggested that HOXA1 played an important role in GC development and might serve as a prognostic marker in GC patients.

Checkpoint kinase 1 (CHK1)

Bargiela et al. investigated the expression and clinical significance of CHK1 in GC and found that CHK1 contributed to radiation resistance (Bargiela-Iparraguirre et al., 2016). CHK1 plays a role in checkpoint-mediated cell cycle arrest in response to DNA damage (Tapia-Alveal et al., 2009). Menoyo et al. were the first to report a potential link between GC and CHK1, whereby inhibition of the DNA damage response pathway including CHK1 were involved in gastric carcinogenesis with microsatellite instability (Menoyo et al., 2001). Yao et al. showed that CHK1 expression was higher in advanced GC than in early GC (Yao et al., 2010). Furthermore, Bargiela et al. demonstrated that CHK1 accumulation in the nuclei of GC tissues significantly correlated with shorter progression-free survival (PFS), and that inhibition of CHK1 led to an incremental increase in sensitivity to bleomycin and radiation. Their results suggested that CHK1 might help in stratifying patients according to their radiation sensitivity and in deciding how to adapt adjuvant radiotherapy to the patient.

Synaptotagmin 8 (SYT8)

We recently focused on molecules specifically involved in the peritoneal metastasis of GC (Kanda et al., 2016b). We extracted candidate genes from a four-group analysis (no recurrence, peritoneal recurrence, hepatic recurrence, and distant nodal recurrence) using

Table 1. Continuation.

NRP1 (10p11.22)	Regulator of cell migration	Tissue	qPCR, WB, IHC	141	-	stage, Histologic classification, Differentiation	Proliferation, Tumor angiogenesis	VEGF, EGF, HGF	Yes	Li et al., 2016b
HNF4α (20q13.12)	nuclear transcription factor	tissue	qPCR, WB, IHC	22	OS	-	Proliferation, Cell cycle	AMPK, WNT	Yes	Chang et al., 2016
Prediction of treatment response										
ATM (11q22.3)	cell cycle checkpoint kinase	-	IHC, WB	-	-	-	Veliparib and Irinotecan sensitivity	P21, P53, PUMA	Yes	Subhash et al., 2016
DCTPP1 (16p11.2)	Metabolic enzyme	Tissue	qPCR, IHC, WB	-	-	-	5-FU sensitivity	-	Yes	Xia et al., 2016
FGFR2 (10q26.13)	fibroblast growth factor receptor	Tissue	IHC	54	PFS	-	Pazopanib and CapeOx sensitivity	-	-	Kim et al., 2016
CHEK1 (11q24.2)	DNA damage response	Tissue	qPCR, IHC, WB	23	OS	-	Bleomycin and radiation sensitivity	RB1/E2F1, P53	-	Bargiela-Iparraguirre et al., 2016
BAK1 (6p21.31)	Apoptosis regulator	tissue	IHC, WB	69	OS, PFS	-	DTX sensitivity	BIM-BH3	-	Kubo et al., 2016
HNRNPC (14q11.2)	pre-mRNA processing and other aspects of mRNA metabolism and transport	-	qPCR	-	OS, TTP		CF and 5-FU sensitivity	-	-	Huang et al., 2016
SYT8 (11p15.5)	neurotransmission and hormone secretion	tissue	qPCR, IHC	340	OS	CA19--9, Tumor location, Tumor size, Macroscopic type, T, Differentiation, Infiltrative growth type, N, CY/P, stage	Proliferation, Migration, Invasion, 5-FU resistance	-	Yes	Kanda et al., 2016b

Pt, number of patients enrolled in expression analysis; Ref., reference; qPCR, quantitative real-time reverse transcription-polymerase chain reaction; IHC, immunohistochemistry; GC, gastric cancer; OS, overall survival; stage, UICC stage; T, tumor depth; N, lymph node metastases; WB, western blot; v, vessel invasion; RFS, recurrence-free survival; CY, peritoneal lavage cytology; DFS, disease-free survival; M, distant metastases; P, peritoneal metastases; ly, lymphatic invasion; DSS, disease-specific survival; CA19-9, carbohydrate antigen 19-9

RNA sequencing performed on a next-generation sequencer. SYT8 mRNA was expressed at a significantly higher level in the peritoneal recurrence group rather than in the three other groups. High SYT8 expression was significantly associated with a shorter OS in all patients regardless of stage, and a high cumulative incidence of peritoneal recurrence in stage II/III patients. Additionally, the therapeutic effect of intraperitoneal injection of small interfering RNAs specific for SYT8 (siSYT8) in a xenograft mice model was explored. Treatment with siSYT8 significantly prolonged the survival time of xenograft mice implanted with GC cells into the peritoneal cavity. Moreover, we showed that SYT8 contributed to 5-FU resistance. While the prognosis of stage II/III GC patients who underwent surgery alone was similar between the high and low SYT8 groups, the prognosis of stage II/III GC patients who received adjuvant S-1 monotherapy after curative resection was significantly different between the two groups; the survival time of the high SYT8 group treated with adjuvant therapy was shorter than that of the low SYT8 group treated with adjuvant therapy, and similar to that of patients who underwent surgery alone. Knockdown of SYT8 increased the sensitivity of GC cells to 5-FU *in vitro*. We concluded that SYT8 could be a promising biomarker for the diagnosis and prediction of peritoneal metastasis of GC and may affect the sensitivity of GC cells to 5-FU.

Downregulated genes in GC

Downregulation of TSGs has been implicated in carcinogenesis and the malignant phenotype of various neoplasms, and contributes to a worse prognosis of patients with cancer. Though downregulated genes are rarely effective for use as therapeutic targets because of their low expression levels in cancer tissues, they can still be useful as biomarkers. In addition, delineating the downstream protein and pathways linked to these TSGs might lead to the development of novel therapeutic

Table 2. Downregulated genes in gastric cancer.

Symbol (location)	Biological function	Specimen	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo*	Ref.
Prediction of survival										
RBMS3 (3p24.1)	DNA replication, gene transcription, cell cycle	Tissue	qPCR, IHC, WB	195	OS	T, Histological grade	-	-	-	Zhang et al., 2016e
TSPAN5 (4q23)	signal transduction	Tissue	IHC, WB	114	OS	Tumor size, T, N, stage	Proliferation, Colony formation, Migration, Cell cycle	p27/p15, Cyclin D1/CDK4/E2F1	Yes	He et al., 2016
LIPF (10q23.31)	gastric lipase	Tissue	IHC	90	OS	T, stage	-	DGKA	-	Kong et al., 2016
RBM4 (11q13.2)	regulating alternative splicing and mRNA translation	Tissue	qPCR, IHC	861	OS, DFS	Differentiation, stage, N, M	-	-	-	Yong et al., 2016
FOXL1 (16q24.1)	transcription factors	Tissue	qPCR, IHC, WB	109	OS	T, N, M	-	-	-	Ertao et al., 2016
SIGLEC8 (19q13.41)	cell surface proteins found predominantly on cells of the immune system	Tissue	IHC	434	OS	-	-	-	-	Cao et al., 2016b
BTG1 (12q22)	Regulator of cell growth and differentiation	Tissue	qPCR, IHC	233	DSF, RFS	Sex, Subtype, Tumor size, N, stage	-	-	-	Kanda et al., 2015a
FOSB (19q13.32)	dimerize with proteins of the JUN family	Tissue	qPCR, IHC	-	OS	Differentiation, N, stage	Proliferation, Clone formation, Migration	-	-	Tang et al., 2016a
Monitoring recurrences										
BARX2 (11q24.3)	homeobox transcription factor	Tissue	qPCR, IHC, WB	264	OS, DFS	T, N, M, stage, v, Nerve invasion, Differentiation, Relapse	Proliferation, Migration, Invasion, Tumorigenesis	Wnt/β-catenin	Yes	Mi et al., 2016
FAM46C (1p12)	mRNA stabilizing factor	Tissue	qPCR	129	OS, DFS	Hepatic recurrence	-	-	-	Tanaka et al., 2016
GPR155 (2q31.1)	Membrane transporter	Tissue	qPCR, IHC	220	-	Age, Sex, , Macroscopic type, T, Differentiation, Infiltrative growth type, Hematogenous metastasis	Proliferation, Invasion	TWIST1, WNT5B, p-ERK1/2, p-STAT1	-	Shimizu et al., 2017

Pt, number of patients enrolled in expression analysis; Ref., reference; qPCR, quantitative real-time reverse transcription-polymerase chain reaction; IHC, immunohistochemistry; WB, western blot; OS, overall survival; T, tumor depth; N, lymph node metastases; stage, UICC stage; DFS, disease-free survival; M, distant metastases; RFS, recurrence-free survival; v, vessel invasion

targets. Table 2 provides a list of newly reported downregulated genes without DNA hypermethylation in GC (Kanda et al., 2015a; Cao et al., 2016b; Ertao et al., 2016; He et al., 2016; Kong et al., 2016; Mi et al., 2016; Tanaka et al., 2016; Tang et al., 2016a; Yong et al., 2016; Zhang et al., 2016e; Shimizu et al., 2017).

Tetraspanin 5 (TSPAN5)

TSPAN5, a member of the TSPAN family that contains 33 members in humans, encodes a four-transmembrane protein. TSPANs engage in several functions and are active in the immune system, fertilization, infection, and malignancies, through interaction with other membranous proteins by forming tetraspanin-enriched microdomains (TEMs) (Hemler, 2008). TSPAN5 was reported to be involved in brain development (Garcia-Frigola et al., 2000, 2001). He et al. reported that TSPAN5 suppressed tumor growth in GC via inhibiting the cell cycle transition from G1-S phase and correlated with p27, p15, cyclin D1, CDK4, pRB, and E2F1 expression (He et al., 2016). TSPAN5 expression was found to be suppressed in GC tissues and was significantly associated with tumor depth, tumor size, lymph node metastasis, and TNM stage. The TSPAN5 expression level was inversely correlated with OS and was an independent prognostic factor in multivariate analysis. Enforced expression of TSPAN5 inhibited proliferation *in vitro* and tumor growth *in vivo*. This study indicated that TSPAN5 might be a prognostic biomarker for predicting outcome in GC patients.

RNA-binding motif 4 (RBM4)

It has been reported that RBM4 is an RNA-binding factor and controls various types of splicing (Markus and Morris, 2009; Wang et al., 2014). Splicing dysregulation is one molecular mechanism of carcinogenesis. RBM4 is thought to control apoptosis, proliferation, and migration of malignant cells. Yong et al. investigated the expression level of RBM4 in GC tissues and found that lower expression of RBM4 contributed to a worse prognosis in GC patients. They showed that expression of RBM4 protein and mRNA were significantly lower in GC tissues compared with adjacent noncancerous mucosae. Low RNM4 expression was significantly associated with poor differentiation, lymph node metastasis, distant metastasis, and TNM stage. Downregulation of RBM4 expression was an independent prognostic factor along with TNM stage of OS in GC patients, and was significantly correlated with poor OS and DFS. RBM4 may serve as a prognostic marker for GC patients.

G protein-coupled receptor 155 (GPR155)

GPR155 is a member of the seven-transmembrane G protein-coupled receptor (GPCR) family (Fredriksson et al., 2003). GPCRs mediate diverse physiological processes such as visual sensing, immune function, cell proliferation, and tumor metastasis (Dorsam and Gutkind, 2007). However, little is known about the function of GPR155. We recently detected GPR155 as a molecule specific for hematogenous metastasis using global expression profiling of GC tissues with synchronous hepatic metastasis and without metastasis to the peritoneal cavity or distant lymph nodes. GPR155 was the most downregulated gene in GC tissues with synchronous hepatic metastasis compared with GC tissues without hepatic metastasis. We showed that the expression level of GPR155 was inversely correlated with expression of TWIST1 and WNT5B, which have been shown to play an important role in epithelial-mesenchymal transition (EMT). Knockdown of GPR155 increased the level of p-ERK1/2 and p-STAT1, and advanced cell proliferation and invasion *in vitro*. In stage IV GC, patients with synchronous hematogenous metastasis had significantly lower expression levels of GPR155 compared with patients without hematogenous metastasis. In stage II/III GC, the cumulative incidence of hematogenous recurrence was significantly higher in the GPR155 low expression group. Multivariate analysis revealed that reduced expression of GPR155 mRNA was an independent predictive factor of hematogenous metastasis. We found that GPR155 may represent a biomarker for diagnosing and predicting hematogenous metastasis in GC.

Methylated genes in GC

DNA methylation of CpG islands in promoters is one mechanism of transcriptional silencing (Nomoto et al., 2007). Global CpG island hypermethylation, which induces epigenetic silencing of TSGs involved in apoptosis, the cell cycle, DNA repair, and transcription, precedes carcinogenesis and malignant behavior of cancer cells (Baba et al., 2014). Epstein-Barr virus (EBV) and Helicobacter pylori (HP) are known to induce aberrant DNA methylation and to participate in gastric carcinogenesis; thus it is important to investigate DNA hypermethylation to understand carcinogenesis of GC (Matsusaka et al., 2014; Shinozaki-Ushiku et al., 2015; Wu et al., 2016). Aberrant DNA methylation is detectable in serum and can be easily measured using liquid biopsies (Mitchell et al., 2016; Tang et al., 2016b). Additionally, hypermethylated genes could serve as therapeutic targets of DNA methyltransferase inhibitors to reactivate TSGs (Fenaux et al., 2009). In Table 3 we show recently reported methylated genes and review the representative genes individually (Guo et al., 2016; Kanda et al., 2014a,c, 2015b, 2016d,e; Pimson et al., 2016; Wang et al., 2016b; Yang et al., 2016b; Yeh et al., 2016; Choi et al., 2017).

Differentially expressed in adenocarcinoma of the lung-1 (DAL-1)

DAL-1 downregulation was reported to be

associated with several cancers (Tran et al., 1999; Charboneau et al., 2002; Yamada et al., 2006; Bernkopf and Williams, 2008). CpG hypermethylation of the DAL-1 promoter has been detected in renal cell carcinoma, lung cancer, and breast cancer. Wang et al. investigated the expression and DNA methylation status of DAL-1 in GC (Wang et al., 2016b). Both DAL-1 mRNA and protein were significantly reduced in GC tissue, and aberrant DNA hypermethylation at the DAL-1 locus occurred in 95% of GC cases. Overexpression of DAL-1 significantly decreased cell proliferation, migration, and invasion. Moreover, DAL-1 suppressed EMT via downregulation of N-cadherin and upregulation of α-1-catenin and β-catenin. DAL-1 is a putative TSG in gastric carcinogenesis and may serve as a useful biomarker for the molecular diagnosis of GC.

Marginal zone B and B1 cell-specific protein (MZB1)

The MZB1 gene, whose cytogenetic location is 5q31.2, was first identified as encoding an endoplasmic reticulum protein that was expressed during the differentiation of B cells to plasma cells (Flach et al., 2010). Matsumura et al. showed that CpG islands in the promoter of MZB1 were hypermethylated in hepatocellular carcinoma, and low MZB1 expression was significantly associated with a poor prognosis (Matsumura et al., 2012). In contrast, high MZB1 expression was associated with shorter survival in chronic lymphocytic leukemia, follicular lymphoma, and

Table 3. Methylated genes in gastric cancer.

Symbol (location)	Biological function	Specimen	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo*	Ref.
Prediction of survival										
PCDH10 (4q28.3)	cadherin-related neuronal receptor	Tissue	WB, MSP	101	OS	stage, M	-	-	-	Pimson et al., 2016
RASSF2 (20p13)	modulating the activity of other pro-apoptotic effectors	Tissue	IHC, WB, Bis-seq	135	OS, RFS	stage, T, N, M, Family history of UGIC	-	-	-	Guo et al., 2016
NR4A3 (9q31.1)	steroid-thyroid hormone-retinoid receptor	Tissue	IHC, qMSP, Bis-seq	88	OS	-	Proliferation, Colony formation, Cell cycle, Tumor growth	JAK/STAT	Yes	Yeh et al., 2016
GDF1 (19p13.11)	secreted ligand of the TGF-beta	Tissue	qPCR, IHC, WB, qMSP, Bis-seq	65	OS	-	Proliferation, Colony formation, Cell cycle	SMAD, p15, p21, c-Myc	Yes	Yang et al., 2016b
PDSS2 (6q21)	Synthesize the prenyl side-chain of coenzyme	Tissue	qPCR, IHC, MSP, Bis-seq	238	DSS, RFS	CA19-9, N	-	-	-	Kanda et al., 2014c
TUSC1 (9p21.2)	unknown	Tissue	qPCR, IHC, MSP, Bis-seq	112	DSS	Age, Sex, T, v, N	-	-	-	Kanda et al., 2014a
DENND2D (1p13.3)	Membrane trafficking protein regulating Rab GTPases	Tissue	qPCR, IHC, MSP, Bis-seq	112	DSS, RFS	Age, Sex, Tumor size, T, v, N, stage	-	-	-	Kanda et al., 2015b
Monitoring recurrences										
MZB1 (5q31.2)	B cell activation	Tissue	qPCR, IHC, Bis-seq	200	OS, RFS	Hematogenous recurrence	Proliferation, Migration, Invasion	ESR1, DESI1	-	Kanda et al., 2016d
MFSD4 (1q32.1)	Membrane transporter	Tissue	qPCR, Bis-seq	200	-	Macroscopic type, Infiltrative growth type, CY, Synchronous hepatic metastasis, Hepatic recurrence	Migration, Invasion	BMP2, NUDTI3, OCLN	-	Kanda et al., 2016e
Others										
TMEM220 (17p13.1)	signal transduction	Tissue	qPCR, Bis-seq	30	-	-	-	-	-	Choi et al., 2017
DAL-1(18p11.31)	cell-cell contact	Tissue	qPCR, IHC, WB, MSP, Bis-seq	38	-	-	Proliferation, Migration, Invasion, Colony formation, EMT	Caspase8, α1-catenin, β-catenin, N-cadherin	-	Wang et al., 2016b

Pt, number of patients enrolled in expression analysis; Ref., reference; WB, western blot; MSP, methylation specific polymerase chain reaction; OS, overall survival; stage, UICC stage; M, distant metastases; IHC, immunohistochemistry; Bis-seq, bisulfite sequencing; RFS, recurrence-free survival; T, tumor depth; N, lymph node metastases; UGIC, upper gastrointestinal carcinoma; qMSP, quantitative MSP; DSS, disease-specific survival; CA19-9, carbohydrate antigen 19-9 v, vessel invasion; CY, peritoneal lavage cytology; EMT, epithelial-mesenchymal transition

diffuse large B-cell lymphoma (Herold et al., 2013). We reported that aberrant hypermethylation of the MZB1 promoter contributed to the downregulation of MZB1 expression and malignant behavior in GC. GC cells with DNA hypermethylation expressed lower levels of MZB1 mRNA, and demethylation treatment restored the expression of MZB1. Knockdown of MZB1 caused an increase in proliferation, migration, and invasion of GC cells. MZB1 expression levels were significantly lower in GC tissues compared with adjacent noncancerous mucosae. Low MZB1 expression was an independent prognostic factor for recurrence-free survival (RFS) and was significantly associated with an increased incidence of hematogenous recurrence. Downregulation of MZB1 expression in GC tissues was a predictive factor of recurrence after curative resection, and aberrant hypermethylation of CpG islands in the MZB1 promoter suppressed MZB1 expression.

Growth differentiation factor 1 (GDF1)

The protein encoded by GDF1 is a member of the transforming growth factor-beta (TGF-β) superfamily (Lee, 1991). Generally, members of the TGF-β superfamily activate SMAD proteins that result in attenuation of cell proliferation (Heldin et al., 1997). Yang et al. identified hypermethylation of the GDF1 promoter through genome-wide methylation scanning of GC tissues in mice. 5-aza-dC treatment restored the downregulated expression of GDF1 and increased phosphorylation of SMAD2/3 in GC cells *in vivo*. Aberrant hypermethylation and suppression of GDF1 was significantly associated with poorer OS in GC patients via reduction of phosphorylated-SMAD2/3. Enforced expression of GDF1 caused an increase in colony formation of GC cells *in vitro* and rapid tumorigenicity *in vivo*. Additionally, overexpressed GDF1 increased the G1 population via upregulation of p21. GC patients with GDF1 promoter hypermethylation had significantly shorter OS compared with that of patients without hypermethylation. Similarly, downregulation of GDF1 was also significantly associated with shorter OS. Their results indicated that the expression and methylation status of DGF1 might be

Table 4. Dysregulated microRNAs in gastric cancer.

Symbol (location)	Specimen	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo*	Ref.
Early detection									
miR-133a (18q11.2)	Tissue, Gastric juice	qPCR	204	-	-	-	-	-	Shao et al., 2016a
miR-196 (17q21.32)	Tissue, Plasma	qPCR	98	OS	Gross type, Tumor size, Histological type, T, N, M, stage, P, v, ly, Perineural invasion	-	-	-	Tsai et al., 2016
miR-26a (3p22.2)	Tissue, Plasma	qPCR	370	-	-	-	-	-	Qiu et al., 2016a
miR-940 (16p13.3)	Plasma	qPCR	110	-	-	-	NF-κB, Wnt/β-catenin	-	Liu et al., 2016
Prediction of survival									
miR-198 (3q13.33)	Tissue	qPCR	106	OS	Tumor size, T, N, stage	-	-	-	Cui et al., 2016
miR-203 (14q32.33)	Serum	qPCR	154	OS, DFS	Sex, ly, v, T, N, H, P, M, stage	-	-	-	Imaoka et al., 2016
miR-204 (9q21.12)	Serum	qPCR	115	OS	N, Differentiation, stage	-	-	-	Chen et al., 2016
miR-23b (9q22.32)	Plasma	qPCR	138	OS, DFS	T, M, Differentiation	-	-	-	Zhuang et al., 2016
miR-26a (3p22.2)	Tissue	qPCR	625	OS	-	Proliferation, Migration, Invasion, Apoptosis	-	-	Qiu et al., 2016b
miR-27b (9q22.32)	Tissue	qPCR	631	-	-	Proliferation, Migration, Invasion, Tumor growth, Metastasis	NR2F2	Yes	Feng et al., 2017
miR-31 (9p21.3)	Tissue	qPCR	40	OS	T, N, M, Differentiation	Proliferation, Migration, Invasion, Apoptosis, Cell cycle	E2F2	Yes	Wang et al., 2016a
Prediction of treatment response									
miR-363 (Xq26.2)	Tissue	qPCR	40	OS	DCF sensitivity	Proliferation	FBW7	-	Zhang et al., 2016d
Monitoring recurrences									
miR-206 (6p12.2)	Serum	qPCR	150	OS, DFS	T, stage, N, Recurrence	-	-	-	Hou et al., 2016a

Pt, number of patients enrolled in expression analysis; Ref., reference; qPCR, quantitative real-time reverse transcription-polymerase chain reaction; OS, overall survival; T, tumor depth; N, lymph node metastases; M, distant metastases; stage, UICC stage; P, peritoneal metastases; v, vessel invasion; ly, lymphatic invasion; DFS, disease-free survival; H, hepatic metastases; DCF, docetaxel, cisplatin and 5-FU

a biomarker that could be used to predict the outcome of GC patients.

Dysregulated microRNAs in GC

MicroRNAs (miRNA) are one group of non-coding RNAs that are approximately 22 nucleotides in length (Ruvkun, 2001). MiRNAs play an important role in the regulation of protein-coding gene expression. By binding to the complementary sequence within the 3'-untranslated region of the targeted messenger RNA (mRNA), miRNAs negatively regulate post-transcriptional processes. MiRNAs have been reported to be involved in many types of diseases, especially malignancies including GC. MiRNAs work like an oncogene of a TSG via expression silencing of cancer-related genes. Because of their stability in fluids including serum, miRNAs derived from fluids might serve as diagnostic and prognostic biomarkers (Matsuzaki and Ochiya, 2017). Many studies have demonstrated the potential value of miRNAs as diagnostic and prognostic markers in GC. Newly identified dysregulated miRNAs in GC are shown in

Table 4, and certain studies are summarized below (Chen et al., 2016; Cui et al., 2016; Hou et al., 2016a; Imaoka et al., 2016; Liu et al., 2016; Qiu et al., 2016, 2017; Shao et al., 2016a; Tsai et al., 2016; Wang et al., 2016a; Zhang et al., 2016d; Zhuang et al., 2016; Feng et al., 2017).

miR-133a

MiR-133a was reported to function as a tumor suppressor in several cancers, such as bladder cancer (Chiyomaru et al., 2010), esophageal squamous cell carcinoma (Kano et al., 2010), prostate cancer (Kojima et al., 2012), colorectal cancer (Dong et al., 2013), breast cancer (Wu et al., 2012), as well as others. Similarly, miR-133a acts as a tumor suppressor in GC (Gong et al., 2015; Lai et al., 2015). Interestingly, Shao et al. detected miR-133a in gastric juice and disclosed that miR-133a in gastric juice had diagnostic value (Shao et al., 2016a). GC tissue and gastric juice were obtained endoscopically. MiR-133a expression was significantly lower in GC tissues compared with that in noncancerous mucosae. Additionally, suppressed expression of miR-

Table 5. Dysregulated long non-coding RNAs in gastric cancer.

Symbol (location)	Specimen	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	In vivo	Ref.
Early detection									
H19 (11p15.5)	Plasma	qPCR	62	-	stage, CEA	-	-	-	Hashad et al., 2016
RMRP (9p13.3)	Tissue, Plasma, Gastric juice	qPCR	132	-	-	Proliferation, Cell cycle, Tumorigenisity	Cyclin D2	Yes	Shao et al., 2016b
HULC (6p24.3)	Serum	qPCR	240	OS	Tumor size, stage, N, M, H. pylori	-	-	-	Jin et al., 2016
PVT1 (8q24.21)	Tissue, Gastric juice	qPCR	111	OS, DFS	T, N, stage	-	-	-	Yuan et al., 2016b
Prediction of survival									
SOX2OT (3q26.33)	Tissue	qPCR	132	OS	stage, T, N, M	Proliferation, Migration, Invasion	-	-	Zhang et al., 2016f
NEAT1 (11q13.1)	Tissue	qPCR	140	OS	Histological type, stage, N, M	Migration, Invasion	Vimentin, N-cadherin, Zo-1, E-cadherin	-	Fu et al., 2016
TUG1 (22q12.2)	Tissue	qPCR	100	OS	T, stage	Proliferation, Colony formation, Cell cycle, Tumorigenesis	P15, P16, P21, P27, P57	Yes	Zhang et al., 2016a
PANDAR (6p21.2)	Tissue	qPCR	100	OS, DFS	T, N, stage	-	-	-	Ma et al., 2016
MIR31HG (9p21.3)	Tissue	-	-	OS	Tumor size, stage	Proliferation	E2F1, p21	Yes	Nie et al., 2016
LINC00982 (1p36.32)	Tissue, Gastric juice	qPCR	106	OS, DFS	T, N, stage	Proliferation, Cell cycle	p15, p16	-	Fei et al., 2016
Prediction of treatment response									
UCA1 (19p13.12)	Tissue	qPCR	77	DFS	tumor size, differentiation, Borrmann type, Lauren type, v, ly, T, N	Proliferation, Adriamycin sensitivity	cleaved PARP, Bcl-2	-	Shang et al., 2016

Pt, number of patients enrolled in expression analysis; Ref., reference; qPCR, quantitative real-time reverse transcription-polymerase chain reaction; stage, UICC stage; CEA, carcinoembryonic antigen; OS, overall survival; N, lymph node metastases M, distant metastases; H. pylori, Helicobacter pylori infection; DFS, disease-free survival; T, tumor depth; v, vessel invasion; ly, lymphatic invasion

133a was also detected in the gastric juice of GC patients. They evaluated the stability of miR-133a in gastric juice incubated at 4°C for 24 hours, and found that the level of miR-133a was reduced by only 15% after 24 hours. ROC curve analysis revealed that the AUC value of the miR-133a expression level was 0.907 for detection of GC, the sensitivity was 85.9%, and the specificity was 84.8%. MiR-133a in gastric juice may serve as a promising biomarker for GC screening.

miR-206

An association of miR-206 with GC was reported for the first time in 2013 (Zhang et al., 2013a). Thereafter, there were additional reports referring to the expression of miR-206 in GC patients, as well as several studies in which miR-206 expression levels in GC tissue samples were determined. Hou et al. found that measuring miR-206 in serum had prognostic value in GC patients (Hou et al., 2016a). MiR-206 in serum from GC patients was downregulated, compared with serum from healthy controls. Decreased miRNA-206 in serum was significantly correlated with tumor depth, lymph node metastasis, and advanced TNM stage. Patients with low serum miR-206 expression had significantly lower OS rates than patients with high serum miR-206 expression. Moreover, decreased miR-206 expression in serum was increased significantly four weeks after surgery. Intriguingly, miR-206 expression in serum recovered to levels close to preoperative expression levels when GC recurred, thus indicating that serum miR-206 might not only serve as a novel diagnostic biomarker for GC, but also to predict cancer recurrence and prognosis.

miR-363

In a previous report, miR-363 was shown to promote cell proliferation, viability, progression, EMT, and tumorsphere formation of GC cells via downregulation of MBP-1 (Hsu et al., 2014). Zhang et al. showed that miR-363 exerted its effects not only on cell proliferation but also on chemoresistance (Zhang et al., 2016d). MiR-363 expression was higher in GC tissues than in adjacent noncancerous tissues. Enforced miR-363 expression promoted cell proliferation and resistance of GC cells to 5-FU and DCF (combination of docetaxel, cisplatin, and 5-FU). Patients with high expression of miR-363 in GC tissues had worse OS and recurrence rates. Furthermore, high expression of miR-363 in GC tissues contributed to significantly shorter PFS in GC patients treated with DCF. MiR-363 might serve as a biomarker for predicting the outcome and response to DCF treatment in GC patients.

Dysregulated long non-coding RNAs in GC

Advances in RNA sequencing technology have revealed that non-coding RNAs make up more than 90% of the transcriptome and play important roles at the transcriptional stage (Kapranov et al., 2007; Guttman et al., 2009). Generally, long non-coding RNAs (lncRNAs) are non-protein coding RNAs that are more than 200 nucleotides in length and are located in the nucleus. LncRNA expression levels are lower and more tissue-specific than those of protein-coding genes (Derrien et al., 2012). LncRNAs are reported to regulate cell differentiation and development (Li and Chang, 2014), and their aberrant expression contributes to the pathopoiesis of various diseases including neoplasms. Recent articles indicate that lncRNAs might be useful biomarkers and therapeutic targets. Listed in Table 5 are recently reported lncRNAs contributing to GC; we have outlined some of them below (Fei et al., 2016; Fu et al., 2016; Hashad et al., 2016; Jin et al., 2016; Ma et al., 2016; Nie et al., 2016; Shang et al., 2016; Shao et al., 2016b; Yuan et al., 2016b; Zhang et al., 2016a,c).

RNA component of mitochondrial RNA processing endoribonuclease (RMRP)

RMRP was detected on chromosome 9p in 1990 (Hsieh et al., 1990) and has been reported to be involved in colon cancer (Park and Jeong, 2015) and lung cancer (Meng et al., 2016), acting as an oncogene. Shao et al. revealed that RMRP promoted gastric carcinogenesis (Shao et al., 2016b). RMRP expression levels in tissues were significantly decreased in GC and gastric dysplasia compared with normal mucosa and benign lesions. Significantly lower expression levels of RMRP could also be detected in plasma and gastric juice of GC patients compared with healthy controls. Additionally, expression of RMRP rebounded dramatically after curative resection of GC. ROC curves for the detection of GC showed that sensitivity and specificity of RMRP expression in plasma were 0.591 and 0.678, respectively, and those in gastric juice were 0.564 and 0.754, respectively. Overexpression of RMRP promoted cell proliferation *in vitro* and tumorigenicity *in vivo*. By using the miRcode algorithm to predict miRNA interaction with RMRP, miR-206 was identified as a putative related molecule. Knockdown of RMRP induced G1 arrest in a small population of GC cells. Their results suggested that RMRP could be a candidate biomarker for early detection of GC.

Taurine upregulated 1 (TUG1)

Some reports revealed that TUG1 was a cancer-related lncRNA, and acted like an oncogene in bladder carcinoma (Han et al., 2013), osteosarcoma (Zhang et al., 2013b), esophageal squamous cell carcinoma (Xu et al., 2015), hepatocellular carcinoma (Huang et al., 2015), and colorectal cancer (Sun et al., 2016), and like a tumor suppressor in lung cancer (Zhang et al., 2014) and glioma (Li et al., 2016a). Zhang et al. explored the expression and significance of TUG1 in GC. TUG1 expression was significantly increased in GC tissues compared with noncancerous mucosae, and high expression of TUG1 in GC tissues was significantly associated with tumor invasive depth and TNM stage.

Patients with high TUG1 expression had a worse prognosis than patients with low TUG1 expression. Inhibition of TUG1 expression induced a decrease in cell proliferation *in vitro* and *in vivo* by promoting the expression of cyclin-dependent protein kinase inhibitors. They concluded that TUG1 may serve as a candidate prognostic biomarker in GC patients.

Urothelial cancer associated 1 (UCA1)

Initially, UCA1 was reported to be a potential biomarker in serum that might have diagnostic value in GC (Dong et al., 2015). Shang et al. revealed that UCA1 was implicated in chemotherapy resistance (Shang et al., 2016). GC tissues expressed high levels of UCA1 and patients with high levels of UCA1 expression had a significantly shorter OS than patients with low UCA1 expression levels. High UAC1 expression was an independent prognostic factor for OS in GC patients. Knockdown of UCA1 downregulated cell proliferation of GC cells *in vitro*. The key result in this article was that UCA1 interfered with GC cell sensitivity to adriamycin (ADM). Silencing of UCA1 expression restored sensitivity to ADM in ADM-resistant GC cells via acceleration of apoptosis. Additionally, ADM treatment induced higher levels of cleaved PARP and decreased Bcl-2 expression in UCA1-silenced GC cells compared with control GC cells. UCA1 may serve as a useful biomarker not only for predicting outcome but also for patient stratification according to chemotherapy sensitivity.

Conclusion

Array and sequencing technologies have been developed in the last few decades. High throughput expression analyses have contributed to the identification of several aberrantly regulated cancer-related molecules. These molecules could be candidate therapeutic targets and biomarkers. Additionally, investigation of cancer-related molecules contributes to our understanding of the epigenetic background of carcinogenesis.

Because GC patients have a high mortality rate, novel therapeutic strategies and useful biomarkers for GC patients are required. To improve the outcome of GC patients, personalized treatment and patient stratification according to their individual risk factors are needed. Our review focused on recently reported GC-related molecules, which might be therapeutic targets or biomarkers that may help with early detection, prediction of survival, and prediction of treatment response, as well as in the monitoring of recurrence. Although many candidate biomarkers or therapeutic targets have been reported, few of them have made it into the clinic. However, with the development of next-generation sequencing technology, we can expect a further increase in newly reported molecules in the future. These molecules will have to be validated in larger cohorts, which will result in bringing novel molecular targets and/or useful biomarkers to the clinic. Multi-marker panels could also be serviceable for patient stratification in clinical practice. Further research in this field will lead to improvements in the prognosis of GC patients.

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