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TOPIC HIGHLIGHT

2015 Advances in Gastric Cancer

Recent advances in the molecular diagnostics of gastric cancer

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Abstract

Gastric cancer (GC) is the third most common cause of cancer-related death in the world, representing a major global health issue. Although the incidence of GC is declining, the outcomes for GC patients remain dismal because of the lack of effective biomarkers to detect early GC and predict both recurrence and chemosensitivity. Current tumor markers for GC, including serum carcinoembryonic antigen and carbohydrate antigen 19-9, are not ideal due to their relatively low sensitivity and specificity. Recent improvements in molecular techniques are better able to identify aberrant expression of GC-related molecules, including oncogenes, tumor suppressor genes, microRNAs and long non-coding RNAs, and DNA methylation, as novel molecular markers, although the molecular pathogenesis of GC is complicated by tumor heterogeneity. Detection of genetic and epigenetic alterations from gastric tissue or blood samples has diagnostic value in the management of GC. There are high expectations for molecular markers that can be used as new screening tools for early detection of GC as well as for patient stratification towards personalized treatment of GC through prediction of prognosis and drug-sensitivity. In this review, the studies of potential molecular biomarkers for GC that have been reported in the publicly available literature between 2012 and 2015 are reviewed and summarized, and certain highlighted papers are examined.

Key words: Gastric cancer; Biomarker; Prognosis; MicroRNA; DNA methylation; Long non-coding RNA

Core tip: Gastric cancer (GC), although declining in incidence in recent decades, is still the fourth most common malignancy and the third leading cause of cancer-related death worldwide. Although reliable biomarkers are necessary to improve the management of GC, conventional tumor markers have insufficient diagnostic performance. Detection of molecular markers in gastric tissue and blood samples may enhance the

sensitivity and specificity of diagnostic and prognostic tests for early stage GC and provide a means to monitor recurrence and predict response to treatment. In this review, we introduce recently reported candidates for GC-related biomarkers and overview important findings.

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INTRODUCTION

Gastric cancer (GC), the third leading cause of global cancer death, is a malignant disease with a high mortality rate despite declining incidence in the recent decade[1,2]. Multimodal treatment strategies including surgery, chemotherapy and radiotherapy can improve local and regional tumor control and decrease the rate of systemic metastasis[3,4]. However, the overall prognosis for advanced disease remains poor. The high mortality rate attributed to GC is mainly due to the lack of both early detection methods and effective medical treatment for advanced stages of the disease[1,5]. Early diagnosis is beneficial and critical for successful surgical removal of GCs because peritoneal dissemination and local/distal metastases often occur in the late stages of GC and greatly reduce the efficacy of surgical intervention[6,7].

Carcinoembryonic antigen, carbohydrate antigen (CA) 19-9 and CA72-4 are the most commonly used biomarkers for GC[8]. Although widely used, they are not ideal markers because of their relatively low sensitivity and specificity in the diagnosis and prognosis of GC[9,10]. Therefore, identification of more specific and sensitive novel markers for GC is urgently required to establish screening strategies and further stratify patients for individualized therapies[3,11]. Modern biomedical research has explored many potential GC biomarker genes by examining serum protein antigens, oncogenic genes or gene families through improved molecular biological technologies, such as microarray and next-generation sequencing analyses[12]. However, there remains room for improvement of molecular-based diagnosis methods in terms of sensitivity, specificity and accessibility; therefore, they have not been utilized in clinical practice.

Recently, it was demonstrated that microRNA (miRNA) and long non-coding RNA (lncRNA) can be effective candidates for molecular diagnostics in GC in addition to altered expression of oncogenes and tumor suppressor genes (TSGs)[8,13,14]. The search for non-invasive tools for diagnosis has led to the investigation of proteins and circulating nucleic acids, including miRNAs and lncRNAs, in plasma and serum samples[15].

The aim of this review is to provide up-to-date information regarding molecular biomarkers for early detection and risk stratification for patients with GC. A prognostic cancer biomarker provides information on the likely course of the disease. In contrast, a predictive biomarker is defined as a marker that can be used to identify subpopulations of patients most likely to respond to a targeted therapy[8,16]. The search for cancer biomarkers is carried out in order to identify tumor cells at early stages and predict treatment response, ultimately leading to a favorable therapeutic outcome[8,17]. The studies of potential molecular biomarkers for GC that have been reported in the publicly available literature between 2012 and 2015 are reviewed, summarized and categorized by based on their suggested clinical implication; early detection, monitoring recurrences, prediction of survival and prediction of treatment response.

UPDATE ON GENES OVEREXPRESSED IN GC

To date, numerous GC-related oncogenes have been reported. Oncogenes are frequently overexpressed in GC and promote cancer cell growth and cell cycle progression[7,18]. They also inhibit apoptosis by silencing growth-inhibition associated genes[19]. Particularly, when the target molecules are minimally expressed in normal gastric mucosa or blood samples from healthy controls, detection of aberrantly activated oncogenes can be of great diagnostic value. Recently reported genes that are overexpressed in GC are listed in Table 1[20-44], and we review certain highlighted studies.

Bone morphogenetic protein 4

Bone morphogenetic protein 4 (BMP4) encodes a secreted protein belonging to the TGFb superfamily. BMP4 binds to BMP type Ⅰ/Ⅱ receptors, resulting in activation of a signaling cascade that culminates in phosphorylation of SMAD1/5/8 and the regulation of gene expression[45]. Ivanova *et al*[24] conducted an integrated epigenomics study to identify genes associated with cisplatin resistance in GC and found that BMP4 was an epigenetically regulated gene that is highly expressed in cisplatin-resistant GC cell lines. BMP4 promoter methylation levels were inversely correlated with BMP4 expression, and patients with high BMP4-expressing GC showed significantly worse prognosis. Inhibition of BMP4 resulted in significant sensitization of GC cells to cisplatin, and BMP4-expressing GC cells did not exhibit cross-resistance to oxaliplatin[24]. These results indicated that BMP4 epigenetic and expression status may represent a promising biomarker for cisplatin resistance in GC.

Dihydropyrimidinase-like 3

Dihydropyrimidinase-like 3 (DPYSL3) has been described as a cell-adhesion molecule; it is actively expressed in

Table 1 Genes upregulated in gastric cancer

Symbol (location)	Biological function	Materials	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo* study	Ref.
Early detection										
ERCC5 (13q33)	DNA repair	Tissue	IHC	176	OS	Depth, smoking, *Helicobacter pylori*	-	-	-	[27]
IFITM1 (11p15.5)	Interferon induced transmembrane protein	Tissue	IHC	151	-	Differentiation	Migration, invasion	-	-	[21]
MMP-9 (20q13.12)	Breakdown of extracellular matrix	Tissue, Circulating	IHC, ELISA	45	-	N, stage	-	-	-	[40]
PTTG1 (5q35.1)	Homolog of yeast securin proteins	Tissue	QPCR, IHC	98	OS	-	-	-	-	[43]
STC1 (8p21.2)	Regulation of renal and intestinal calcium and cell metabolism	Tissue, circulating	IHC, ELISA	83	PFS	N, stage	-	-	-	[30]
Monitoring recurrences										
CD147 (19p13.3)	Plasma membrane protein involved in spermatogenesis	Tissue	IHC	223	OS, RFS	Depth, N, stage	-	-	-	[26]
CEACAM6 (19q13.2)	Cell adhesion	Tissue	IHC	106	-	T, N, vascular invasion	-	HER2	-	[28]
ERBB3 (12q13)	Epidermal growth factor receptor family of receptor tyrosine kinases	Tissue	QPCR, IHC	167	OS, RFS	Depth	-	IGF-1R, EphA2	-	[29]
NUAK1 (12q23.3)	Regulator of whole-body and cellular energy homeostasis	Tissue	IHC	117	OS, RFS	Differentiation, depth, N, stage	-	-	-	[37]
SULF1/2 (8q13.2)	Extracellular heparan sulfate endosulfatase	Tissue	QPCR, IHC	450	OS, RFS	Size, depth, N, stage	Proliferation	-	Yes	[20]
Prediction of survival										
B7-H4 (1p13.1)	Cell surface protein interacting with ligand bound to T cell receptors	Circulating	ELISA	132	OS	Size, depth, N, stage	-	-	-	[35]
CCND1 (11q13)	Regulators of cell cycles *via* CDK kinases	Tissue	IHC	211	OS	Age	-	-	-	[42]
DPYSL3 (5q32)	Cell-adhesion factor involved in the metastatic process of tumor cells	Tissue	QPCR, IHC	238	OS, RFS	Differentiation, depth, N, CY, stage	-	VEGF, FAK, EZR	-	[33]
IL-17 (6p12)	Proinflammatory cytokine produced by activated T cells	Tissue, circulating	IHC, ELISA	50	-	N, stage	-	-	-	[22]
KDM4A (1p34.1)	Trimethylation-specific demethylase	Tissue	QPCR, IHC	123	OS, RFS	N, stage	Proliferation, apoptosis	-	-	[32]
MAGED2 (Xp11.2)	Unknown	Tissue, Circulating	QPCR, IHC	225	OS, RFS	N, stage	-	-	-	[44]
MYCL1 (1p34.2)	Transcription factor involved in cell differentiation and apoptosis	Tissue	IHC	176	OS	Age, differentiation, stage	-	-	-	[39]
NEDD4 (15q)	Regulation of degradation of epithelial sodium channel	Tissue	IHC	214	OS	Depth, N, stage	Migration, invasion	-	-	[36]
S100A6 (1q21)	Regulation of cell cycle progression and differentiation	Circulating	ELISA	103	OS	Vascular invasion, perineural invasion, N, stage	Proliferation, invasion, apoptosis	-	Yes	[38]
SATB1 (3p23)	Matrix protein which binds nuclear matrix and scaffold-associated DNAs	Tissue	IHC	175	OS, RFS	Age, N	-	-	-	[31]
SERPINA1 (14q32.1)	Serine protease inhibitor	Tissue	QPCR, IHC	400	OS	Age, size, depth, N	Migration, invasion	MMP8	-	[34]

XPO1 (2p15)	Mediator of leucine-rich nuclear export signal-dependent protein	Tissue	IHC	120	OS, PFS	HER2, CEA, stage	-	-	-	[25]
YBX1 (1p34)	Modulator of gene transcription and protein translation	Tissue	IHC	167	-	N, perforation	Migration, invasion	-	-	[41]
Prediction of treatment response										
BMP4 (14q22-23)	Endochondral bone formation	Tissue	IHC	197	OS	Chemoresistance	-	EMT	-	[24]
TUBB3 (16q24.3)	Formation of microtubules	Circulating	ELISA	128	OS	Sex, chemoresistance	-	-	-	[23]

Pt: Number of patients enrolled in expression analysis; ELISA: Enzyme-linked immunosorbent assay; IHC: Immunohistochemistry; QPCR: Quantitative real-time reverse transcription-polymerase chain reaction; OS: Overall survival; RFS: Recurrence free survival; PFS: Progression free survival; N: Lymph node metastasis.

normal tissues in cardiac myocytes, brain, pineal body, retina and smooth muscle and is moderately expressed in various tissues, including gastric mucosa[46]. DPYSL3 is involved in the metastatic process of tumor cells[47,48]. We recently investigated the expression status of DPYSL3 in GC cells and tissues and found that DPYSL3 mRNA expression levels positively correlated with those of potentially interacting genes (vascular endothelial growth factor, focal adhesion kinase and ezrin)[33,49]. Tissues from patients with stage Ⅳ GC showed increased expression of DPYSL3 mRNA. High DPYSL3 mRNA expression in GCs was significantly associated with more malignant phenotypes, including recurrence, and was an independent prognostic factor. The potential of DPYSL3 as a biomarker for the progression of GC was demonstrated.

Erb-b2 receptor tyrosine kinase 3

Erb-b2 receptor tyrosine kinase 3 (ERBB3), alternatively named human epidermal growth factor receptor (HER) 3, is a key member of the ErbB family and preferentially signals through the phosphatidylinositol 3-kinase pathway[50]. ERBB3 heterodimerizes with other HER family members to initiate signal transduction[51]. Ema *et al*[29] conducted an integrated immunohistochemical analysis of receptor type tyrosine kinases, including ERBB3, in stage Ⅱ/Ⅲ GC and found that ERBB3 expression was significantly associated with shorter recurrence-free survival. Additionally, ERBB3 expression was closely correlated with IGF-1R and EphA2 expression levels and was identified as the only independent prognostic factor regardless of the stage[29]. ERBB3 is proposed to be a prognostic marker for GC after curative gastrectomy.

Serpin peptidase inhibitor, clade A member 1

Serpin peptidase inhibitor, clade A member 1 (SERPINA1) is primarily synthesized in the liver and is also produced in certain cells, such as GC, colon cancer and lung cancer cells[34,52]. SERPINA1 has been reported to have major roles in physiologic and pathologic processes, including angiogenesis, intravascular fibrinolysis, wound healing, and tumor invasion and metastasis[52]. Kwon *et al*[34] evaluated the clinical significance of SERPINA1 expression by immunohistochemical staining in 400 GC tissues and found that SERPINA1 expression was significantly associated with a more aggressive phenotype of GC and shorter overall survival. In the functional analysis, upregulation of SERPINA1 increased the release of metalloproteinase-8, migration and invasion in GC cells.

Extracellular heparan sulfate 6-O-endosulfatase 1

Extracellular heparan sulfate 6-O-endosulfatase 1 (SULF1) has been identified in mammals, and the encoded protein is secreted to the cell surface to modulate the sulfation of heparan sulfate proteoglycans[53,54]. Hur *et al*[20] conducted an expression analysis on SULF1 in 450 GC tissues to evaluate the potential of SULF1 as a biomarker for GC. The expression of SULF1 was identified as a predictive factor of lymph node metastasis, recurrence and worse prognosis. Moreover, they found that hypomethylation of CpG islands within the SULF1 gene promoter imparts oncogenic potential in GC. Expression level and methylation status of SULF1 are promising biomarkers for patients with GC.

GENES DOWNREGULATED IN GC

Loss of expression of GC-related TSGs leads to accelerated cell growth, cell cycle progression, and impaired inhibition of oncogenic gene expression[7]. Similar to oncogenes, altered expression levels of GC-related TSGs in gastric tissues can be as diagnostic molecular markers for the early detection or progression of GC[13,55]. Table 2 provides a list of updated genes that are suppressed in GC without hypermethylation[56-62], and certain representative genes are reviewed individually.

B-cell translocation gene 1

B-cell translocation gene 1 (BTG1) is a translocation partner of the c-Myc gene in the context of B-cell chronic lymphocytic leukemia and belongs to a family of antiproliferative genes[63,64]. BTG1 is constitutively expressed in quiescent cells, and its expression is downregulated as cells enter the growth cycle[65]. In breast and ovarian cancers, artificial expression of BTG1

Table 2 Genes suppressed in gastric cancer

Symbol (location)	Biological function	Materials	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo* study	Ref.
Early detection										
TMEFF2 (2q32.3)	Unknown	Tissue	QPCR, IHC	105	OS	-	Proliferation, apoptosis	SHP-1	Yes	[61]
Monitoring recurrences										
BTG1 (12q22)	Regulator of cell growth and differentiation	Tissue	QPCR, IHC	233	OS, RFS	Sex, location, size, N, stage	-	-	-	[59]
eIF3f (11p15.4)	Unknown	Tissue	IHC	195	RFS	CEA, stage	-	-	-	[57]
Prediction of survival										
ITIH5 (10p14)	Extracellular matrix stabilization	Tissue	QPCR, IHC	331	OS	Differentiation, N, stage	-	-	-	[60]
JAMA (1q21.2-3)	Regulator of tight junction assembly in epithelia	Tissue	IHC	167	OS	Size, lymphovascular invasion, N, stage	Migration, invasion	-	-	[58]
SEMA3A (7p12.1)	Neuronal pattern development	Tissue	IHC	128	OS	Differentiation, depth, N, stage	Proliferation, migration	-	-	[62]
STUB1 (16p13.3)	Ubiquitin ligase/ cochaperone	Tissue	IHC	493	OS	Size, depth, N, stage	Proliferation	NF-κB, IL-8	Yes	[56]

Pt: Number of patients enrolled in expression analysis; IHC: Immunohistochemistry; QPCR: Quantitative real-time reverse transcription-polymerase chain reaction; OS: Overall survival; RFS: Recurrence free survival; N: Lymph node metastasis.

mediates Bcl-2-regulated apoptosis and suppresses the proliferation of cancer cells[66,67]. We recently evaluated the clinical implication of BTG1 expression in GC and examined the genetic diversity among histopathologic and anatomic subtypes[59]. BTG1 expression was downregulated in the majority of GCs, but promoter hypermethylation events or sequence mutations were not detected[68,69]. Patients with downregulated BTG1 mRNA in GCs had significantly shorter recurrence-free survival and overall survival. BTG1 mRNA expression was more strongly suppressed in proximal non-diffuse and diffuse GC compared with distal non-diffuse GC, and subgroup analysis revealed that BTG1 downregulation led to adverse prognosis, specifically in patients with proximal non-diffuse and diffuse GC[59].

Inter-a-trypsin inhibitor 5

Inter-a-trypsin inhibitor 5 (ITIH5) is a new member of the ITIH family of plasma protease inhibitors and is the only ITIH gene with a CpG-rich promoter region, which contains two domains that are conserved in all known ITIHs[70]. Although the precise function of ITIH5 is unclear, it has been reported that the loss of ITIH5 expression is involved in breast cancer development[71]. Mai *et al*[60] investigated ITIH5 expression and its predictive value in 331 clinical GC tissues. Low ITIH5 expression was significantly associated with lymph node metastasis and advanced stage, and patients with low ITIH5 expression showed shorter survival times than those with high ITIH5 expression, suggesting that ITIH5 may be a potential prognostic biomarker for GC[60]. The mechanisms of ITIH5 silencing and oncological functions of ITIH5 in GC are expected to be clarified.

STIP1 homology and U-box containing protein 1

STIP1 homology and U-box containing protein 1 (STUB1) includes a tetratricopeptide repeat domain at its amino terminus that interacts with the molecular chaperones Hsc70-Hsp70 and the Hsp90 protein[72]. It also contains a U-box domain at its carboxy terminus with E3 ubiquitin ligase activity, which functions as a link between the chaperone and proteasome systems[73]. STUB1 induces ubiquitination and degradation of several oncogenic proteins, such as mutant p53, estrogen receptor a, c-ErbB2/neu, hypoxia inducible factor 1a and SRC-3[73,74]. Wang *et al*[56] evaluated the prognostic value of STUB1 expression by immunohistochemical staining in 493 patients and the role of STUB1 in tumorigenicity and angiogenesis *in vitro* and *in vivo*. Decreased STUB1 expression in GC tissues was significantly associated with advanced stage and diffuse type and was an independent prognostic factor. Forced expression of STUB1 reduced the formation of anchorage-independent colonies in soft agar, suppressed the growth of xenografts in nude mice and inhibited endothelial cell growth and tube formation by suppressing NF-κB-mediated interleukin 8 expression[56]. STUB1 acts as a TSG and represents a promising biomarker for GC.

METHYLATED MARKERS OF GC

Aberrant DNA methylation is an epigenetic alteration that occurs in an organ-disease-specific manner, and therefore, it has been studied as a molecular diagnostic marker[75,76]. To date, frequent promoter hypermethylation and subsequent loss of protein expression has been demonstrated in GC-related

Table 3 Methylated markers in gastric cancer

Symbol (location)	Biological function	Materials	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo* study	Ref.
Early detection										
APBA2 (15q11-12)	Neuronal adapter protein interacting with the Alzheimer's disease amyloid precursor protein	Tissue, Circulating	MSP	90	OS	Size, differentiation, depth, invasive growth, N, CY, stage	-	-	-	[89]
GADD45 (1p31.2)	Responding to environmental stresses	Tissue	QPCR, IHC	138	OS	Stage	-	-	-	[84]
OSR1 (2p24.1)	Development of intermediate mesoderm	Tissue	QPCR, IHC	164	OS	-	Proliferation, cell cycle, apoptosis	β-catenin, TCF-1	-	[94]
RASGRF1 (15q24.2)	Mediator of Ras-GEF signaling pathway	Tissue	QPCR	130	-	-	Proliferation, invasion	-	-	[82]
SPG20 (13q13.3)	Regulating endosomal trafficking and mitochondria function	Tissue, Circulating	IHC, MSP	119	OS	-	-	-	-	[95]
TUSC1 (9p21.2)	Unknown	Tissue	QPCR, IHC	112	OS	Age, sex, depth, vascular invasion, N	-	-	-	[92]
XAF1 (17p13.1)	Inhibitory factor of inhibitor of apoptosis proteins	Tissue, Circulating	QPCR, IHC	202	OS, RFS	Size, depth, N, stage, *Helicobacter pylori*	-	-	-	[85]
Monitoring recurrences										
DENND2D (1p13.3)	Membrane trafficking protein regulating Rab GTPases	Tissue	QPCR, IHC	112	OS, RFS	Age, sex, size, depth, N, stage	-	-	-	[96]
PDSS2 (6q21)	Synthesize the prenyl side-chain of coenzyme Q	Tissue	QPCR, IHC	238	OS, RFS	CA19-9, N	-	-	-	[91]
Prediction of survival										
PAX5 (9p13)	B-cell lineage specific activator protein that is expressed at early stages of B-cell differentiation	Tissue	QPCR	187	OS	Stage	Proliferation, migration, invasion, apoptosis	p53	Yes	[81]
PEBP1 (12q24-23)	Inhibitor of Raf1-mediated phosphorylation	Tissue	IHC	135	OS	Differentiation, N, stage	-	-	-	[93]
RASSF5A (1q32.1)	Suppressor of cell growth in response to activated Ras family	Tissue	QPCR, IHC	132	OS	Differentiation, depth, N, stage	-	-	-	[90]
SOCS4 (14q22.1)	suppressor of cytokine signaling	Tissue	QPCR	50	OS	Depth, N	-	-	-	[80]
SOX17 (8q11.23)	Transcription factor involved in the regulation of embryonic development	Circulating	MSP	73	OS	Differentiation	-	-	-	[83]
TCF21 (6q23.2)	Mesoderm specifictranscription factor	Tissue	QPCR, IHC	200	OS	Differentiation, depth, N	-	-	-	[97]
TFF1 (21q22.3)	Protecting the gastrointestinal mucosa	Tissue	QPCR, IHC	182	OS	Depth	Invasion	-	-	[87,88]
Prediction of treatment response										
RPRM (2q23.3)	Regulator of cell cycles in a p53-dependent manner	Tissue	QPCR	83	OS	Chemoresistance	Proliferation, apoptosis	-	Yes	[86]

Pt: Number of patients enrolled in expression analysis; IHC: Immunohistochemistry; QPCR: Quantitative real-time reverse transcription-polymerase chain reaction; OS: Overall survival; RFS: Recurrence free survival; N: Lymph node metastasis.

TSGs, and their methylation statuses in gastric tissues and blood samples have been proposed as diagnostic markers[5,77]. Because epigenetic alterations are thought to be an early event that possibly precedes gastric carcinogenesis, DNA hypomethylation and CpG island hypermethylation in pre-neoplastic or early neoplastic stages may serve as indicators or biomarkers for screening patients with an increased risk for GC[78,79]. Novel genes proposed as candidates for methylated markers of GC are listed in Table 3[80-97].

Amyloid beta precursor protein-binding, family A, member 2

Amyloid beta precursor protein-binding, family A, member 2 (APBA2) is a multimodular adapter protein encoded by a member of the X11 protein family and functions in membrane transport and organization[98]. Furthermore, APBA2 has been reported to be involved in signal transduction processes and is also regarded as a putative vesicular trafficking protein in the brain that can form a complex with the potential to couple synaptic vesicle exocytosis to neuronal cell adhesion[89]. Han *et al*[89] performed quantitative methylation-specific PCR analysis to detect APBA2 methylation using gastric tissues, peritoneal lavage fluids and blood samples. Notably, methylation of APBA2 was found in approximately 40% of peritoneal lavage fluids and blood samples from patients with GC, but not in healthy controls. In addition, positive methylation in peritoneal lavage fluids and blood samples was associated with peritoneal dissemination, advanced tumor and poor prognosis[89]. Methylation status of APBA2 can be a good biomarker that is applicable in multiple types of samples.

DENN/MADD domain-containing 2D

DENN/MADD domain-containing 2D (DENND2D) regulates Rab GTPases and represents a newly recognized class of membrane trafficking proteins[99]. DENND2D interacts directly with Rab35 and functions as a guanine nucleotide exchange factor for this GTPase[100]. We evaluated the expression level and methylation status of DENND2D in 112 pairs of gastric tissues and found that GC tissues showed a significantly lower mean mRNA expression level and a higher frequency of promoter hypermethylation of DENND2D than corresponding noncancerous tissues[96]. These findings were independent of tumor differentiation, location, and morphology. Downregulation of DENND2D mRNA in GC tissues was significantly associated with factors related to more advanced GC, recurrence and a subsequent poor prognosis[96]. Expression level and methylation status of DENND2D can serve as novel tumor biomarkers that predict progression and early recurrence of all types of GC.

Paired box gene 5

Paired box gene 5 (PAX5) was recently characterized as the key nuclear protein in the paired box-containing family of transcription factors that are involved in control of organ development and tissue differentiation[101]. PAX5 also plays a role in the early stages of B-cell differentiation, as well as neural development and spermatogenesis[102]. Li *et al*[81] investigated the expression, methylation and function of PAX5 in GC cells and tissues. PAX5 was frequently downregulated in GC concomitant with promoter hypermethylation. Artificial forced expression of PAX5 inhibited proliferation, migration and invasion of GC cells, arrested the cell cycle, induced apoptosis, and repressed tumorigenicity in mouse xenografts. The antitumorigenic function of PAX5 was shown to be mediated by upregulating downstream targets of p53, p21, and metastasis suppressor 1 and downregulating BCL2, cyclin D1 and mesenchymal–epithelial transition factor. Hypermethylation of PAX5 was detected in approximately 80% of GC tissues and identified as an independent prognostic factor[81]. PAX5 serves as a TSG, and its methylation status would be a prognostic marker for GC.

Reprimo

Reprimo (RPRM) is a highly glycosylated protein localized predominantly in the cytoplasm, and it has been reported to be a mediator of the cell cycle[103]. Forced expression of RPRM induces G2 arrest of the cell cycle by inhibiting Cdc2 activity and nuclear translocation of the Cdc2–cyclin B1 complex in various cell lines[104]. Ooki *et al*[86] evaluated the epigenetic inactivation of RPRM and its biologic function as well as its clinical relevance in GC. Frequent promoter hypermethylation was specifically detected in GCs. Forced RPRM expression inhibited proliferation, anchorage-independent colony formation of GC cells and enhanced DNA damage-induced apoptosis. Furthermore, the tumor inhibitory effect of RPRM was proven in an *in vivo* study. Methylation of RPRM was significantly associated with a poor response to chemotherapy and poor patient prognosis[86]. RPRM is a novel putative TSG, and promoter methylation of RPRM may serve as a predictive marker for chemotherapy and the malignant behavior of GC.

DIAGNOSTIC POTENTIAL OF miRNAS IN GC

Extensive studies in the past decade have indicated the existence and importance of an additional epigenetic mechanism for regulation of gene function by means of small non-coding miRNAs[105]. Currently, miRNAs are recognized as one of the major regulatory gatekeepers of protein-coding genes in the human genome[106]. Mature miRNAs measuring 20 to 23 nucleotides in length are incorporated into miRNA-induced silencing complexes[107]. These complexes then bind to imperfect complementary sequences in the 3′-untranslated region of target mRNAs and negatively regulate gene expression through either mRNA degradation or translational inhibition[108]. MiRNAs can be released from cancer cells into body fluids *via* secreting exosome particles, which could protect them from RNase degradation in the circulation[108]. With the surprising stability of miRNAs in tissues, serum or other body fluids, miRNAs have emerged as a new type of cancer biomarker with immeasurable clinical potential[12]. Here, we introduce newly identified miRNAs that potentially represent biomarkers for GC

(Table 4)[109-136].

MiR-25

Li *et al*[124] investigated the expression level of miR-25 in plasma and GC tissues and found overexpression of miR-25 in patients with lymph node metastasis. Inhibition of miR-25 significantly suppressed metastasis, invasion and proliferation *in vitro* and reduced the metastatic capacity of GC cells *in vivo* through repression of transducer of ERBB2, 1 expression. Furthermore, patients with high plasma expression of miR-25 had poor prognoses[124]. MiR-25 is related to GC progression through repression of transducer of ERBB2, 1 and may represent a noninvasive biomarker for GC.

MiR-129

It has been reported that miR-129 is a cancer-associated miRNA[137]. In previous studies, miR-129 levels were significantly altered in cancerous tissues, including GC, when compared to noncancerous tissues. MiR-129 has been shown to play an important role in regulating cell proliferation by downregulation of cyclin-dependent kinase 6[118,138]. Yu *et al*[118] assessed the diagnostic values of miR-129-1/2 in gastric secretion samples to propose a new screening tool for GC. After examining 141 secretion samples, patients with GC showed significantly lower levels of miR-129-1 and miR-129-2. Gastric secretions may be a good resource for the molecular diagnosis of GC.

MiR-199a-3p

Li *et al*[115] performed microarray profiling of plasma samples to compare expression patterns in GC patients and healthy controls and to identify circulating miRNAs that may be novel diagnostic markers for GC. MiRNA-199a-3p was found to be significantly elevated in GC patients and was reduced after resection of the primary tumors in the training set. In the validation stage in a large cohort, plasma miR-199a-3p was elevated in GC patients compared to healthy controls, with a high under the receiver operating characteristic curve area (0.837), and was significantly associated with tumor depth, lymph node metastasis and stage[115]. Plasma miRNA-199a-3p was shown to be a potential biomarker both for early detection and progression of GC.

MiR-630

MiR-630 has been reported to be elevated in lung, head and neck, and pancreatic cancers, and reports show that it can modulate chemosensitivity[139]. Chu *et al*[120] examined expression levels of miR-630 in 236 GC and adjacent normal tissues and found that miR-630 was elevated in GC tissues. Increased expression of miR-630 was significantly associated with depth of the tumor, lymph node metastasis, distant metastasis and poor overall survival, indicating that miR-630 may serve as a potential marker for the initiation and progression of GC.

SIGNIFICANCE OF lncRNAS IN GC

The genome sequencing projects revealed that the human genome is composed of less than 2% protein-coding genes and that more than 90% of the genome is transcribed as noncoding RNAs[107,140]. LncRNAs are a class of newly identified noncoding RNAs, > 200 nucleotides in length, that are currently being studied for their roles in cellular processes[141]. Changes in the expression levels of lncRNAs have been increasingly reported in various malignancies, suggesting that lncRNAs may play a role in tumorigenesis and tumor progression[142]. Interestingly, recent studies have suggested that lncRNAs also exist in serum, plasma and other body fluids, and certain lncRNAs have been described as candidate biomarkers[142,143]. Here, we introduce reported GC-related lncRNAs from recent publications (Table 5)[140,142,144-147].

Colon cancer associated transcript 1

Colon cancer associated transcript 1 (CCAT1) was found to be generally upregulated in colon cancer and correlated with the rs6983267 allele, which was associated with increased cancer susceptibility[148]. The MYC enhancer region physically interacts with the promoter region of CCAT1, suggesting that the cancer-associated variant rs6983267 as an MYC enhancer could regulate CCAT1 expression[140]. Additionally, CCAT1 was reported to have a role in cell-cycle regulation and development of colon cancer[148]. Zhang *et al*[140] reported that CCAT1 was upregulated in GC tissues compared to paired adjacent normal tissues and that knockdown of CCAT1 significantly inhibited proliferation of GC cells by inducing G0/G1 cell-cycle arrest, apoptosis and inactivation of the ERK/MAPK signaling pathway. Diagnostic performance of CCAT1 is expected to be evaluated in a large cohort in the future.

Hypoxia inducible factor 1 alpha antisense RNA-2

Hypoxia inducible factor 1 alpha antisense RNA-2 (HIF1A-AS2) is an antisense long noncoding RNA, which is a natural antisense transcript of hypoxia-inducible factor 1alpha (HIF-1α)[149]. Although earlier reports indicated that HIF1A-AS2 plays a crucial role in cancer development, *via* regulation of the cancer-relevant HIF-1α pathway, its oncological role in GC remains to be determined[150,151]. Chen *et al*[146] reported that upregulation of HIF1A-AS2 was found in GC tissues and significantly correlated with tumor depth, lymph node metastasis, advanced stage and poor prognosis. Furthermore, knockdown of HIF1A-AS2 in GC cells inhibited proliferation *in vitro* and tumorigenesis *in vivo*. HIF1A-AS2 may be considered as a promising biomarker for GC.

Gastric adenocarcinoma predictive long intergenic noncoding RNA

Hu *et al*[145] conducted global microarray and in situ

Table 4 Dysregulated microRNAs in hepatocellular carcinoma

Symbol (location)	Materials	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo* study	Ref.
Early detection									
miR-21 (17q23.1)	Circulating	QPCR	103	-	Size, depth	-	-	-	[116]
miR-22 (17p13.3)	Tissue	QPCR	32	-	-	Proliferation, migration, invasion	CD151	-	[117]
miR-29c (1q32.2)	Tissue	QPCR	274	-	-	Proliferation, adhesion, invasion, migration	ITGB1	Yes	[135]
miR-30b (8q24.22)	Tissue	QPCR	21	-	-	Apoptosis	PAI-1	Yes	[134]
miR-106b (7q22.1)	Circulating	QPCR	40	-	Age	-	-	-	[132]
miR-129 (7q32.1)	Gastric juice	QPCR	141	-	-	-	-	-	[118]
miR-141 (12p13.31)	Tissue	QPCR	30	-	-	Proliferation, migration, invasion	HDGF	-	[119]
miR-148a (7p15.2)	Tissue	QPCR	64	-	Size	-	-	-	[127]
miR-181c (19p13.13)	Tissue, circulating	QPCR	30	-	-	-	-	-	[113]
miR-191 (3p21.31)	Tissue, circulating	QPCR	75	-	T, stage	Proliferation, migration, invasion, cell cycle	-	-	[126]
miR-199a-3p (12)	Tissue, circulating	QPCR	180	-	T, N, stage	-	-	-	[115]
miR-223 (Xq12)	Circulating	QPCR	60	-	*Helicobacter pylori*	-	-	-	[109]
miR-233 (X)	Circulating	QPCR	50	-	Size, differentiation, stage	-	-	-	[130]
Monitoring recurrences									
miR-26a (3p22.2)	Tissue	QPCR	40	OS, RFS	N, stage	Proliferation, metastasis	FGF9	Yes	[114]
miR-34b/c (11q23.1)	Noncancerous tissue	Pyrosequencing	129	RFS	Age	-	-	-	[128]
miR-185 (22q11.21)	Tissue	QPCR	126	OS, RFS	N, stage	Proliferation, metastasis	-	Yes	[129]
miR-196a (17q21.32)	Tissue, circulating	QPCR	72	-	-	Migration, invasion	-	-	[110]
miR-200c (12p13.31)	Circulating	QPCR	52	OS, PFS	-	-	-	-	[111]
miR-222 (Xp11.3)	Circulating	QPCR	114	OS, RFS	N, stage	-	-	-	[121]
Prediction of survival									
miR-25 (7q22.1)	Tissue, circulating	QPCR	70	OS	N, stage	Proliferation, migration, invasion	TOB1	Yes	[124]
miR-132 (17p13.3)	Tissue	QPCR	79	OS	Lymphovascular invasion, N, stage	-	-	-	[125]
miR-183 (7q32.2)	Tissue	QPCR	80	-	Depth, N, stage	Proliferation, migration, invasion, apoptosis	PDCD4	-	[122]
miR-192 (11q13.1)	Tissue	QPCR	38	-	Sex, vascular invasion, N	Invasion	-	-	[136]
miR-214 (1q24.3)	Tissue	QPCR	80	-	Size, N	Proliferation, migration, invasion	CSF1	-	[131]
miR-630 (15q24.1)	Tissue	QPCR	236	OS	Depth, N, stage	-	-	-	[120]
Prediction of treatment response									
miR-17-5p (13q31.3)	Circulating	QPCR	65	OS	Differentiation, stage	-	-	-	[112]
miR-27a (19p13.13)	Circulating	QPCR	82	OS	Chemoresistance	-	-	-	[123]

Pt: Number of patients enrolled in expression analysis; QPCR: Quantitative real-time reverse transcription-polymerase chain reaction; OS: Overall survival; RFS: Recurrence free survival; PFS: Progression free survival; N: Lymph node metastasis.

Table 5 Gastric cancer-associated long non cording RNAs

Symbol (location)	Materials	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo* study	Ref.
Early detection									
CUDR (19p13.12)	Circulating	QPCR	106	OS	-	-	-	-	[142]
HOTAIR (12q13.13)	Tissue	QPCR	60	-	Perineural invasion, stage	-	-	-	[144]
Prediction of survival									
BLACAT1 (1q32.1)	Tissue	QPCR	85	OS	Size, N, stage	Proliferation, migration, invasion	-	-	[147]
CCAT1 (8q24.21)	Tissue	QPCR	62	-	Size, stage	Proliferation, apoptosis	ERK/MAPK pathway	-	[140]
GAPLINC (18)	Tissue	Microarray	90	OS	Size, N	Proliferation, migration	CD44	-	[145]
HIF1A-AS2 (14q23.2)	Tissue	QPCR	83	OS	Depth, N, stage	Proliferation	-	Yes	[146]

Pt: Number of patients enrolled in expression analysis; QPCR: Quantitative real-time reverse transcription-polymerase chain reaction; OS: Overall survival; N: Lymph node metastasis.

hybridization analyses to explore novel GC-related lncRNAs and identified gastric adenocarcinoma predictive long intergenic noncoding RNA (GAPLINC) as an aberrantly expressed lncRNA. Suppression of GAPLINC led to alterations in cell migration pathways, particularly in CD44. GAPLINC induced increased the cell migration and proliferation abilities of GC cells, and the positive effects of GAPLINC were neutralized by suppression of CD44[145]. Patients with high GAPLINC expression in GC tissues had a significantly worse prognosis, suggesting that GAPLINC may represent a promising biomarker for GC.

CONCLUSION

Exhaustive research performed over recent years and the development of new genetic technologies have built the foundation for a better understanding of the molecular pathogenesis of GC[18,19]. This review aimed to describe the relevance of genomics as a novel diagnostic and prognostic tool in GC, to give an overview of epigenetics in GC (methylation, miRNA and lncRNA) and to discuss how the application of molecular data to the management of GC might improve the accuracy of prognosis prediction and lead to more efficient personalized treatments for GC.

Improvement of the treatment outcomes for GC in the future is dependent on the development of sophisticated biomarkers[8,17]. High-performance biomarkers for early detection, potential distant metastasis and prediction of chemosensitivity, recurrence and prognosis enable personalized therapy[152]. Even with many putative biomarker molecules identified, the outcomes for GC patients remain dismal due to modest improvements in clinical treatment strategies. Increased translational medicine efforts should be made to globally encourage standardized systematic biomarker validation studies in GC. On the basis of recent data, this review highlights the potential of recently reported molecular markers as biomarkers for GC and explores their relationship to disease susceptibility, diagnosis, prognosis and response to treatment.

Despite these encouraging results, there are still many issues to be resolved in the field of GC-related molecular biomarker research. First, a major challenge to identifying reliable biomarkers is inter-individual variability of expression levels influenced by various factors such as pathology, hypoxia, infection and cytotoxic treatment, response to targeted therapy and drug resistance[8]. Second, there is not yet enough data available on circulating molecular profiles to be used as potential biomarkers for the diagnosis and prognosis of GC. Ultimately, blood samples can represent noninvasive screening tools without other invasive procedures such as endoscopy and surgery. Third, we require more robust platforms and quick analytical methods because DNA/RNA extraction and bisulfite conversion is too time-intensive for clinical use. Finally, most studies demonstrating the diagnostic potential of molecular markers have involved small sample sets. Thus, these candidate molecules must be validated in large independent cohorts to confirm the existence of a predictive value.

Although there are still many challenges in the field of GC-related molecular biomarker research, the accumulation of genetic and epigenetic data is of key importance to improve the diagnosis and management of GC and overcome this disease in the future.

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