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REVIEW **Open Access**

Update on molecular biomarkers for diagnosis and prediction of prognosis and treatment responses in gastric cancer

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Summary. Gastric cancer (GC) is one of the leading causes of cancer-related deaths worldwide, and its high mortality rate is a serious problem in many regions. To improve prognosis, it is necessary to identify novel biomarkers for the early detection of GC, along with its prognosis, risk of metastatic recurrence, and predicted response to chemotherapy, and to develop individualized treatment strategies. Advances in microarray and sequencing techniques have led to the elucidation of cancer-related gene mutations and aberrant expression levels, which have deepened our knowledge of GC. Further searches for sensitive biomarkers are needed to improve the management of patients with GC. In this review article, we update the current knowledge of GC biomarkers, examine recently published literature, and introduce some representative molecules.

Key words: Gastric cancer, Biomarker, Prognosis, Expression

Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide and is the third leading cause of cancer-related deaths, resulting in approximately 800,000 deaths each year, making it an important global health issue (Bray et al., 2018). The understanding of the pathogenesis, diagnosis, and treatment of GC is constantly improving. However, the prognosis of advanced GC is still poor due to its high recurrence rate after resection and its resistance to chemotherapy at recurrence (Kanda et al., 2018a). To improve GC's prognosis, it is desirable to establish useful prognostic markers to guide the early detection and treatment efficacy of GC. The tumor-node-metastasis (TNM) classification is currently used in clinical practice to assess the risk of GC, and carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19–9 are widely used as serum tumor markers to estimate GC's grade of malignancy, its recurrence, and the predicted effects of treatment. However, we often experience a clinical course that differs from the TNM classification, where the CEA and CA19-9 values do not necessarily reflect the clinical features (Kanda et al., 2020a,b); their role is limited due to their insufficient sensitivity and specificity in the early identification of GC, its recurrence, and its prognosis (Baniak et al., 2016; Kanda et al., 2018b).

GC is a heterogeneous disease at the clinical and molecular levels (Wadhwa et al., 2013). Genes involved in the development and progression of GC have been identified, and there have been many reports of genetic changes involved in the malignancy of GC. Recently, next-generation sequencing technology and bioinformatic analyses have been widely used to screen genetic alterations. These developments will advance our understanding of GC, contribute to the further development of therapeutic strategies, and lead to improved prognosis.

The purpose of this paper is to describe the latest findings on GC biomarkers. We focused on and reviewed the most recent GC biomarkers reported between 2018 and 2020 (Fig. 1). In addition, these identified molecules were classified as follows: oncogenes, tumor suppressor genes (TSGs), methylated DNA, microRNAs (miRNAs), and long non-coding RNAs (lncRNAs). Further, we addressed their clinical applications that may lead to early detection, the monitoring of recurrence, and the ability to predict patient survival and treatment responses. For each category, some characteristic molecules are described and introduced below.

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Protein coding genes overexpressed in GC

Oncogenes play an important role in carcinogenesis and are involved in cancer cell proliferation, invasion, and migration. Identification of genes that are highly expressed in comparison to normal tissues and blood may be useful for the early detection of GC and for estimating its grade of malignancy (Kanda et al., 2018 c). The following list of genes has been reported to be overexpressed in GC (Table 1). The key genes that should be mentioned are briefly described below (Ajani et al., 2018; Fang et al., 2018; Kanda et al., 2018c,d; Kasurinen et al., 2018; Kiyozumi et al., 2018; Sawaki et al., 2018; Shimizu et al., 2018; Ueta et al., 2018; Xu et al., 2018a,b; Jiang et al., 2019; Liu et al., 2019, 2020; Miwa et al., 2019; Qiao et al., 2019; Takeuchi et al., 2019; Yuan et al., 2019; Cai et al., 2020; Lu et al., 2020; Nakamura et al., 2020; Necula et al., 2020; Wang et al., 2020; Wu et al., 2020; Zhang et al., 2020; Zhiwei et al., 2020).

Collagen Type X Alpha 1 Chain (COL10A1)

COL10A1 is a member of the collagen family involved in tissue architecture and acts as a barrier to the migration of epithelial cells under normal conditions. COL10A1 is a gene with limited expression in most normal tissues and elevated expression in several tumor types (Huang et al., 2018). Increased levels of stromal COL10A1 are correlated with a poor pathologic response in ER+/HER2+ breast tumors (Brodsky et al., 2016). Necura et al. found a significant increase in COL10A1 gene expression and protein levels in gastric tumor tissues compared to adjacent normal tissues. COL10A1 appears to show elevated expression from the beginning of carcinogenesis, in the early stages, and its increased level remains elevated during cancer progression. A significant increase in COL10A1 plasma levels in gastric adenocarcinoma patients was also identified. Increased COL10A1 plasma levels were associated with poor patient survival (Necula et al., 2020). Circulating expression levels of COL10A1 were significantly increased in gastric adenocarcinoma patients; these expression levels are associated with poor survival and act as potential biomarkers for the early detection of GC.

Synaptotagmin XIII (SYT13)

SYT13 resides on human chromosome 11p11.2, and encodes a predicted single-pass 47-kDa transmembrane protein (Poser Von et al., 2001). The synaptotagmin family includes proteins that mediate membrane trafficking (Jahn and Coleman, 2008). SYT13 lacks the extracellular N-terminus and critical residues required for calcium binding (Jahn et al., 2010). These distinctive characteristics, as well as their widespread distribution in the brain, indicate that SYT13 is involved in constitutive vesicular transport (Jahn et al., 2010), but little is known about its role in cancer. We identified SYT13 as a candidate molecule that contributes to the formation of peritoneal metastasis in patients with GC. Transcriptome

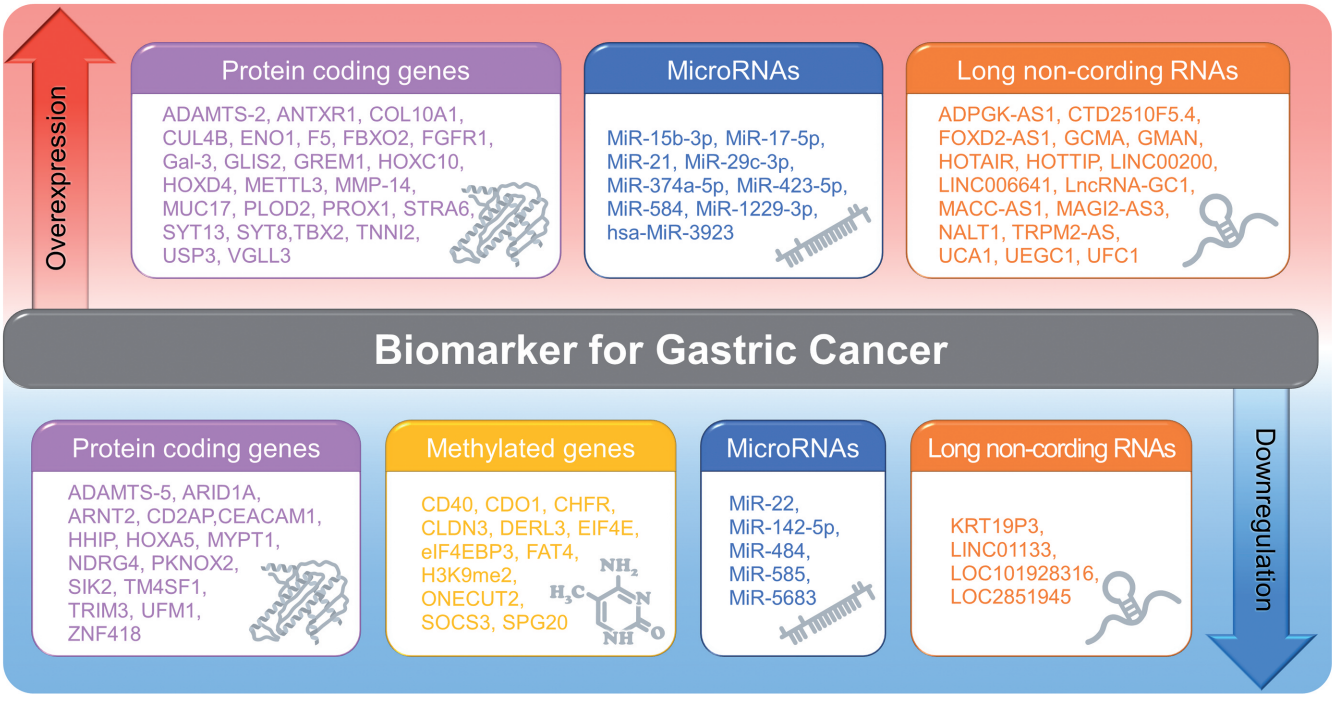

Fig. 1. Overview of current molecular biomarkers for GC.

Table 1. Genes up-regulated in gastric cancer.

Symbol (location)	Biological function	Specimen	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo*	Reference
Early detection										
COL10A1 (6p22.1)	tissue architecture	Tissue, Circulating	QPCR WB	49	OS	Stage	(-)	(-)	(-)	Necula et al., 2020
Monitoring recurrences										
CEACAM1 (19q13.2)	Transmembrane protein and cell-cell adhesion	Tissue	IHC	235	OS	Peritoneal metastasis	Proliferation invasion	TGF-β	Yes	Takeuchi et al., 2019
HOXC10 (12q13.3)	Morphogenesis in multicellular organisms	Tissue	QPCR	300	OS	Hepatic and peritoneal metastases	Proliferation, invasion, migration, apoptosis	SOX10, FGFBP1, MAPK	Yes	Miwa et al., 2019
PLOD2 (3q24)	Mediates extracellular matrix	Tissue	QPCR IHC, WB	179	OS DFS	Peritoneal metastasis	Proliferation, invasion, migration	HIF-1	(-)	Kiyozumi et al., 2018
SYT13 (11p11.2)	Membrane trafficking protein	Tissue	QPCR, IHC	200	OS DFS	Peritoneal metastasis	Proliferation, invasion, migration, apoptosis	(-)	Yes	Kanda et al., 2018a-d
SYT8 (11p15.5)	Neurotransmission and hormone secretion	Tissue	QPCR, IHC	227	OS	Peritoneal metastasis	Invasion, migration	(-)	Yes	Kanda et al., 2018a-d
TNNI2 (11p15.5)	Calcium-sensitive regulation of contraction	Tissue	QPCR, IHC	262	OS	Peritoneal metastasis	(-)	TIMP1, VPS13A	(-)	Sawaki et al., 2018
Prediction of survival										
ADAMTS2 (5q23-24)	Cleaves the propeptides of type I and II collagen	Tissue	IHC	655	OS	Lauren classification, stage, vascular invasion, depth, N, age, Her2	(-)	(-)	(-)	Jiang et al., 2019
ANTXR1 (2p13.3)	Cell attachment and migration	Tissue	QPCR, IHC, WB	103	OS	Depth, N, stage	Proliferation, invasion, migration, apoptosis	PI3K/AKT/mTOR	Yes	Cai et al., 2020
CUL4B (Xq24)	gene expression, DNA damage and cell cycle	Tissue	QPCR, IHC	190	OS DFS	Differentiation, M, stage	Proliferation, invasion, tumorigenicity	DDB1, RBX1	Yes	Wu et al., 2020
ENO1 (1p36.23)	The synthesis of pyruvate	Tissue	QPCR, IHC, WB	94	OS DFS	Differentiation, depth, N, stage	Proliferation, apoptosis, colony formation	c-FOS, SBFS, MAP3K20, DET1	(-)	Qiao et al., 2019
F5 (1q24.2)	Blood coagulation cascade	TCGA dataset		351	OS	Stage	(-)	metabolic pathway,	(-)	Liu et al., 2020
FBXO2 (5p13.1)	Mediates the ubiquitination	Tissue	QPCR, IHC, WB	89	OS	N	Proliferation, invasion, migration, EMT	(-)	(-)	Sun et al., 2018a,b
FGFR1 (8p11.23)	Fibroblast growth factor receptor	Tissue	QPCR, WB	395	OS RFS	Lauren classification, depth, M, undifferentiated type, CY/P positive	Proliferation, invasion, migration,	EMT, CDH1, SNAI1, VIM, ZEB1	(-)	Shimizu et al., 2018
Gal-3 (14q22.3)	b-galactoside binding protein	Tissue	IHC, WB	184	OS RFS	Lauren classification, differentiation	Proliferation, invasion, migration	YAP1/BET	(-)	Ajani et al., 2018
GREM1 (15q13.3)	Regulating angiogenesis	Tissue	QPCR, WB	321	OS PFS	Depth, N, stage	Proliferation, adhesion, invasion, migration	BMP, EMT	(-)	Sun et al., 2020
HOXD4 (2q31.1)	Early embryo development and cell differentiation	Tissue	QPCR, IHC	127	DFS	Tumor size, depth, N	Proliferation, invasion, migration	c-Myc, cyclin D1	(-)	Liu et al., 2019
METTL3 (14q11.2)	mRNA stability, processing, translation efficiency and editing	Tissue	QPCR, WB	83	OS	N, stage	Proliferation, angiogenesis, invasion, migration, glycolysis	HDGF, GLUT4, ENO2	Yes	Wang et al., 2020
MMP14 (14q11.2)	Breakdown of extracellular matrix	Circulating	ELISA	240	DFS	M, stage	(-)	(-)	(-)	Kasurinen et al., 2018
PROX1 (1q32.3)	Transcription regulator	Tissue	IHC, WB	99	OS RFS	N, stage, lymphatic invasion, vascular invasion	Proliferation, invasion, migration	(-)	(-)	Ueta et al., 2018
STRA6 (15q24.1)	Retinol transporter	Tissue	QPCR	228	OS DFS	Stage	(-)	JAK2/STAT3	(-)	Nakamura et al., 2020
USP3 (15q22.3)	Regulates p53 stability	Tissue	QPCR, IHC	147	OS DFS	Lauren classification, depth, N, M, stage, differentiation, vascular invasion	Proliferation, invasion, migration, cell cycle	cyclinsD E, MMP-2	Yes	Fang et al., 2018
VGLL3 (3p12.1)	Transcription factor	Tissue	IHC	317	OS	Depth, stage, histological grade	(-)	MAPK, JAK/STAT, WNT	(-)	Zhang et al., 2020
Prediction of treatment response										
GLIS2 (16p13.3)	Promotes neuronal differentiation	TCGA dataset		238	OS DFS	Histological type, depth, stage, microsatellite instability, drug response	(-)	TGF-β, p53	(-)	Yuan et al., 2019
TBX2 (17q23.2)	Embryonic development	Tissue	WB	401	OS RFS	Lymphovascular invasion, lymph node metastasis	(-)	(-)	(-)	Lu et al., 2020

Pt, number of patients; QPCR, quantitative real-time reverse transcription-polymerase chain reaction; IHC, immunohistochemistry; WB, western blotting; ELISA, Enzyme-Linked Immuno-Sorbent Assay; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; stage; RFS, relapse-free survival; UICC stage.

analysis revealed that SYT13 was expressed at significantly higher levels in patients with peritoneal recurrence. Inhibition of SYT13 expression in a GC cell line was associated with decreased invasion and migration ability of the cells. Intraperitoneal administration of siSYT13 significantly inhibited the growth of peritoneal nodules and prolonged survival in mice. Patients with high SYT13 expression experience shorter overall survival (OS) and recurrence-free survival (RFS). A high level of SYT13 expression in primary GC tissues was an independent risk factor for peritoneal recurrence (Kanda et al., 2018d). These findings suggest that SYT13 expression in GC is associated with peritoneal metastases and is a potential target for treatment.

Anthrax toxin receptor 1 (ANTXR1)

Anthrax toxin receptor 1 (ANTXR1), a type I transmembrane protein, is one of the receptors that facilitates the entrance of anthrax toxin into cells. ANTXR1 is overexpressed in tumor cells and the vasculature of developing carcinoma. However, the biological function of ANTXR1 in GC remains unknown. Cai et al. found that ANTXR1 expression was significantly upregulated in GC tissues, and its overexpression was associated with poor prognoses in GC patients. A high protein expression level of ANTXR1 was positively associated with tumor depth, lymph node metastasis, clinical stage, and shorter OS in GC patients. Silencing ANTXR1 increased the percentage of G0/G1 phase cells and reduced S phase cells, whereas overexpression of ANTXR1 significantly decreased the percentage of G0/G1 phase cells and increased the proportion of S phase cells. ANTXR1 induced proliferation, cell cycle progression, invasion and migration, and tumorigenicity; it induced suppressed apoptosis in GC, and exerted its promoting effects on GC through activation of the PI3K/AKT/mTOR signaling pathway. Overexpression of ANTXR1 promoted tumor growth in a nude mouse model (Cai et al., 2020). These findings suggest that ANTXR1 plays a crucial role in the development and progression of GC and mightserve as a novel prognostic biomarker and potential therapeutic target for GC.

Matrix metalloproteinase-14 (MMP-14)

Matrix metalloproteinases (MMPs), which are zinc-containing genetically distinct but structurally related endopeptidases, exhibit diverse biochemical functions, such as the capability to promote cancer cell invasion and the formation of metastases (Egeblad and Werb, 2002). Among the 26 identified MMPs, matrix metalloproteinase-14 (MMP-14), also known as membrane-type matrix metalloproteinase-1, belongs to the membrane-bound MMP family. Kasurinen et al. revealed a positive association between a high serum MMP-14 level and cancer stages III–IV, and between high serum MMP-14 and distant metastasis. Furthermore, survival was worse among patients with a high serum MMP-14, particularly among men, patients with pT3–4 tumors, in the presence of lymph node metastases, or when accompanying an intestinal cancer. The serum MMP-14 level remained an independent prognostic factor in multivariate survival analyses (Kasurinen et al., 2018). These results indicate that high serum soluble MMP-14 levels in GC serve as a marker for its poor prognosis, possibly indicating the presence of distant metastases.

Methyltransferase like3 (METTL3)

N^6-methyladenosine (m^6A) RNA methylation and its associated methyltransferase METTL3 are involved in tumor initiation and progression via the regulation of RNA function (Meyer and Jaffrey, 2014). Wang et al. found that the level of m^6A RNA was significantly increased in GC, and METTL3 was the main regulator involved in the abundant m^6A RNA modification. METTL3 expression was significantly elevated in GC tissues and was associated with poor prognosis. Patients with GC with increased METTL3 mRNA levels had worse overall survival (OS). The protein expression of METTL3 in the GC cohort was significantly correlated with clinicopathological features such as lymph node metastasis, as well as tumor, node, and metastases (TNM) stages. A multivariate Cox regression analysis revealed that METTL3 expression was an independent prognostic factor and an effective predictor in human patients with GC. Knockout or knockdown of METTL3 obviously suppressed the efficiency of soft agar colony formation as well as its clonogenic ability. METTL3 overexpression promoted GC proliferation and liver metastasis *in vitro* and *in vivo*. Moreover, METTL3 promotes GC malignant progression through the upregulation of HDGF expression (Wang et al., 2020). They concluded that elevated METTL3 expression promotes tumor angiogenesis and glycolysis in GC, indicating that METTL3 expression is a potential prognostic biomarker and therapeutic target for human GC.

Protein coding genes downregulated in GC

TSGs are involved in DNA damage repair, the inhibition of cell division, the induction of apoptosis, and the suppression of metastasis. Uncontrolled cell growth and the ability to invade other tissues are the result of silencing TSGs. The expression levels of TSGs can serve as diagnostic molecular biomarkers for the early detection and progression of GC (Sun and Yang, 2010). Table 2 provides a list of recently reported downregulated genes without DNA hypermethylation in GC (Fu et al., 2018; Hui et al., 2018; Peng et al., 2018a,b; Sun et al., 2018a,b; Wang and Sun, 2018; Zhang et al., 2018c,d, 2019; Ashizawa et al., 2019; Huang et al., 2019a,b; Jia et al., 2019; Lin et al., 2019;

Yang et al., 2019; Dai et al., 2020; Xie et al., 2020).

Tripartite motif-containing 3 (TRIM3)

Tripartite motif-containing 3 (TRIM3) is a member of the TRIM protein family, which maps to chromosome 11p15.5 (El-Husseini et al., 1999). TRIM proteins are one of the subfamilies of the RING-type E3 ubiquitin ligases, which are regarded as critical regulators of neoplastic processes. These proteins play important roles in a variety of biological processes, such as cell proliferation, cell differentiation, DNA repair,

Table 2. Genes suppressed in gastric cancer.

Symbol (location)	Biological function	Specimen	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo*	Reference
Early detection										
MUC17 (7q22.1)	Mucosal barrier	Tissue	QPCR, IHC	163	OS	Age, differentiation, depth, N	Proliferation, cell cycle	CDX1, NFkB, myosin-9, p53, RhoA, p38	Yes	Yang et al., 2019
Monitoring recurrences										
TRIM3 (11p15.5)	Regulators of neoplastic processes	Circulating	QPCR, IHC, WB	160		(-)	Proliferation, migration	miR-20a	Yes	Fu et al., 2018
Prediction of survival										
ADAMTS5 (21q21.3)	Tumor suppressor	Tissue	QPCR, IHC	176	OS	Gender, histological type, differentiation, M, stage, vascular invasion	Adhesion Invasion, migration, wound healing,	ETS1	(-)	Huang et al., 2019a,b
ARID1A (1p36.11)	Transcriptional activation	Tissue	IHC	420	OS	Depth, stage, lymphatic invasion, venous invasion	(-)	PD-L1, p53	(-)	Ashizawa et al., 2019
ARNT2 (15q25.1)	Transcription factor	Tissue	QPCR, IHC, WB	89	OS	Gender, differentiation, depth	Proliferation	PI3K/AKT, Bcl-2	(-)	Jia et al., 2019
CD2AP (6p12.3)	Regulating cytoskeleton assembly and intercellular adhesion	Tissue	IHC, WB	564	OS DFS	Lauren classification, bowman's type pathological type, Depth, N, stage	Proliferation, adhesion, invasion, migration	CAPZA1	(-)	Xie et al., 2020
HHIP (4q31.21)	Mediators of many fundamental processes	Tissue	QPCR, IHC	165	OS DFS	N, stage, nervous system invasion	Invasion, migration,	(-)	(-)	Sun et al., 2018a,b
HOXA5 (7p15.2)	Regulating human embryonic development	Tissue	QPCR, IHC, WB	81	OS	Histological grade, tumor site	Proliferation	p21, c-Myc, Ki-67	Yes	Peng et al., 2018a,b
MYPT1 (12q21.2)	Regulating the depolymerization	Tissue, Circulating	QPCR, WB	68	OS	Stage	Proliferation, invasion, migration, cell cycle	E-cadherin, TIMP-2, MMP-2	(-)	Wang and Sun, 2018
NDRG4 (16q21)	Regulation of mitogenic signalling	Tissue	QPCR, IHC	286	OS DFS	Differentiation, depth, N, M, stage	Proliferation, apoptosis, colony formation	PI3K/AKT	(-)	Zhang et al., 2018a-d
PKNOX2 (11q24.2)	Transcription factor	Tissue	QPCR	28	OS	(-)	Proliferation, invasion, migration, apoptosis, cell cycle	IGFBP5, p53	Yes	Zhang et al., 2019
SIK2 (11q23.1)	Regulator in intracellular signaling pathways	Tissue	QPCR, IHC, WB	180	OS	N, stage, lymphatic invasion, venous invasion	Invasion, migration	AKT/GSK3β β-catenin PHLPP2, PP2A	Yes	Dai et al., 2020
TM4SF1 (3q25.1)	Regulation of cell development, activation, growth and motility	Tissue	IHC, WB	152	OS	Lauren classification, depth, N, stage	(-)	(-)	(-)	Peng et al., 2018a,b
UFM1 (13q13.3)	Regulation of tumor development	Tissue	QPCR, IHC, WB	437	OS	Stage	Invasion, migration	PDK1, PI3K/AKT	Yes	Lin et al., 2019
ZNF418 (19q13.43)	Transcriptional repressor	Tissue, Circulating	QPCR	84	OS	Depth, stage	(-)	(-)	(-)	Hui et al., 2018

Pt, number of patients; QPCR, quantitative real-time reverse transcription-polymerase chain reaction; IHC, immunohistochemistry; WB, western blotting; OS, overall survival; DFS, disease-free survival; stage, UICC stage.

transcriptional regulation, and apoptosis (Hatakeyama, 2011). Fu et al. found that the expression levels of TRIM3 mRNA and protein were decreased in GC tissues compared to the matched control tissues. In addition, the TRIM3 protein levels in the serum exosomes of GC patients were lower than in healthy controls. Overexpression of TRIM3 markedly upregulated E-cadherin expression and downregulated N-cadherin and vimentin expression. Exosomal TRIM3 inhibits the proliferation and migration of GC cells *in vitro*. Moreover, TRIM3 knockdown promoted the growth and metastasis of GC *in vitro* and *in vivo* through the regulation of stem cell factors and epithelial-mesenchymal transition (EMT) regulators. Exosome-mediated delivery of TRIM3 protein might suppress GC growth and metastasis *in vitro* and *in vivo* (Fu et al., 2018). These findings suggest that exosomal TRIM3 may serve as a biomarker for GC diagnosis, and the delivery of TRIM3 by exosomes may provide a new avenue for GC therapy.

Ubiquitin fold modifier 1 (UFM1)

UFM1 is a small molecule ubiquitin protein that was first discovered by Komatsu et al. in 2004. It consists of 85 amino acids and has a modification function similar to that of ubiquitin, which is covalently bound to other proteins such as ubiquitin molecules. UFM1 and its modification system are involved in a variety of pathophysiological processes, and participate in biological processes such as cell cycle, cell survival, hypoxia tolerance, and fatty acid β oxidation (Ha et al., 2011). Lin et al. found that the transcription levels and protein expression levels of UFM1 in GC tissues were significantly downregulated compared to the corresponding adjacent tissues. The downregulation of UFM1 expression was closely related to the more advanced TNM stage, and GC patients with low expression levels of UFM1 had a poor prognosis. High expression of UFM1 had an inhibitory effect on the tumorigenicity, invasion, and migration of GC cells *in vitro* and *in vivo*. Furthermore, UFM1 can inhibit the phosphorylation of AKT and downstream GSK3β by binding to PDK1 and increasing its ubiquitination, thereby inhibiting EMT of GC cells and exerting a tumor suppressor function (Lin et al., 2019). These findings indicate that UFM1 may be a potential new marker for the treatment of GC.

Myosin phosphatase target subunit 1 (MYPT1)

MYPT1 serves as a subgroup of myosin phosphatases and contains a C-terminal leucine zipper domain, which can regulate depolymerization and protein interaction (Tan et al., 2001). The MYPT family plays important roles in the development of diseases such as cancer, hypertension, and Parkinson's disease (Grassie et al., 2011). Wang et al. found that MYPT1 was downregulated in GC tissues. MYPT1 expression was significantly decreased in phase I and II compared with normal tissues, and was significantly downregulated in phases III and IV compared to phase I and II. Furthermore, MYPT1 expression was higher in postoperative patients than in preoperative patients. GC patients with high MYPT1 expression had dramatically longer survival times compared to those with low MYPT1 expression. Overexpression of MYPT1 can inhibit cell proliferation, cell cycle progression, and migration and invasion of GC cells, and can suppress RhoA phosphorylation (Wang and Sun, 2018). They concluded that MYPT1 might serve as a novel prognostic marker and candidate drug target for GC.

Methylated DNA

In the human genome, there are approximately 28 million CpG sites, of which approximately 70% are methylated in normal somatic cells. Unmethylated CpG sites within promoter CpG islands provide a binding platform for the complements of transcription factors to control gene activity. The hypermethylation of CpG islands is frequently associated with silencing of TSGs, genes that control cell growth, and downstream signaling pathways. Epigenetic alterations, such as DNA methylation of CpG islands, play an important role in the regulation of expression cancer-associated genes and may be initial events that precede the development of GC. Therefore, DNA hypermethylation of CpG islands in preneoplastic and early neoplastic periods may serve as molecular biomarkers to identify patients with an increased risk of GC (Skvortsova et al., 2019). We have summarized in Table 3 the aberrant DNA methylation detected in the cancerous tissue or serum of GC patients. The findings from several studies listed in Table 3 are summarized below (Ge et al., 2018; Sun et al., 2018b; Zhang et al., 2018d; Dai et al., 2019; Harada et al., 2019; Li et al., 2019b, 2020b; Wei et al., 2019; Amini et al., 2020; Han et al., 2020; Seo et al., 2020; Zhai et al., 2020).

ONECUT2 (OC2)

The ONECUT family in mammals is comprised of three members: OC1, OC2, and OC3. The encoded proteins activate genes involved in controlling cell differentiation in the liver and pancreas as well as the patterning of trigeminal sensory neurons (Hodge et al., 2007). However, the role of OC2 in GC is not well defined. Seo et al. validated the hypomethylation of the promoter-proximal DNA of OC2 in 160 primary GCs, in which the methylation level correlated negatively with OC2 mRNA level. Intestinal metaplasia (IM) and GC cells stained positively for OC2. Stable transfection of OC2 in GC cells promoted colony formation, cell migration, invasion, and proliferation. Moreover, OC2 knockdown with short hairpin RNA suppressed tumorigenesis in nude mice. Chromatin immuno-precipitation coupled with DNA sequencing and RNA-

seq analyses revealed that OC2 triggered ACSL5, which is strongly expressed in the IM of the stomach but not in the gastric mucosa. OC2 and ACSL5 may cooperate to promote intestinal differentiation or the development of GC (Seo et al., 2020). These results indicate that OC2 and its downstream target ACSL5 might be used to develop early detection biomarkers and to prevent gastric carcinogenesis.

Eukaryotic translation initiation factor 4E binding protein 3 (eIF4EBP3)

eIF4EBP3 is located on chromosome 5q31.3, and is the last identified member of the family of mammalian eukaryotic translation initiation factor 4E binding proteins, which includes three 4E-BP homologs in mammals: 4EBP1, 4EBP2, and 4EBP3 (Peter et al., 2015). eIF4EBPs bind to eukaryotic translation initiation factor 4E (eIF4E) and regulate its assembly into EIF4F, a multi-subunit translation initiation factor that recognizes the mRNA cap structure (Siddiqui and Sonenberg, 2015). Zhai et al. elucidated that eIF4EBP3 plays a TSG role in GC and found that the expression level of eIF4EBP3 was downregulated in GC due to methylation in the promoter region and was associated with poor survival and tumor progression. eIF4EBP3 protein expression was significantly correlated with TNM stage and pathologic differentiation. Ectopic expression of

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*	Reference
Early detection										
CD40 (20q11.23)	Induction of isotype switching and affinity maturation	Tissue	MSP	25	OS	Stage	(-)	(-)	(-)	Amini et al., 2020
DERL3 (22q11.23)	Degradation of misfolded glycoprotein	TCGA dataset		397	OS	Stage, race, gender, age, tumor grade	Proliferation, invasion	TNFRSF17, ADAM6, PIM2	(-)	Li et al., 2020a-c
ONECUT2 (18q21.31)	Controlling cell differentiation	Tissue	QPCR, IHC	160		(-)	Proliferation, invasion, migration,	ACSL5	Yes	Seo et al., 2020
SOCS3 (17q25.3)	Regulation of cytokines	Tissue	Methylation-sensitive high-resolution melting assay	751		Tumor site, histological type differentiation, helicobacter pylori	(-)	STAT1	(-)	Han et al., 2020
SPG20 (13q13.3)	Protein binding	Tissue, Circulation	QPCR, MSP	120		(-)	(-)	JAK/STAT	(-)	Wei et al., 2019
Prediction of survival										
CDO1 (5q22.3)	Iron-containing metalloenzyme	Tissue	QPCR, MSP	138	OS	Age, depth, N, P, CY, stage, lymphatic invasion, venous invasion	Proliferation	(-)	(-)	Harada et al., 2019
CHFR (12q24.33)	Controlling chromosomal instability	TCGA, GEO dataset		1994	OS	Differentiation	(-)	(-)	(-)	Dai et al., 2019
CLDN3 (7q11.23)	Formation, integrity and function of tight junctions	Tissue	IHC, MSP	122	OS	Lauren classification, stage	(-)	(-)	(-)	Zhang et al., 2018a-d
EIF4E (4q23)	Translation initiation	TCGA dataset		269	OS	Age, depth, stage	(-)	(-)	(-)	Ge et al., 2018
eIF4EBP3 (5q31.3)	Translation initiation	Tissue	QPCR, IHC, WB	151	OS	Differentiation, stage	Proliferation, invasion, migration	eIF4E/β-catenin	Yes	Zhai et al., 2020
H3K9me2	Regulating gene expression	Tissue	IHC	133	PFS	Differentiation, N, stage	(-)	(-)	(-)	Li et al., 2019a,b
Others										
FAT4 (4q28.1)	Controlling the size of organs	Circulating	Methylation-sensitive high-resolution melting assay	769		(-)	(-)	SOX11	(-)	Sun et al., 2018a,b

Pt, number of patients; QPCR, quantitative real-time reverse transcription-polymerase chain reaction; IHC, immunohistochemistry; WB, western blotting; MSP, methylation specific polymerase chain reaction; OS, overall survival; PFS, progression-free survival; stage; UICC stage.

eIF4EBP3 significantly inhibited tumor cell growth, migration, and invasion both *in vitro* and in liver metastasis *in vivo*. Moreover, eIF4EBP3 downregulated β-catenin protein levels. Overexpression of β-catenin reversed the inhibitory effects of eIF4EBP3 on cell growth and migration, indicating that eIF4EBP3 acts on GC cells by targeting the eIF4E/β-catenin axis (Zhai et al., 2020). They concluded that eIF4EBP3 is a novel TSG methylated in GC that may play important roles in GC development and liver metastasis. eIF4EBP3 might be used as a potential metastasis and survival biomarker of GC.

MicroRNA

MicroRNAs (miRNAs) are a series of short non-coding RNAs, approximately 20–24 nucleotides in length, which play vital roles in the regulation of gene expression at the posttranscriptional level via binding to the 3-UTR of target mRNAs (Zhang et al., 2013). miRNAs participate in the regulation of a variety of human proteins, which allows them to affect genetic pathways (Filipowicz et al., 2008). miRNAs have been reported to act as oncogenes or tumor suppressors in the initiation and development of various cancers (Wang et al., 2019a). miRNAs are found in serum and other body fluids, and function as biomarkers of diseases due to their differential expression between patients and healthy individuals (Mori et al., 2019). We have introduced the recently identified miRNAs that may be potential biomarkers for GC (Table 4) (Hu et al., 2018; Li et al., 2018, 2020c; Yang et al., 2018a, 2020; Cui et al., 2019; Ji et al., 2019; Wang et al., 2019b; Yan et al., 2019; Zheng et al., 2019b; Ebrahimi Ghahnavieh et al., 2020; Miao et al., 2020; Nishibeppu et al., 2020; Wei et al., 2020a).

Table 4. Dysregulated microRNAs in gastric cancer.

Symbol (location)	Specimen	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo*	Reference
Early detection									
MiR-584 (5q32)	Tissue	QPCR	37	OS	Depth, N, stage, Helicobacter. pylori	(-)	STAT1, PTEN, CCND1, PIK3CA	(-)	Ghahnavieh et al., 2020
MiR-15b-3p (3q15.33)	Tissue, Circulating	QPCR, IHC, WB	108	OS	Alcohol abuse, tumor size, histological grade, stage, lymphovascular invasion	Proliferation, invasion, migration, apoptosis	DYNLT1, Caspase3, Caspase9	Yes	Wei et al., 2020a,b
MiR-17-5p (13q31.3)	Tissue, Circulating	QPCR	268	OS	N, stage	(-)	DC, IL-10, IL-12, p70	(-)	Cui et al., 2019
MiR-142-5p (17q22)	Tissue	QPCR	101	OS	(-)	Invasion, migration	CYR61 Wnt/β-catenin	Yes	Yan et al., 2019
MiR-423-5p (17q11.2)	Tissue, Circulating	QPCR	160	OS, DFS	N	Proliferation, migration	SUFU	Yes	Yang et al., 2018a,b
MiR-484 (16p13.11)	Tissue	QPCR	124	OS	Differentiation, N, M, stage	Proliferation, Invasion, migration	(-)	(-)	Li et al., 2020a-c
MiR-585 (5q35.1)	Tissue	QPCR, WB	65	OS	Depth, N, stage	Proliferation, migration, cell cycle, apoptosis	MAPK1	Yes	Hu et al., 2018
MiR-5683 (6p25.1)	Tissue	QPCR	70	OS, DFS	Tumor size	Proliferation, apoptosis, cell cycle	PDK4	Yes	Miao et al., 2020
Hsa-miR-3923 (3p12.3)	TCGA, GEO dataset		452	OS	Vital status, depth, N, histological grade	(-)	(-)	(-)	Yang et al., 2020
Prediction of treatment response									
MiR-374a-5p (Xq13.2)	Circulating	QPCR, WB	105		Tumor size	Proliferation, apoptosis	Neurod1	Yes	Ji et al., 2019
MiR-1229-3p (5q35.3)	Circulating	QPCR	60	OS, RFS	Depth, recurrence	(-)	TS, DPD, SLC22A7	Yes	Nishibeppu et al., 2020
Others									
MiR-21 (17q23.1)	Circulating	QPCR, WB	32		(-)	(-)	PD-1/PD-L1 Th17/Treg cells	(-)	Zheng et al., 2019a,b
MiR-22 (17p13.3)	Tissue	QPCR, IHC, WB	90	OS	Helicobacter pylori	Proliferation	NLRP3, CCND1	Yes	Li et al., 2018
MiR-29c-3p (1q32.2)	Tissue	QPCR, IHC	60		(-)	Migration	KIAA1199, EBP11, FGFR4, PTP4A3	Yes	Wang et al., 2019a,b

Pt, number of patients; QPCR, quantitative real-time reverse transcription-polymerase chain reaction; IHC, immunohistochemistry; WB, western blotting; OS, overall survival; DFS, disease-free survival; RFS, relapse-free survival; UICC stage.

MiR-15b-3p

As important gene regulators, the miR-15b family is involved in the cell cycle, cellular proliferation, and apoptosis, and has been found to be dysfunctional in various diseases (Sun et al., 2017). Wei et al. validated the miR-15b-3p mRNA levels in tissues, serum, cells, and exosomes. They found that the expression levels of miR-15b-3p mRNA were upregulated in exosomes obtained from the serum samples of 108 GC patients, as compared to corresponding non-GC controls. A statistically significant correlation was observed between high serum exo-miR-15b-3p expression and alcohol abuse, tumor size (≥3.5 cm in diameter), poorly differentiated histological type, TNM stage (III and IV), and lymph vascular invasion. In addition, high exo-miR-15b-3p expression in serum was found to accurately predict worse overall survival. Furthermore, MiR-15b-3p overexpression enhanced GC cell proliferation, invasion, and migration and inhibited apoptosis *in vivo* and *in vitro* via the DYNLT1/Caspase-3/Caspase-9 signaling pathway (Wei et al., 2020a). These results indicate that serum exo-miR-15b-3p in humans may function as a potential GC diagnostic and prognostic biomarker, acting as a significant novel GC therapeutic target.

MiR-423-5p

Yang et al. found that the expression level of exosomal miR-423-5p in patients with GC was significantly higher than in healthy volunteers. The level of exosomal miR-423-5p was remarkably correlated with lymph node metastasis. Overall survival and disease-free survival analyses showed that patients with higher levels of exosomal miR-423-5p had a poorer prognosis. MiR-423-5p overexpression and knockdown decreased the proliferation and migration of GC cells *in vitro* and *in vivo*. Moreover, miR-423-5p enriched exosomes enhanced cell proliferation and migration both *in vitro* and *in vivo*. MiR-423-5p inhibited the expression of the suppressor of fused protein (SUFU) to enhance the proliferation and migration of GC cells. The expression levels of SUFU were significantly decreased in GC cells and in the tumor tissues of GC patients (Yang et al., 2018a). They concluded that exosomes might deliver miR-423-5p to promote cancer growth and metastasis, and serum exosomal miR-423- 5p may serve as a potential marker for GC diagnosis and prognosis.

MiR-374a-5p

Ji et al. assessed miR-374a-5p expression in the serum of GC patients and explored the effects of miR-374a-5p on drug resistance in GC cells. Reichl et al. reported that the diagnostic value of serum miR-374a-5p was higher than that of traditional diagnostic markers, such as AFP or CEA (Reichl and Mikulitis, 2016). Ji et al. found that the serum level of miR-374a-5p was elevated in GC patients compared to gastritis patients and healthy controls. High expression levels of miR-374a-5p were positively associated with tumor size. The expression level of circulating miR-374a-5p was notably reduced in the post-operative group compared to the preoperative group. MiR-374a-5p overexpression promoted GC chemoresistance *in vitro* and *in vivo*, while miR-374a-5p knockdown inhibited chemoresistance. High levels of miR-374a-5p expression were correlated with a poor prognosis. Furthermore, miR-374a-5p bound to Neurod1 to antagonize its effect on chemoresistance. Exosome-mediated delivery of miR-374a-5p inhibitors might increase Neurod1 expression, promote cell apoptosis, and suppress chemoresistance (Ji et al., 2019). They concluded that miR-374a-5p expression was elevated in patients with GC and was able to predict the response of GC patients to chemotherapy. These findings indicate that miR-374a-5p is a new target for the diagnosis and drug resistance therapy of GC.

Long non-coding RNAs in GC

Long non-coding RNAs (lncRNAs) are non-coding RNAs that are >200 nucleotides in length. Recently, lncRNAs have been found to be important regulators of human cancers. Increasing evidence suggests that lncRNAs are involved in cancer initiation, growth, metastasis, and therapy resistance (Schmitt and Chang, 2016). Numerous lncRNAs are aberrantly expressed in GC. However, the functional roles of lncRNAs in GC and the mechanisms of their aberrant expression have not been well elucidated. Here, we list recent papers that discuss GC-related lncRNAs (Table 5) (Lin et al., 2018; Xu et al., 2018b; Yang et al., 2018b; Zhang et al., 2018a,b; Zhao et al., 2018a,b; He et al., 2019; Huang et al., 2019a,b; Huang and Yang, 2019; Li et al., 2019a, 2020a; Piao et al., 2019; Wang et al., 2019c; Zheng et al., 2019a; Zhuo et al., 2019; Guo et al., 2020; He et al., 2020; Hu et al., 2020; Tian et al., 2020; Wei et al., 2020b; Zhong et al., 2020).

The GC-associated long noncoding RNA1 (lncRNA-GC1)

LncRNA-GC1 functions as a modular scaffold by binding to histone acetyltransferases WDR5 and KAT2A, which leads to histone modifications that are associated with the target gene SOD2, which promotes the progression of GC (Sun et al., 2016). However, the role of lncRNA-GC1 in circulating exosomes of patients with GC has not been clarified. Guo et al. investigated the diagnostic efficacy of circulating exosomal lncRNA-GC1 levels in GC. The circulating levels of exosomal lncRNA-GC1 were significantly higher in patients with GC compared to the healthy donor individuals (HDs). Moreover, the area under the curve (AUC) values of circulating exosomal lncRNA-GC1 were higher than those of CEA, CA72-4, and CA19-9 in regards to distinguishing between patients with GC and HDs. The

Table 5. Gastric cancer-associated long noncoding RNAs.

Symbol (location)	Specimen	Detection methods	Pt	Survival	Relevant clinical factors	Functional analyses	Interacting molecules	*In vivo*	Reference
Early detection									
HOTTIP (7p15.2)	Circulating	QPCR	246	OS	Depth, stage	(-)	(-)	(-)	Zhao et al., 2018a,b
LncRNA-GC1	Tissue, Circulating	QPCR,	862		Lauren classification, pathological grade, stage	(-)	(-)	(-)	Guo et al., 2020
UEGC1	Circulating	QPCR, WB	69		stage	(-)	(-)	(-)	Lin et al., 2018
UFC1 (1q23.3)	Tissue, Circulating	QPCR, WB	205	OS	Tumor size, N, stage	Proliferation, invasion, migration	MiR-498/Lin28b	Yes	Zhang et al., 2018a-d
Prediction of survival									
ADPGK-AS1 (15q24.1)	Tissue	QPCR WB	60	OS	(-)	Proliferation, migration, apoptosis	MiR-3196, KDM1B	(-)	Huang et al., 2019a,b
CTD2510F5.4	Tissue	QPCR, ISH, microarray	407	OS	Pathological grade, stage, serous membrane invasion, vascular or nerve invasion	Proliferation, cell cycle, apoptosis	E2F3, DTL, RBL1, MCM10, ATAD2, KIF18B, NUSAP1, RAD54L, BUB1, KPNA2	(-)	Wang et al., 2019a-c; Wang and Qui, 2019
FOXD2-AS1 (1p33)	Tissue	QPCR, microarray	106	DFS	Tumor size, depth, N, stage	Proliferation, cell cycle	EZH2, LSD1	Yes	Xu et al., 2018a,b
GCMA	Tissue	QPCR microarray	71	OS DFS	N	Proliferation, invasion, migration	MiR-124, MiR-34a	(-)	Tian et al., 2020
GMAN (1q22)	Tissue	QPCR, IHC microarray	322	OS	M	Proliferation, invasion, migration	ephrin A1	Yes	Zhuo et al., 2019
HOTAIR (12q13.13)	Tissue	QPCR, IHC, WB	348	OS	Tumor grade, depth	Proliferation, invasion, migration	COL5A1, MiR1277-5p	Yes	Wei et al., 2020a,b
KRT19P3 (4q25)	Tissue	QPCR, microarray	84	OS DFS	Lauren classification, tumor size, N, stage	Proliferation, invasion, migration, apoptosis	COPS7A, KRT193P	Yes	Zheng et al., 2019a,b
LINC01133 (1q23.2)	Tissue	QPCR	200	OS PFS	N, stage	Proliferation, migration, EMT	MiR-106a-3p, APC, Wnt/β-catenin	Yes	Yang et al., 2018a,b
LOC285194 (3q13.31)	Tissue	QPCR, IHC, WB	72	OS	Tumor size, depth, N, stage	Proliferation, invasion, migration, apoptosis	Wnt/β-catenin	Yes	Zhong et al., 2020
MACC1-AS1 (7q21.1)	Tissue	IHC, ISH	123	OS	Depth, N, stage, recurrence	Proliferation, apoptosis	AMPK/Lin28	Yes	Zhao et al., 2018a,b
MAGI2-AS3 (7q21.11)	Tissue	QPCR, microarray	373	OS DFS	Differentiation, depth, stage	Invasion, migration	MiR-141/200a, ZEB1	(-)	Li et al., 2020
MT1JP (16q12.2)	Tissue	QPCR	75	OS	N, stage	Proliferation, invasion, migration, apoptosis	FBXW7, MiR-92a-3p	Yes	Zhang et al., 2018a-d
NALT1 (9q34.3)	Tissue	QPCR, WB	336	OS DFS	Differentiation, depth, N, stage	Invasion, migration	NOTCH	(-)	Piao et al., 2019
TRPM2-AS (21q22.3)	Tissue	QPCR	124	OS	Depth, N, stage	Proliferation, invasion, migration	MiR-195/HMGA1	(-)	Huang et al., 2019a,b
UCA1 (19p13.12)	Tissue	QPCR	60	OS	Depth, stage	Proliferation, invasion, migration	p21, SPRY1	Yes	He et al., 2019
Prediction of treatment response									
LINC00641 (14q11.2)	Tissue	QPCR, WB	173	OS	sex, M, L-OHP resistance	Proliferation, migration, autophagy	MiR-582-5p	(-)	Hu et al., 2020
Others									
LINC00200 (10p15.3)	Tissue	QPCR	372		(-)	Proliferation, invasion, migration	MiR-143-3p, SERPINE1	Yes	He et al., 2021
LOC101928316 (11p14.1)	Tissue	QPCR, ISH	90		Differentiation, stage	Proliferation, invasion, migration	PI3K/Akt/mTOR	Yes	Li et al., 2019a,b

Pt, number of patients; QPCR, quantitative real-time reverse transcription-polymerase chain reaction; IHC, immunohistochemistry; WB, western blotting; ISH, in situ hybridization; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; stage; UICC stage.

levels of circulating exosomal lncRNA-GC1 in patients with stage I or II GC were significantly upregulated compared to the levels in HDs and in patients with chronic atrophic gastritis or intestinal metaplasia. In addition, the levels of circulating exosomal lncRNA-GC1 that were strictly correlated with tumor burden significantly increased with the progression of GC in the early to advanced stages (Guo et al., 2020). These results suggest that circulating exosomal lncRNA-GC1 may serve as a noninvasive biomarker for detecting the early stages of GC and for monitoring the disease progression.

Homeobox transcript antisense intergenic RNA (HOTAIR)

HOTAIR, a trans-acting lncRNA with 2158 nucleotides and 6 exons, has been found to interact with polycomb repressive complex 2, leading to epigenetic silencing and tumorigenesis of many cancer types, including breast cancer and bladder cancer (Hajjari and Salavati, 2015). Accumulating evidence has revealed that HOTAIR exerts its biological function by interacting with miRNAs to regulate gene expression and participate in tumorigenesis molecular pathways (Liu et al., 2014). Wei et al. explored the role of the HOTAIR/miR-1277-5p/COL5A1 axis in GC and its underlying mechanisms. HOTAIR was highly expressed in GC cells and enhanced the proliferation and metastasis of GC, which was mediated by sponging miR-1277-5p and upregulating COL5A1. A Kaplan–Meier analysis showed that GC patients with higher HOTAIR expression levels had poorer prognoses. Furthermore, miR-1277-5p suppressed the growth and metastasis of GC, while COL5A1 promoted the growth of GC, and COL5A1 was positively correlated with GC immune infiltration. Mouse xenograft models revealed that knockdown of HOTAIR suppressed GC growth *in vivo* (Wei et al., 2020b). They concluded that the HOTAIR/miR-1277-5p axis regulates GC tumorigenesis by affecting COL5A1 levels, which may provide new targets for GC treatments.

LOC285194

LOC285194 serves as a carcinoma inhibitor by targeting p53 through the KRAS/BRAF/SMEK pathway in non-small cell lung carcinoma (Zhou et al., 2019). In esophageal squamous cell carcinoma, LOC285194 also participates in chemoradiotherapy resistance (Tong et al., 2014). Zhong et al. investigated the biological function of LOC285194 in the progression and development of GC. LOC285194 was lowly expressed in both human GC tissues and GC cell lines compared to corresponding normal controls. A Kaplan-Meier analysis showed that GC patients with high lncRNA LOC285194 expression levels had higher overall survival rates than those with low LOC285194 expression levels. LOC285194 overexpression suppressed MKN45 and HGC-27 cell proliferation and promoted cell apoptosis. In contrast, silencing of LOC285194 remarkably induced GC cell viability and cell proliferation, increased its colony formation abilities, cell migration, and invasive capacities, and blocked the apoptotic rates of GC cells. Furthermore, LOC285194 inhibited GC progression by targeting Wnt signaling in an *in vivo* nude mouse model (Zhong et al., 2020). These results indicate that LOC285194 may serve as a novel treatment biomarker for GC.

LINC00641

A previous study indicated that LINC00641 might act as a competing endogenous RNA (ceRNA) by binding to miR-153-3p to relieve its transcriptional suppression of ATG5, and then promote the initiation of autophagy during intervertebral disc degeneration (Wang et al., 2019c). However, the biological function of LINC00641 in GC remains unclear. Hu et al. found that LINC00641 was highly expressed in GC tissues compared with para-cancer tissues, and miR-582-5p expression was lower in GC tissues. High LINC00641 expression was significantly associated with L-OHP resistance, low miR-582-5p expression, M stage, patient sex, and poor prognosis. LINC00641 promoted cell proliferation and migration by inhibiting miR 582 5p *in vitro*, whereas upregulation of miR-582-5p resulted in decreased cell proliferation (Hu et al., 2020).

Autophagy enables cells to maintain metabolism and survival by recycling intracellular proteins to cope with stress (Galluzzi et al., 2014). Therefore, it has been suggested that autophagy may be involved in chemoresistance. LINC00641 and miR 582 5p were aberrantly expressed in L OHP-resistant GC cells. In addition, downregulation of LINC00641 inhibited the autophagy process, making GC cells more sensitive to oxaliplatin (Hu et al., 2020). These findings indicate that LINC00641 and miR 582 5p serve as biomarkers for predicting GC prognosis, as they are involved in regulating oxaliplatin resistance by altering autophagy in gastric adenocarcinoma.

Conclusion

We introduced updated evidence regarding the molecular biomarkers of GC according to the following categories: oncogenes, TSGs, methylated DNA, miRNAs, and lncRNAs. Although knowledge and information about biomarkers is increasing, there remains scope for improvement in the treatment of GC. Treatment interventions tailored to each risk may contribute to the early detection, prevention of recurrence, and improved prognosis of GC. There is a lack of information on serum biomarkers. They are non-invasive and simple diagnostic tools that can be measured repeatedly without a heavy burden on the patient. Although we are still a long way from reaching our goal, we need to search for new biomarkers and deepen our understanding and knowledge of further

biomarkers and apply them to clinical practice.

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