Recent advances in the molecular diagnostics of gastric cancer

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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.

Kanda M, Kodera Y. Recent advances in the molecular diagnostics of gastric cancer. World J Gastroenterol 2015; 21(34): 9838-9852 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i34/9838.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i34.9838

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[11,12]. 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)[6,13,14]. The search for non-invasive tools for diagnosis has led to the investigation of proteins and circulating nucleic acids, including miRNAs and IncRNAs, 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[16,17]. 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]. 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]. Therefore, they are used in preclinical models for GC and are typically expressed in a synergistic fashion in the majority of GC cases[20]. However, they inhibit apoptosis by silencing growth-inhibition associated genes[19].

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[20]. Ivanova et al[21] 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[22]. These results indicate 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
| 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] |
| IFTM1 (11p15.5)  | Interferon induced transmembrane protein | Tissue | IHC               | 151| -        | Differentiation           | Migration, invasion | -                  | -              | [21] |
| MPP-9 (20q13.12) | Breakdown of extracellular matrix | Tissue, Circulating | IHC, ELISA        | 45 | -        | N, stage                 | -                   | -                  | -              | [40] |
| PTTG1 (5q35.1)   | Homolog of yeast securin proteins | Tissue | ELISA             | 98 | OS       | -                        | -                   | HER2               | -              | [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] |
| NUA1 (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)   | Trimmethylation-specific demethylase | Tissue | QPCR, IHC         | 123| OS, RFS  | N, stage                 | Proliferation, apoptosis | -                  | -              | [32] |
| MAGED2 (Xp11.2)  | Unknown            | Tissue | QPCR, IHC         | 225| OS, RFS  | N, stage                 | -                   | -                  | -              | [44] |
| MYCL1 (1p34.2)   | Transcription factor involved in cell differentiation and apoptosis | Tissue | QPCR, 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, apoptosis | -                  | Yes             | [38] |
| SATB1 (3p23)     | Matrix protein which binds nuclear matrix and scaffold-associated DNAs | Tissue | IHC               | 175| OS, RFS  | Age, N                   | -                   | -                  | -              | [31] |
| SERPIN1A (14q32.1) | Serine protease inhibitor | Tissue | QPCR, IHC         | 400| OS       | Age, size, depth, N       | Migration, invasion | MMP8               | -              | [34] |
normal tissues in cardiac myocytes, brain, pineal body, retina and smooth muscle and is moderately expressed in various tissues, including gastric mucosa. DPYSL3 is involved in the metastatic process of tumor cells. 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)\(^{32,49}\). 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\(^{41}\) 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...
mediates Bcl-2-regulated apoptosis and suppresses the proliferation of cancer cells\cite{66,67}. We recently evaluated the clinical implication of BTG1 expression in GC and examined the genetic diversity among histopathologic and anatomic subtypes\cite{59,60}. BTG1 expression was downregulated in the majority of GCs, but promoter hypermethylation events or sequence mutations were not detected\cite{59,60,68,69}. 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\cite{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\cite{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\cite{71}. Mai et al\cite{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\cite{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\cite{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\cite{73}. STUB1 induces ubiquitination and degradation of several oncopgenic proteins, such as mutant p53, estrogen receptor a, c-ErbB2/neu, hypoxia inducible factor 1a and SRC-3\cite{74,75}. Wang et al\cite{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 anchorange-independent colonies in soft agar, suppressed the growth of xenografts in nude mice and inhibited endothelial cell growth and tube formation by suppressing NF-kB-mediated interleukin 8 expression\cite{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\cite{75,76}. To date, frequent promoter hypermethylation and subsequent loss of protein expression has been demonstrated in GC-related
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\[^80-97\].

### 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. |
|-------------------|---------------------|-----------|-------------------|-----|----------|--------------------------|--------------------|----------------------|--------------|------|
| APBA2 (15p11-12)  | 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                  | Proliferation, cell cycle, apoptosis | β-catenin, TCF-1   | -            | [84] |
| OSR1 (2p24.1)     | Development of intermediate mesoderm | Tissue | QPCR, IHC | 164 | OS       | -                      | Proliferation, invasion               | -                  | -            | [82] |
| RASGRF1 (15q24.2) | Mediator of Ras-GEF signaling pathway | Tissue | QPCR | 130 | -        | -                      | -                                | -                  | -            | [94] |
| SFG20 (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] |
| 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] |
| 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 (1q21.1)  | Suppressor of cell growth in response to activated Ras family suppressor of cytokine signaling | Tissue | QPCR, IHC | 132 | OS       | Differentiation, depth, N, stage | -                  | -             | -             | [90] |
| SOCS4 (1q22.1)    | Transcription factor involved in the regulation of embryonic development | Tissue | QPCR | 50  | OS       | Depth, N | -                     | -           | -             | [80] |
| SOX17 (8q11.23)   | Mesoderm specific transcription factor | Circulating | MSP | 73  | OS       | Differentiation          | -                  | -             | -             | [83] |
| TCF21 (6q23.2)    | Transcription factor involved in the p53-dependent manner | Tissue | QPCR, IHC | 200 | OS       | Differentiation, depth, N | -                  | -             | -             | [97] |
| TFF1 (21q22.3)    | Regulator of cell cycles in a p53-dependent manner | Tissue | QPCR, IHC | 182 | OS       | Depth                | Invasion            | -               | -             | [87,88] |
| RFRM (2q33.3)     | Preventing treatment responses | Tissue | QPCR | 83  | OS       | Chemosensitivity         | 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.
**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[89]. 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[109]. Here, we introduce newly identified miRNAs that potentially represent biomarkers for 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.[141] 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.[140] conducted global microarray and in situ
| Symbol (location) | Early detection | Materials | Detection methods | Pt | Survival | Relevant clinical factors | Functional analyses | Interacting molecules | In vivo study | Ref. |
|------------------|----------------|-----------|-------------------|----|----------|-------------------------|-------------------|----------------------|--------------|------|
| miR-21 (17q21.3) | Circulating    | QPCR      | 103               | -  | Size, depth | -                       | Proliferation, migration, invasion | CD151            | -    | [116] |
| miR-22 (17p13.3) | Tissue         | QPCR      | 32                | -  | -         | -                       | Proliferation, adhesion, invasion migration | -                | -    | [117] |
| miR-29c (1q32.2) | Tissue         | QPCR      | 274               | -  | -         | -                       | Proliferation, adhesion, invasion migration | ITGB1 Yes        | -    | [135] |

**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. |
|------------------|-----------|-------------------|----|----------|-------------------------|-------------------|----------------------|--------------|------|
| miR-30b (8q24.22)| Tissue    | QPCR              | 21 | -        | Age                     | Apoptosis          | PAI-1 Yes            | -            | [134] |
| miR-106b (7q32.1)| Gastric juice | QPCR             | 40 | -        | Age                     | -                 | -                    | -            | [132] |
| miR-129 (7q32.1) | Tissue (12p13.3) | QPCR          | 141 | -       | -                       | -                 | -                    | -            | [118] |
| miR-141 (12p13.3)| Tissue     | QPCR              | 30 | -        | -                       | Proliferation, migration invasion | HDGF            | -    | [119] |

**Monitoring recurrences**

| Symbol (location) | Materials | Detection methods | Pt | Survival | Relevant clinical factors | Functional analyses | Interacting molecules | In vivo study | Ref. |
|------------------|-----------|-------------------|----|----------|-------------------------|-------------------|----------------------|--------------|------|
| miR-148a (7p15.2)| Tissue    | QPCR              | 64 | -        | Size                    | -                 | -                    | -            | [127] |
| miR-181c (19p13.13)| Tissue, circulating | QPCR  | 30 | -       | -                       | -                 | -                    | -            | [113] |

| Symbol (location) | Early detection | Materials | Detection methods | Pt | Survival | Relevant clinical factors | Functional analyses | Interacting molecules | In vivo study | Ref. |
|------------------|----------------|-----------|-------------------|----|----------|-------------------------|-------------------|----------------------|--------------|------|
| miR-199a-3p (12) | Tissue, circulating | QPCR     | 180 | -       | T, N, stage          | Proliferation, migration, invasion, cell cycle | -                | -    | [115] |
| miR-223 (X1q21)  | Circulating    | QPCR      | 60    | -       | Helicobacter pylori    | -                 | -                    | -            | [109] |
| miR-233 (X)      | Circulating    | QPCR      | 50    | -       | Size, differentiation, stage | -                | -                    | -            | [130] |

| Symbol (location) | Early detection | Materials | Detection methods | Pt | Survival | Relevant clinical factors | Functional analyses | Interacting molecules | In vivo study | Ref. |
|------------------|----------------|-----------|-------------------|----|----------|-------------------------|-------------------|----------------------|--------------|------|
| miR-25 (7q22.1)  | Tissue, circulating | QPCR    | 70    | OS      | N, stage          | Proliferation, metastasis | FGF9 Yes         | -    | [114] |
| miR-34b/c (11q23.1) | Noncancerous tissue | Pyrosequencing 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)| Tissue, circulating | QPCR | 52    | OS, RFS | -       | Migration, invasion   | - | - | [111] |
| miR-222 (Xp11.3)    | Tissue, circulating | QPCR | 114   | OS, RFS | N, stage          | -                 | -                    | -            | [121] |

| Symbol (location) | Early detection | Materials | Detection methods | Pt | Survival | Relevant clinical factors | Functional analyses | Interacting molecules | In vivo study | Ref. |
|------------------|----------------|-----------|-------------------|----|----------|-------------------------|-------------------|----------------------|--------------|------|
| miR-26a (3p22.2) | Tissue        | QPCR      | 40    | OS, RFS | N, stage          | Proliferation, metastasis | FGF9 Yes         | -    | [114] |

| Symbol (location) | Prediction of survival | Materials | Detection methods | Pt | Survival | Relevant clinical factors | Functional analyses | Interacting molecules | In vivo study | Ref. |
|------------------|--------------------------|-----------|-------------------|----|----------|-------------------------|-------------------|----------------------|--------------|------|
| miR-192 (11q13.1)| Tissue                   | QPCR      | 38    | -       | Sex, vascular invasion, N | Proliferation, migration, invasion apoptosis, repression | PDLC4            | -    | [122] |
| miR-214 (1q24.3) | Tissue                   | QPCR      | 80    | -       | Size, N            | Proliferation, migration, invasion      | CSF1             | -    | [131] |

| Symbol (location) | Early detection | Materials | Detection methods | Pt | Survival | Relevant clinical factors | Functional analyses | Interacting molecules | In vivo study | Ref. |
|------------------|----------------|-----------|-------------------|----|----------|-------------------------|-------------------|----------------------|--------------|------|
| miR-630 (15q24.1)| Tissue        | QPCR      | 236   | OS      | Depth, N, stage | Proliferation, invasion      | -                | -    | [120] |
| miR-17-5p (13q31.3)| Circulating | QPCR | 65    | OS      | Differentiation, stage Chemoresistance | - | - | [112] |
| miR-27a (19p13.13)| Circulating | QPCR | 82    | OS      | Depth, N, stage | Proliferation, invasion      | -                | -    | [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.
hybridization analyses to explore novel GC-related IncRNAs and identified gastric adenocarcinoma predictive long intergenic noncoding RNA (GAPLINC) as an aberrantly expressed IncRNA. 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 IncRNA) 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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P-Reviewer: Larentzakis A, Li Y S-Editor: Ma YJ L-Editor: A E-Editor: Ma S
