Non-coding RNAs that regulate the Wnt/ β -catenin signaling pathway in gastric cancer: Good cop, bad cop? (Review)

ZHAOZHAO SHAO¹, DIAN GAO², LI CHEN¹, WENJIE DING¹ and QIONGFANG YU¹

¹Department of Gastroenterology and Hepatology, Second Affiliated Hospital of Nanchang University;

²Department of Pathogen Biology and Immunology, Medical College of Nanchang University,
Nanchang, Jiangxi 330006, P.R. China

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Abstract. Gastric cancer (GC) is one of the most common causes of cancer-related mortality worldwide. Despite remarkable progress in the diagnosis and treatment of GC, a large number of cases are diagnosed as advanced GC, and treatment failure occurs. Emerging evidence has shown that non-coding RNAs (ncRNAs), especially microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play a vital role in the tumorigenesis and development of GC. Moreover, the pathogenesis of GC is closely related to aberrant activation of the Wnt (Wingless-type MMTV integration site family) signaling pathway. ncRNAs serve as potential novel biomarkers in the clinical examination, prognosis and therapeutic targeting of GC. Furthermore, dysregulation of ncRNAs has been demonstrated to affect tumor initiation, epithelial-mesenchymal transition (EMT), angiogenesis, tumor development, invasion, metastasis and resistance to therapy via the Wnt/ β -catenin signaling pathway. This review focuses on the role of ncRNAs in modulating the Wnt/ β -catenin signaling pathway in the pathogenesis of GC, which may provide a reference for the clinical diagnosis and treatment of GC.

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Correspondence to: Dr Qiongfang Yu, Department of Gastroenterology and Hepatology, Second Affiliated Hospital of Nanchang University, 1 Minde Road, Nanchang, Jiangxi 330006, P.R. China
E-mail: qiongfangyu@yeah.net

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1. Introduction

Globally, gastric cancer (GC) is the leading cause of cancer-related mortality and one of the most common types of cancers (1). The number of newly discovered GC cases worldwide reached over 1,000,000 in 2018, with 783,000 GC-related deaths, making it the fifth most commonly diagnosed cancer (2). East Asia is one of the major regions with a high incidence of GC (3). For example, GC ranks as the second leading cause of cancer-related death in China (4). Despite a large amount of progress in diagnosis and therapeutic strategies, the overall survival of GC patients remains unsatisfactory (5). Furthermore, due to the lack of sensitive predictive markers at an early stage and the lack of specific symptoms, the majority of GC patients are diagnosed with advanced GC or metastasis (6). Therefore, it is urgent to explore the molecular mechanism and critical signaling pathways underlying the initiation and progression of GC.

In recent decades, numerous studies have demonstrated that non-coding RNAs (ncRNAs), primarily microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are closely related to every stage of GC, including tumorigenesis, growth, development, apoptosis, invasion, metastasis, and drug resistance (7). The role of ncRNAs as promising biomarkers in the diagnosis of GC has also been deeply studied (8). It is worth noting that activation of the wingless-type MMTV integration site family (Wnt)/ β -catenin signaling pathway has a vital role in a variety of cancers, such as breast cancer (9), colon cancer (10) and liver cancer (11). Indeed, continual activation of Wnt/ β -catenin signaling pathway is closely related to the carcinogenesis of GC (12-14). Thus, efforts to further understand the mechanism by which ncRNAs modulate the Wnt/ β -catenin signaling pathway may provide early effective diagnosis and potential novel therapeutic strategies for GC. Therefore, in this review, we summarize the role of ncRNAs in regulating the Wnt/ β -catenin signaling pathway in the pathogenesis of GC.

2. Search methods

In the current main literature databases, PubMed is the most widely used premier bibliographic database in the life sciences and biomedicine fields. In addition, Web of Science is the

largest comprehensive academic information resource with the most disciplines in the world. Therefore, we identify eligible studies using the following terms: 'β-catenin', 'Wnt', 'gastric cancer' and 'non-coding RNA' in the PubMed and Web of Science databases. The search began on February 1, 2020, and the last retrieval was on March 15, 2020. The citation lists associated with the studies were used to identify additional eligible studies. Reviews and bibliographies were also manually inspected to identify related articles. The role of ncRNAs in regulating the Wnt/β-catenin signaling pathway in the pathogenesis of GC was analyzed.

3. Wnt pathway

Classification. The Wnt signaling pathway is a highly conserved extracellular signal transduction pathway that is triggered by the binding of the ligand protein Wnt to its membrane protein receptor. In 1982, the *Wnt* gene was first discovered in mouse breast cancer. As activation of this gene relies on the insertion of mouse breast cancer-associated viral genes, it was named '*Int1*' (15). Subsequent studies discovered that the *Int1* gene plays an essential role in the normal embryonic development of mice and that its function is similar to that of the *Wingless* gene of *Drosophila*, which controls axial development of the fruit fly embryo. Due to the similarity between these two genes, *Wingless* and *Int1* were combined and named '*Wnt*' (16-19).

The Wnt pathway is mainly divided into three pathways: i) The canonical Wnt or β-catenin dependent pathway, which activates expression of target genes in nucleus planar cells; ii) the polarity (PCP) pathway, which participates in Jun N-terminal kinase (JNK) activation and cytoskeletal rearrangement; and iii) the Wnt/Ca²⁺ pathway, which participates in activation of phospholipase C (PLC) and protein kinase C (PKC) (20-23). The last two pathways together are called the 'non-classical' or 'β-catenin-independent' pathways (24).

Wnt/β-catenin signaling pathway and GC. The Wnt/β-catenin signaling pathway is a classical Wnt pathway by which β-catenin accumulates in the cytoplasm and eventually translocates to the nucleus and coactivates transcription with TCF/LEF (T cytokine/lymphoid enhancer factor) family members (21). The Wnt signal is induced when the Wnt protein binds to a cysteine-rich domain of the N-terminal of the Frizzled (Fz) family of receptors (25). Following gene transduction and TCF/LEF transcription, the factor induces transcription of the target gene that ultimately acts on Wnt, inducing subsequent cellular responses (Fig. 1) (26,27).

Among these Wnt signaling pathways, the Wnt/β-catenin signaling pathway is highly evolutionarily conserved. It is involved in the pathogenesis of gastric carcinoma (28). According to statistics, activation of Wnt/β-catenin signaling pathway can be found in ~30-50% of GC tissues (29).

4. Non-coding RNAs and gastric cancer

Non-coding RNAs (ncRNAs) are a group of RNA transcribed from the genome that do not have protein-coding functions (30). In the past, most ncRNAs were considered 'evolutionary junk', but developments in molecular biology

suggest that mutation or aberrant expression of ncRNAs has a huge impact on the occurrence and development of diseases, including cancers (31). Recently, ncRNAs have attracted widespread attention. It has also been confirmed that abnormal expression of miRNAs strongly contributes to the initiation and development of carcinoma (32). lncRNAs exert potent tumor-suppressive or -promoting effects on the pathogenic processes underlying GC tumorigenesis and progression (33). In addition, miRNAs have been verified to have deep connections to the occurrence, development, proliferation, metastasis, and invasion of GC (33-37).

5. lncRNAs

lncRNAs act on members of the Wnt/β-catenin signaling pathway to regulate GC. Glycogen synthase kinase-3β (GSK-3β) is an evolutionarily highly conserved serine/threonine kinase that is ubiquitous in mammalian eukaryotic cells. It acts on many signaling proteins, structural proteins and transcription factors, regulating cell differentiation, proliferation, survival and apoptosis (38,39). One study revealed that lncRNA LINC01225 activates the Wnt/β-catenin signaling pathway mainly by inhibiting GSK-3β to promote the proliferation, migration, invasion and EMT of GC (40). In another study, GSK-3β was identified as a target gene of lncRNA small nucleolar RNA host gene 20 (SNHG20) in GC cells. Promoting expression of lncRNA SNHG20 suppresses that of GSK-3β to activate the Wnt/β-catenin signaling pathway in GC (41).

In addition to activating Wnt/β-catenin signaling pathway, some lncRNAs play a completely opposite role. For instance, upregulation of lncRNA GATA6 antisense RNA 1 (GATA6-AS1) suppresses the Wnt/β-catenin signaling pathway by recruiting enhancer of Zeste homolog 2 (EZH2) to the Frizzled family receptor 4 (FZD4) promoter region, enhancing H3K27me3 and downregulating expression of FZD4, both of which reduce the occurrence, development, and invasion of GC (42).

lncRNAs regulate GC by inhibiting mediators of the Wnt/β-catenin signaling pathway. Desmoplakin (DSP), a class of proteins found in desmosomes, can decrease the level of β-catenin both in the cytoplasm and nucleus. Upregulation of lncRNA MIR4435-2HG diminishes the activity of DSP, thus promoting GC growth and metastasis (43). In addition, knock-down of lncRNA zinc finger antisense (ZFAS)1 increases expression of miR-200b, which targets Wnt1 to inhibit the induction of cell proliferation, cell cycle progression and activation of Wnt/β-catenin signaling pathway in GC (44,45).

Furthermore, lncRNAs act as tumor suppressors by altering Wnt/β-catenin signaling pathway via their mediators. lncRNA LINC01314 is expressed at low levels in GC tissue, and enhancing its expression was found to inhibit GC tumor growth, invasion and migration in nude mice by directly suppressing the Wnt/β-catenin signaling pathway via downregulation of kallikrein 4 (KLK4) (46).

lncRNAs act as ceRNAs to regulate GC via the Wnt/β-catenin signaling pathway. Competing endogenous RNA (ceRNA) refers to a new mechanism of interaction between RNAs; that is, ceRNA binds to miRNA via microRNA response

Figure 1. The Wnt/β-catenin signaling pathway. When the signal is activated, the Wnt ligand binds to the Frizzled (Fz) receptor and coreceptor lipoprotein receptor-related protein (LRP 5/6), causing adaptor protein Dishevelled (Dvl) to inhibit the destruction complex, which is composed of adenoma colon polyp (APC), glycogen synthase kinase 3β (GSK3β), axin and casein kinase 1 (CK1). This allows β-catenin to accumulate and translocate to the nucleus and combine with T-cytokine (TCF)/lymphocyte enhancer-binding factor (LEF) transcription factors for target gene expression. In contrast, when the signal is inactivated, Dvl fails to inhibit the destruction complex, and β-catenin is phosphorylated by GSK3β. Phosphorylated β-catenin is decomposed by the ubiquitin (Ub)-proteasome system.

elements (MERs) to regulate target gene expression (47,48). A large number of studies have demonstrated that ceRNAs may be inextricably linked to multiple cancers, including GC (49-51).

lncRNA Homeobox A11 (HOXA11) antisense RNA (HOXA11-AS) serves as a ceRNA by sponging miR-148a, which deactivates the Wnt/β-catenin signaling pathway by directly targeting Wnt1. Thus, lncRNA HOXA11-AS promotes the migration and invasion of GC cells, leading to a poor clinical survival rate (52). Consistent with this finding, lncRNA LIN01606 was verified to increase expression of Wnt3a by acting as a ceRNA of miR-423-5p, thereby promoting cell migration and invasion of GC through activation of the Wnt/β-catenin signaling pathway (53).

In addition, some lncRNAs can serve as tumor suppressors in GC. LINC01133 regulates adenoma colon polyp (APC) by acting as a ceRNA of miR-106a-3p. LINC01133 also inhibits nuclear accumulation of the β-catenin protein by inhibiting miR-106a-3p and promoting APC expression to inhibit activation of Wnt/β-catenin signaling pathway, thus suppressing EMT and metastasis in GC (54).

Similarly, lncRNA TOB1 antisense RNA 1 (TOB1-AS1) functions as a ceRNA of miR-23a to abolish its inhibitory effector on neuraminidase 1 (NEU1), promoting apoptosis and inhibiting the metastasis of GC via the Wnt/β-catenin signaling pathway (55).

6. MicroRNAs

miRNAs act on members of the Wnt/β-catenin signaling pathway to regulate GC. In addition to participating in

Wnt/β-catenin signaling pathway regulation via lncRNA-mediated mechanisms, some miRNAs directly exert regulatory effects on the Wnt/β-catenin signaling pathway in GC. miR-214 was discovered to downregulate expression of GSK3β. As a downstream gene of *GSK3β*, β-catenin was significantly upregulated by decreased levels of *GSK3β*, thus facilitating proliferation potency and suppressing apoptosis in GC cells (56). Additionally, miR-501-5p has been proven to directly target Dickkopf Wnt signaling pathway inhibitor 1 (DKK1), naked cuticle homolog 1 (NKD1), and GSK3β and suppress their expression, which enhances the stem cell-like phenotype in GC (57).

Wnt ligands, which are involved in a variety of signaling pathways, have been demonstrated to play an active role in mediating the occurrence and progression of several types of human cancers (58). Moreover, the combination of Wnt1 synergistically activates Wnt/β-catenin signaling pathway (59). For instance, miR-140-5p suppresses Wnt/β-catenin signaling pathway activation by binding to Wnt1 to inhibit GC proliferation and invasion *in vitro* (60). Similar to miR-140-5p, miR-200b and miR-22 act as tumor suppressors in GC cells by binding to Wnt1. Furthermore, miR-200b and miR-22 synergistically contribute to the efficacy of diallyl disulfide both *in vivo* and *in vitro* (61-63). Consistent with these findings, miR-491-5p inhibits progression and induces apoptosis and cell cycle arrest in GC by targeting Wnt3a through the Wnt/β-catenin signaling pathway (64).

In addition, miRNAs mediate genes downstream of the Wnt ligand, acting as tumor suppressors in GC. *Dishevelled* and *axin* are both downstream genes of the Wnt ligand.

Figure 2. Dual roles of non-coding RNAs (ncRNAs) in modulating the Wnt/ β -catenin signaling pathway in gastric cancer (GC). ncRNAs directly or indirectly act on members of the Wnt/ β -catenin signaling pathway to regulate the biological behavior of GC. The biological effect of ncRNAs that act as mediators of the pathway can be reversed. In addition, miRNAs act as tumor suppressors by interacting with pathway mediators, but the specific targets and mechanisms by which they regulate the Wnt/ β -catenin signaling pathway remain to be elucidated; thus, they are not shown in the figure. Once the signal is activated, the Wnt ligand binds to the Frizzled protein (Fz) receptor and coreceptor lipoprotein receptor-related proteins, causing the adaptor protein Dishevelled (Dvl) to inhibit the destruction complex. This allows β -catenin to accumulate, be translocated to the nucleus and bind to T-cytokine (TCF)/lymphocyte enhancer-binding factor (LEF) transcription factors to activate expression of target genes, such as *c-myc*, *c-jun*, *matrix metalloproteinase 7* (MMP7), and *cyclin D1*.

The Dishevelled-axin domain contains a type of protein named DIXDC1, which is an activator of the Wnt/ β -catenin signaling pathway. Interestingly, miR-154 can directly inhibit DIXDC1 to suppress the proliferation and invasion of GC via the Wnt/ β -catenin signaling pathway (65). Another study revealed that miR-338 decreases *c-myc* and promotes phosphorylation of GSK-3 β to regulate Wnt/ β -catenin signaling pathway, inhibiting the proliferation, migration, and invasion of GC cells (66). As another inactivator of the Wnt/ β -catenin signaling pathway, miR-503 is beneficial for inhibiting the progression and invasion of GC through upregulation of GSK-3 β and p- β -catenin (67). The role of ncRNAs in GC was further clarified by Cong *et al* who discovered that expression of miR-200a is downregulated in gastric carcinoma cells. Furthermore, upregulated miR-200a directly target β -catenin to suppress activation of the Wnt/ β -catenin signaling pathway, thus inhibiting tumorigenesis in GC (68).

miRNAs regulate GC by modulating mediators of the Wnt/ β -catenin signaling pathway. miR-188-5p has been validated as targeting phosphatase and tensin homolog (PTEN), a tumor suppressor involved in a variety of cancers, including GC (69-73). miR-188-5p suppresses PTEN and further promotes phosphorylation of GSK3 β to activate the Wnt/ β -catenin signaling pathway, leading to metastasis and poor prognosis in GC patients (74).

Suppressor of Fused (SUFU), a major negative regulator of the Hedgehog signaling pathway (75-77), as well as the Wnt signaling pathway (78-80), is reported to be abnormally

activated in GC (81-83). Oncogenic miR-194 inhibits SUFU; then, massive amounts of β -catenin accumulate in the cytoplasm, leading to translocation of β -catenin to the nucleus, which promotes GC carcinogenesis (84,85).

Consistently, miR-324-3p activates Wnt/ β -catenin signaling pathway by inhibiting expression of the Wnt/ β -catenin signaling pathway antagonist SMAD family member 4 (Smad4) to promote tumorigenesis and inhibit apoptosis in GC cells. Such increased expression of miR-324-3p is accompanied by the expansion and increased proliferation rate of gastric organoids (86).

miRNAs can also act as inhibitors of the Wnt/ β -catenin signaling pathway by targeting its mediators. Overexpression of miR-200a upregulates expression of E-cadherin by targeting zinc finger E-box-binding homeobox 1 (ZEB1) and zinc finger E-box binding homeobox 2 (ZEB2), which transfers β -catenin from the nucleus to the cytoplasm, suppressing activation of the pathway (68). Furthermore, miR-219-5p targets liver receptor homolog-1 (LRH-1) to inhibit Wnt/ β -catenin signaling pathway, further suppressing the proliferation, migration, and invasion of GC (87).

Moreover, miR-302b inhibits expression of cyclin D1 and *c-myc* by targeting erythropoietin-producing hepatocellular (Eph) A2 via the Wnt/ β -catenin signaling pathway (88). Consistently, the level of miR-19 in GC clinical samples is significantly decreased compared with that noted in normal gastric tissue. Further analysis revealed that the transcription factor myocyte enhancer factor 2D (MEF2D) functions as a potential target of miR-19. Indeed, high expression of MEF2D promotes activation of the Wnt/ β -catenin signaling

Table I. ncRNAs act as oncogenes or tumor suppressors to regulate GC pathogenesis by targeting specific components of the Wnt/ β -catenin signaling pathway.

Effect	ncRNAs	Functional target	Promote	Specific role	(Refs.)
Oncogene	lncRNA				
	ZFAS1	miR-200b/Wnt1 axis	Promote	Proliferation and the cycle procession	(44)
	HOXA11-AS	miR-148a/Wnt1		Migration and invasion	(52)
	LINC01606	miR-423-5p/Wnt3a		Metastasis and invasion	(53)
	MIR4435-2HG	DSP		Growth and metastasis	(43)
	LINC01225	GSK-3 β		EMT and tumorigenesis	(40)
	SNHG20	GSK-3 β		Progression	(41)
	miRNA				
	miR-214	GSK-3 β		Proliferation	(56)
	miR-501-5p	GSK-3 β , NKD1, DKK1		Stem cell-like phenotype	(57)
	miR-188-5p	PTEN		Metastasis and poor survival	(74)
	miR-194	SUFU		Migration, invasion, angiogenesis and tumor growth	(84)
	miR-324-3p	Smad4		Progression	(86)
Tumor suppressor	lncRNA		Inhibit		
	GATA6-AS1	FZD4	Inhibit	LNM and EMT	(42)
	LINC01133	miR-106a-3p/APC axis		EMT, progression and metastasis	(54)
	LINC01314	KLK4		Migration, invasion, angiogenesis and tumor growth	(46)
	TOB1-AS1	miR23a/NEU1 axis		Cell proliferation	(55)
	miRNA				
	miR-140-5p	Wnt1		Proliferation and invasion	(60)
	miR-200b/miR-22	Wnt1		Progression	(61)
	miR-491-5p	Wnt3a		Growth and progression	(64)
	miR-154	DIXDC1		Proliferation and invasion	(65)
	miR-338	GSK-3 β , c-myc		Proliferation, migration, and invasion	(66)
	miR-503	GSK-3 β , β -catenin		Cell proliferation and invasion	(67)
	miR-200a	ZEB1/ZEB2, β -catenin		EMT and tumor growth	(68)
	miR-219-5p	LRH-1		Proliferation, migration, and invasion	(87)
	miRNA				
	miR-302b	EphA2		Tumorigenesis	(88)
	miR-19	MEF2D		Proliferation	(89)
	miR381/miR489	CUL4B		Proliferation and invasion	(90)

GC, gastric cancer; ncRNAs, non-coding RNAs; EMT, epithelial mesenchymal transition; ZFAS1, ZNF1 antisense RNA 1; HOXA11-AS, lncRNA Homeobox A11 (HOXA11) antisense RNA; SNHG20, lncRNA small nucleolar RNA host gene 20; GATA6-AS1, lncRNA GATA6 antisense RNA 1; TOB1-AS1, lncRNA TOB1 antisense RNA 1; DSP, desmoplakin; LNM, lymph node metastasis; PTEN, phosphatase and tensin homolog; SUFU, suppressor of fused; Wnt, wingless-type MMTV integration site family; DIXDC1, Dishevelled-axin domain containing 1; ZEB1/2, zinc finger E-box-binding homeobox 1/2; RH-1, liver receptor homolog-1; DKK-1, Dickkopf Wnt signaling pathway inhibitor 1; NKD1, naked cuticle homolog 1; KLK4, kallikrein 4; NEU1, neuraminidase 1; EphA2, erythropoietin-producing hepatocellular A2; MEF2D, myocyte enhancer factor 2D; CUL4B, cullin 4B.

pathway and contributes to the tumorigenesis and growth of GC. However, such effects of MEF2D can be reversed by miR-19 (89). Additionally, synergistic upregulation of miR381 and miR489 exerts phenotypic effects such as inhibiting cell migration, invasion and EMT through inactivation of the Wnt/ β -catenin signaling pathway by directly targeting cullin 4B (CUL4B) (90).

As mentioned above, ncRNAs can serve as underlying novel biomarkers and therapeutic targets in human GC diagnosis and treatment. Thus, efforts to thoroughly understand the role of ncRNAs in modulating the Wnt/ β -catenin signaling pathway in GC is crucial (Fig. 2).

7. Conclusions and perspectives

GC is still a global concern and a great threat to humans (91). Despite tremendous effort in recent decades to elucidate the role of ncRNAs and the Wnt/ β -catenin signaling pathway in the initiation and progression of GC, the specific molecular mechanism remains unclear. This review summarizes recent studies on the role of ncRNAs in modulating the Wnt/ β -catenin signaling pathway (Table I). These findings support the hypothesis that modulation by ncRNAs can promote or inhibit downstream Wnt/ β -catenin signaling pathway in GC.

Various ncRNAs contribute to target directly or indirectly the members of the Wnt/ β -catenin signaling pathway in GC. It remains unknown whether some microRNAs that interacts with lncRNAs are involved in this regulatory process. Interestingly, some substances that act as mediators of the ncRNAs are also regulators of other signaling pathways. It means further study is needed to explore whether the lncRNA-Wnt/ β -catenin signaling pathway is the main signaling pathway affecting the progression of GC.

In addition, compared with that in normal gastric tissue, expression of ncRNAs is abnormal in GC tissue and cells; hence, detecting changes in ncRNA expression may serve as a diagnostic factor in the early stage of GC. In addition, ncRNAs directly or indirectly act on members of the Wnt/ β -catenin signaling pathway to regulate the biological behavior of GC, and EMT, angiogenesis and other pathogenic processes that may be involved in GC can serve as effective entry points for GC research. Thus, determining specific targets is paramount, and the development of targeted drugs, improvement in the accuracy of targeted drugs and reduction in drug resistance rates will offer a glimmer of hope to patients with GC. We firmly believe that a better understanding of the precise underlying molecular mechanisms will increase our knowledge of the basic mechanism of GC and provide new clues to developing valuable diagnostic and therapeutic strategies for GC.

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Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request. All information reported in this Review is based on relevant and current references.

Authors' contributions

ZS, DG, LC, WD and QY were all involved in selection of the review topic, literature data search, writing, figure and table design, and editing of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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