Crosstalk between the Notch signaling pathway and non-coding RNAs in gastrointestinal cancers (Review)

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Abstract. The Notch signaling pathway is one of the main signaling pathways that mediates direct contact between cells, and is essential for normal development. It regulates various cellular processes, including cell proliferation, apoptosis, migration, invasion, angiogenesis and metastasis. It additionally serves an important function in tumor progression. Non-coding RNAs mainly include small microRNAs, long non-coding RNAs and circular RNAs. At present, a large body of literature supports the biological significance of non-coding RNAs in tumor progression. It is also becoming increasingly evident that cross-talk exists between Notch signaling and non-coding RNAs. The present review summarizes the current knowledge of Notch-mediated gastrointestinal cancer cell processes, and the effect of the crosstalk between the three major types of non-coding RNAs and the Notch signaling pathway on the fate of gastrointestinal cancer cells.

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1. Introduction

Notch signaling is a highly conserved cell signaling pathway that is involved in multiple aspects of metazoan growth and development, including cell proliferation, differentiation and apoptosis (1). It has been suggested to be one of the most commonly activated signaling pathways in neoplastic diseases, most notably in gastrointestinal malignancies including stomach, colorectal and esophageal cancer, as well as liver and pancreatic cancers (1-3). Furthermore, the abnormal activation of Notch signaling may result from the mutation or amplification of Notch signaling components (1). As Notch signaling may regulate a plethora of genes, the dysregulation of Notch signaling often promotes tumor formation (4).

Noncoding RNAs (ncRNAs) include microRNAs (miRNAs), long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), transfer RNAs, ribosomal RNAs and small nucleolar RNAs. These nucleic acids affect every stage of gene expression, from transcription and mRNA stability to mRNA translation (5,6). At present, research has uncovered the critical function of ncRNAs in cancer pathogenesis (7). The dysregulated expression and dysfunction of specific ncRNAs has been demonstrated to drive the process of tumorigenesis in human cells. Three forms of ncRNAs that are particularly important for the regulation of gene expression in cells are miRNA, lncRNA and circRNA (8). An increasing number of studies have demonstrated that specific ncRNAs may interact with the Notch signaling pathway and serve important functions in tumor progression (9-12). Therefore, in the present review, the functional association between ncRNAs and the Notch signaling pathway is described.

2. The Notch signaling pathway

The Notch signaling pathway is composed of Notch receptors, Notch ligands, intracellular effector molecules, DNA-binding proteins and regulatory molecules. At present, four different Notch receptors have been identified in mammalian cells, which are Notch1-4. Notch receptors are single transmembrane proteins consisting of extracellular, transmembrane and intracellular domains (13). Previous studies have refined our understanding of Notch ligands. In addition to the commonly known Jagged (JAG) 1-2 and delta like canonical Notch ligand (DLL), other Notch ligands have been identified

including delta like non-canonical Notch ligand (DLK)-1 and DLK-2/epidermal growth factor-like protein 9 (14). Notch receptors and a majority of Notch ligands have also been revealed to be type I transmembrane proteins (14). In canonical Notch signaling, Notch1-4 activate the same basic signaling pathway through the use of CBF-1, suppressor of hairless, lag-1 (CSL) transcription factors (15,16). The Notch signaling pathway is activated when a Notch ligand interacts extracellularly with its specific Notch receptor between two neighboring cells (10). Upon activation, the Notch receptor is proteolytically cleaved by unidentified γ-secretase-like protease activity, which is dependent on presenilin proteins, and releases the Notch intracellular domain (NICD) (10,16). NICD then translocates into the nucleus and interacts with recombination signal binding protein for immunoglobulin κJ region (CBF-1/RBPJκ), one of the mammalian CSL transcription factors. Then, with the mastermind protein, it forms a ternary complex with CSL proteins (CBF-1/RBPJκ, Su(H), Lag-1) that binds Notch target genes in order to promote their transcription (Fig. 1) (10,14,15,17,18).

Since Notch signaling regulates the expression of multitudinous genes and modulates cell growth and metabolism, the alteration of Notch signaling activity or the deregulated expression of Notch receptors and ligands may disrupt cell physiology, thus promoting numerous disorders, including tumor malignancies (19-21). Based on its influence on various downstream functions, Notch signaling may serve oncogenic and anti-tumor functions in different types of human cancer, depending on the cellular context (22-24). In specific types of tumor or tumor stages, aberrant Notch signaling is involved in cancer recurrence, metastasis, epithelial to mesenchymal transition (EMT) and resistance to treatment (4,25-28).

3. Crosstalk between the Notch signaling pathway and ncRNAs in gastrointestinal cancers

The Notch signaling pathway and miRNAs. miRNAs are small ncRNAs ~22 nucleotides in length with important functions that include development, cell differentiation, regulation of the cell cycle and apoptosis of cells (29). They regulate gene expression by inhibiting translation or degrading mRNA transcripts (8). With further research, additional novel miRNAs have been demonstrated to function as oncogenes or tumor-suppressor genes in cancer, including gastrointestinal cancer. miRNA expression is frequently deregulated in cancer via a variety of mechanisms including amplification, deletion, mutation and epigenetic silencing (29). Furthermore, miRNAs are stable and present in various biofluids, and the level of miRNAs in body fluids reflect specific pathological states (30). These characteristics make them novel and effective biomarkers for human cancer diagnosis. It has been well documented that the Notch signaling pathway is one of the most important pathways in the regulation of the carcinogenesis and progression of gastrointestinal cancer. It may function alone, or in crosstalk with other pathways and regulatory factors that serve critical functions in tumor development. There is a notable association between miRNAs and the Notch signaling pathway, and several miRNAs both regulate and are regulated by the Notch pathway (13). In the present study, a number of typical miRNAs that interact with
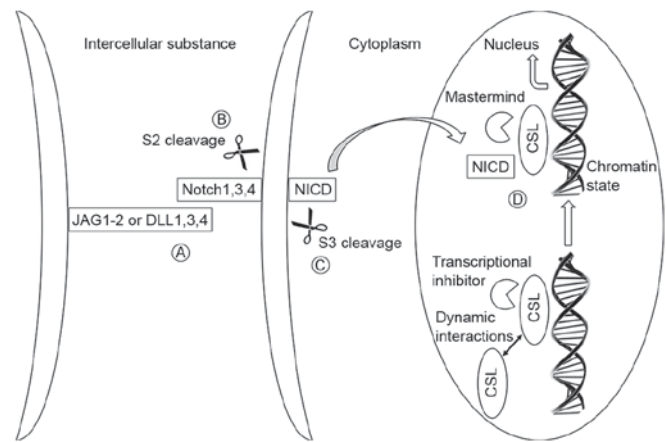

Figure 1. Functional mechanism of the Notch signaling pathway. (A) The Notch extracellular domain comes into contact with Notch ligands including JAG1,2 and DLL1, 3 and 4; (B) The NICD is then released via disintegrin- and metalloproteinase-dependent cleavage at the S2 site at the extracellular position of the membrane-spanning domain; (C) Intramembranous γ-secretase-dependent cleavage then occurs at the S3 site to transport NICD into the nucleus. (D) In the nucleus, NICD interacts with cell-specific factors CSL and Mastermind to form a ternary complex and bind Notch target genes to promote their transcription. JAG1, Jagged1; JAG2, Jagged2; DLL, delta like canonical Notch ligand; NICD, Notch intracellular domain; CSL, CBF-1, suppressor of hairless, lag 1.

Notch signaling and their functions in gastrointestinal cancer are highlighted (Table I).

Esophageal cancer. Esophageal cancer is one of the ten most common malignant tumors with the highest incidence in 2012 globally, and is more common in less developed areas than developed areas (31). The two main types of esophageal cancer are esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (31). Notch1 is one of the well-known ESCC-associated genes (32). Deviant activation of Notch signaling has been identified as associated with the initiation and evolution of esophageal cancer, and a number of miRNAs are linked with this pathway (33).

The expression level of miR-29a has been demonstrated to be markedly downregulated in ESCC tissue and the ESCC TE-1 cell line when compared with matched normal esophageal tissue and cells. In addition, induced expression of miR-29a significantly prevented cell growth and migration in the TE-1 cell line (34). Furthermore, the aforementioned study identified that the exogenous expression of miR-29a repressed ESCC cell proliferation by downregulating nuclear factor I A (NFIA) and upregulating the Hes family BHLH transcription factor 1 (Hes1). Target Scan prediction identified a potential binding site for miR-29a at the position 240-246 of the NFIA 3' untranslated region (UTR) mRNA, and identified that the knockdown of NFIA may increase Hes1 expression and inhibit the growth of TE-1 cells (34). Since Hes1 is one of the key effectors of the Notch signaling pathway, miR-29a may indirectly activate the Notch pathway, although it has no effect on the expression of Notch1 (34).

The miR-200 family is downregulated in numerous types of cancer, including ESCC. It negatively regulates the zinc finger E-box binding homeobox (ZEB), a cluster of transcription factors indispensable in cancer stem cell function and

Table I. miRNAs are associated with the Notch signaling pathway in gastrointestinal cancers.

Author, year	Names	Expression[a]	Targets	Biological events	(Refs.)
Liu et al, 2015	miR-29a	↓	Hes1	Esophageal cancer	(34)
Furukawa et al, 2013	miR-1	↓	Notch3	Colorectal cancer	(46)
Xiong et al, 2014	miR-21	↑	Notch1	Colorectal cancer	(47)
Bu et al, 2013; Ji et al, 2008; Roy et al, 2012; Ji et al, 2009; Cifarelli et al, 2015	miR-34a	↑↓[b]	Notch1	Gastric cancer/colorectal cancer/pancreatic cancer	(9,38,48,72,73)
Yang et al, 2015	miR-100	↑	HS3ST2	Gastric cancer	(37)
Jiang et al, 2016	miR-124	↓	JAG1	Gastric cancer	(40)
Sureban et al, 2011; Sureban et al, 2011	miR-144	↓	Notch1	Colorectal cancer/ pancreatic cancer	(51,74)
Jung et al, 2016	miR-148a	↓	Notch1	Liver cancer	(58)
Hashimoto et al, 2010	miR-181	↓	Notch4	Gastric cancer	(42)
Ohashi et al, 2011; Bao et al, 2011; Brabletz et al, 2011	miR-200b/c	↓	Notch3/Notch1	Esophageal cancer/ pancreatic cancer	(35,68,76)
Wang et al, 2015; Liu et al, 2014	miR-206	↓	Notch3	Colorectal cancer/ liver cancer	(56,63)
Giovannini et al, 2014	miR-221	↓	Notch3	Liver cancer	(65)
Ma et al, 2015	miR-223	↑	Notch1	Pancreatic cancer	(78)
Zhang et al, 2014	miR-224	↓	JAG1	Pancreatic cancer	(81)
Yan et al, 2016	miR-935	↓	Notch1	Gastric cancer	(43)

[a]Representing the expression of miRNAs in specific types of cancer. [b]miR-34a is upregulated in esophageal cancer while downregulated in the other gastrointestinal cancers. miRNA/miR, microRNA; Hes1, Hes family BHLH transcription factor 1; HS3ST2, heparan sulfate-glucosamine 3-sulfotransferase 2; JAG1, Jagged1.

EMT (35). Previous research has revealed that the inhibition of Notch3 leads to a downregulation of the miR-200 family and promotes EMT via the upregulation of ZEBs in ESCC (35). Additionally, transforming growth factor (TGF)-β induces ZEB1 and ZEB2 to increase the production of EMT markers in Notch3 knockdown ESCC cells, thus demonstrating that the inhibition of Notch3 promotes TGF-β-mediated EMT via the upregulation of ZEBs as a result of the decreased level of miR-200 family members in ESCC (35).

Gastric cancer. Although there is an overall downward trend of morbidity, gastric cancer remains a high-incidence neoplastic disease, particularly in eastern Asia (31). Previous studies have identified that the Notch signaling pathway serves oncogenic and tumor suppressor functions in gastric cancer (36,37). A number of miRNAs are regarded as oncogenic genes, whilst others are thought to possess tumor-suppressor capacities. Several miRNAs have been considered to possess a regulatory effect on Notch signaling, or be regulated by Notch signaling in gastric cancer.

One such miRNA that serves a tumor-suppressor function is miR-34. The miR-34 family consists of miR-34a, b and c (38). It has been demonstrated to regulate various types of digestive system tumors, including pancreatic, colorectal and gastric cancer (Table I). Notch is one of the targets of miR-34, which has an oncogenic effect on gastric cancer cells (39). Notch1 is inhibited by miR-34a, b, c, while Notch2 and 4 are inhibited by miR-34b, and Notch1-4 are all inhibited by miR-34c (38). miR-34 partially restores tumor protein P53 (p53) tumor-suppressing functions, including inhibiting cell growth and inducing apoptosis, which leads to the chemosensitization of p53-deficient gastric cancer cells (38). Furthermore, miR-34 inhibits cancer stem cell self-renewal partially through the modulation of the following downstream targets: B-cell lymphoma protein 1, Notch and high mobility group AT-hook 2 (38).

Another cancer-associated miRNA is miR-100, which was identified as an oncogene that was significantly upregulated in human epithelium-derived gastric cancer cells in a previous study (37). Silencing of miR-100 may activate Notch through an increase in the expression level of heparan sulfate-glucosamine 3-sulfotransferase 2 (HS3ST2), a target gene of miR-100 (37). miR-100 antagonism has also been demonstrated to sensitize cancer cells to chemotherapy in gastric epithelial tumor cells (37). The results of this previous study suggest that the antagonism of miR-100 may increase apoptosis in epithelium-derived gastric cancer cells via the upregulation of HS3ST2, subsequently activating the Notch signaling pathway (37). The dual function of the Notch signaling pathway in cancer genesis and development is

present in many types of cancer, however further research is required to identify the reason for these opposing effects in gastric cancer.

miR-124 is an important miRNA affecting gastric cancer progress. A previous study has revealed that miR-124 is down-regulated in gastric cancer, and that the ectopic expression of miR-124 suppresses cell growth, migration and invasion, and induces cell cycle arrest in gastric cancer cells (40). miR-124 may negatively regulate Notch1 signaling by targeting the Notch ligand JAG1, whilst the activation of Notch1 signaling via the overexpression of Notch intracellular domain (NICD) led to the repression of miR-124 expression, suggesting the existence of a regulatory feedback loop between miR-124 and the Notch1 signaling pathway in gastric cancer cells (40). miR-124-3p was also demonstrated to be significantly down-regulated in gastric cancer tissues compared with adjacent normal gastric tissues, and the mir-124-3p low-expression group demonstrated increased lymph node metastasis and lymphatic invasion than the high-expression group (41).

miR-181c has been revealed to be downregulated in gastric cancer tissues due to the methylation status in CpG islands in a region from -1297 to -987 upstream (42). A previous study demonstrated that the overexpression of miR-181c inactivated several tumorigenesis-associated pathways, including the Notch and δ-Notch signaling pathways (42). Furthermore, the aforementioned study demonstrated that there is a significant reduction of gastric cancer cell proliferation in pre-miR-181c-transfected cells, and that Notch2 and Notch4 are down-regulated by miR-181c. However, a luciferase assay revealed that miR-181c has a binding site at the Notch4 3'UTR but not at the Notch2 3'UTR, indicating that Notch4 may be a more likely target of miR-181c than Notch2 (42). The results of this previous study indicated that the inhibitory effect on cell proliferation, mediated by miR-181c may act partially through Notch4, one of its targets (42).

miR-935 has been revealed to serve a tumor suppressor function in gastric signet ring cell carcinoma (GSRCC), a unique pathological type of gastric carcinoma with high invasiveness and poor prognosis. Notably, the expression of miR-935 has been demonstrated to be lower in gastric cancer tissues compared with paired normal tissues, and is mark-edly lower in GSRCC than in non-GSRCC (43). miR-935 was revealed to suppress Notch1 expression by directly targeting the Notch1 mRNA 3'UTR, and there was a significant inverse correlation between miR-935 and Notch1 expression in gastric carcinoma (43). Furthermore, the overexpression of miR-935 negatively regulated GSRCC cell proliferation, migration and invasion, and the forced expression of NICD may rescue the tumor suppressive effects of miR-935 overexpression on GSRCC (43). This data suggests that miR-935 acts as an anti-carcinoma gene by inactivating the Notch signaling pathway in gastric cancer, particularly in GSRCC (43).

Colorectal cancer. Colorectal cancer is the second and third most frequently diagnosed cancer in 2012 globally in women and men, respectively (31). Its incidence and mortality are higher in developed areas compared with underdeveloped areas (31). Numerous cellular events are involved in the occur-rence of colorectal cancer, one of which is the deregulation of miRNAs. miRNAs are known to be associated with processes

of growth and metastasis in colorectal cancer (44). In addition, previous studies have demonstrated that the Notch signaling pathway is indispensable in the self-renewal capability of tumor-initiating cells and the inhibition of the differentiation of normal colonic epithelial cells (45), thus serving a carcinogenic function in colorectal cancer development. To date, numerous miRNAs associated with the Notch signaling pathway have been uncovered, which function together to affect the fate of colorectal cancer cells.

miR-1 is downregulated in colorectal cancer tissues, and restoring the expression of miR-1 may suppress Notch3 expression by directly binding to the Notch3 mRNA 3'UTR region (46). Notch3 signaling is involved in aberrant overex-pression of Rho guanine nucleotide exchange factor 4 (Asef), a guanine-nucleotide exchange factor (46). Activating the miR-1-Notch3-Asef pathway inhibits colorectal tumorigen-esis, as well as the migration and invasion of colorectal tumor cells (46). In addition, of the five Notch ligands, DLL4 has been suggested to induce Notch3-Asef pathway-mediated cell migration (46).

miR-21, an onco-miRNA, is upregulated in numerous solid tumors including colorectal cancer (47). Xiong *et al* (47) measured Notch1 and miR-21 expression in colorectal cancer tissues and adjacent non-tumor tissues of 102 patients by reverse transcription polymerase chain reaction analysis, western blotting and immunohistochemistry. The expres-sion levels of Notch1 and miR-21 were demonstrated to be upregulated in advanced-stage colorectal cancer and positively correlated with tumor stages. Thus, it may be theorized that crosstalk exists between Notch-1 and miR-21 in colorectal cancer development, though the mechanisms remain unclear.

miR-34 exerts a similar tumor suppressive effect on colon cancer cells, to that on gastric cancer cells. It was revealed that miR-34a and miR-34c expression were downregulated in colon cancer tissues, and that the decreased level of miR-34 in colon cancer is partially due to the hyper-methylation of the miR-34 gene promoter (48). Notch1 has been identified as a direct target of miR-34b and 34c in HeLa cells (48,49). miR-34a may reduce the expression of Notch-1 in colon cancer cells (48). Notably, research has also demonstrated that miR-34a may act as a bimodal switch to regulate Notch1, to determine the cell fate of early state dividing colon cancer stem cells (CCSCs) (9). High miR-34a levels suppress Notch signaling and promote asymmetric division, whereas low miR-34a levels upregulate Notch signaling and promote the self-renewing symmetric division of CCSCs (9).

miR-144 is regarded as a tumor suppressor gene in colorectal cancer, and the silencing of miR-144 has been associated with poor prognosis in patients with colorectal cancer (50). miR-144 targets Notch1 by binding to its 3' UTR (51). In addition, doublecortin like kinase 1 (DCAMKL1), a novel putative intes-tinal stem cell marker, has been revealed to negatively regulate miR-144 expression in colorectal cancer cells, which in turn regulates the post-transcriptional control of Notch1. Finally, the inhibition of DCAMKL1 or Notch is capable of arresting tumor growth in colorectal cancer (51).

miR-206 is downregulated in numerous types of human malignancies, including several gastrointestinal cancers, for example colorectal (52) and gastric cancer (53). Previous studies have demonstrated that Notch3 is a target of miR-206

in myoblasts and HeLa cells (54,55). Another previous study has revealed that the interaction between miR-206 and Notch3 also occurs in colorectal cancer cells (56). It was reported that miR-206 inhibited cancer cell proliferation and migration, and induced apoptosis though numerous pathways, including the Notch signaling pathway (56). The aforementioned study additionally demonstrated that miR-206 is linked with Notch-associated molecules, including JAG1 and Hes related family BHLH transcription factor with YRPW motif 1 (56). The results of this previous study suggest that miR-206 serves a tumor suppressor function in colorectal cancer cells partially via the negative control of the Notch signaling pathway.

Liver cancer. Liver cancer is the second leading cause of cancer mortality in men in 2012 worldwide (31). The rates of liver cancer mortality are highest in the east and south-east of Asia as well as in northern and western Africa, whilst China alone accounts for ~50% of the total number of cases and mortalities (31). The Notch-signaling pathway is becoming increasingly recognized to be involved in liver physiological metabolism and biological functions including liver regeneration and repair, inflammation, and carcinogenesis (3,57). Furthermore, miRNAs have been recognized to have close contact with Notch signaling and to exert a substantial biological effect on the progression of hepatocellular carcinoma (HCC). The interplay between differing miRNAs and the Notch signaling pathway is elaborated on below.

miR-148a is downregulated in HCC, and the restoration of miR-148a expression levels may reduce liver fibrosis and inhibit tumor growth (58). Conserved helix-loop-helix ubiquitous kinase (IKKa) is a direct target of miR-148a, which binds to the 3'UTR site of IKKa mRNA. It has been reported that IKKα may mediate Notch signaling activation through regulation of NUMB, Endocytic Adaptor Protein (NUMB), as NUMB may inhibit Notch signaling in HCC (59-61). The silencing of IKKa may induce hepatocytic differentiation, a similar effect to the upregulation of miR-148, whilst the overexpression of Notch2 may reverse this phenomenon (58). The results of this previous study suggest that miR-148a is a novel negative regulator of the IKKα/NUMB/Notch signaling pathway that directly targets IKKα expression (58), and that miR-148a may be a potential target for molecular therapy and allow the prevention of HCC.

miR-206 is known to regulate cell proliferation and migration and is involved in numerous malignancies, and its tumor suppressor function in colorectal cancer has been elaborated above. Previous studies have demonstrated that miR-206 has a similar effect in HCC (62). Notch3 has been demonstrated to be significantly upregulated in the cytoplasm of HCC samples. Additionally, Notch3 and one of its targets, Hes1, were downregulated in miR-206 overexpressing HepG2 cells (63). This previous study also revealed that miR-206 overexpression promotes apoptotic cell death, induces cell cycle arrest and impairs cellular migration in HepG2 cells (63). Taken together, the results of the aforementioned study indicate that the effects of miR-206 on HCC cells are potentially partially dependent on the Notch3 signaling pathway (63). Nevertheless, the specific underlying mechanisms of this action remain unclear.

miR-221, a tumor suppressor gene may be indirectly regulated by the Notch signaling pathway. Previous studies have demonstrated that Notch3 controls miR-221 expression through Hes1, one of the primary targets of Notch signaling (64), and it was later demonstrated that it may bind to the miR-221 gene promoter (65). Furthermore, miR-221 has been revealed to be significantly decreased in HCC, and the restoration of miR-221 resulted in the increase of the expression level of p53, a well-known tumor suppressor gene, through the repression of mouse double minute protein 2 (MDM2) (66). The silencing of Notch3 is strengthened by the effect of MDM2 inhibitors (65). Therefore, the suppression of p53 by Notch3 is controlled partially by the feed-forward circuit involving p53, miR-221 and MDM2 (65).

Pancreatic cancer. Pancreatic cancer is the leading cause of cancer associated mortality worldwide in 2012 (31). In previous years there has been a trend of growing rates of morbidity, particularly in less developed areas (31,67). The one factor responsible for the poor prognosis of this disease is the absence of specific symptoms to allow for early detection (68,69). It has been noted that Notch signaling is required for pancreatic ductal adenocarcinoma (PDAC) progression (70). One previous study revealed that Notch signaling serves an oncogenic function at an early stage, and serves a tumor suppressive function at an advanced stage in pancreatic intraepithelial neoplasia pancreatic cancer, one of the precursor lesions of PDAC (71). This previous study also suggested that a number of miRNAs are associated with Notch signaling and may have a major impact on the occurrence and development of pancreatic cancer. Elucidating the underlying mechanism of disease is necessary in order to further our understanding of this malignancy.

The miR-34 family, a well-known tumor suppressor miRNA family, has functions in other gastrointestinal cancers that were elaborated on earlier in this review. Previously, the interaction between miR-34 and Notch signaling has been confirmed to also exist in pancreatic cancer. The miR-34 family has differing effects on Notch signaling members, as miR-34a, b and c negatively control the expression of Notch1 and Notch2, but have a limited effect on Notch3 in the pancreatic cancer cell line MiaPaCa2 (72). In addition, the overexpression of miR-34a by metformin and rapamycin was demonstrated to inactivate the Notch signaling pathway by directly binding to Notch, which resulted in the prevention of pancreatic cancer growth in obese pre-diabetic mice (73).

The function of miR-144 in pancreatic cancer is similar when compared with colorectal cancer. It has been demonstrated that miR-144 may negatively regulate Notch1 expression levels by binding to the 3'UTR site in human pancreatic cells (74). Furthermore, it was also demonstrated that DCAMKL1, a microtubule-associated kinase regarded as a pancreatic stem cell marker, downregulates pre-miR-144 levels in human pancreatic cancer cells and normal mouse pancreas cells (74). The results of this previous study suggest that DCAMKL1 may induce the activation of Notch signaling by silencing miR-144 expression, which regulates EMT in pancreatic cancer (74).

The miR-200 family is composed of miR-200a, miR-200b, miR-200c, miR-141 and miR-429. Research has identified that Notch1 is one of the target genes of the miR-200 family which includes (miR-200b, miR-200c), whilst JAG1 may be regulated by miR-200b, c and miR-141 by direct binding to

Table II. Long noncoding RNAs and their association with the Notch signaling pathway in cancer.

Author, year	Names	Expression	Targets	Biological events	(Refs.)
Pei and Wang, 2015	GAS5	↓	Notch1	Breast cancer	(101)
Wang *et al*, 2015	NALT	↑	Notch1	Pediatric T-cell acute lymphoblastic leukemia	(11)
Hang *et al*, 2015	AK022798	↑	Notch1	Gastric cancer	(85)
Tang *et al*, 2014	Linc00974	↑		Hepatocellular carcinoma	(87)
Trimarchi *et al*, 2014	LUNAR1	↑	Notch1	T-cell acute lymphoblastic leukemia	(102)

GAS5, growth arrest specific 5; NALT, NOTCH1 associated lncRNA in T-cell acute lymphoblastic leukemia 1; AK022798, *Homo sapiens* cDNA FLJ12736 fis, clone NT2RP2000327; Linc00974, long intergenic non-protein coding RNA 974; LUNAR1, leukemia-associated non-coding IGF1R activator RNA 1.

the JAG1 3'UTR (75,76). The inhibition of Notch signaling activity via the knockdown of JAG1 may reduce the proliferation and increase the apoptosis of the Panc1 cell line (76). The EMT activator, ZEB1, has also been revealed to activate Notch signaling by silencing miR-200 family members (miR-141 and 200c) in pancreatic cancer cells (76). In addition, miR-200b may regulate EMT partially through targeting Notch1 in pancreatic cancer cells (68).

miR-223 has been demonstrated to serve a critical function in the regulation of cell proliferation, apoptosis, migration and invasion in pancreatic cancer cells (77,78). Ma *et al* (78) revealed that the inhibition of miR-223 may reduce cell motility and invasion, as well as reverse EMT in gemcitabine-resistant (GR) pancreatic cancer cells. Furthermore, it was identified that F-box and WD repeat domain-containing 7 (Fbw7) was markedly decreased in GR cells whilst the Fbw7 substrate Notch1 expression level was significantly increased. Silencing miR-223 may upregulate Fbw7 expression levels and downregulate Notch1 expression levels in GR pancreatic cancer cells (78). As previously mentioned, Notch signaling has the potential to mediate EMT in pancreatic cancer, and the results of this previous study suggest that the EMT-mediating effect of miR-223 on pancreatic cancer may be partially due to the activation of the Notch signaling pathway, via the downregulation of Fbw7.

miR-224 has been revealed to be upregulated in various types of tumor when functioning as an oncogene (79-81). Nevertheless, a previous study identified that miR-224 was downregulated in mucinous cystic neoplasms (MCNs) of the pancreas (81). It has been demonstrated that JAG1 expression levels are significantly upregulated in tumor tissues when compared with normal tissues, and miR-224 regulates JAG1 expression by binding JAG1 mRNA at its 3'UTR (81). Notch signaling is well-documented to be associated with various pancreatic diseases (81,82), including tumorigenesis and tumor progression (81). Therefore, it may be speculated that miR-224 has the capacity to stimulate oncogenesis in MCNs through the negative control of JAG1 (81).

In addition, Notch1 has been revealed to be negatively correlated with let-7b and c expression, yet is positively correlated with miR-21 expression in the pancreatic cancer cell line AsPC-1. Furthermore, the overexpression of Notch1 increased the expression of miR-21, a potential oncogenic regulator, whilst decreasing the expression of miR-200b, miR-200c, let-7b and let-7c in AsPC-1 cells, suggesting that Notch1 may be involved in regulating the expression of these genes (68), although the mechanism and potential function remains unclear.

The Notch signaling pathway and lncRNAs. LncRNAs, which may be >200 nucleotides in size, account for the largest portion of RNA genes transcribed in cells. These transcripts seem to exert an effect on a diverse number of cellular maintenance functions including protein scaffolding, chromatin looping and the regulation of mRNA stability (8). LncRNAs are now regarded as a novel class of non-coding RNAs that contribute to cancer development and progression (83). Identical to miRNAs, different lncRNAs may serve tumor-promoting or tumor-suppressing functions in the formation and development of a tumor (84). Despite the limited number of studies demonstrating the association between lncRNA and the Notch signaling pathway, certain studies have revealed several lncRNAs that are associated with Notch signaling in gastrointestinal cancers (Table II).

The lncRNA AK022798 is upregulated in gastric cancer and serves important functions in tumorigenesis, as a previous study suggested (85). The silencing of lncRNA AK022798 by specific siRNAs not only decreases the expression of multidrug resistance-associated protein 1 (MRP1) and P-glycoprotein, but also enhances the apoptotic activity of certain cisplatin-resistant gastric cancer cell lines (including SGC7901/DDP and BGC823/DDP cell lines) (85). This previous study also suggested that Notch1 is significantly upregulated in SGC7901/DDP and BGC823/DDP cells (85). The activation of Notch1 via transfection of the Notch1 overexpression vector plasmid may promote lncRNA AK022798 expression and increase the expression of MRP1, P-glycoprotein, and reduce the apoptosis of SGC7901 and BGC823 cells (85). The results of this previous study suggest that Notch1 may promote cisplatin-resistant gastric cancer formation and inhibit apoptosis, at least partially through upregulating the expression of lncRNA AK022798 (85), whilst the regulation mechanism remains unclear.

An accumulating number of studies have demonstrated that a class of lncRNAs are dysregulated in HCC and are associated with tumorigenesis, metastasis, prognosis and diagnosis (86).

Table III. Circular RNAs as potential biomarkers for gastrointestinal cancer.

Author, year	Names	Expression	Biological events	(Refs.)
Li *et al*, 2015	ITCH	↓	Esophageal cancer	(103)
Li *et al*, 2015	hsa-circ-002059	↓	Gastric cancer	(95)
Wang *et al*, 2015	hsa-circ-001988	↓	Colorectal cancer	(96)
Xie *et al*, 2016	hsa-circ-001569	↑	Colorectal cancer	(94)
Qin *et al*, 2016	hsa-circ-0001649	↓	Hepatocellular carcinoma	(97)
Shang *et al*, 2016	hsa-circ-0005075	↑	Hepatocellular carcinoma	(98)

ITCH, Itchy E3 ubiquitin protein ligase.

An example of such an lncRNA is Linc00974. It was demonstrated that Linc00974 was upregulated in HCC owing to an abnormal hypo-methylation in the promoter. Furthermore, Pearson correlation analysis indicated a positive correlation between Linc00974 and KRT19 expression that was later reported as a biomarker for tumor growth and metastasis in HCC (87). Knockdown of Linc00974 or keratin 19 (KRT19) by short hairpin RNA inhibited cell proliferation and migration, and induced cell apoptosis in HCC. Furthermore, KRT19 expression levels were downregulated when Linc00974 was knocked down, and this was reversed when miR-642 was absent, indicating that Linc00974 may act as a 'sponge' to absorb miR-642, which would normally suppress KRT19 (87). In addition, the same previous study also revealed a markedly reduced level of Notch1, JAG1, and deltex E3 ubiquitin ligase 1 in KRT19 knockdown Huh7 cells. (87). Based on the results of this previous study, it was proposed that Linc00974 may induce the upregulation of KRT19 via competing endogenous RNA interactions, resulting in the activation of the Notch signaling pathway (87).

The Notch signaling pathway and circRNAs. CircRNAs are a novel class of ncRNAs characterized by the presence of a covalent bond linking the 3' and 5' ends generated by back-splicing (88). They have previously demonstrated substantial capabilities as gene regulators in human cell progression, including in tumor development, and have been revealed to be abundant, conserved and stable in the cytoplasm (89,90). Despite the limited recognition of the functional mechanisms of circRNAs in the progression of tumors, circRNAs may act as miRNA 'sponge'. For instance, ciRS-7 was demonstrated to bind miR-7 specifically to prevent the partial biological function of the latter, including regulating epidermal growth factor receptor signaling in tumor cells (91,92). Similarly, in another circRNA sex-determining region Y (SRY), functions by controlling the expression level of miR-138 and inhibits its biological effects, mainly including the enhancement of proliferation, migration and invasion in tumor cells (92). Previously, a novel circRNA, circHIPK3, was reported to be significantly upregulated in HCC compared with corresponding normal tissues and promoted HCC cell proliferation (93). This previous study also noted that circHIPK3 served as a sponge for multiple miRNAs and may directly bind to miR-124 in order to inhibit the activity of the latter (93). miR-124, as

aforementioned, possesses the capability to negatively regulate the Notch signaling pathway, thus it may be hypothesized that circHIPK3 activates the Notch signaling pathway by preventing miR-124 expression. Additionally, circ001569 has been demonstrated to be upregulated in colorectal cancer tissues, and may promote colorectal cancer cell proliferation and invasion by regulating miR-145 and its targets (94).

CircRNAs are not only associated with cancer-related miRNAs, but also regulate cancer-associated pathways (92). Since miRNAs participate in various signaling pathways to exert an effect on the fate of tumor cells, there is the potential that circRNA-miRNAs may also contribute to this function. Furthermore, circRNAs may regulate mRNA transcription and control protein production (90). In addition, several specific circRNAs possess the potential to become novel biomarkers in gastrointestinal cancers (Table III), including has-circ-002059, hsa-circ-001988, hsa-circ-0001649 and circ-0005075. Hsa-circ-002059, hsa-circ-001988 ahashsa-circ-0001649 were revealed to be significantly downregulated in gastric cancer, colorectal cancer and HCC tissues, respectively (95-98), whilst circ-0005075 expression level was significantly higher in HCC (98). At present, there is no study that specifically investigates the association between circRNAs and the Notch signaling pathway. However, considering that circRNAs are believed to act as inhibitors of miRNA function by binding to a specific miRNA (88), this may indicate a potential association with the Notch signaling pathway similar to miRNAs (47).

4. Conclusion

NcRNAs, including miRNAs, lncRNAs and circRNAs, are the main focus of the present review and have the potential to be used as novel biomarkers for cancer in clinical applications. Thus, they may be used for the early detection of cancer, prognostic prediction and sensitivity assessment of chemotherapy and radiotherapy in the future (99). Emerging data suggests that ncRNAs are closely associated with the Notch signaling pathway, and that they serve functions in a variety of types of tumor. At present, there is a comparatively thorough understanding of the interactions between miRNAs and Notch signaling in the development of gastrointestinal cancers. Nevertheless, the exact mechanism by which the other two types of ncRNA (lncRNAs and circRNAs) interact with Notch signaling in gastrointestinal cancer remains unclear. Further

studies are required to explore the structure and functional features of these ncRNAs, as well as their effects on malignancies. In therapy, contraposing the oncogenic potential of Notch signaling, Notch inhibitors including γ-secretase inhibitors (GSIs), are effective in inhibiting Notch signaling (4). GSIs have been demonstrated to prevent cell proliferation, migration and invasion in pancreatic cancer (100). Therefore, the present review hypothesizes that the use of a combination of Notch inhibitors and ncRNA analogues may be a beneficial treatment for gastrointestinal cancers. Nevertheless, further studies examining Notch signaling are required, and the novel ncRNAs associated with Notch signaling remain to be identified, notably circRNAs.

Acknowledgements

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