Pathology - Research and Practice 215 (2019) 152620

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

NOTCH signaling pathway and non-coding RNAs in cancer

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ARTICLE INFO

Keywords:
Non-coding RNA
Notch signaling
Cancer

ABSTRACT

Malignant tumors, known as cancer, seriously threaten human life and health. Cancer has the characteristics of abnormal cell differentiation, proliferation, invasion and metastasis. As a result, cancer often accompanied by poor prognosis and a lower survival rate. Notch signaling pathway is a highly conserved system in many multicellular organisms, and which has been proved to play a biological role in many cancers. In recent years, increasing evidence has shown that non-coding RNA can not only activate or inhibit NOTCH pathway, but also regulate the occurrence and development of cancer through NOTCH pathway. Therefore, we focus on the cancer-NOTCH-non-coding RNA axis in this review, and provide new ideas for cancer therapy.

1. Introduction

1.1. Progresses in cancer research

Malignant tumors, collectively known as cancer. Cancer cells have the characteristics of rapid proliferation and metastasis. According to GLOBOCAN 2018, there were more than 18 million new cancer cases and 9 million cancer deaths [1]. Due to the self-sustaining and adaptive process that interacts dynamically with its microenvironment, cancer continues to threat patients, researchers, and clinicians. So that how to prevent and treat cancer more effectively is a big problem we are facing. At present, lung cancer, breast cancer (BC), prostate cancer (PCa) and colorectal cancer (CRC) are high-risk cancers threatening human health.

Among the most prevalent and fatal cancer diagnosed with the frequency, lung cancer is considered as a major concern. It is the second deadly cause of cancer-related deaths in both male and female [1]. Lung cancer includes non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC can further divided into lung squamous cell carcinoma (LUSC), lung adenocarcinoma (LUAD) and large cell type. About 40% of NSCLC patients have brain metastasis (BM) during the disease [2–4].

Worldwide, BC is the first deadly cause of cancer-related deaths in female [1]. There were more than two million newly diagnosed BC cases in 2018, accounting for approximately 30% of new cancer cases among women. China is one of the countries with lower morbidity of BC. However, in recent years, the incidence increased significantly. An annual increase of 3% to 4%, more than 1% to 2% of the world level [1]. Resistance to drugs and metastasis of BC cells are major challenges with current therapy. Almost 40% of advanced HER2-positive BC patients will transfer to central nervous system (CNS), and a half of them will die from the course of brain progression [5–7].

PCa is one of the most common cancer in men, ranking as the second most prevalent cancer [1]. In the past year, there was almost one million PCa new cases and more than three hundred thousand associated deaths worldwide, being the fifth leading cause of cancer death in men. Only a few patients present with metastatic disease, but up to half of detected cases will eventually develop metastasis [8–10].

In 2018, CRC ranks third in terms of incidence meanwhile second in terms of mortality. In the past decade, cancer incidence and mortality have increased in many countries, including China, Russia and Brazil [1]. Almost one in four of patients present with metastatic disease and approximately half of patients will develop metastases. There are many reasons for CRC. Gender, diet, environment, microorganisms and immunity can affect the development of CRC [11–14].

1.2. NOTCH signaling pathway

In 1917, Morgan et al. discovered the Notch gene in the mutant Drosophila. The deletion of the Notch gene would lead to a breach in the wings of Drosophila, so it known as 'Notch'. In 1983, Artavanis et al. reported that they cloned Notch gene and found that it encoded Notch protein [15]. Later studies found that Notch was widely expressed in many species and highly conservative in evolution, affecting cell differentiation, proliferation and apoptosis, and related to the occurrence and development of cancer.

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https://doi.org/10.1016/j.prp.2019.152620
Received 21 June 2019; Received in revised form 20 August 2019; Accepted 1 September 2019

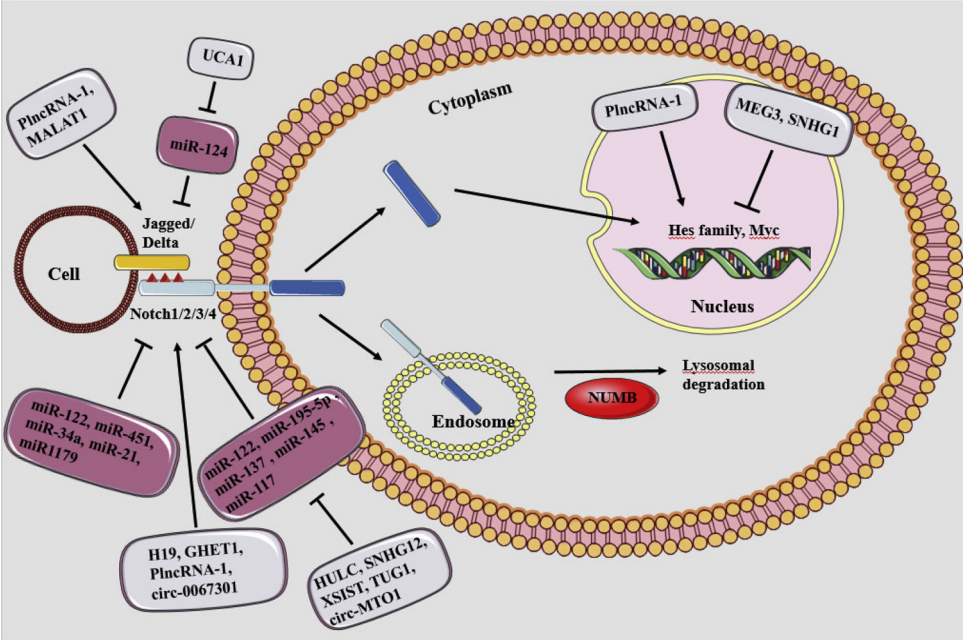

Fig. 1. Non-coding RNAs takes parts in cancer regulation through NTOCH signaling pathway.

There are four different Notch receptors in mammals: *Notch1*, *Notch2*, *Notch3* and *Notch4*. Notch signaling is essential in neurogenesis, angiogenesis, hematopoiesis, myocyte production, epithelial-mesenchymal transition (EMT) and regulation of homeostasis in tissues. Notch receptor is a transmembrane protein. It consists a large extracellular domain, which binds to Notch's extracellular domain in a calcium-dependent manner. Abnormal NOTCH signals can lead to important signaling events in cancer and autoimmune diseases [16–19].

2. Non-coding RNAs take parts in cancer regulation through NOTCH signaling pathway

Researches have explored many mechanisms for non-coding RNAs (ncRNAs), such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs). NcRNAs can regulate gene transcription, translation and protein modification, participate in important life processes such as metabolism and development, and play a certain role in the occurrence and recovery of human diseases. NcRNA can take parts in NOTCH signaling pathway through functioning as regulators of respective target genes (Fig. 1).

2.1. MiRNAs and NOTCH signaling pathway in cancers

Recently, emerging evidences showed that miRNAs could serve as regulators during biological and pathological tumor progression. Notch signaling was affected by many pathways and factors jointly where miRNAs appears to play a major role (Table 1).

Among the most prevalent and fatal cancer diagnosed with the frequency, lung cancer is considered as major concern. Nisansala Chandimali et al. found a low miR-122 level in NSCLC. Meanwhile, miR-122 negatively correlated with the level of peroxiredoxin-II. Overexpressed miR-122 reduced *Notch1* and *Hes1* in A549 stem cells. Through blocking NOTCH signaling pathway, miR-122 decreased gefitinib resistance of A549 stem cells, suppressed cell proliferation and migration [20]. Haiwei Zhang et al. reported that high miR-223 level arrested NOTCH signaling pathway in NSCLC, and abated cell resistance to erlotinib [21]. Jiayuan Huang et al. discovered that in LUAD, AP-1 negatively regulated miR-451, and the later directly targeted *MDR-1*. *Notch1* also opposite regulated miR-451, and further enhanced cell chemotherapy tolerance [22].

BC often accompanied by high mortality. In BC, Xianhui Wang et al. proved that miR-146a directly targeted the 3′-untranslated coding regions (UTR) of *NUMB* for inhibiting translation. Moreover, KLF8-up-regulated expression of miR-146a led to activating of Notch signaling, and induced pro-tumorigenic mammary stem cells [23]. Le Kang et al. testified that miR-34a exerted anti-tumor effects in BC. Via functionally targeting *Notch1*, miR-34a blocked NOTCH pathway, consequently adjusted cell propagation, migration, and invasion [24]. Xiaoli Peng et al. identified that deletion of miR-34a or upsurged miR-21 significantly lessened the effects of 3,6-dihydroxyflavone (3,6-DHF) on *Notch1* and *PTEN*. Then further suppressed BC cells development [25]. Sabrina De Carolis et al. illustrated that over-expressed Carbonic Anhydrase isoenzyme 9 (CA9) acted as an endogenous miRNA sponge, increased two miR-34a targets *JAG1* and *Notch3* [26]. Xiongwei Deng et al. concluded that miR-34 was an endogenous tumor suppressor in triple-negative BC. Intracellular restoration of miR-34a inhibited BC cell migration via directly targeting *Notch1* [27]. W.-J. Li et al. gave the evidence that low miR-1179 level was associated with shorter overall survival. Up-regulating miR-1179 reduced *Notch1*, *Notch4* and *Hes1*, finally blocked cells proliferation, and metastasis in BC [28]. Yifang-Shui et al. showed that miR-130b-3p directly targeted *DLL1* and then arrested NOTCH signaling. High level of miR-130b-3p suppressed invasion and migration of BC [29]. Haitao Guan et al. revealed that levels of *JAG1*, *Hes1* and *Hey1* were reduced significantly after miR-101 mimic transfected. Through blocking NOTCH pathway, miR-101 inhibited BC cell proliferation and promoted cell apoptosis [30]. Wang HL et al. put forward that *Notch1* was the target gene of miR-449a. Up-regulation of miR-449a promoted cell proliferation and migration [31].

In PCa, Maria Kashat et al. raised evidence that the down-regulation of miR-34a was partly due to hypermethylation of its promoter. Lower miR-34a level activated NOTCH pathway because of directly targeting *Notch1* [32]. Jayant K Rane et al. sorted out conclusions from transcriptomic microarray data that miR-542-5p negatively related to NOTCH reporters, *Hes1* and Survivin in PCa stem-like cells [33].

In the study of neuroblastoma cells, microarray-based miRNA expression analyses results showed that miR-200a/b/c and miR-34b/c could influence NOTCH signaling pathway. They respectively targeted *Notch1* in vitro. Furthermore, overexpression of miR-200 and miR-34 led to abated *Notch1* and raised cell toxicity and cell death markers [34]. P. Bettinsoli et al. found that miRNA-34 family members directly

Table 1
MiRNAs targeting NOTCH pathway related cancer progress.

Cancer types	MicroRNAs	Genes or pathway	Functions	Reference
Lung cancer	miR-122	*Notch1, Hes1*	Inhibited gefitinib resistance	[20]
	miR-223	NOTCH	Inhibited erlotinib resistance	[21]
	miR-451	*MDR-1, Notch1*	Promoted cell chemotherapy tolerance	[22]
Breast cancer	miR-146a	*NUMB*	Induced stemness	[23]
	miR-34a	*Notch1, PTEN, JAG1, Notch3*	Inhibited cell propagation, migration, and invasion	[24,25,26] [27]
	miR-21	*Notch1, PTEN*	Inhibited cell propagation, migration, and invasion	[25]
	miR-1179	*Notch1, Notch4, Hes1*	Inhibited cell propagation, migration, and invasion	[28]
	miR-130b-3p	*DLL1*	Inhibited invasion and migration	[29]
	miR-101	*Hes1, Hey1*	Inhibited cell proliferation and promoted cell apoptosis	[30]
	miR-449a	*Notch1*	Promoted cell proliferation and migration	[31]
Prostate cancer	miR-34a	*Notch1*	Inhibited cell propagation	[32]
	miR-542-5p	*Hes1*	Inhibited stemness	[33]
Neuroblastoma	miR-200	*Notch1*	Rised cell toxicity	[34]
	miR-34	*Notch1, Notch2, DLL1, c-Met*	Inhibited cell proliferation and rised cell toxicity	[34,35,36]
	miR-524	*Smad2, Tead1, Hes1*	Inhibited cell propagation, migration, and arrested cell cycle	[37]
Glioma	miR-139-5p	*Notch1*	Inhibited EMT	[38]
	miR-524-5p	*Jagged1, Hes1*	Inhibited cell growth	[39]
	miR-129	*Notch1*	Promoted autophagy	[40]
	miR-92-3p	*Notch1*	Inhibited cell growth	[41]
Gastric cancer	miR-124	*JAG1, NICD, Hes1, Hes5*	Inhibited cell propagation, migration, and invasion	[42,43,44]
	miR-34	*Notch1-4*	Inhibited cell growth and stemness	[45]
	miR-935	*Notch1*	Inhibited cell propagation, migration, and invasion	[46]
	miR-449a	NOTCH	Inhibited cell propagation, migration, and invasion	[47]
	miR-140-5p	NOTCH	Inhibited cell propagation, migration, and invasion	[48]
	miR-181c	*Notch4*	Inhibited cell growth	[49]
	miR-133a	*Notch1-3*	Inhibited cell propagation, migration, and invasion	[50]
	miR-151	*Notch1*	Promoted tumorsphere formation and metastasis	[51]
Colorectal carcinoma	miR-34a	*Notch1, NUMB, JAG1*	Inhibited cell growth	[52] [53]
	miR-200	*Notch1-3, Hey1*	Inhibited cell growth	[54]
	miR-142-3p	NOTCH	Induced stemness	[55]
	miR-1280	*JAG2*	Inhibited cell growth	[56]
	miR-598	*JAG1*	Promoted cell metastasis and EMT	[57]
	miR-195-5p	*Notch2*	Inhibited stemness	[58]
	miR-449a	*Notch1*	Inhibited cell propagation, migration, and invasion	[59]
	miR-139-5p	*Notch1*	Induced cell sensitized to 5-FU	[60]
Hepatocellular carcinoma	miR-34	*Notch1*	Lessened resistance to sorafenib or chemotherapeutic drugs	[61]
	miR-1388	NOTCH	Promoted cell growth	[62]
	miR-148a	*Notch2, Hes1, Hey1*	Inhibited cell growth	[63]
	miR-760	*Notch1, Hes1*	Inhibited cell growth	[64]
	miR-199a-3p	*JAG1*	Inhibited cell growth	[65]

targeted *DLL1*, and high miR-34 level dropped cell proliferation [37]. KaiZhao et al. reported that miR-524 functioned as an anti-oncogene in glioblastoma (GBM). MiR-524-3p directly hindered *Smad2*, miR-524-5p impeded *Tead1*, and they both targeted *Hes1*. Through restraining NOTCH pathway, miR-524 inhibited cell proliferation and migration, and arrested GBM cell cycle [36]. Yunqing Li et al. achieved experimental data that miR-34a bound to the 3′-UTRs of multiple genes, such as *c-Met*, *Notch1* and *Notch2* [38].

In GBM, Jianlong Li et al. discovered that miR-139-5p directly attenuated *Notch1*, and then suppressed the EMT process of GBM [39]. Lingchao Chen et al. proved that miR-524-5p directly targeted *Jagged1* and *Hes1*. Higher miR-524-5p levels was associated with better survival rates [40]. Xiong Chen et al. testified that over-expressed miR-129 specifically bound to *Notch1* to promote cell autophagy. Thus to restrain tumor growth [41]. Hang Song et al. identified that miR-92-3p could bind to the 3′-UTR of *Notch1* in GBM stem-like cells (GSCs) [42].

Gastric signet ring cell carcinoma (GSRCC)–a rare pathological gastric carcinoma (GC)–has an extremely invasion ability and with a poor prognosis. Haijuan Xiao et al. illustrated that expression level of miR-124 negatively related with *JAG1*, *NICD*, *Hes1* and *Hes5*. Through blocking NOTCH, miR-124 inhibited cell invasion, migration, and proliferation, arrested cell cycle and promoted cell apoptosis [43]. Lei Jiang et al. concluded that miR-124 negatively regulated *JAG1* and then blocked NOTCH pathway. Excessive miR-124 could suppress cell growth, migration and invasion and arrested cell cycle in GC [44]. Yangyang Pan et al. gave evidences that high level of miR-124 restrained cell proliferation, migration and invasion. Furthermore, miR-124 obstructed *JAG1* in terms of mechanism [45]. Qing Ji et al. showed some experimental results between miR-34a/b/c and NOTCH signaling pathway. MiR-34a/b/c mimics all blocked *Notch1* and HMGA2 protein level, miR-34b mimic decreased protein level of *Notch2* and *Notch4*, and miR-34c mimic down-regulated *Notch1-4*. All in all, overexpressed miR-34 inhibited GC development and stem cell self-renewal or differentiation [35]. Chao Yan et al. revealed a lower level of miR-935, which directly targeted *Notch1*. Down-regulation of *Notch1* inhibited cell proliferation, migration and invasion of GSRCC [46]. Fangxi Xue et al. put forward that high miR-449a level was adverse to cell proliferation and migration of gastrointestinal stromal tumor (GIST) via inactivating NOTCH signaling pathway [47]. Wu K et al. raised evidences that miR-140-5p negatively regulated THY1 and suppressed NOTCH signaling pathway. Up-regulated of miR-140-5p arrested cell proliferation, migration and invasion, and promoted cell apoptosis of GC [48]. Yutaka Hashimoto et al. demonstrated that *Notch4* was one target of miR-181c. MiR-181c was silenced through methylation and served as an anti-oncogene [49]. Xinbo Chen et al. found that miR-133a directly targeted PSEN1, further down-regulated expression of *Notch1/2/3*. Over-expressed miR-133a blocked GC cell growth and metastasis abilities [50]. Kai-Wen Hsu et al. reported that miR-151 could induce *Notch1* and elevated tumorsphere formation and metastasis [51].

In CRC, Pengcheng Bu et al. discovered that miR-34a directly suppressed *Notch1* and *NUMB*. However, they formed an incoherent feed-forward loop (IFFL) motif. In detail, miR-34a binded to the 3′-UTRs of *Notch1* and *NUMB*, however, *NUMB* inhibited *Notch1* via promoting its internalization and degradation [52]. Xuemei Zhang et al. proved that

miR-34a specifically targeted 3′-UTRs of *Notch1* and *JAG1*. Consequently, abundant miR-34a restrained CRC metastasis via suppressing NOTCH pathway [53]. MiR-200 family includes miR-200a/b/c, miR-141 and miR-429. Mohammed A. Suliman et al. testified that, under treated with niclosamide, there was a negative relation between miR-200 family level and NOTCH related proteins (*Notch1/2/3* and *Hey1*) [54]. Hongdan Li et al. identified that miR-142-3p was conducive to NOTCH signaling pathway via directly decreasing *NUMB*. MiR-142-3p spurred bone marrow-derived mesenchymal stem or stromal cells (BM-MSC) to release exosomes and then promoted CRC stemness [55]. Bingqing Huang et al. recently illustrated that *JAG2* was one of the downstream targets for tRF/miR-1280. High level of tRF/miR-1280 repressed CRC cell growth in vivo and vitro [56]. Chen et al. concluded that miR-598 displayed a notable loss expression level. *JAG1*, which could interact with *Notch1* and *Notch2* to activate NOTCH pathway, worked as a target of miR-598. Up-regulation of miR-598 promoted cell metastasis and EMT progress [57]. Yinghu Jin et al. gave evidences that miR-195-5p binded to the 3′-UTR of *Notch2*. High level of miR-195-5p decreased *Notch2* and inhibited the stemness of CRC cells [58]. Yun Feng et al. showed that miR-449a directly targeted *Notch1* to suppress cell growth and metastasis [59]. Heyong Liu et al. put forward that miR-139-5p targeted *Notch1*, and inhibited MRP-1 and BCL-2 as well. High level of miR-139-5p blocked NOTCH pathway and induced cell sensitized to 5-FU [60].

Multi-drug resistance (MDR) is a significant barrier to effective treatment of advanced hepatocellular carcinoma (HCC). Hui Jia et al. raised a microRNA-34a could knockdown *Notch1* significantly, and miR-34b/c decreased *Notch1* with lower effect than miR-34a. MiR-34a contributed mainly to *Notch1* knockdown in HCC cells. Up-regulation of miR-34a reduced *Notch1* and then lessened MDR to sorafenib or chemotherapeutic drugs [61]. Shao-jun Zhou et al. expressed that the HBx-miR-3188-ZHX2-*Notch1* signaling pathway regulated the pathogenesis and development of hepatitis B virus (HBV)-related HCC. MiR-1388 directly inhibited ZHX2. Repressed ZHX2 led to promoting CREB-mediated induction of miR-3188 and NOTCH signaling [62]. Kwang Hwa Jung et al. found that miR-148a positively correlated to *NUMB*, but negatively related to *Notch2*, *Hes1* and *Hey1*. MiR-148a inhibited NOTCH pathway to block tumor growth [63]. Tao Tian et al. reported that miR-760 decreased, and negatively regulated *Notch1* and *Hes1* [64]. Kewei Ren et al. discovered that miR-199a-3p significantly down in HCC. Through cutting *JAG1*, miR-199a-3p reduced HCC cell growth [65].

2.2. LncRNAs and NOTCH signaling pathway in cancers

LncRNAs are usually over 200 nt, hence their mechanisms are more complex. They cannot only target genes to affect NOTCH pathway, but also affect the transcription of downstream genes in nucleus. Furthermore, lncRNAs in cytoplasm can act as sponges of miRNA (Table 2).

In NSCLC, Xi Wang et al. proved that miR-137 was down-regulated and directly targeted *Notch1*. LncRNA XIST acted as an oncogene and absorbed miR-137. Excessive XIST was advantageous to cell growth and EMT progress [66]. Trimarchi et al. T testified that in Estrogen Receptor-α positive (ER +) BC, lncRNA H19 was regulated by NOTCH and HGF signaling together. Blocking of NOTCH and HGF inhibited H19 and decreased cell resistance to Fulvestrant and Tamoxifen [67]. In PC, Zhu Y et al. identified that up-regulated lncRNA GHET1 increased *Notch1* and induced cell growth [69].

In GBM, Gao K et al. illustrated that lncRNA ZFAS1 expressed a lot and correlated with poor survival. Loss of ZFAS1 caused deactivation of NOTCH pathway and decreased EMT process of GBM cells [71]. Wang X et al. concluded that lncRNA PlncRNA-1 significantly activated the Notch signal pathway through regulating *Notch1*, *JAG1*, and *Hes1* expression. Consequently promoted cell proliferation, colony formation, and inhibited cell apoptosis [72]. Zhankun Zhu et al. gave evidences that the lncRNA LINC00152 adsorbed miR-4775. The target gene CKD6 of miR-4775 could active NOTCH pathway, thus, the LINC00152/ miR-4775/ CKD6 axis regulated GBM cell growth, migration, and invasion [73]. In GBM stem cells (GSCs), Keisuke Katsushima et al. showed that high level of *Notch1* directly induced lncRNA TUG1. TUG1 was the sponge of miR-145, and induced GSCs self-renewal [74].

Osteosarcoma, has a high fatality rate in youngsters and children, is the most common primary malignant bone tumor. Zhang SZ et al. put forward that lncRNA MEG3 inhibited *Notch1* and *Hes1*, and further blocked cell growth and metastasis [75]. Daliang Kong et al. raised evidences that lncRNA HULC exerted tumorigenic function. HNF4G was the target of miR-122. HULC absorbed miR-122 as its sponge, and the loss of miR-122 activated NOTCH pathway through inhibiting HNF4G [76]. Sheng Zhou et al. demonstrated that lncRNA SNHG12 served as a sponge of miR-195-5p, and the latter directly targeted *Notch2*. Higher SNHG12 level led to lower miR-195-5p level, and less miR-195-5p brought overexpression of *Notch2*. So that the SNHG12/miR-195-5p/ *Notch2* axis played an important role in osteosarcoma cell cycle, proliferation, invasion and migration abilities [77].

In GC cells, Pei Liu et al. expressed that lncRNA INK4 locus (ANRIL) induced tumorigenesis. MiR-99a, negatively regulated by ANRIL, inhibited BMI1, and further blocked NOTCH pathway. Hang Q et al. found that *Notch1* could elevate lncRNA AK022798 expression and drug resistance [79].

Zhang HF et al. reported that in HCC, lncRNA reduced *Notch1* and *Hes1* expression, and further inhibited cell proliferation and invasion [89]. Bingjie Cai et al. identified a lncRNA BANCR expressed high level in melanoma. BANCR directly down-regulated miR-204 and the later binded *Notch2* [80]. Tongue cancer exhibits a massive threat to human health. Tonghan Zhang et al. discovered the regulation effects of UCA1/ miR-124/*JAG1* axis on tongue cancer. LncRNA urothelial cancer associated 1 (UCA1) binded to miR-124 mechanismly, and miR-124 targeted *JAG1* directly. There was another lncRNA metastasis-associated LUAD transcript 1 (MALAT1) showed similar function. High level of UCA1 and MALAT1 both promoted EMT process of tongue cancer cells [81]. Zhihui Xu et al. proved the relationship between NOTCH pathway and bladder cancer (BCa). LncRNA HCG18 absorbed miR-34c-5p, led to increase of *Notch1*, and finally restrained BCa development. Because of that *Notch1* was the target gene of miR-34c-5p [82]. Han Q et al. testified that in polycystic ovary syndrome (PCOS) cell line, lncRNA-LET inhibited cell viability, migration and EMT process and stimulated apoptosis in PCOS KNG cells [90]. In endometrial carcinoma (EC), Guo Q identified that lncRNA MEG3 negatively related with *Notch1* and *Hes1*. Expression of MEG3 inhibited cell growth evidently [83]. Liu Z et al. illustrated that in oral squamous cell carcinoma (OSCC), high lncRNA HNF1A-AS1 level accompanied by with poor prognosis. Expression of HNF1A-AS1 induced *Notch1* and *Hes1* mechanically, and promoted cell development [84]. Liu ZB et al. concluded that in nasopharyngeal carcinoma (NPC), lncRNA SNHG12 actived NOTCH pathway and promoted cell proliferation and migration [85]. Zhang Y et al. gave evidences that lncRNA small nucleolar RNA host gene 1 (SNHG1) actived NOTCH pathway through increasing *Notch1* and *Hes1*. Deletion of SNHG1 inhibited cell growth, invasion, and EMT process in esophageal squamous cell cancer [86].

2.3. CircRNAs and NOTCH signaling pathway in cancers

Circular RNAs (circRNAs) are special non-coding RNAs that are the latest research hotspot in RNA field. Unlike linear RNAs (containing 5′and 3′ ends), circRNAs are closed ring structure and play pivotal roles in carcinogenesis. They will not affected by RNA exonuclease, so that they exist more stably. Due to the difference in the first step of circRNA production, there are two modes of circRNA generation. Newly researches reported that some circRNAs were rich in miRNA binding sites. CircRNAs functioned as miRNAs sponges or competing endogenous RNAs (ceRNAs) that competitively inhibit miRNAs [91–95].

Table 2
LncRNAs targeting NOTCH pathway related cancer progress.

Cancer types	lncRNAs	Genes or pathway	Functions	Reference
Lung cancer	XIST	*Notch1*	Promoted cell growth and EMT	[66]
Breast cancer	H19	NOTCH	Induced cell resistance to Fulvestrant and Tamoxifen	[67]
	SNHG7	*Notch1*	Promoted cell growth and EMT	[68]
Prostate cancer	GHET1	*Notch1*	Promoted cell growth	[69]
Colorectal carcinoma	FAM83H-AS1	*Notch1, Hes1*	Promoted cell growth	[70]
Glioma	ZFAS1	NOTCH	Promoted EMT	[71]
	PlncRNA-1	*Notch1, JAG1, Hes1*	Promoted cell propagation, migration, and invasion and inhibited apoptosis	[72]
	LINC00152	NOTCH	Promoted cell propagation, migration, and invasion	[73]
	TUG1	*Notch1*	Promoted cell self-renewal	[74]
Osteosarcoma	MEG3	*Notch1, Hes1*	Inhibited cell growth and metastasis	[75]
	HULC	NOTCH	Promoted cell growth	[76]
	SNHG12	*Notch2*	Promoted cell growth and cell cycle	[77]
Gastric cancer	ANRIL	NOTCH	Inhibited cell growth	[78]
	AK022798	*Notch1*	Induced drug resistance	[79]
Melanoma	BANCR	*Notch2*	Promoted cell growth	[80]
Tongue cancer	UCA1	*JAG1*	Promoted EMT	[81]
	MALAT1	*JAG1*	Promoted EMT	[81]
Bladder cancer	HCG18	*Notch1*	Inhibited cell growth	[82]
Endometrial carcinoma	MEG3	*Notch1, Hes1*	Inhibited cell growth	[83]
Oral squamous cell carcinoma	HNF1A-AS1	*Notch1, Hes1*	Promoted cell growth	[84]
Nasopharyngeal carcinoma	SNHG12	NOTCH	Promoted cell proliferation and migration	[85]
Esophageal squamous cell cancer	SNHG1	*Notch1, Hes1*	Inhibited cell growth, invasion and EMT	[86]
Pancreatic cancer	SNHG1	*Notch1, Hes1*	Promoted cell proliferation and migration	[87]
Cervical cancer	SRA	NOTCH	Promoted cell proliferation and migration	[88]

In LUAD, Binbin Zhang et al. illustrated that circ-MTO1 served as a sponge of miR-17, and then blocked NOTCH pathway. Overexpressed circ-MTO1 inhibited LUAD growth [87]. Haiyang Xu et al. showed evidences that circNFIX positively regulated GBM cell growth. Through absorbed miR-34a-5p, circNFIX induced *Notch1* and then activated NOTCH signaling [70]. Endometriosis biologically behaves as tumor. Mengmeng Zhang et al. made a study that has-circ-0067301 deletion increased expression of *Notch1*, *Hes1*, vimentin and N-cadherin. Furthermore, lower has-circ-0067301 negatively regulated the EMT process [96].

3. Conclusion and perspective

With the development of modern medical technology, precision medicine has also been widely applied to treatment of cancers. However, different solutions should be proposed for different symptoms and causes of patients at each stage. The NOTCH signaling pathway is considered to be an important signaling pathway in the cancer process. NcRNA can participate in the regulation of NOTCH pathway, which can promote or inhibit cancer cells. The mechanism of ncRNA and NOTCH provides new ideas for clinical treatment and drug development of cancer.

There are more than 150 anticancer drugs and many different clinical treatment methods, such as chemotherapy and chemo-immunotherapy. Researches expressed that gold nanoparticles involves afatinib showed better drug efficacy and biocompatibility in the treatment of NSCLC [97]. Cisplatin (Cis-Pt) is one of antineoplastic drugs widely used in various tumors, but which accompanied by a non-specific effect and high toxicity [98]. Programmed death-ligand 1 (PD-L1), also called cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1). It is an immune checkpoint molecule. PD-L1 can expressed on both infiltrating immune cells and tumor cells. Immunotherapy based on PD1/PD-L1 revealed the critical role of tumor immune escape [99,100]. A growing number of studies proved effect of PD1/PD-L1 inhibitors in diversified cancers. Although more and more anti-cancer drugs have been found, drug resistance of tumors remains a challenge. Notch pathway plays an important role in tumorigenesis, and targeting NOTCH pathway will provide new ideas for cancer treatment. In this paragraph, we list several hot anticancer drugs so far. Actually, there have been many kinds of anticancer drugs, but most of them are chemotherapeutic drugs, and fewer targeted drugs. On the one hand, the complexity mechanisms in human body make it difficult for ordinary drugs to exert their efficacy. On the other hand, cancer cells have strong self-renewal ability and tolerant to the drug. Therefore, we need to explore some new treatment directions, such as combining signal pathway with non-coding RNA.

This review systematically summarized ncRNAs that regulate the NOTCH pathway and then influence the development of various cancers. They stimulated or attenuated the NOTCH pathway by targeting the ligands, receptors or downstream target genes, thereby promoting or inhibiting cancer growth. With the deepening and expanding of research, studies will explore the mechanism role of lncRNA and circRNA in NOTCH pathway-related cancers gradually. These studies will also provide new strategies for cancer drug treatment.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgements

Our work was funded by Shanghai Key Laboratory of Molecular Andrology, Institute of Biochemistry and Cell Biology, Shanghai Academy of Life Sciences. We thank Dr. Yang Shao (Fudan University Shanghai Cancer Center) for his help in this review.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424.
[2] A. Leonetti, F. Facchinetti, G. Rossi, R. Minari, A. Conti, L. Friboulet, M. Tiseo, D. Planchard, BRAF in non-small cell lung cancer (NSCLC): pickaxing another brick in the wall, Cancer Treat. Rev. 66 (2018) 82–94.
[3] E. El Rassy, A. Botticella, J. Kattan, C. Le Pechoux, B. Besse, L. Hendriks, Non-small cell lung cancer brain metastases and the immune system: from brain metastases development to treatment, Cancer Treat. Rev. 68 (2018) 69–79.
[4] H. Zhang, J. Shen, L. Yi, W. Zhang, P. Luo, J. Zhang, Efficacy and safety of ipilimumab plus chemotherapy for advanced lung Cancer: a systematic review and meta-analysis, J. Cancer 9 (2018) 4556–4567.
[5] R. Duchnowska, S. Loibl, J. Jassem, Tyrosine kinase inhibitors for brain metastases in HER2-positive breast cancer, Cancer Treat. Rev. 67 (2018) 71–77.
[6] X. Bai, J. Ni, J. Beretov, P. Graham, Y. Li, Cancer stem cell in breast cancer therapeutic resistance, Cancer Treat. Rev. 69 (2018) 152–163.

[7] O.M. Gannon, A. Antonsson, I.C. Bennett, N.A. Saunders, Viral infections and breast cancer - A current perspective, Cancer Lett. 420 (2018) 182–189.
[8] Y. Zhao, H. Huang, C. Chen, H. Liu, H. Liu, F. Su, J. Bi, T.B. Lam, J. Li, T. Lin, J. Huang, Efficacy and safety of different interventions in castration resistant prostate cancer progressing after docetaxel-based chemotherapy: Bayesian network analysis of randomized controlled trials, J. Cancer 9 (2018) 690–701.
[9] Y. Loriot, S. Supiot, J.B. Beauval, F. Schlurmann, G. Pasticier, P. Sargos, P. Barthelemy, G. Pignot, D. Maillet, S. Vincendeau, E. Gross, G. Ploussard, M.O. Timsit, D. Borchiellini, Management of non-metastatic castrate-resistant prostate cancer: a systematic review, Cancer Treat. Rev. 70 (2018) 223–231.
[10] N. Howard, M. Clementino, D. Kim, L. Wang, A. Verma, X. Shi, Z. Zhang, R.S. DiPaola, New developments in mechanisms of prostate cancer progression, Semin. Cancer Biol. (2018).
[11] L.E. Harrison, M. Bleiler, C. Giardina, A look into centrosome abnormalities in colon cancer cells, how they arise and how they might be targeted therapeutically, Biochem. Pharmacol. 147 (2018) 1–8.
[12] K.M. Peters, B.A. Carlson, V.N. Gladyshev, P.A. Tsuji, Selenoproteins in colon cancer, Free Radic. Biol. Med. 127 (2018) 14–25.
[13] P. Ahechu, G. Zozaya, P. Marti, J.L. Hernandez-Lizoain, J. Baixauli, X. Unamuno, G. Fruhbeck, V. Catalan, NLRP3 inflammasome: a possible link between obesity-associated low-grade chronic inflammation and colorectal Cancer development, Front. Immunol. 9 (2018) 2918.
[14] Y. Hu, M. Ding, C. Yuan, K. Wu, S.A. Smith-Warner, F.B. Hu, A.T. Chan, J.A. Meyerhardt, S. Ogino, C.S. Fuchs, E.L. Giovannucci, M. Song, Association between coffee intake after diagnosis of colorectal Cancer and reduced mortality, Gastroenterology 154 (2018) 916–926 e919.
[15] S. Artavanis-Tsakonas, M.A. Muskavitch, B. Yedvobnick, Molecular cloning of Notch, a locus affecting neurogenesis in Drosophila melanogaster, Proc. Natl. Acad. Sci. U. S. A. 80 (1983) 1977–1981.
[16] C.R. Balistreri, R. Madonna, G. Melino, C. Caruso, The emerging role of Notch pathway in ageing: focus on the related mechanisms in age-related diseases, Ageing Res. Rev. 29 (2016) 50–65.
[17] L. Alberi, S.E. Hoey, E. Brai, A.L. Scotti, S. Marathe, Notch signaling in the brain: in good and bad times, Ageing Res. Rev. 12 (2013) 801–814.
[18] J. Chung, L.V. Riella, I. Maillard, Targeting the notch pathway to prevent rejection, Am. J. Transplant. 16 (2016) 3079–3085.
[19] J.C. Aster, W.S. Pear, S.C. Blacklow, The varied roles of notch in Cancer, Annu. Rev. Pathol. 12 (2017) 245–275.
[20] N. Chandimali, D.L. Huynh, J.J. Zhang, J.C. Lee, D.Y. Yu, D.K. Jeong, T. Kwon, MicroRNA-122 negatively associates with peroxiredoxin-II expression in human gefitinib-resistant lung cancer stem cells, Cancer Gene Ther. (2018).
[21] H. Zhang, F. Chen, Y. He, L. Yi, C. Ge, X. Shi, C. Tang, D. Wang, Y. Wu, W. Nian, Sensitivity of non-small cell lung cancer to erlotinib is regulated by the Notch/miR-223/FBXW7 pathway, Biosci. Rep. 37 (2017).
[22] J. Huang, Y. Chen, J. Li, K. Zhang, J. Chen, D. Chen, B. Feng, H. Song, J. Feng, R. Wang, L. Chen, Notch-1 confers chemoresistance in lung adenocarcinoma to Taxanes through AP-1/microRNA-451 mediated regulation of MDR-1, Mol. Ther. Nucleic Acids 5 (2016) e375.
[23] < Krüppel-like factor 8 promotes tumorigenic mammary stem cell induction by targeting miR-146a.pdf > .
[24] L. Kang, J. Mao, Y. Tao, B. Song, W. Ma, Y. Lu, L. Zhao, J. Li, B. Yang, L. Li, MicroRNA-34a suppresses the breast cancer stem cell-like characteristics by downregulating Notch1 pathway, Cancer Sci. 106 (2015) 700–708.
[25] X. Peng, H. Chang, Y. Gu, J. Chen, L. Yi, Q. Xie, J. Zhu, Q. Zhang, M. Mi, 3,6-Dihydroxyflavone suppresses breast carcinogenesis by epigenetically regulating miR-34a and miR-21, Cancer Prev. Res. Phila. (Phila) 8 (2015) 509–517.
[26] S. De Carolis, S. Bertoni, M. Nati, L. D'Anello, A. Papi, A. Tesei, M. Cricca, M. Bonafe, Carbonic anhydrase 9 mRNA/microRNA34a interplay in hypoxic human mammospheres, J. Cell. Physiol. 231 (2016) 1534–1541.
[27] X. Deng, M. Cao, J. Zhang, K. Hu, Z. Yin, Z. Zhou, X. Xiao, Y. Yang, W. Sheng, Y. Wu, Y. Zeng, Hyaluronic acid-chitosan nanoparticles for co-delivery of MiR-34a and doxorubicin in therapy against triple negative breast cancer, Biomaterials 35 (2014) 4333–4344.
[28] < Increased expression of miR-1179 inhibits breast cancer cell metastasis by modulating Notch signaling pathway and correlates with favorable prognosis.pdf > .
[29] Y. Shui, X. Yu, R. Duan, Q. Bao, J. Wu, H. Yuan, C. Ma, miR-130b-3p inhibits cell invasion and migration by targeting the Notch ligand Delta-like 1 in breast carcinoma, Gene 609 (2017) 80–87.
[30] H. Guan, Z. Dai, Y. Ma, Z. Wang, X. Liu, X. Wang, MicroRNA-101 inhibits cell proliferation and induces apoptosis by targeting EYA1 in breast cancer, Int. J. Mol. Med. 37 (2016) 1643–1651.
[31] H.L. Wang, Y. Xiao, L. Wu, D.C. Ma, [Effects of miR-449a on proliferation and migration of human breast cancer cell line MCF-7], Zhongguo Ying Yong Sheng Li Xue Za Zhi 33 (2017) 508–513.
[32] < Inactivation of AR and Notch-1 signaling by miR-34a attenuates prostate cancer aggressiveness.pdf > .
[33] J.K. Rane, A. Ylipaa, R. Adamson, V.M. Mann, M.S. Simms, A.T. Collins, T. Visakorpi, M. Nykter, N.J. Maitland, Construction of therapeutically relevant human prostate epithelial fate map by utilising miRNA and mRNA microarray expression data, Br. J. Cancer 113 (2015) 611–615.
[34] < Integrative genetic, epigenetic and pathological analysis of paraganglioma reveals complex dysregulation of NOTCH signaling.pdf > .
[35] Q. Ji, X. Hao, Y. Meng, M. Zhang, J. Desano, D. Fan, L. Xu, Restoration of tumor suppressor miR-34 inhibits human p53-mutant gastric cancer tumorspheres, BMC Cancer 8 (2008) 266.
[36] K. Zhao, Q. Wang, Y. Wang, K. Huang, C. Yang, Y. Li, K. Yi, C. Kang, EGFR/c-myc axis regulates TGFbeta/Hippo/Notch pathway via epigenetic silencing miR-524 in gliomas, Cancer Lett. 406 (2017) 12–21.
[37] P. Bettinsoli, G. Ferrari-Toninelli, S.A. Bonini, C. Prandelli, M. Memo, Notch ligand Delta-like 1 as a novel molecular target in childhood neuroblastoma, BMC Cancer 17 (2017) 352.
[38] Y. Li, F. Guessous, Y. Zhang, C. Dipierro, B. Kefas, E. Johnson, L. Marcinkiewicz, J. Jiang, Y. Yang, T.D. Schmittgen, B. Lopes, D. Schiff, B. Purow, R. Abounader, MicroRNA-34a inhibits glioblastoma growth by targeting multiple oncogenes, Cancer Res. 69 (2009) 7569–7576.
[39] J. Li, Q. Li, L. Lin, R. Wang, L. Chen, W. Du, C. Jiang, R. Li, Targeting the Notch1 oncogene by miR-139-5p inhibits glioma metastasis and epithelial-mesenchymal transition (EMT), BMC Neurol. 18 (2018) 133.
[40] L. Chen, W. Zhang, W. Yan, L. Han, K. Zhang, Z. Shi, J. Zhang, Y. Wang, Y. Li, S. Yu, P. Pu, C. Jiang, T. Jiang, C. Kang, The putative tumor suppressor miR-524-5p directly targets Jagged-1 and Hes-1 in glioma, Carcinogenesis 33 (2012) 2276–2282.
[41] < MiR-129 triggers autophagic flux by regulating a novel Notch-1 E2F7Beclin-1 axis to impair the viability of human malignant glioma cells.pdf > .
[42] H. Song, Y. Zhang, N. Liu, S. Zhao, Y. Kong, L. Yuan, miR-92a-3p exerts various effects in glioma and glioma stem-like cells specifically targeting CDH1/beta-catenin and Notch-1/Akt signaling pathways, Int. J. Mol. Sci. 17 (2016).
[43] H.J. Xiao, Q. Ji, L. Yang, R.T. Li, C. Zhang, J.M. Hou, In vivo and in vitro effects of microRNA-124 on human gastric cancer by targeting JAG1 through the Notch signaling pathway, J. Cell. Biochem. 119 (2018) 2520–2534.
[44] L. Jiang, T. Lin, C. Xu, S. Hu, Y. Pan, R. Jin, miR-124 interacts with the Notch1 signalling pathway and has therapeutic potential against gastric cancer, J. Cell. Mol. Med. 20 (2016) 313–322.
[45] Y. Pan, A. Wu, F. Xu, C. Chen, L. Jiang, R. Jin, Lentivirus-mediated overexpression of miR-124 suppresses growth and invasion by targeting JAG1 and EZH2 in gastric cancer, Oncol. Lett. 15 (2018) 7450–7458.
[46] C. Yan, J. Yu, W. Kang, Y. Liu, Z. Ma, L. Zhou, miR-935 suppresses gastric signet ring cell carcinoma tumorigenesis by targeting Notch1 expression, Biochem. Biophys. Res. Commun. 470 (2016) 68–74.
[47] F. Xue, Z. Liu, J. Xu, X. Xu, X. Chen, F. Tian, Neferine inhibits growth and migration of gastrointestinal stromal tumor cell line GIST-T1 by up-regulation of miR-449a, Biomed. Pharmacother. 109 (2019) 1951–1959.
[48] K. Wu, J. Zou, C. Lin, Z.G. Jie, MicroRNA-140-5p inhibits cell proliferation, migration and promotes cell apoptosis in gastric cancer through the negative regulation of THY1-mediated Notch signaling, Biosci. Rep. (2019).
[49] Y. Hashimoto, Y. Akiyama, T. Otsubo, S. Shimada, Y. Yuasa, Involvement of epigenetically silenced microRNA-181c in gastric carcinogenesis, Carcinogenesis 31 (2010) 777–784.
[50] X.B. Chen, W. Li, A.X. Chu, MicroRNA-133a inhibits gastric cancer cells growth, migration, and epithelial-mesenchymal transition process by targeting presenilin 1, J. Cell. Biochem. 120 (2019) 470–480.
[51] < Notch1 pathway-mediated microRNA-151-5p promotes gastric cancer progression.pdf > .
[52] P. Bu, L. Wang, K.Y. Chen, T. Srinivasan, P.K. Murthy, K.L. Tung, A.K. Varanko, H.J. Chen, Y. Ai, S. King, S.M. Lipkin, X. Shen, A miR-34a-Numb feedforward loop triggered by inflammation regulates asymmetric stem cell division in intestine and colon cancer, Cell Stem Cell 18 (2016) 189–202.
[53] X. Zhang, F. Ai, X. Li, L. Tian, X. Wang, S. Shen, F. Liu, MicroRNA-34a suppresses colorectal cancer metastasis by regulating Notch signaling, Oncol. Lett. 14 (2017) 2325–2333.
[54] M.A. Suliman, Z. Zhang, H. Na, A.L. Ribeiro, Y. Zhang, B. Niang, A.S. Hamid, H. Zhang, L. Xu, Y. Zuo, Niclosamide inhibits colon cancer progression through downregulation of the Notch pathway and upregulation of the tumor suppressor miR-200 family, Int. J. Mol. Med. 38 (2016) 776–784.
[55] H. Li, F. Li, Exosomes from BM-MSCs increase the population of CSCs via transfer of miR-142-3p, Br. J. Cancer 119 (2018) 744–755.
[56] B. Huang, H. Yang, X. Cheng, D. Wang, S. Fu, W. Shen, Q. Zhang, L. Zhang, Z. Xue, Y. Li, Y. Da, Q. Yang, Z. Li, L. Liu, L. Qiao, Y. Kong, Z. Yao, P. Zhao, M. Li, R. Zhang, tRF/miR-1280 suppresses stem cell-like cells and metastasis in colorectal cancer, Cancer Res. 77 (2017) 3194–3206.
[57] J. Chen, H. Zhang, Y. Chen, G. Qiao, W. Jiang, P. Ni, X. Liu, L. Ma, miR-598 inhibits metastasis in colorectal cancer by suppressing JAG1/Notch2 pathway stimulating EMT, Exp. Cell Res. 352 (2017) 104–112.
[58] Y. Jin, M. Wang, H. Hu, Q. Huang, Y. Chen, G. Wang, Overcoming stemness and chemoresistance in colorectal cancer through miR-195-5p-modulated inhibition of notch signaling, Int. J. Biol. Macromol. 117 (2018) 445–453.
[59] Y. Feng, Y.W. Dong, Y.N. Song, J.H. Xiao, X.Y. Guo, W.L. Jiang, L.G. Lu, MicroRNA449a is a potential predictor of colitisassociated colorectal cancer progression, Oncol. Rep. 40 (2018) 1684–1694.
[60] H. Liu, Y. Yin, Y. Hu, Y. Feng, Z. Bian, S. Yao, M. Li, Q. You, Z. Huang, miR-139-5p sensitizes colorectal cancer cells to 5-fluorouracil by targeting NOTCH-1, Pathol. Res. Pract. 212 (2016) 643–649.
[61] H. Jia, Q. Yang, T. Wang, Y. Cao, Q.Y. Jiang, H.D. Ma, H.W. Sun, M.X. Hou, Y.P. Yang, F. Feng, Rhamnetin induces sensitization of hepatocellular carcinoma cells to a small molecular kinase inhibitor or chemotherapeutic agents, Biochim. Biophys. Acta 1860 (2016) 1417–1430.
[62] S.J. Zhou, Y.L. Deng, H.F. Liang, J.C. Jaoude, F.Y. Liu, Hepatitis B virus X protein promotes CREB-mediated activation of miR-3188 and Notch signaling in hepatocellular carcinoma, Cell Death Differ. 24 (2017) 1577–1587.
[63] K.H. Jung, J. Zhang, C. Zhou, H. Shen, M. Gagea, C. Rodriguez-Aguayo, G. Lopez-Berestein, A.K. Sood, L. Beretta, Differentiation therapy for hepatocellular carcinoma: multifaceted effects of miR-148a on tumor growth and phenotype and liver

fibrosis, Hepatology 63 (2016) 864–879.
[64] T. Tian, X. Fu, J. Lu, Z. Ruan, K. Nan, Y. Yao, Y. Yang, MicroRNA-760 inhibits doxorubicin resistance in hepatocellular carcinoma through regulating Notch1/Hes1-PTEN/Akt signaling pathway, J. Biochem. Mol. Toxicol. 32 (2018) e22167.
[65] K. Ren, T. Li, W. Zhang, J. Ren, Z. Li, G. Wu, miR-199a-3p inhibits cell proliferation and induces apoptosis by targeting YAP1, suppressing Jagged1-Notch signaling in human hepatocellular carcinoma, J. Biomed. Sci. 23 (2016) 79.
[66] X. Wang, G. Zhang, Z. Cheng, L. Dai, L. Jia, X. Jing, H. Wang, R. Zhang, M. Liu, T. Jiang, Y. Yang, M. Yang, Knockdown of LncRNA-XIST suppresses proliferation and TGF-beta1-Induced EMT in NSCLC through the Notch-1 pathway by regulation of miR-137, Genet. Test. Mol. Biomarkers 22 (2018) 333–342.
[67] P. Basak, S. Chatterjee, V. Bhat, A. Su, H. Jin, V. Lee-Wing, Q. Liu, P. Hu, L.C. Murphy, A. Raouf, Long non-coding RNA H19 acts as an estrogen receptor modulator that is required for endocrine therapy resistance in ER+ breast Cancer cells, Cell. Physiol. Biochem. 51 (2018) 1518–1532.
[68] X. Sun, T. Huang, Z. Liu, M. Sun, S. Luo, LncRNA SNHG7 contributes to tumorigenesis and progression in breast cancer by interacting with miR-34a through EMT initiation and the Notch-1 pathway, Eur. J. Pharmacol. 856 (2019) 172407.
[69] Y. Zhu, Y. Tong, J. Wu, Y. Liu, M. Zhao, Knockdown of LncRNA GHET1 suppresses prostate cancer cell proliferation by inhibiting HIF-1alpha/Notch-1 signaling pathway via KLF2, Biofactors 45 (2019) 364–373.
[70] H. Xu, Y. Zhang, L. Qi, L. Ding, H. Jiang, H. Yu, NFIX circular RNA promotes glioma progression by regulating miR-34a-5p via notch signaling pathway, Front. Mol. Neurosci. 11 (2018) 225.
[71] K. Gao, Z. Ji, K. She, Q. Yang, L. Shao, Long non-coding RNA ZFAS1 is an unfavourable prognostic factor and promotes glioma cell progression by activation of the Notch signaling pathway, Biomed. Pharmacother. 87 (2017) 555–560.
[72] X. Wang, Y. Yan, C. Zhang, W. Wei, X. Ai, Y. Pang, Y. Bian, Upregulation of lncRNA PlncRNA-1 indicates the poor prognosis and promotes glioma progression by activation of Notch signal pathway, Biomed. Pharmacother. 103 (2018) 216–221.
[73] Z. Zhu, J. Dai, Y. Liao, J. Ma, W. Zhou, Knockdown of long noncoding RNA LINC00152 suppresses cellular proliferation and invasion in glioma cells by regulating miR-4775, Oncol. Res. 26 (2018) 857–867.
[74] K. Katsushima, A. Natsume, F. Ohka, K. Shinjo, A. Hatanaka, N. Ichimura, S. Sato, S. Takahashi, H. Kimura, Y. Totoki, T. Shibata, M. Naito, H.J. Kim, K. Miyata, K. Kataoka, Y. Kondo, Targeting the Notch-regulated non-coding RNA TUG1 for glioma treatment, Nat. Commun. 7 (2016) 13616.
[75] S.Z. Zhang, L. Cai, B. Li, MEG3 long non-coding RNA prevents cell growth and metastasis of osteosarcoma, Bratisl. Lek. Listy 118 (2017) 632–636.
[76] D. Kong, Y. Wang, Knockdown of lncRNA HULC inhibits proliferation, migration, invasion, and promotes apoptosis by sponging miR-122 in osteosarcoma, J. Cell. Biochem. 119 (2018) 1050–1061.
[77] S. Zhou, L. Yu, M. Xiong, G. Dai, LncRNA SNHG12 promotes tumorigenesis and metastasis in osteosarcoma by upregulating Notch2 by sponging miR-195-5p, Biochem. Biophys. Res. Commun. 495 (2018) 1822–1832.
[78] P. Liu, M. Zhang, Q. Niu, F. Zhang, Y. Yang, X. Jiang, Knockdown of long non-coding RNA ANRIL inhibits tumorigenesis in human gastric cancer cells via microRNA-99a-mediated down-regulation of BMI1, Braz. J. Med. Biol. Res. 51 (2018) e6839.
[79] Q. Hang, R. Sun, C. Jiang, Y. Li, Notch 1 promotes cisplatin-resistant gastric cancer formation by upregulating lncRNA AK022798 expression, Anticancer Drugs 26 (2015) 632–640.
[80] B. Cai, Y. Zheng, S. Ma, Q. Xing, X. Wang, B. Yang, G. Yin, F. Guan, BANCR contributes to the growth and invasion of melanoma by functioning as a competing endogenous RNA to upregulate Notch2 expression by sponging miR204, Int. J. Oncol. 51 (2017) 1941–1951.
[81] T.H. Zhang, L.Z. Liang, X.L. Liu, J.N. Wu, K. Su, J.Y. Chen, Q.Y. Zheng, LncRNA UCA1/miR-124 axis modulates TGFbeta1-induced epithelial-mesenchymal transition and invasion of tongue cancer cells through JAG1/Notch signaling, J. Cell. Biochem. 120 (2019) 10495–10504.
[82] Z. Xu, B. Huang, Q. Zhang, X. He, H. Wei, D. Zhang, NOTCH1 regulates the proliferation and migration of bladder cancer cells by cooperating with long non-coding RNA HCG18 and microRNA-34c-5p, J. Cell. Biochem. 120 (2019) 6596–6604.
[83] Q. Guo, Z. Qian, D. Yan, L. Li, L. Huang, LncRNA-MEG3 inhibits cell proliferation of endometrial carcinoma by repressing Notch signaling, Biomed. Pharmacother. 82 (2016) 589–594.
[84] Z. Liu, H. Li, S. Fan, H. Lin, W. Lian, STAT3-induced upregulation of long noncoding RNA HNF1A-AS1 promotes the progression of oral squamous cell carcinoma via activating Notch signaling pathway, Cancer Biol. Ther. 20 (2019) 444–453.
[85] Z.B. Liu, C. Tang, X. Jin, S.H. Liu, W. Pi, Increased expression of lncRNA SNHG12 predicts a poor prognosis of nasopharyngeal carcinoma and regulates cell proliferation and metastasis by modulating Notch signal pathway, Cancer Biomark. 23 (2018) 603–613.
[86] Y. Zhang, X. Jin, Z. Wang, X. Zhang, S. Liu, G. Liu, Downregulation of SNHG1 suppresses cell proliferation and invasion by regulating Notch signaling pathway in esophageal squamous cell cancer, Cancer Biomark. 21 (2017) 89–96.
[87] B. Zhang, M. Chen, N. Jiang, K. Shi, R. Qian, A regulatory circuit of circ-MTO1/miR-17/QKI-5 inhibits the proliferation of lung adenocarcinoma, Cancer Biol. Ther. (2019) 1–9.
[88] M. Zhang, S. Wang, L. Tang, X. Wang, T. Zhang, X. Xia, X. Fang, Downregulated circular RNA hsa_circ_0067301 regulates epithelial-mesenchymal transition in endometriosis via the miR-141/Notch signaling pathway, Biochem. Biophys. Res. Commun. 514 (2019) 71–77.
[89] H.F. Zhang, W. Li, Y.D. Han, LINC00261 suppresses cell proliferation, invasion and Notch signaling pathway in hepatocellular carcinoma, Cancer Biomark. 21 (2018) 575–582.
[90] Q. Han, W. Zhang, J. Meng, L. Ma, A. Li, LncRNA-LET inhibits cell viability, migration and EMT while induces apoptosis by up-regulation of TIMP2 in human granulosa-like tumor cell line KGN, Biomed. Pharmacother. 100 (2018) 250–256.
[91] S. Shen, Y. Wu, J. Chen, Z. Xie, K. Huang, G. Wang, Y. Yang, W. Ni, Z. Chen, P. Shi, Y. Ma, S. Fan, CircSERPINE2 protects against osteoarthritis by targeting miR-1271 and ETS-related gene, Ann. Rheum. Dis. 78 (2019) 826–836.
[92] L. Peng, X. Yuan, G. Li, The emerging landscape of circular RNA ciRS-7 in cancer (Review), Oncol. Rep. 33 (2015) 2669–2674.
[93] W.R. Jeck, N.E. Sharpless, Detecting and characterizing circular RNAs, Nat. Biotechnol. 32 (2014) 453–461.
[94] J. Salzman, Circular RNA expression: its potential regulation and function, Trends Genet. 32 (2016) 309–316.
[95] T.B. Hansen, J. Kjems, C.K. Damgaard, Circular RNA and miR-7 in cancer, Cancer Res. 73 (2013) 5609–5612.
[96] A.R. Mire-Sluis, R.G. Wickremasinghe, A.V. Hoffbrand, A.M. Timms, G.E. Francis, Human T lymphocytes stimulated by phytohaemagglutinin undergo a single round of cell division without a requirement for interleukin-2 or accessory cells, Immunology 60 (1987) 7–12.
[97] A.M. Cryer, C. Chan, A. Eftychidou, C. Maksoudian, M. Mahesh, T.D. Tetley, A.C. Spivey, A.J. Thorley, Tyrosine kinase inhibitor gold nanoconjugates for the treatment of non-small cell lung cancer, ACS Appl. Mater. Interfaces 11 (2019) 16336–16346.
[98] S. Prylutska, I. Grynyuk, T. Skaterna, I. Horak, A. Grebinyk, L. Drobot, O. Matyshevska, A. Senenko, Y. Prylutskyy, A. Naumovets, U. Ritter, M. Frohme, Toxicity of C60 fullerene-cisplatin nanocomplex against Lewis lung carcinoma cells, Arch. Toxicol. 93 (2019) 1213–1226.
[99] J.P. Zhang, Z. Song, H.B. Wang, L. Lang, Y.Z. Yang, W. Xiao, D.E. Webster, W. Wei, S.K. Barta, M.E. Kadin, L.M. Staudt, M. Nakagawa, Y. Yang, A novel model of controlling PD-L1 expression in ALK+ anaplastic large cell lymphoma revealed by CRISPR screening, Blood (2019).
[100] C. Van Berckelaer, C. Rypens, P. van Dam, L. Pouillon, M. Parizel, K.A. Schats, M. Kockx, W.A.A. Tjalma, P. Vermeulen, S. van Laere, F. Bertucci, C. Colpaert, L. Dirix, Infiltrating stromal immune cells in inflammatory breast cancer are associated with an improved outcome and increased PD-L1 expression, Breast Cancer Res. 21 (2019) 28.