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Review article

Cross-regulation between Notch signaling pathway and miRNA machinery in cancer

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ABSTRACT

Despite their simple structure, the Notch family of receptors regulates a wide-spectrum of key cellular processes including development, tissue patterning, cell-fate determination, proliferation, differentiation and, cell death. On the other hand, accumulating date pinpointed the role of non-coding microRNAs, namely miRNAs in cancer initiation/progression via regulating the expression of multiple oncogenes and tumor suppressor genes, as such the Notch signaling. It is now documented that these two partners are in one or in the opposite directions and rule together the cancer fate. Here, we review the current knowledge relevant to this tricky interplay between different miRNAs and components of Notch signaling pathway. Further, we discuss the implication of this crosstalk in cancer progression/regression in the context of cancer stem cells, tumor angiogenesis, metastasis and emergence of multi-drug resistance. Understanding the molecular cues and mechanisms that occur at the interface of miRNA and Notch signaling would open new avenues for development of novel and effective strategies for cancer therapy.

1. Introduction

Contrary to its simple architecture, the evolutionarily conserved Notch family of receptors regulates a myriad of fundamental cellular processes including development, tissue patterning, cell-fate determination, proliferation, differentiation and, cell death [1,2].

In mammals, this family of receptors incorporates four type I transmembrane proteins, namely Notch 1–4. Each Notch receptor consists of (i) an extracellular domain which contains almost 30 epidermal growth factor (EGF)-like repeats that are involved in ligand-binding; (ii) a transmembrane domain, and (iii) an intracellular domain consisting of the RAM domain, the ankyrin repeats, a transcriptional activator domain (TAD), and the PEST (proline, glutamate-, serine-, threonine-rich) sequence [3]. The Five Notch ligands include Jagged1, Jagged2, delta-like 1 (DLL1), DLL3, and DLL4 that are composed of EGF-like repeats in their extracellular domain, a highly conserved DSL domain (Delta and Serrate from Drosophila and Lag-2 from C. elegans), and a cysteine-rich region (CR) in Serrate. Not to mention that the DSL domain is vital for Notch activity [4].

For activation, Notch proteins undergo three proteolytic events. Upon the first cleavage by furin-like convertase, a heterodimeric form of the receptor is transported to the cell surface (S1 cleavage). The second cleavage occurs following the ligand binding to the Notch receptor of an adjacent cell through DSL domains and results in a Notch activation in which an ADAM disintegrin and metalloprotease family, catalyzes the S2 cleavage of the receptor [5]. Subsequently, a presenilin-dependent gamma-secretase complex mediates the third cleavage (S3) and liberates the NICD (intracellular domain of Notch receptor). NICD translocates to the nucleus and binds to the ubiquitous transcription factor CBF-1/suppressor of hairless/Lag1 (CSL) complex and displaces the co-repressor (Co-R) complex by engaging a co-activator (Co-A) complex composed of mastermind-like 1 (MAML1), resulting in the transcriptional activation of Notch target genes [6] (Fig. 1).

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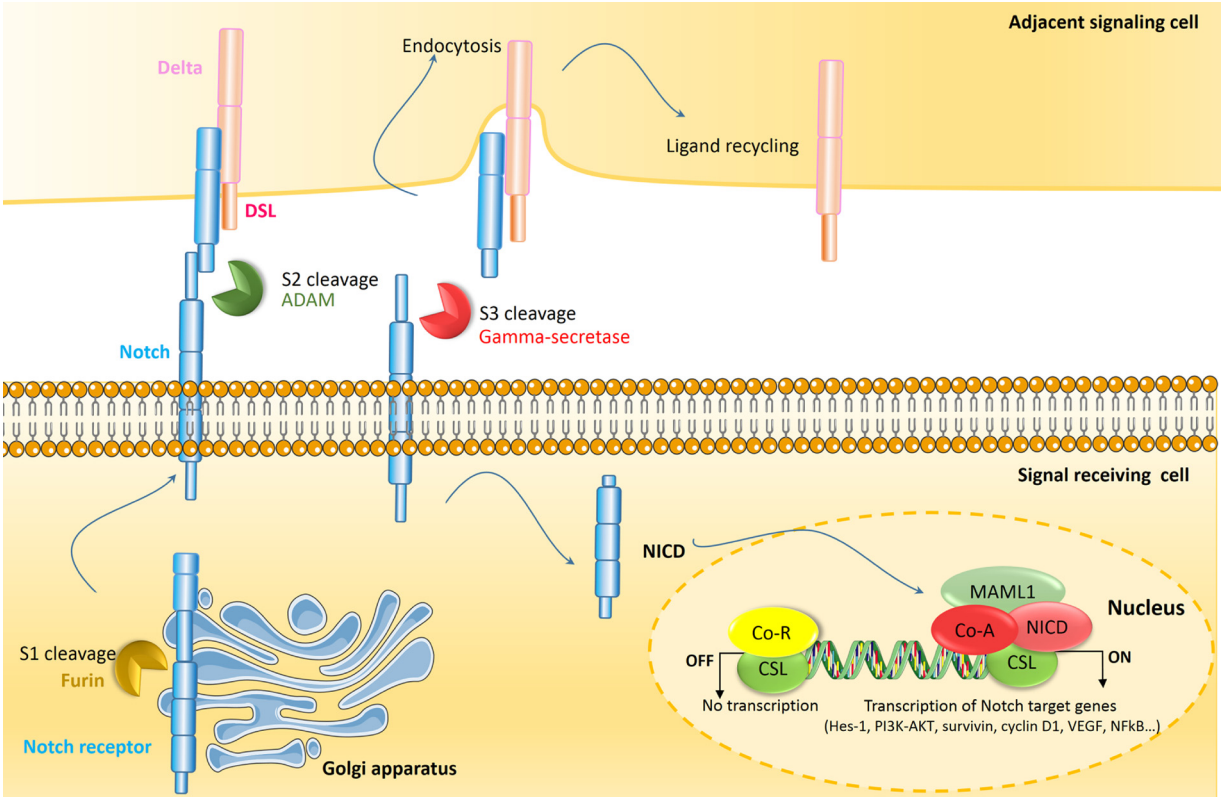

Fig. 1. Schematics of Notch signaling.

2. Notch signaling in cancer

In light of the pleiotropic role of notch receptors in regulating various cellular pathways, deregulation of Notch is intertwined with the development and progression of various disease states [1,7]. It is demonstrated that dysregulated Notch signaling could contribute to tumor state acting as tumor suppressor protein or an oncoprotein [4].

The primary evidence for the oncogenic effects of Notch is validated in hematological malignances. It is shown that Notch1 mutations (e.g. mutations in PEST domain which is a negative regulator of Notch, or an amplification of wild-type Notch receptors/ligands) account for almost 60% of T-cell acute lymphoblastic leukemia (T-ALL) [6]. Additionally, the hyperactivation of Notch signaling has been documented in the oncogenic process of solid cancers such as melanoma, lung, breast, prostate, colorectal, hepatocellular as well as malignancies of the central nervous system (CNS). The results from a recent study showed that Notch 1 overexpression promotes hepatocellular carcinoma cell growth by increasing the expression levels of nuclear receptor NR4A2 which dampen the tumor suppressor activity of p21 and p63 [8,9]. Likewise, regarding melanoma, it is validated that it is among the most lethal cancers owing to its high propensity to metastasize, Notch3 signaling-mediated melanoma-endothelial crosstalk regulates melanoma stem-like cell homeostasis and niche morphogenesis [10] which culminates into tumor heterogeneity and resistance to current therapies.

Notch signaling also elicits tumor suppressive roles in several malignancies. As a proof of this concept, the loss of function mutations in the Notch1 gene has been reported in a significant proportion of the patients with head and neck squamous cell carcinoma [11]. The Notch mediated proliferative and anti-apoptotic effects during carcinogenesis involve several molecules such as p27cip1/waf1, cyclin D1, c-Myc, p21, Bcl-2, survivin, slug, and nanog, etc. [6]. Though the full mechanisms by which Notch pathway can lead to tumor promoting or suppressive effects are not fully addressed, the binary effects include differential tissue and cell specific target genes and are highly context dependent.

3. Cross regulation of the Notch signaling pathway

The oncogenic influence of the Notch signaling pathway could be explained by its communication with more than fifty other signaling pathways including the developmental signals, transcriptional factors, inflammatory cytokines, as well as growth factors [12]. The crosstalk among Notch and other prominent molecules/signaling pathways includes but is not restricted to the urokinase-type plasminogen activator (uPA)/urokinase plasminogen activator receptor (uPAR) axis, phosphatidylinositol 3-kinase (PI3 K/AKT), STAT3, receptor tyrosine kinases (RTKs), Hedge Hog (HH), Janus kinase/signal transducers and activators of transcription (Jak/STAT), transforming growth factor-β (TGF-β), Wnt, hypoxia-inducible factor (HIF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF/PDGFR), Ras, mammalian target of rapamycin (mTOR), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), cytokines interleukin-6 (IL-6), IL-1, estrogen receptor signaling, as well as microRNAs. This deadly cross regulation of Notch signaling fuel the vital requisites of an oncogenic process which are proliferation, development, angiogenesis, differentiation, morphogenesis, and epithelial-to-mesenchymal transition (EMT) for generation of cancer stem cells [13,14].

4. DNA damage response

Genomic instability which is caused by several environmental and endogenous genotoxic agents, is one the most important causes of developing diseases including cancers, infertility, neurodegenerative diseases and immune deficiency [15]. Therefore, protection of genomic integrity is essential to prevent development of these disorders [15]. Several chemotherapeutic agents, ultraviolet (UV), ionizing radiation (IR), activation of oncogenes, as well as lack of tumor suppressors and normal cell metabolism agents like reactive oxygen species (ROS) can lead to DNA damages [16]. DNA damage response (DDR) is a sophisticated system in cells which sense these threats and counteract with

them. It is computed that each cell is faced with almost 10^4–10^5 damages per day, demonstrating that elimination of genomic damages is a significant task to retain convenient genome function [17]. According to the source of lesions, DNA can be impressed in various ways which varies from single-strand breaks (SSBs), double-strand breaks (DSBs), a basic site and changed bases to highly toxic damages like small or bulky adducts to interstrand cross links (ICLs) [17]. Transcription and replication which are basic genome processes are extremely affected by DNA damages [18]. Replication on DNA lesions causes mutations, which may initiate and increase carcinogenesis. Harmful effects occur when lesions block transcription and lead to cellular aging or apoptosis [18]. Cells have developed DNA repair mechanisms, damage tolerance procedures, and cell-cycle checkpoint pathways to find and fix different types of DNA damages [19]. DSBs can be fixed by homologous recombination (HR) or through non-homologous end joining (NHEJ). Nucleotide excision repair (NER) repairs UV- induced DNA damages resulted from methylation, deamination, oxidation or spontaneous loss of the DNA base, which are corrected by base excision repair (BER) [19]. Crosslinks can be repaired through Fanconi anemia (FA) pathway, whereas mismatch repair (MMR) corrects DNA base mismatches [20]. Among several types of DNA damages, DSBs are the most harmful ones. Mutations, chromosome breaks or rearrangements, cell death or development of cancer could be the consequences of failure to repair DSBs [21]. Generally, the DDR pathways comprised a similar set of consequential steps: primary detection of DNA damage, transferring the signal of damage and recruitment of DNA repair factors to the damage site and finally repair DNA damages and return cells to normal status [21]. It has been known that the DDR process is severely controlled by post-translational modifications (PTM) that refers to the covalent and usually enzymatic modifications. PTM are functionally responsible for protein stability, activity and localization and includes: glycosylation, phosphorylation, sumoylation, ubiquitination, methylation and acetylation [22].

5. Notch signaling in DNA damage response

DDR is a complex protein kinase based- signaling pathway which is conducted by the members of the phosphoinositide 3-kinase-like kinase (PIKK) family, such as ataxia telangiectasia mutated (ATM), ATM and Rad3-related (ATR), and DNA-dependent protein kinase catalytic subunit (DNA-PKcs) [22]. DDR is triggered by sensing any potentially detrimental damages in DNA, then continued by transduction of damage signal and finished by exerting an appropriate effect, such as cell cycle arrest, activation of DNA repair machinery, or induction of apoptosis and quiescence [23]. Therefore, the key players of DDR include DDR sensors, transducers, mediators, and effectors. Following any DNA damage, sensor protein, which include MRE11/RAD50/NBS1 (MRN) complex and RAD9/RAD1/HUS1 (9-1-1) complex recognize damaged site and recruit DDR transducers. MRN complex senses double strand breaks (DSBs) and through interaction with NBS1, activates ATM, and subsequently phosphorylate the downstream proteins[24]. One of the well-known targets of ATM is histone-variant H2AX, and its ATM-mediated phosphorylation generates γH2AX, as one of the earliest events in DDR signaling [25]. The next step is transmission of the signal from sensors to transducers and amplifying of damage signal in order to activate the effectors. The serine/threonine kinases, ATM/ATR are important DDR transducers that initiated a cascade of phosphorylation events [25]. ATM activation is occurred following autophosphorylation and monomerization of the ATM dimer. ATR-interacting protein (ATRIP) is also involved in the recruitment of ATR to single strand breaks (SSB) [26]. Both ATM and ATR phosphorylate SQ/TQ motifs and share substrates, including breast cancer susceptibility gene 1(BRCA1), NBS1, p53, checkpoint kinase (CHK)1, and CHK2 [26]. Therefore, CHK1 and CHK2 are phosphorylated and activated in an ATM/ATR-dependent manner. CHK1 and CHK2 also share many common substrates similar to ATM and ATR, such as BRCA1, p53, E2F1, and CDC25A [27]. Effectors receive amplified damage signal form transducers and determine cell fate, in which cells arrest progression through cell cycle, evaluate the intensity of DNA damage and either activate DNA repair machinery or enter cell death pathways. In this context, tumor suppressor, p53 plays a pivotal role [27]. Due to considerable importance of Notch signaling pathway in critical aspects of cellular biology, particularly cell fate determination, recent studies have been focused on the crosstalk between DDR and this signaling pathway, and showed that various component of DDR are potential targets of Notch. In a recent study, it was reported that NOTCH1 is a direct inhibitor of ATM, independent from its transcriptional activity [28]. Investigating the underlying mechanisms revealed that *NOTCH1* inactivates ATM by preventing FOXO3a binding to the FRAPATM- TRRAP-C-terminal (FATC) domain of ATM. Additionally, FOXO3a is necessary for KAT5 binding to ATM and the formation of an ATM, FOXO3a, and KAT5 protein complex, hereinafter referred to as the ATM activation complex (AAC). NOTCH1-mediated FOXO3a displacement results in the impairment of KAT5- ATM interaction and ATM inactivation. Therefore, pharmacological induction of FOXO3a nuclear localization sensitizes NOTCH1- driven cancers to DNA damage-induced cell death [29]. Notch signaling pathway was also reported to target downstream DDR effectors, particularly key proteins involved in the apoptosis and cell cycle arrest. For example, disruption in signaling through Notch pathway increased the apoptosis of colon cancer cells and hence overcame drug resistance against oxaliplatin [30]. Suppression of the protein subunit nicastrin with siRNA and using a sulfonamide GSI (GSI34) prevented NICD induction after oxaliplatin and blunted Hes-1 activation. Therefore, inhibition of Notch-1 with siRNA enhanced chemosensitivity whereas overexpression of NICD increased chemoresistance. Down-regulation of Notch signaling also prevented the induction of prosurvival pathways, most notably phosphoinositide kinase-3/Akt, after oxaliplatin treatment [30]. In another study by Runzi et al. [31]. Notch1 signaling inhibits growth of human hepatocellular carcinoma through induction of cell cycle arrest and apoptosis. The authors observed that Notch1 mediated G0/G1 arrest in cancer cells through decreasing the expression of cyclin A, cyclin D1, cyclin E, CDK2, upregulation of p21waf/cip1, and p53 protein, and the phosphorylated form of retinoblastoma protein. In another study, inhibition of Notch signaling by GSI-XII, another GSI inhibitor, induced apoptosis of myeloma cells via Hes-1 and upregulation of the proapoptotic protein Noxa [32]. CSL is a key transcriptional repressor and mediator of Notch signaling. Downregulation of CSL, as a key transcriptional repressor and mediator of Notch signaling leads to conversion of human dermal fibroblasts (HDFs) into cancer associated fibroblasts (CAF), promoting keratinocyte tumors [33]. Additionally, CSL transcript levels have negative correlation with genes involved in DNA damage/repair. CSL expression is negatively regulated by stress/DNA damage caused by UVA, ROS, smoke extract, and doxorubicin treatment. P53, a key effector of the DDR, negatively controls CSL gene transcription, through suppression of CSL promoter activity and, indirectly, by increased p21 expression. CSL was previously shown to bind p53 suppressing its activity. It was indicated that p53, in turn, decreases CSL expression, which can serve to enhance p53 activity in acute DNA damage response of cells [33].

6. Notch ligands/inhibitors

Since the Notch signaling is one of the most commonly implicated signaling pathways in cancer, the pharmacological intervention of this pathway may favor the outcome of the current oncogenic practice. The current Notch inhibitors in the pre-clinical and clinical settings include monoclonal antibodies (mAb), Notch decoys, and Gamma-secretase inhibitors (GSIs).

The monoclonal antibodies are developed to target Notch receptors (anti-Notch1, Notch2, or Notch3) or its ligands (e.g., anti-DLL4 antibody). For example, the MAb604.107 exhibit a high affinity for the “gain-of-function” mutants of the negative regulatory region of Notch1

Table 1
Role of miRNA/Notch signaling in cancer initiation and progression.

Cancer type	miRNA	Notch targeted gene	Other target gene	Major finding	Ref.
Prostate cancer	miR-8/200	JAGGED1, HES1	ZEB1	miR-8/200 blocks tumourigenesis by inhibiting Notch ligand signaling	[54]
T-cell acute lymphoblastic leukemia	miR-19	Notch1	Bim, Prkaa1, PTEN, PP2A	miR-19 is sufficient to promote leukaemogenesis in Notch1-induced T-cell acute lymphoblastic leukemia	[46]
Colorectal cancer	miR-21	Notch1	PTEN	The expressions of Notch-1 and miR-21 were positively correlated with colorectal cancer development, especially in advanced-stages	[48]
Glioblastoma	mi*R*-33a	NICD	PKA, CREB, PDE8A, UVRAG	mi*R*-33a promotes glioma-initiating cell self-renewal via Notch pathway	[113]
	mir-34a	Notch-1, Notch-2	CDK6, cMet	Transient transfection of mi*R*-34a into glioma and medulloblastoma cell lines strongly inhibited cell proliferation, cell cycle progression, cell survival.	[56]
	mir-34a	Notch1	N/A	mi*R*-34a suppress the proliferation and induce apoptosis of cancer cells by decreasing the expression of target gene Notch1	[114]
Medulloblastoma	Mi*R*-34a	Dll1	Cyclin D1, cMyc, CDK4	mi*R*-34a overexpression reduces tumor burden in cerebellum xenografts of mice.	[115]
Pancreatic cancer	mi*R*-34a	Notch1	Snail1	mi*R*-34a inhibits cancer cell proliferation and induces apoptosis by targeting Notch1 expression	[55]
Gastric cancer	Mir-100	NICD, NRARP, Hey2	HS3ST2, Bcl-2, Bcl-xL, p21, CDKN1A	Antagonism of miR-100 increased the expression level of HS3ST2, the target gene of miR-100, and further resulted in the activation of the Notch-apoptosis pathway in tumor cells	[47]
Glioma cells	Mir-107	Notch-2	CDK6	miR-107 was down-regulated in glioma tissues and cell line Transfection of wild-type p53 into glioma cells stimulates miR-107 expression. miR-107 inhibits cellular proliferation and arrests the cell cycle at the G0–G1 phase miR-107 inhibits CDK6 and Notch-2 protein expression in glioma cells.	[57]
Glioma cells	MiR-129	Notch-1	E2F7, Beclin-1	Forced expression of miR-129 could induce autophagic flux by targetedly suppressing Notch-1 in glioma cells.	[58]
Endometrial cancer	MiR-134	Notch-1, CBF1, HES1	POGLUT1, p27	miR-134 overexpression affected the G2/M phase of cancer cells and suppressed the growth of xenograft tumors formed	[74]
Glioblastoma	MiR-141	Jagged1	N/A	miR-141 expression levels are suppressed in cancer stem cells and inhibit the self-renewal of stem cells	[75]
Melanoma	miR-146a	NOTCH	BRAF, KRAS, MAP	miR-146a promotes the initiation and progression of melanoma via activation of Notch signaling by downregulating NUMB	[45]
T cell acute lymphoblastic leukemia (T-ALL)	mir-181a-1/b-1	Notch1, NICD1		NOTCH oncogene activity in tumor development can be selectively inhibited by targeting the molecular networks controlled by mir-181a-1/b-1	[49]
Osteosarcoma	Mir-199b-5p	Notch1, HES1, HES5, DLL1, JAG1, DTX1	BLCAP, DMRTA2, PURB, AFF4	Mir-199b-5p was upregulated in cancer tissue in comparison with normal tissue	[53]
Hepatocellular carcinoma	miR-199a-3p	Jagged1, NICD, HES1	YAP1	miR-199a-3p regulate cell proliferation and apoptosis through Jagged1-Notch signaling	[59]
Pancreatic adenocarcinoma and basal type of breast cancer	miR-200	Jagged1, Maml2, Maml3	ZEB1	ZEB1 can trigger Notch signaling in cancer cells by stabilizing the expression of Notch pathway components, through inhibition of miR-200 expression	[116]
T-ALL	miR-223	Notch3, Notch1	FBXW7, P-p65, IkBα, Cyclin-E, C/EBPα	the Notch-mediated activation of miR-223 represses the tumor suppressor there is an inverse correlation of miR-223 and FBXW7 expression in a panel of T-ALL patient-derived xenografts	[63]
Gliomas	mi*R*-326	Notch-1,Notch-2	PARP	miRNA-326 was downregulated in gliomas Transfection of microRNA-326 into both established and stem cell-like glioma lines was cytotoxic, and rescue was obtained with Notch restoration	[60]
Embryonic carcinoma	mi*R*-375	Notch1, HES1, DLL1,	BAX, Bcl-2	mi*R*-375 overexpression influences cell proliferation, apoptosis and differentiation through the Notch signaling pathway	[50]
Merkel Cell Carcinoma	mi*R*-375	Notch2, RBPJ	AKT	Enforced mi*R*-375 expression in cells induced neuroendocrine differentiation, and opposed cancer cell viability, migration, invasion, and survival.	[61]
Cervical cancer	miR424-5p	Notch1, Notch2, JAG1	KDM5B	miR424-5p functions as an anti-oncogene cell growth by targeting KDM5B via the Notch signaling pathway	[62]
B- and T-cell Malignancies	mi*R*-30a	NOTCH1, NOTCH2	MYC	Intracellular NOTCH1 and NOTCH2, by inducing MYC, suppressed mi*R*-30a. Pharmacological inhibition of NOTCH decreased MYC expression and ultimately de-repressed mi*R*-30a	[117]
Cholangiocarcinoma	mi*R*-34a	Notch1, Notch2, Jagged 1	EZH2	mi*R*-34a mimic decreased cell proliferation, colony formation and migration	[69]
T-ALL	miR-223	Notch	IGF-1, insulin receptor, PTEN, ERK5	Up- or down-modulation of miR-223 in established T-ALL cells does not have significant effects on overall cell growth/viability	[118]

NICD, Notch intracellular domain; NRARP, Notch-regulated ankyrin repeat protein; CBF1, C promoter-binding factor 1.

(NRR) associated with T-ALL. The antibody decreased proliferation of the primary T-ALL cells by inhibiting elevated ligand-independent Notch1 signaling of NRR mutants and depleted leukemia initiating a CD34/CD44 high population as well as therapy resistant cancer stem cells in breast and colon solid tumors [34]. Other Notch1 monoclonal antibodies (mAb) with therapeutic potential are developed targeting the EGF-repeats. The monoclonal antibody 602.101, which specifically recognizes Notch1, inhibited the ligand-dependent expression of downstream target genes of Notch such as HES-1, HES-5, and HEY-L in the breast cancer cell line MDA-MB-231. The mAb also decreased cell proliferation, induced apoptotic cell death, and modulated expression of genes associated with the stemness and epithelial-mesenchymal transition [35].

The JAG/Notch signaling positively regulates angiogenesis by suppressing sVEGFR-1/sFlt-1 and promoting mural/endothelial cell interactions. Interestingly, soluble decoys such as N110-24 effectively inhibit angiogenesis and tumor growth by suppressing JAG1/JAG2-mediated Notch1 signaling [36].

The gamma-secretase inhibitors (GSIs) consists another class of Notch inhibitors which have entered into the clinical assessments. Though they mainly act as competitive inhibitors of presenilin activity [13], in vitro studies show that the GSI effectively represses cancer stem cells (CSCs), as well. Another mechanism of action described for cytotoxic effects of GSI is the induction of apoptosis of tumor cells by inhibiting proteasome activity. GSI I (Z-Leu-Leu-Nle-CHO) is shown to induce apoptosis in chronic lymphocytic leukemia cells (CLL) by simultaneous targeting of three important apoptosis regulators including proteasome inhibition, endoplasmic reticulum stress increase, and Notch down-regulation [37]. Most of the T-ALL cases can be therapeutically targeted with γ-secretase inhibitors. The mutant Notch1 can activate cMyc and PI3K-AKT-mTOR1 signaling in T-ALL. In the T-ALLs with the wild-type phosphatase and tensin homolog deleted on chromosome ten (PTEN), Notch1 transcriptionally represses PTEN, an effect reversible by the GSIs. Notch1 also promotes the growth factor receptor (IGF1R and IL7Rα) signaling to PI3K-AKT [38].

The GSI engagement of the CDK4/RB pathway is another important mechanism of GSI action which increases sensitivity of the T-ALL cells to apoptosis. The inhibition of the Notch pathway activity signature correlates with the induction of the cyclin-dependent kinase inhibitors CDKN2D (p19(INK4d)) and CDKN1 B (p27(Kip1)), leading to the derepression of RB and the subsequent exit from the cell cycle [39]. At present, GSIs are the most extensively explored Notch inhibitors. The completed clinical trials of the GSIs in cancer are reviewed elsewhere [6].

7. miRNAs

The MicroRNAs (miRNAs) are 21–23 nucleotide single stranded and non-coding RNA molecules which regulate the gene expression through the RNA-induced silencing complex (RISC). The MiRNAs are transcribed as precursors by RNA polymerases II and III, later they form mature miRNA after a series of cleavage events. For regulatory functions, microRNA assembles into RISC to activate the complex to target mRNA specified messenger RNA (mRNA) [40]. The miRNAs elicit their regulatory effects in post-transcriptional regulation by binding to the 3′ untranslated region (3′UTR) of target mRNA. Either perfect or near perfect complimentary base pairing results in the degradation of the mRNA, while the partial base pairing leads to translational inhibition as well as functional proteins [41].

Recently, overwhelming literature has emerged, documenting the biological significance of miRNAs in tumor progression. After discovery of the first miRNA in 1993, over 4500 miRNAs have been identified of which several are classified as oncomirs because they elicit oncogenic effects, meanwhile several others are recognized as tumor suppressor miRNAs [42]. It is well established that the miRNAs are fundamental players in cancer biology. They are implicated in a wide range of cellular processes, including cell proliferation, differentiation, apop

tosis, and angiogenesis. The deregulated expression of certain miRNAs is correlated with development and progression, cellular transformation, carcinogenesis, and tumor metastasis [43]. The up (oncomirs) or down (tumor suppressor miRNAs) regulation pattern of miRNAs could have diagnostic, prognostic, and therapeutic value. For example, up-regulation of miR-21 is strongly associated with both a high Ki-67 proliferative index and the presence of liver metastasis [44].

8. Crosstalk between miRNAs and Notch signaling

8.1. Cancer initiation/progression

An increasing body of previous studies demonstrates that the miRNAs have pivotal functions in cancer initiation/progression via regulating the expression of multiple oncogenes and tumor suppressor genes. As discussed earlier, miRNAs could be either oncogenic, which promote malignant transformation of cells or tumor suppressive, which inhibit cancer promotions (Table 1). Therefore, recently, researchers have been focused on the investigation of the relationship between the miRNAs and potential aberrant signaling pathways involved in cancer such as the Notch signaling pathway. Small RNA molecules such as miR-146a [45], miR-19 [46], miR-100 [47], miR-21 [48], miR-181a-1/b-1 [49], miR-375 [50], miR-483-5p, and various other miRNAs are among those that target the Notch signaling pathway to promote cancer initiation/progression. In a study by Farloni et al. [45], it was reported that the expression of miR-146a increased the ability of the human melanoma cells to proliferate in culture and form tumors in mice, whereas a knockdown of miR-146a had the opposite effects. It was demonstrated that these oncogenic activities are due to the miR-146a targeting the NUMB mRNA, a repressor of Notch signaling. A single nucleotide polymorphism (SNP) was also shown to affect the oncogenic potential of the miRNA, such that the ability of pre-miR-146a/G to activate the Notch signaling and promote oncogenesis was significantly higher than that of pre-miR-146a/C. Additionally, during the melanoma progression pre-miR-146a/G was enriched relative to pre-miR-146a/C, resulting from a C-to-G somatic mutation in pre-miR-146a/C. In a genome-wide RNA-mediated interference screen done by Mavrakis et al. [46], it showed that the miR-19 is sufficient to promote leukaemogenesis in Notch1-induced T-cell acute lymphoblastic leukemia (T-ALL) in vivo. Another miRNA investigated in T-ALL, was mir-181a-1/b-1, which modulate the strength and threshold of the Notch oncogenic signals in part by dampening the multiple negative feedback regulators downstream of the NOTCH and pre-T cell receptor (TCR) signaling pathways [49]. The deletion of mir-181a-1/b-1 expression inhibited the development of Notch1 oncogene-induced T-ALL. In addition, it was demonstrated that mir-181a-1/b-1, but not mir-181a-2b-2 and mir-181-c/d, controlled the development of normal thymic T cells and leukemia cells [49]. Xiong et al. [48] reported that Notch1 and miR-21 were over-expressed in the colorectal cancer tissues, particularly in the advanced stages, compared with the matched adjacent non-tumor tissues. The expressions of Notch1 and miR-21 were positively correlated with colorectal cancer development, especially in the advanced-stages. This finding indicated that the crosstalk between Notch1 and miR-21 is involved in colorectal cancer development. Moreover, the silencing of miR-100, which was specifically upregulated in the human epithelium-derived gastric cancer cells, initiated a robust apoptotic response in vitro [47]. In addition, the development of gastric cancer was inhibited by the miR-100 antagonism via initiating apoptosis of the tumor. The antagonism of miR-100 increased the expression level of HS3ST2, the target gene of miR-100, and further resulted in the activation of the Notch-apoptosis pathway in the tumor cells [47]. Xu et al. [51] characterized the microRNA profile in human cumulus granulosa cells and identified microRNAs such as the miR-483-5p that regulated the Notch signaling and was associated with polycystic ovary syndrome (PCOS). A total of 59 known miRNAs were identified that differentially expressed

in the PCOS cumulus granulosa cells, including 21 miRNAs increase and 38 miRNAs decrease. The members of the Notch signaling and ERK-MAPK pathway, Notch3 and MAPK3, were demonstrated to be regulated by miR-483-5p, based on the negative expression correlation validation and detection of Notch3/MAPK3 expression after miR-483-5p mimics transfection. It was suggested that Notch3 and MAPK3 were directly targeted by miR-483-5p. They suggested that miRNAs and their targeted pathways (e.g. Notch signaling pathway) play important roles in the etiology and pathophysiology of PCOS [51]. In another study by Galoian et al. [52], the differentially expressed miRNA and their targets was compared and analyzed in the human chondrosarcoma cell lines. They reported that the most significantly upregulated ten miRNAs with their significant/unique target genes were miR-551a and miR-105, whereas among the 18 differentially expressed significantly down-regulated human miRNAs, there were miR-886-3p and miR-143. Notch1, CLE11A, and NOTCH-related pathway target genes were among the predicted targets for these miRNAs [52]. Won et al. [53] performed miRNA microarray analysis on osteosarcoma tissue samples. They showed that the expression of 10 miRNAs had increased compared with normal controls. Among the 10 miRNAs, 3 miRNAs (miR-199b-5p, miR-338-3p, and miR-891a) were confirmed to have been up-regulated. After transfection of four osteosarcoma cell lines with miR-199b-5p inhibitor, the expression of the Notch pathway components in the transfected cell lines was changed. The results revealed that miR-199b-5p plays a role in the Notch signaling in osteosarcoma [53]. Some other miRNAs such as miR-8/20 [54], miR-34a [55,56], miR-107 [57], miR-129 [58], miR-199a-3p [59], miR-326 [60], miR-375 [61], and miR424-5p [62] act as the anti-oncogene miRNAs, which inhibit the cancer progression through the various mechanisms such as induction of cell cycle arrest, activation of apoptotic and autophagic pathways, and imbibition of cell proliferative pathways, through cross talk with the key component of the Notch signaling pathways. In addition to this fact that most players of the Notch signaling pathway are potential targets of the miRNA molecules, the reverse is true for some molecules. For example, Kumar et al. [63] reported that the Notch signaling pathway regulated the miR-223/FBXW7 axis in T-ALL. The miR-223 consistently regulated by overexpressing or silencing Notch3. In another study, it was found that hsa-let-7b and hsa-let-7d miRNAs respond to Notch activation specifically in primary melanoma cells. The hsa-let-7b and hsa-let-7d were down-regulated, respectively when the Notch1 pathway was constitutively activated [64]. Therefore, the hsa-let-7b and hsa-let-7d were identified as Notch-regulated specific miRNAs in the primary melanoma cells [64]. Through the undeniable importance of the miRNAs and their relationship with the Notch signaling pathway in the development of cancer, it is suggested that pharmacologic inactivation of Notch signaling or silencing of the miRNA molecules may have potential therapeutic applications in the treatment of various cancers. In this context, Suliman et al. [65] reported that niclosamide, an anthelminthic drug, potentially inhibited the progression of colon cancer by downregulating the Notch signaling and by upregulating the miR-200 family members. It was demonstrated that niclosamide suppressed the growth and migration of colon cancer cells through induction of the cell apoptosis. This was associated with the decreased protein expression of Notch1, Notch2, Notch3, and Hey1, and the increased expression of the tumor suppressor miR-200 family members (miR-200a, miR-200b, miR-200c, miR-141 and miR-429) that are typically downregulated in colon cancer [65]. In another study, Ji et al. [66] showed that the inhibition of non-small cell lung cancer cells (NSCLC) cell growth and induction of apoptosis by delta-tocotrienol due to the modulation of the Notch-1 pathway occurred via alteration of specific miRNA expression. They observed that the downregulation of the Notch-1 pathway, by delta-tocotrienol, was correlated with the upregulation of miR-34a. Moreover, the re-expression of miR-34a by transfection in the NSCLC cells resulted in the inhibition of cell growth and invasiveness, induction of apoptosis, and enhanced p53 activity. Furthermore, the cellular mechanism studies revealed that the induction of miR-34a decreased the expression of Notch1 and its downstream targets including Hes-1, Cyclin D1, Survivin, and Bcl-2. Therefore, it was suggested that delta-tocotrienol was a nontoxic activator of miR-34a which can inhibit the NSCLC cell proliferation, induce apoptosis, and inhibit invasion, and thus offering a potential starting point for the design of novel anticancer agents [66]. Luteolin, as a nontoxic flavonoid, was reported to significantly inhibit the survival, cell cycle, and expression of the Notch signaling- related proteins and regulated miRNAs in breast cancer. Introducing the Notch1 siRNA, miR-34a, and miR-224 mimics resulted in the reduction of the Notch signaling components and decreased tumor survival [67]. Additionally, it was demonstrated that the nanoparticle-based delivery of siRNA against DCAMKL-1, novel putative intestinal, and pancreatic stem cell marker, increased miR-144 and inhibited colorectal cancer tumor growth via a Notch1 dependent mechanism [68]. On the other hand, DAPT-mediated inhibition of Notch1 also resulted in tumor growth arrest and down regulation of Notch1 via a miR-144 dependent mechanism [68]. In another study by Kwon et al. [69], it was indicated that the epigenetic silencing of miR-34a promoted the cholangiocarcinoma growth by regulating the Notch pathway. The treatment of human cholangiocarcinoma cells with the DNA methylation inhibitors enhanced the expression of miR-34a, which was epigenetically silenced in the human cholangiocarcinoma cells. Moreover, the DNA methylation independently repressed the miR-34a expression in cancer cells. They also identified Notch1, Notch2, and Jagged 1, which are the major receptors and ligands of the Notch pathway, as the miR-34a target genes in cholangiocarcinoma cells. Accordingly, the forced over-expression of miR-34a significantly decreased the expression of Notch1, Notch2, and Jagged1 [69].

8.2. Cancer stem cells

In addition to the critical role of the Notch pathway in the development of cancer, it has been demonstrated that this highly conserved signaling pathway has a consequential role during the lineage-specific differentiation of pluripotent stem cells (Fig. 2). For example, miR-34a targets Notch2 and Hes1 and suppresses the Notch signaling pathway in stem cells, as a consequence, the Notch signaling pathway represses the odontogenic and osteogenic differentiation and enhances the miR-34a expression level [70]. The over-expression of miRNA-34b/c targets the Notch1 BMP2-induced C2C12 osteoblast differentiation [71]. The loss of the Notch signaling pathway results in the induction of the miR-155 and NF-kB activation in the bone marrow endothelial cells [72]. Interestingly, Notch signaling is involved in the regulation of the pMN progenitor cells differentiation into motor neurons via enhancing the expression levels of Hes5 and reducing the expression of motor neuron markers Ngn2, Hb9, and Lhx3 [73]. On the other hand, the significance of the Notch signaling pathway in cancer stem cells (CSCs) is associated with the involvement of Notch in tumorigenesis, CSCs management, and crosstalk between the Notch transduction with other oncogenes or pathways. It was reported that the expression level of miR-134 differed significantly between endometrial cancer stem cells and human endometrial cancer cells. The exogenous miR-134 overexpression down-regulated protein O-glucosyltransferase 1 (POGLUT1) and Notch pathway proteins in CSCs and resulted in G2/M arrest of CSCs [74]. The miR-141 inhibited the self-renewal of glioblastoma stem cells via targeting Jagged1. Moreover, miR-141 was suppressed in the CD133+ glioblastoma stem cells compared with CD133-non-glioblastoma stem cells from patient samples. In addition, the miR-141 overexpression inhibited the sphere formation ability of CSCs through targeting the 3'-untranslated region of Jagged1 [75]. The miR-34a suppressed the breast cancer stem cell-like characteristics by downregulating the Notch-1 pathway [76]. The expression of miR-34a correlated negatively with tumor stages, metastasis, and Notch1 expression in breast cancer tissues. The Mammosphere formation and expression of the stemness factor ALDH1 were also reduced in the cells treated with miR-34a [76].

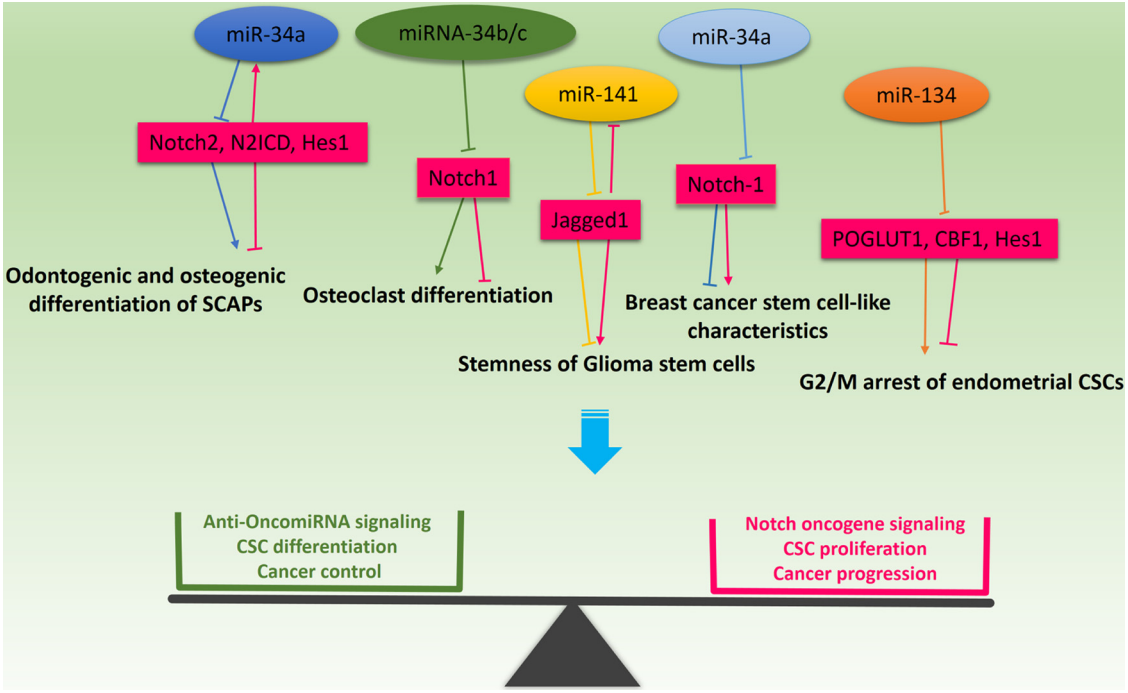

Fig. 2. Interplay between miRNA and Notch signaling in determining CSC fate.

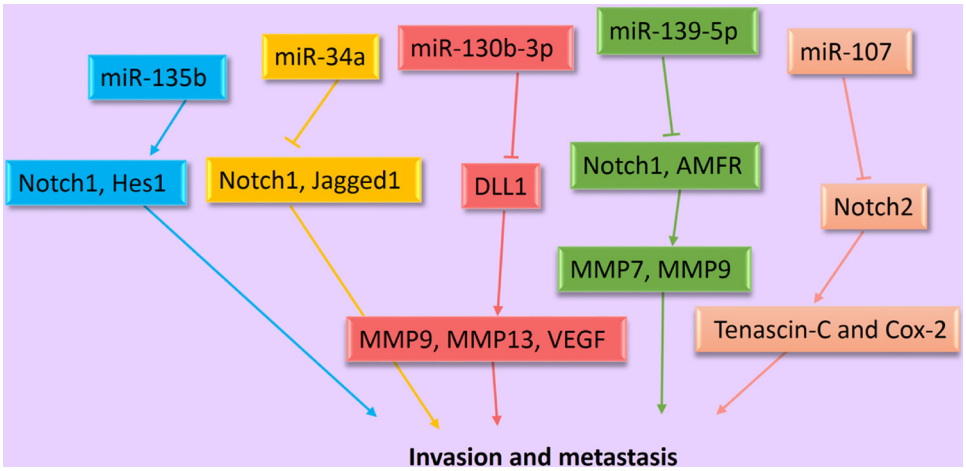

Fig. 3. Crosstalk between miRNA and Notch signaling in promoting cancer metastasis.

Furthermore, the miR34a loss of function and gain of function also altered the balance between self-renewal and differentiation in the colon CSCs [77]. It was shown that the miR34a sequestered Notch1 mRNA to generate a sharp threshold response where a bimodal Notch signal specifies the choice between self-renewal versus differentiation, which introduced a unique microRNA regulated mechanism that converts a noisy input into a toggle switch for robust cell fate decisions in the colon CSCs [77]. The crosstalk between other miRNAs and the Notch signaling process in CSCs' biology is confirmed, but further in-depth research is needed to understand their mechanisms.

8.3. Metastasis

The miRNAs have a significant function in each step of the cancer metastasis process (Fig. 3). Of note, the members of the mi*R*-34 family and their implication in metastasis have been intensively investigated in various types of cancer. In other words, the inhibitory role of this family on the developing aggressive phenotype of cervical carcinoma, prostate cancer, colorectal cancer, and bladder cancer has been studied previously. Pang et al. [78] reported that the mi*R*-34a inhibited the invasion of cervical cancer cells through downregulation of Notch1 and Jagged1. They showed that the forced expression of mi*R*-34a suppressed the invasiveness of cancer cells. The inhibition of the Notch signaling pathway confirmed that the downregulation of Notch1 reduced the invasiveness of the cells. In prostate cancer, mi*R*-34a attenuated the aggressiveness through inactivation of the androgen receptor and Notch1 [79]. In colorectal cancer, it was shown that mi*R*-34a expression was negatively associated with distant metastasis, and positively associated with differentiation and survival of human colorectal cancer specimens [80]. In addition, Notch1 and Jagged1 were the direct targets of mi*R*-34a, and thereby attenuated the migration and invasion of the colon cancer cells. It was further reported that the mi*R*-34a downregulated the expression of vimentin and fibronectin via Notch1 and Jagged1 [80]. The mi*R*-34a also exerts inhibitory effects on the cell migration and invasion of aggressive urothelial bladder carcinoma by targeting Notch1 [81]. In other words, the mi*R*-34a antagonized Notch1 and inhibited cell migration and invasion of bladder cancer cells, which indicated the tumor-suppressive function of

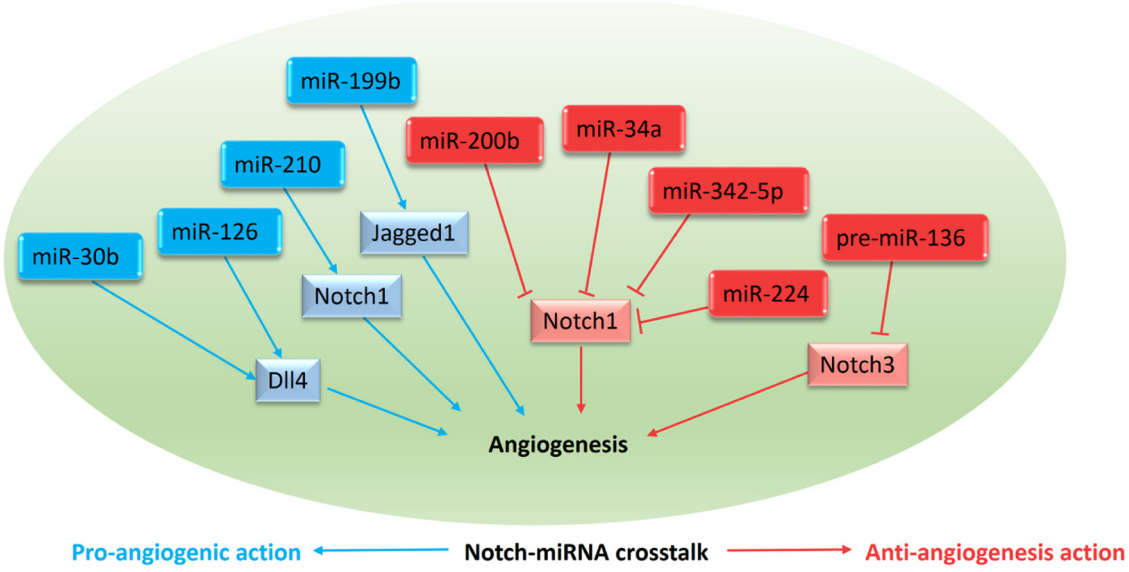

Fig. 4. Implication of miRNA-Notch signaling in tumor angiogenesis.

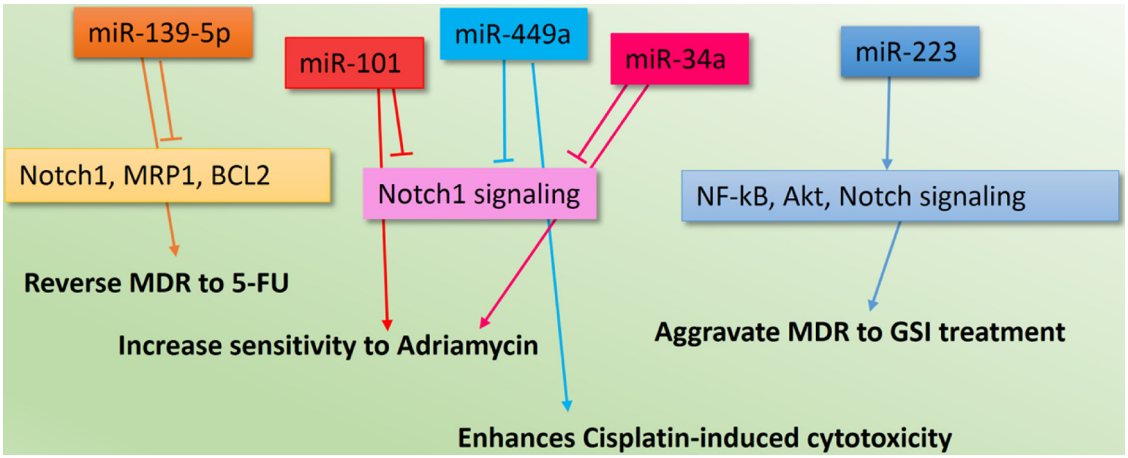

Fig. 5. Crosstalk between miRNA and Notch signaling and MDR in cancer.

microRNA-34a in bladder cancer [81]. In addition to the mi*R*-34 family, Shui et al. [82] showed that the miR-130b-3p inhibited cell invasion and migration by targeting the DLL1, one of the important ligands in the Notch signaling. In breast carcinoma, it was also demonstrated that the suppressive function of the miR-130b-3p on the cancer migration and invasion was mediated by the inhibition of the MMP-9, MMP-13, and VEGF expression [82]. Moreover, the miR-139-5p inhibited the migration and invasion of colorectal cancer by downregulating Notch1 and AMFR, which is an ubiquitin E3 ligase involved in the degradation of proteins through the endoplasmic reticulum pathway [83]. The knockdown of the two genes also phenocopied the inhibitory effect of miR-139-5p on colorectal cancer metastasis [83]. In another study, miR-139-5p was reported to inhibit cellular migration and invasiveness through the inhibition of Notch1, MMP-7, and MMP-9 in colorectal cancer [84]. The inhibitory effects of miR-107 also target Notch2 to suppress the glioma cell migration and invasion [85]. Chen et al. [85] showed that miR-107 was down-regulated in glioma tissues and cell lines, and its overexpression led to suppression of the migratory and invasive ability of glioma cells via direct targeting of Notch2, which was known to transactivate Tenascin-C and Cox-2. It was reported that the invasion of cancer cells was suppressed by the miR-206 targeting Notch3 [86], the mi*R*-375 targeting Notch2 and RBPJ [61], the miR-23b targeting Notch2 [87], the miR-200 targeting Jagged1 [88], and the miR-1 targeting Notch3 and Asef [89]. However, unlike the above mentioned miRNAs that are involved in the inhibition of cancer metastasis, there is another miRNA that was reported to stimulate cancer metastasis in a Notch- dependent manner. Yang et al. [90] demonstrated that the upregulation of miR-135b promoted lung metastasis and tumor recurrence in osteosarcoma. Additionally, overexpression of miR-135b simultaneously targeted the key component of Notch signaling pathways, including Notch1 and Hes1. Notably, the authors showed that antagonizing miR-135b potently inhibited osteosarcoma lung metastasis, cancer cell stemness, CSC-induced tumor formation, and recurrence in xenograft animal models [90].

8.4. Angiogenesis

Given that some miRNAs are expressed in vascular endothelial cells, and a subset of miRNAs are involved in the regulation of angiogenesis, several reports indicate that the miRNAs are essential determinants of vascular endothelial cell biology and angiogenesis. However, the crosstalk between the miRNAs and Notch signaling pathway has been limitedly investigated in cellular biology, particularly cancer pathogenesis (Fig. 4). The overexpression of miR-210 was shown to significantly enhance the angiogenesis and formation of more capillary-like structures through increase in the expression level of Notch1 [91].

Table 2
miRNA/Notch signaling as a therapeutic target for the anti-MDR treatment of multiple cancers.

Cancer type	miRNA	Target genes	Mechanism of MDR	Chemotherapeutic agent	Major finding	Ref.
Confer						
Breast cancer	miR-221/222	Notch, p53, MAPK, TGF-β, Wnt	Inhibition of cell death	fulvestrant	miR-221/222 overexpression resulted in deregulation of multiple oncogenic signaling pathways previously associated with drug resistance.	[111]
	mi*R*-34a	Notch1	Inhibition of apoptosis	Adriamycin	Ectopic miR34a expression reduced cancer stem cell properties and increased sensitivity to doxorubicin treatment by directly targeting NOTCH1	[119]
Lung Adenocarcinoma	miR-451	Notch-1, MDR-1, AP-1	Increase in the expression of drug efflux proteins	Docetaxel	MDR-1 is a direct target of miR-451 and influences chemoresistance of cancer cells	[120]
Non-small cell lung cancer	miR-223	FBXW7,	Inhibition of cell death	erlotinib	Cancer cells can upregulate their levels of miR-223 expression via the Akt and Notch signaling pathways	[112]
Inhibit						
Breast cancer	mi*R*-34a	Notch1	Induction of cell death	Adriamycin	Notch1-siRNA could partially reverse the effect of mi4a inhibitor in inducing chemoresistance of cancer cells to Adriamycin	[110]
Ovarian cancer	miR-499a	NOTCH1	Induction of apoptosis	cisplatin	miR-449a were significantly downregulated in the cisplatin-resistant ovarian cell lines	[109]
Ovarian cancer	miR-199b-5p	JAG1, Notch1	Induction of cell death	cisplatin	re-expression of miR-199b-5p and siRNA-mediated JAG1 knockdown or treatment with Notch specific inhibitor γ-secretase (GSI) attenuated JAG1-Notch1 signaling activity, thereby enhancing cisplatin-mediated cell cytotoxicity.	[121]
Colorectal cancer	miR-139-5p	Notch1, MRP-1, BCL-2	Induction of apoptosis decrease in the expression of drug efflux proteins	to 5-fluorouracil	up-regulation of NOTCH-1 abrogated miR-139-5p-mediated sensitization to 5-FU.	[106]
	MiR-139-5p	Notch1	induction of apoptosis	Oxaliplatin, vincristine	Silencing NOTCH1 exerted an effect similar to overexpression of miR-139-5p by inhibiting the CD44+ and CD133+ population and reversing the drug-resistant phenotype.	[107]
T-ALL	MiR-101	Notch1	induction of apoptosis	adriamycin	miR-101 was significantly downregulated in the blood samples of patients with T-ALL compared with the healthy controls	[108]
Non-small Cell Lung Cancer	miR-3*R*-34a	Notch1	inhibition of epithelial-mesenchymal transition (EMT)	radiation	Reduced Notch-1 expression promoted apoptosis through significant down-regulation of the nuclear factor-kB pathway, resulting in a radiosensitizing effect on cancer cells.	[122]

The miR-497 ~ 195 cluster regulates angiogenesis by maintaining the endothelial Notch and HIF-1a activity via targeting the F-box and WD-40 domain protein (Fbxw7) and Prolyl 4-hydroxylase possessing a transmembrane domain (P4HTM), respectively [92]. The over-expression of pro-angiogenic miR-296 markedly enhanced the formation of capillary-like structures via the upregulation of vascular endothelial growth factor (VEGF) and VEGF receptor 2, and downregulation of the DLL4 and Notch1 [93]. The miR-126 was responsible for an increase in angiogenic factors including VEGF and bFGF being released and activating Dll-4, thus enhancing angiogenesis [94]. The miR-199b modulates angiogenesis by targeting the Jagged1 and enhancing VEGF Signaling [95]. The overexpression of mi*R*-30b in endothelial cells led to an increased vessel number and length via up-regulation of the Dll-4 [96]. The mi*R*-342-5p acts as a multifunctional angiogenic repressor and a Notch downstream molecule, which regulates multiple angiogenic pathways including Notch, VEGF, and bFGF signaling [97]. In ovarian cancer, it was reported that pre-miR-136 enhanced apoptosis and decreased angiogenesis by directly targeting of the Notch3 [98]. MicroRNAs such as mi*R*-34a and miR-200b are typically lost in osteosarcoma, however their re-expression leads to the reduced expression of Notch1, thus resulting in the inhibition of osteosarcoma cell angiogenesis, which is indicated by the miRNA- related inhibition of VEGF expression and activities [99]. Moreover, mi*R*-34a and miR-224 regulated Notch signaling and inhibited breast cancer cell angiogenesis through suppression of VEGF expression and release [67].

8.5. Drug resistance

An increasing body of evidence now declares that the miRNA levels within the cell can be a major determinant of multidrug resistance (MDR) or sensitivity. Several researchers have identified miRNAs associated with sensitivity or resistance to many types and classes of chemotherapeutic drugs through targeting important players of the Notch signaling pathway (Fig. 5). In general, several molecular mechanisms are responsible for the acquisition of the MDR in cancer cells, including alterations of apoptosis; DNA repair mechanisms and cell cycle; alterations of drug efflux system; drug metabolism; drug target structure; alternation in cell membrane composition; regulation of cancer stem cells; and epithelial–mesenchymal transition (EMT) [100–105]. The overexpression of some miRNAs confers MDR, while upregulation of some others sensitize cancer cells to various chemotherapeutics. For instance, miR-139-5p reversed the resistance to 5-fluorouracil (5-FU) in colorectal cancer cells by targeting Notch1 [106]. Furthermore, the miR-139-5p was down-regulated either in the colorectal cancer tumors receiving chemotherapy or in 5-FU-resistant CRC cell lines. The miR-139-5p induced sensitization of cancer cells to 5-FU was mediated by increasing 5-FU-induced apoptosis, as well as the inhibition of the Notch1 and its downstream molecules MRP-1 and BCL-2, two key MDR-associated genes [106]. Additionally, the overexpression of miR-139-5p reversed CD44 + /CD133 + associated MDR in colorectal cancer [107]. Silencing Notch1 exerted an effect similar to over-expression of miR-139-5p by inhibiting the CD44 + and CD133 + population and reversing the drug-resistant phenotype [107]. miR-101 enhanced the sensitivity to Adriamycin in T-cell acute lymphoblastic leukemia [108]. Notch1 mediates the effects of miR-101 on Jurkat cell proliferation, apoptosis, and invasion [108]. Notch1 is a target for another miRNA, miR-449a, which reduces cell survival and enhances cisplatin-induced cytotoxicity via downregulation of Notch1 in ovarian cancer cells [109]. The mi*R*-34a also modulates chemosensitivity of breast cancer cells to Adriamycin by targeting Notch1 [110]. In addition, Notch1-siRNA could partially reverse the effect of mi*R*-34a inhibitor in inducing chemoresistance of cancer cells to Adriamycin [110]. On the other hand, miR-221/222 confers breast cancer fulvestrant resistance by regulating the multiple signaling pathways including Notch signaling [111]. An increase in miR-223 expression induces cell resistance to erlotinib in non-small cell lung cancer cells [112]. It was reported that blocking either the Akt or Notch signaling pathway and reducing miR-223 expression resulted in a decreased resistance in cancer cells [112]. Notch and NF-kB are reported to be novel co-regulatory signals of miR-223 expression and its inhibition prevents T-ALL resistance to gamma-secretase inhibitor (GSI) treatment, suggesting that miR-223 could be involved in GSI-sensitivity and its inhibition may be exploited in the target therapy protocols in T-ALL [63]. Collectively, this data suggests that the miRNA/Notch signaling may be a promising therapeutic target for the anti-MDR treatment of multiple cancers (Table 2).

9. Conclusions

While angiogenesis and metastatic potential are indispensable for cancer progression, establishment of tumor cells with characteristics of cancer stem cells assures cancer cell survival and promote multi-drug resistance, consequently translate into therapy failure and cancer relapse. Tumor cells adopt various tactics to meet these vital requisites for their growth and survival, among the recently uncoupled strategies, the interplay of two prominent signaling pathways, miRNA and Notch signaling have been demonstrated in the progression and MDR of many cancers. Accordingly, approaches to target miRNA/Notch signaling may offer a promising therapeutic approach to fight cancer, however further in-depth research is desirable to depict the whole picture of possible underling mechanisms.

Conflict of interest

Authors declare none.

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