Non-coding RNA Research 10 (2025) 1–15

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: www.keaipublishing.com/en/journals/non-coding-rna-research

Review Article

Emerging roles of non-coding RNAs in modulating the PI3K/Akt pathway in cancer

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ARTICLE INFO

Keywords:
Non-coding RNAs
Cancer therapy
Cancer progression
PTEN
Chemotherapy
Radiotherapy

ABSTRACT

Cancer progression results from the dysregulation of molecular pathways, each with unique features that can either promote or inhibit tumor growth. The complexity of carcinogenesis makes it challenging for researchers to target all pathways in cancer therapy, emphasizing the importance of focusing on specific pathways for targeted treatment. One such pathway is the PI3K/Akt pathway, which is often overexpressed in cancer. As tumor cells progress, the expression of PI3K/Akt increases, further driving cancer advancement. This study aims to explore how ncRNAs regulate the expression of PI3K/Akt. NcRNAs are found in both the cytoplasm and nucleus, and their functions vary depending on their location. They can bind to the promoters of PI3K or Akt, either reducing or increasing their expression, thus influencing tumorigenesis. The ncRNA/PI3K/Akt axis plays a crucial role in determining cell proliferation, metastasis, epithelial-mesenchymal transition (EMT), and even chemoresistance and radioresistance in human cancers. Anti-tumor compounds can target ncRNAs to modulate the PI3K/Akt axis. Moreover, ncRNAs can regulate the PI3K/Akt pathway both directly and indirectly.

1. Introduction

1.1. Cancer definition and dysregulation of molecular pathways

Neoplasms or malignant disorders are significant threats to human health, encompassing a variety of diseases that can occur in different organs and tissues [1]. The most characteristic feature of tumors is their abnormal growth and spread throughout the body, forming new colonies at secondary sites [2,3]. Cancer cells are heterogeneous in nature, and the incidence rate of cancer is projected to rise significantly. By

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https://doi.org/10.1016/j.ncrna.2024.08.002
Received 28 November 2023; Received in revised form 25 July 2024; Accepted 8 August 2024
Available online 9 August 2024

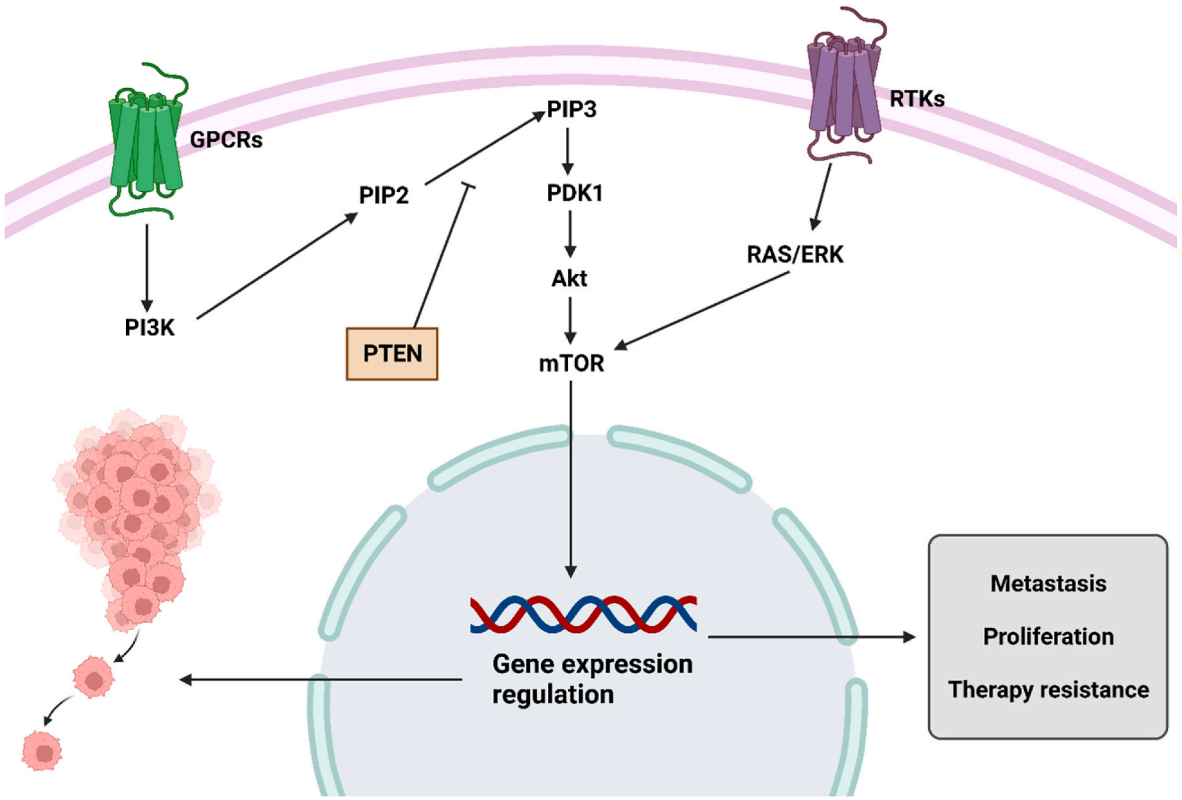

Fig. 1. An overview of the PI3K/Akt/mTOR axis: PI3K can be activated by GPCRs, facilitating the conversion of PIP2 to PIP3. This conversion then activates the PDK1/Akt axis, which enhances mTOR levels. Subsequently, mTOR is translocated to the nucleus to regulate gene expression, impacting proliferation, metastasis, therapy resistance, and other mechanisms such as cell death and metabolism. PTEN can suppress the conversion of PIP2 to PIP3. Additionally, RTKs can activate the RAS/ERK axis, contributing to mTOR signaling activation.

2040, the number of cancer cases is estimated to reach 28.4 million, representing a 47 % increase compared to 2020 [4]. Clinical management of cancer remains a significant challenge for physicians. Despite various therapies, patient mortality rates are still high. Therefore, conventional therapies need to be evolved, and new approaches, such as gene therapy, should be considered either alone or in combination with other treatments to improve cancer care. Recent studies have highlighted the importance of targeting dysregulated molecular pathways and mechanisms that occur during tumor progression. Consequently, there is a growing emphasis on understanding, identifying, and therapeutically targeting key molecular pathways involved in tumorigenesis.

1.1.1. An introduction PI3K/Akt

Phosphatidylinositol-3-kinase (PI3K), protein kinase B (Akt), and mammalian target of rapamycin (mTOR) are dysregulated during tumorigenesis and play regulatory roles in proliferation, viability, migration, and metabolic reprogramming [5–7]. PI3Ks in mammals are classified into three categories as lipid kinases [8] and they have always been of interest due to their crucial roles in normal and pathological conditions. The most well-established type of PI3K is class I, which has shown a strong association with the initiation and development of cancer [9]. In each class IA PI3K, there are two subunits with catalytic and regulatory functions. The catalytic subunit of class I PI3K is p110, which can be p110α, p110β, p110γ, or p110δ, encoded by PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively. The regulatory subunit is p85, which includes p85α, p85β, and p85γ, encoded by PIK3R1, PIK3R2, and PIK3R3, respectively. PI3K activation can occur in two ways: directly by Ras and indirectly by Src homology 2 and the presence of phosphotyrosine residues on growth factor receptors [10]. Class IA enzymes are involved in the induction of PI3K signaling by facilitating the conversion of PIP2 to PIP3 [11,12]. The transformation of PIP2 to PIP3 is considered crucial for the activation of two downstream kinases, PDK1 and Akt [13]. Akt, a serine/threonine kinase, can be activated by PDK1. It has three isoforms—Akt1, Akt2, and Akt3—which are expressed in various tissues [14]. Phosphorylation of Akt leads to its activation, but this phosphorylation must occur at specific sites. Full activation of Akt occurs when it is phosphorylated at threonine 308 by PDK1 and at serine 473 by various kinases [15,16], including Akt itself [17], integrin-linked kinase [18], DNA-dependent protein kinase [19], and mTOR complex 2 (mTORC2) [20]. Akt can target various pathways in regulating proliferation and survival [21]. mTOR, a well-known downstream target of PI3K/Akt, is a serine/threonine kinase that exists in two complexes: mTORC1 and mTORC2. The mTORC1 complex is involved in protein translation through its substrates, including S6K1 and eukaryotic initiation factor 4E-binding protein 1 [22]. mTORC2 induces phosphorylation of S473 regulatory domain of Akt [20] and also modulates PKC-α phosphorylation, actin cytoskeleton organization, and cell migration [23,24].PTEN is a crucial tumor suppressor gene that negatively regulates the PI3K/Akt pathway. It functions by dephosphorylating PIP3 back to PIP2, thereby acting as a brake on PI3K/Akt signaling. Loss or mutation of PTEN is common in many cancers, leading to unchecked activation of the PI3K/Akt pathway, which promotes cell survival, proliferation, and resistance to apoptosis. By maintaining the balance between PIP2 and PIP3, PTEN is essential for controlling the cellular processes regulated by PI3K/Akt [25–29]. The RAS/ERK pathway, also known as the MAPK pathway, is another crucial signaling cascade involved in cell proliferation, differentiation, and survival. RAS, a small GTPase, directly activates PI3K, thereby linking the RAS/ERK pathway with PI3K/Akt signaling. Activation of ERK can further modulate components of the PI3K/Akt pathway, creating a network of interactions that finely tune cellular responses to growth signals. Aberrations in the RAS/ERK pathway, like those in the PI3K/Akt pathway, are commonly

observed in various cancers, highlighting the interconnected nature of these signaling networks. For more information, refer to these reviews [30,31]. Fig. 1 depicts PI3K/Akt/mTOR signaling.

1.2. PI3K/Akt function in human cancers

The PI3K/Akt pathway promotes cell growth and proliferation by enhancing protein synthesis and inhibiting apoptosis. Activation of mTORC1 increases protein translation and cell growth [32]. Akt phosphorylates and inactivates pro-apoptotic factors such as BAD and procaspase 9, thereby promoting cell survival. Additionally, Akt activates NF-κB signaling, further enhancing cell survival [33]. The PI3K/Akt pathway shifts cellular metabolism towards glycolysis, known as the Warburg effect, to support rapid cell proliferation. Akt enhances glucose uptake by upregulating GLUT1 and stimulating glycolytic enzymes [34]. PTEN is a tumor suppressor that dephosphorylates PIP3 back to PIP2, thereby antagonizing PI3K/Akt signaling. Loss or mutation of PTEN is common in many cancers, resulting in hyperactivation of the PI3K/Akt pathway [35]. The RAS/ERK pathway can directly activate PI3K. RAS binds to the p110 catalytic subunit of PI3K, leading to its activation. Cross-talk between the PI3K/Akt and RAS/ERK pathways is essential for regulating cell growth and survival [36]. PI3K/Akt signaling regulates key metabolic pathways, including glycolysis and lipid metabolism. Activation of Akt results in increased glucose uptake and lipid synthesis, which support the anabolic needs of proliferating cancer cells [37]. The PI3K/Akt pathway is a pivotal component in cancer biology, integrating signals from various receptors and interacting with multiple molecular pathways to regulate essential cellular processes for cancer development and progression. Targeting this pathway presents potential therapeutic opportunities, as evidenced by numerous ongoing clinical trials exploring PI3K, Akt, and mTOR inhibitors in cancer treatment.

The role of the PI3K/Akt pathway in cancer is crucial, and the modulatory functions of upstream mediators have been extensively evaluated. Additionally, the effects of anti-tumor compounds on the regulation of PI3K/Akt signaling and the reduction of carcinogenesis have been investigated. Connexin32 (Cx32) shows low expression in liver cancer and is associated with poor prognosis. Restoring Cx32 expression impairs cancer stem cells in liver tumors by suppressing the PI3K/Akt pathway [38]. In bladder tumors, the stimulation of the PI3K/Akt/mTOR axis by STIL enhances c-Myc expression, promoting carcinogenesis s [39]. Upregulation of RGS20 in penile cancer leads to increased growth and invasion of tumor cells through the stimulation of PI3K/Akt, while silencing RGS20 impairs tumorigenesis in animal models [40]. Stabilization of EGFR by UBE2C as an upstream mediator induces PI3K/Akt signaling, elevating pancreatic cancer progression [41]. It can be concluded that key tumor hallmarks such as proliferation, metastasis, cell cycle progression, and even vasculogenic mimicry formation are modulated by PI3K/Akt as central players in molecular pathways [42–46]. On the other hand, inhibition of PI3K/Akt by anti-tumor compounds such as alisol A [47], jujuboside B [48], calycosin [49] and berberine [50] plays a significant role in reducing tumor cell progression. Conversely, activation of PI3K/Akt by upstream mediators drives increased tumor cell progression. For example, microcystin-leucine arginine induces PI3K/Akt to increase Wnt/β-catenin expression, enhancing the growth rate of colorectal tumor cells [51].

Significant genomic changes in tumor cells accumulate over time, ultimately leading to tumorigenesis. One of the key dysregulated factors in human cancers is the PI3K/Akt pathway, which is known to be upregulated during tumorigenesis. Since PI3K/Akt can increase proliferation, metastasis, and drug resistance, understanding the related molecular pathways is crucial. This review focuses on the association between PI3K/Akt and ncRNAs in regulating tumorigenesis. While the PI3K/Akt pathway has oncogenic functions and contributes to cancer progression in various cancers, ncRNAs have dual roles and can either stimulate or suppress PI3K/Akt in cancer therapy. The underlying pathways are discussed in this review to pave the way for developing novel therapeutics in the future. Although numerous reviews have been published recently, they often focus on specific cancers, such as gastric cancer [52], prostate cancer [53], breast cancer [54], gastrointestinal tumors [55] and colorectal cancer [56]. Additionally, interactions of PI3K/Akt with other factors, such as ubiquitination, deubiquitination [57], and m6A modification [58], have been explored. Two reviews in 2024 specifically address the regulation of PI3K/Akt by ncRNAs in hepatocellular carcinoma [59] and the lncRNA/PI3K-Akt axis in lung cancer [60]. Therefore, this review aims to provide a comprehensive overview of the regulation of the PI3K/Akt axis by ncRNAs across different human cancers.

2. microRNAs and PI3K/Akt signaling

2.1. An overview of microRNAs

miRNAs are single-stranded RNA molecules, 18–25 nucleotides in length, that do not encode proteins. They are encoded by endogenous genes and exhibit tissue-specific expression [61]. The first report of miRNAs was in Caenorhabditis elegans, where they regulate the expression of the lin-14 gene through antisense RNA-RNA interactions [62]. miRNAs degrade target messenger RNA (mRNA) by binding to the 3′-UTR, thus regulating various genes and molecular pathways [63]. Recent studies have highlighted that dysregulation of miRNAs is common in cancer, making them important regulators of molecular pathways. The function of miRNAs in each cancer can vary, being either pro-survival or pro-death, and one miRNA can target multiple genes. For example, miR-137 suppresses metastasis in lung cancer cells by downregulating COX-2 [64]. miR-22-3p inhibits proliferation and metastasis in colorectal cancer by reducing KDM3A expression, thereby suppressing Hippo signaling [65]. miR-26a-5p, which is expressed at low levels in cervical cancer, induces apoptosis in tumor cells by suppressing HSDL2 expression [66]. These studies demonstrate the versatile functions of miRNAs in cancer and their importance as regulators of molecular pathways, which will be discussed in association with the PI3K/Akt axis in the next section.

2.2. Tumorigenesis regulation

2.2.1. Tumor suppression

The role of certain miRNAs in cancer is well-documented, and when most studies support their anti-tumor activity, they can be classified as tumor suppressors. However, as scientific understanding evolves and more studies are conducted, the role of a tumor-suppressor miRNA may be reconsidered, as these RNA transcripts can act like a double-edged sword. For example, miR-30e is suggested to be a tumor suppressor; it reduces the levels of met-adherin, thereby impairing the growth and metastasis of bladder tumor cells [67]. Reduced expression of miR-30e can increase cancer progression [68]. However, melatonin administration decreases the levels of miR-30e and miR-21, inducing apoptosis by activating PTEN signaling [69]. miR-30e-3p specifically suppresses cancer progression by reducing THOC2 expression and impairing the PI3K/Akt/mTOR axis, thus decreasing the progression and development of gastric tumors [70]. A recent experiment focused on developing a miR-19a/b sponge to increase PTEN and TP53INP1 expression at the mRNA level, which resulted in the inhibition of Akt and significantly reduced the progression of lung tumor cells [71]. These studies demonstrate that miRNAs can directly and indirectly affect the PI3K/Akt axis in cancer progression regulation. However, based on experiments, miRNAs primarily use indirect methods in cancer therapy. High levels of miR-30d-5p suppress the progression of ovarian cancer by diminishing SOX4 expression, thereby suppressing the PI3K/Akt axis and increasing sensitivity to cell death in cancer [72]. Another example of the indirect impact of miRNAs on the PI3K/Akt axis is miR-122-5p, which decreases cholangiocarcinoma progression. High expression levels of FUT8 are observed in cholangiocarcinoma, enhancing tumor progression and

mediating poor prognosis. Through post-transcriptional action, miR-122-5p reduces FUT8 expression, thereby suppressing the PI3K/Akt axis and decreasing the proliferation and metastasis of cholangiocarcinoma cells [73].

The previous study also supports the notion that miRNAs indirectly affect the PI3K/Akt pathway in tumor cells. Laminin subunit beta-3 (LAMB3) is a key component of laminin, and its upregulation has been linked to the progression of various human cancers, including pancreatic and lung tumors [74,75]. The expression level of hsa-mir-133a-2 is reduced in cervical tumors, impairing the growth and metastasis of tumor cells. Hsa-mir-133a-2 functions by reducing LAMB3 expression, which suppresses the PI3K/Akt axis and inhibits tumorigenesis in cancer [76]. HM13, also known as SPP, is a protein localized in the endoplasmic reticulum (ER) [77,78]. HM13 is suggested to have oncogenic functions, and its upregulation in hepatocellular carcinoma is associated with poor prognosis and increased growth and invasion [79]. Overexpression of HM13 in breast tumors induces the PI3K/Akt pathway, promoting tumor growth and metastasis. However, miR-760 reduces HM13 expression by binding to its 3′-UTR, thereby inactivating the PI3K/Akt pathway [80].

Another metabolic change in tumor cells is the alteration of glucose metabolism. Metabolic adaptation is crucial for cancer cell survival, involving a shift from oxidative phosphorylation to glycolysis [81–84]. This shift increases lactate accumulation and promotes tumor proliferation. miR-129-5p suppresses the phosphorylation of PI3K/Akt and binds to SLC2A3, reducing its expression and impairing glycolysis in gastric tumors [85].

So far, we have discussed how both miRNAs and the PI3K/Akt pathway can regulate each other's expression. The miRNA/PI3K/Akt axis is involved in regulating proliferation, metastasis, lipid metabolism, and glycolysis in cancer cells. Moreover, miRNAs can directly and indirectly control the PI3K/Akt pathway. Interestingly, it has been shown that the miRNA/PI3K/Akt axis can be modulated by anti-tumor compounds in cancer therapy. For instance, saponin from Platycodi radix is an anti-tumor compound that can suppress the progression of colorectal cancer by reducing the expression levels of miR-181c/d-5p, thereby inhibiting the PI3K/Akt axis and decreasing tumor growth and invasion [86]. The PI3K/Akt pathway is also a critical regulator of immunotherapy. In recent years, the induction of immunotherapy [87,88] and factors involved in immune evasion have gained importance [89]. Therefore, future studies should focus on the role of miRNAs in the regulation of PI3K/Akt in immune evasion.

2.2.2. Tumor progression

In Section 2, it was discussed that PTEN inhibits PI3K/Akt signaling. Thus, if a certain miRNA binds to the 3′-UTR of PTEN and decreases its expression, it plays an oncogenic role in cancer. miR-548k interacts with PTEN and mechanistically decreases PTEN expression, thereby inducing PI3K/Akt signaling, reducing apoptosis and cell death, and promoting progression in breast tumors [90]. Consequently, if a miRNA sponge is designed to increase PTEN expression, it could significantly reduce tumor cell progression by impacting PI3K/Akt signaling. SOX4 is a new emerging target in cancer therapy. USP20 promotes SOX4 stability by preventing its degradation and ubiquitination, thereby increasing colorectal cancer progression [91]. Additionally, circ-0000218 increases SOX4 expression by inhibiting miR-139-3p, which suppresses apoptosis in gastric tumors [92]. Therefore, high levels of SOX4 expression are associated with increased tumor cell progression.

LZTS1 plays an important role in cancer, and its upregulation is crucial for increasing the sensitivity of breast tumor cells to paclitaxel chemotherapy [93]. In gastric cancer, there appears to be an interaction between LZTS1 and the PI3K/Akt pathway, where high LZTS1 expression hinders the activation of PI3K/Akt. miR-762 has been shown to promote gastric cancer progression by reducing LZTS1 expression, thereby inducing the PI3K/Akt axis and enhancing tumor development and progression [94]. Similarly, upregulation of SGTB in lung cancer leads to downregulation of PI3K/Akt, inducing apoptosis and reducing cancer cell progression [95].

Apelin, a member of the adipokine family [96], plays a vital role in physiological processes such as metabolic reprogramming [97], angiogenesis [98], growth, and migration [99]. High expression of apelin leads to the induction of the PI3K/Akt pathway, which enhances cancer proliferation [100]. In prostate tumors, apelin increases cell invasion by inducing the PI3K/Akt pathway through the phosphorylation of c-Src. This activation results in the overexpression of miR-106a-5p, which reduces TIMP2 levels, thereby promoting cancer metastasis [101]. Additionally, miR-205-5p reduces VEGF-A expression to suppress angiogenesis. However, the PI3K/Akt pathway undergoes phosphorylation by vWF, leading to decreased miR-205-5p expression and increased VEGF-A expression, which promotes angiogenesis [102]. These studies indicate that the PI3K/Akt axis can regulate miRNA expression in cancers. Metabolic reprogramming and changes in tumor cell metabolism can result from miRNA dysregulation. The PTEN/PI3K/Akt axis is known to regulate lipid metabolism in lung cancer, with PTEN suppressing metabolism [103]. However, PTEN expression decreases during tumor progression. miR-421 increases lipid metabolism in lung tumors to promote carcinogenesis by reducing PTEN expression, thereby inducing the PI3K/Akt axis and accelerating lipid metabolism.

Two crucial aspects are essential for glycolysis in cancers: the availability and uptake of glucose into cells, and the proper functioning of glycolytic enzymes. GLUT1, a transmembrane protein, facilitates glucose entry into cells, while hexokinase II (HKII) participates in the glycolytic process. miR-124 impairs growth and the Warburg effect in lung tumors by suppressing Akt signaling, leading to decreased levels of GLUT1 and HKII, which are important for reducing cancer proliferation [104]. Conversely, some miRNAs promote glycolysis and tumor progression. miR-193a-3p enhances glycolysis under hypoxic conditions by increasing Akt phosphorylation and upregulating PFKFB3, another key glycolytic enzyme [105]. The interaction between PTEN and Akt is also critical in regulating glycolysis in cancers. In breast tumors, the expression of miR-181a-5p increases while NDRG2 expression decreases. miR-181a-5p downregulates NDRG2, leading to increased Akt expression through PTEN downregulation, thereby accelerating growth and glycolysis in breast tumors [106]. Therefore, the interaction of miRNAs with other molecular pathways, including the PI3K/Akt pathway, is crucial in modulating glycolysis and controlling tumorigenesis [107–111].

Icariin is another compound that can suppress tumor proliferation by increasing miR-1-3p expression and inhibiting the Wnt/β-catenin pathway [112]. Additionally, loading icariin onto functionalized nanostructures not only enhances its anti-tumor activity but also reduces adverse effects [113]. A recent experiment showed that icariin decreases miR-205-5p expression, thereby inducing PTEN signaling. This results in the inhibition of the PI3K/Akt axis and impairs the progression of lung tumor cells [114]. These studies underscore that the miRNA/PI3K/Akt axis can be effectively regulated by anti-tumor compounds [115–117]. However, most research has focused on natural products, suggesting a need for future studies on small molecule inhibitors. Furthermore, the use of nanoparticles to deliver natural products and increase their potential in cancer suppression is highly recommended.

2.3. Therapy response

2.3.1. Introduction to PI3K/Akt function in cancer drug resistance

The previous section clearly demonstrated that miRNAs can target the PI3K/Akt axis to regulate tumor progression. The final impact on tumorigenesis depends on the function of the miRNAs and whether they induce or inhibit the PI3K/Akt axis. However, the concept of carcinogenesis extends beyond just the proliferation and metastasis of tumor cells. Dysregulation of oncogenic pathways can also lead to the development of chemoresistance or radio-resistance in cancer cells. Recent studies have evaluated the role of the PI3K/Akt axis in modulating

chemoresistance and radio-resistance in tumors. In gastric cancer, ATXN2 increases the levels of PI3K/Akt, leading to 5-fluorouracil (5-FU) resistance and decreasing the anti-tumor activity of $CD8^+$ T cells [118]. Additionally, interactions between cancer-associated macrophages and cancer cells upregulate CXCL5, which induces the PI3K/Akt axis and reduces the cytotoxicity of 5-FU on gastric tumor cells [119]. Furthermore, stimulation of the PI3K/Akt axis can result in radio-resistance in human cancers [120,121]. This section focuses on the role of miRNAs in regulating the PI3K/Akt axis and the subsequent impact on the chemotherapy response of tumor cells.

2.3.2. An overview to PI3K/Akt regulation by miRNAs in drug resistance

One of the key aspects of cancer biology is the presence of feedback loops among molecular pathways that regulate each other's expression levels. These loops can either promote or inhibit tumor progression, and their overall impact on chemotherapy response varies depending on the specific pathway involved. For example, upregulation of miR-567 in gastric cancer inhibits the PI3K/Akt pathway and enhances drug sensitivity. However, when PI3K/Akt is upregulated, it induces c-Myc signaling, which then reduces miR-567 expression, thereby reactivating the PI3K/Akt pathway and promoting gastric cancer progression and chemoresistance [122]. This feedback loop demonstrates that c-Myc signaling can regulate miR-567 expression, influencing the development of chemoresistance in tumor cells. Additionally, c-Myc is not the only pathway involved in regulating the miRNA/PI3K/Akt axis; other factors also play a role. For instance, SOX9 is an oncogenic factor that, in cooperation with HMGB3, transactivates NANOG, thereby promoting prostate tumor progression [123]. SOX9 also increases CXCL5 expression, enhancing the proliferation and metastasis of hepatocellular carcinoma [124]. In esophageal cancer, SOX9 regulates the miRNA/PI3K/Akt axis by binding to the promoter of miR-203a and reducing its expression. This leads to the stimulation of the PI3K/Akt pathway, increasing the proliferation rate of colorectal tumor cells. Notably, reducing SOX9 expression enhances the efficacy of cisplatin in suppressing colorectal cancer progression, suggesting that down-regulation of the PI3K/Akt pathway can increase the cytotoxicity of anti-tumor compounds [125]. Furthermore, miR-199a can reduce Akt levels, impair tumorigenesis, and increase sensitivity to temozolomide chemotherapy in glioma. This highlights the importance of miRNA regulation in modulating the PI3K/Akt axis and influencing chemotherapy response in cancer treatment [126].

An interesting aspect is that the expression levels of miRNAs can be regulated by the PI3K/Akt axis, which significantly influences tumor cell progression. In ovarian tumors, a combination of ascitic fluid shear and hepatocyte growth factor (HGF) stimulates the PI3K/Akt axis, leading to a reduction in miR-199a-3p levels. Patients with low miR-199a-3p expression tend to have a poor response to platinum chemotherapy [127]. Therefore, the relationship between miRNAs and the PI3K/Akt axis is mutual, with each capable of regulating the other's expression levels. VPS33B, a member of the Sec-1 domain family, encodes the human ortholog of the rat Vps33b and is homologous to the yeast class C Vps33 protein [128]. VPS33B functions as a tumor suppressor, and its expression decreases in the presence of nicotine [129]. The interaction of VPS33B with NESG1 is crucial for increasing the sensitivity of ovarian cancer to cisplatin [130]. VPS33B also modulates miRNA expression in cancer cells [131]. In nasopharyngeal cancer, upregulation of VPS33B increases the sensitivity of tumor cells to 5-FU chemotherapy. VPS33B positively interacts with NESG1 to suppress the EGFR/PI3K/Akt axis, enhancing the expression of miR-133a-3p, which is vital for promoting 5-FU sensitivity in ovarian tumor cells [132]. While many studies have focused on the role of oncogenic miRNAs in regulating the PI3K/Akt axis and chemotherapy response in tumor cells, there is evidence that miRNAs can also suppress the PI3K/Akt axis to enhance chemosensitivity. In breast tumors, CBLB stimulates the PI3K/Akt axis, increasing cancer cell progression. Additionally, GRB2, upregulated by the EGF/EGFR axis, leads to Ras upregulation and induction of the PI3K/Akt axis. However, miR-27b reduces the expression levels of GRB2 and CBLB, suppressing the PI3K/Akt axis and increasing paclitaxel sensitivity in breast tumors [133]. Thus, the function of miRNAs in regulating the PI3K/Akt axis and chemotherapy response is highly complex in tumors [134].

Table 1
The role of miRNAs regulating PI3K/Akt axis in cancers.

Molecular pathway	Cancer type	Remark	Ref
miR-183/ PTEN/Akt	Pancreatic cancer	Low expression of miR-183 leads to PTEN down-regulation Upregulation of Akt and development of insensitivity to 5-fluorouracil and gemcitabine chemotherapy	[144]
miR-590-3p	Colorectal cancer	Exosomal miR-590-3p stimulates PI3K/Akt axis in mediating radio-resistance	[145]
miR-214/ netrin-1	Bladder cancer	miR-214 decreases netrin-1 expression to increase cisplatin sensitivity Netrin-1 upregulation prevents cisplatin-mediated apoptosis and increases Akt levels	[146]
miR-501/BLID/ Akt	Gastric cancer	miR-501 reduces BLID expression to induce Akt signaling and doxorubicin resistance	[147]
miR-1269b/ PTEN/PI3K/ Akt	Lung cancer	miR-1296b reduces PTEN expression to induce PI3K/Akt axis in mediating cisplatin resistance	[148]
miR-205-5p/ TGFA/Akt	Triple-negative breast cancer	miR-205-5p reduces TGFA expression to suppress Akt and drug resistance	[149]
miR-181c/ GRP78/ PI3K/Akt	Ovarian cancer	miR-181c suppresses GRP78/ PI3K/Akt axis in enhancing paclitaxel sensitivity of tumor cells	[150]
miR-222-3p/ TSC1/PI3K/ Akt	Pancreatic cancer	miR-222-3p reduces TSC1 expression to induce PI3K/Akt signaling in mediating gemcitabine resistance	[151]
miR-3682-3p/ PI3K/Akt/c-Myc	Hepatocellular carcinoma	miR-3682-3p stimulates the PI3K/Akt axis in increasing cancer stemness	[152]
miR-4268/ keratin 80/ PI3K/Akt	Gastric cancer	miR-4268 reduces keratin 80 to suppress PI3K/Akt axis in reducing cancer progression	[153]
miR-124-3p/ PI3K/Akt	Lung cancer	miR-124-3p reduces PI3K/Akt expression to suppress invasion	[154]
miR-498/ DNMT3b/ PI3K/Akt	Esophageal cancer	DNMT3b down-regulation by miR-498 to suppress Akt signaling, leading to radio-sensitivity	[155]
miR-181a/ PTEN/PI3K/ Akt	Lung cancer	miR-181a reduces PTEN expression to induce PI3K/Akt signaling in mediating radio-resistance	[156]

2.3.3. Exosomes, miRNAs and PI3K/Akt

Exosomes are membrane-bound compartments ranging in size from 20 to 100 nm, facilitating communication between cancer cells and immune cells, and are abundantly present in the tumor microenvironment [135,136]. These exosomes can transfer genetic materials, lipids, and proteins among cells [137,138]. Recently, exosomal miRNAs and their roles in drug resistance have garnered significant attention. Exosomes can be secreted by macrophages, leading to the delivery of miR-223 to epithelial ovarian tumor cells. This process results in PTEN down-regulation, subsequent upregulation of the PI3K/Akt pathway, and the development of drug resistance [139]. Given the growing interest in exosomes, studies have focused on the role of exosomal miRNAs in regulating the PI3K/Akt axis and the development of chemoresistance in cancers [140]. Exosomal miR-92b-3p has shown potential in inducing

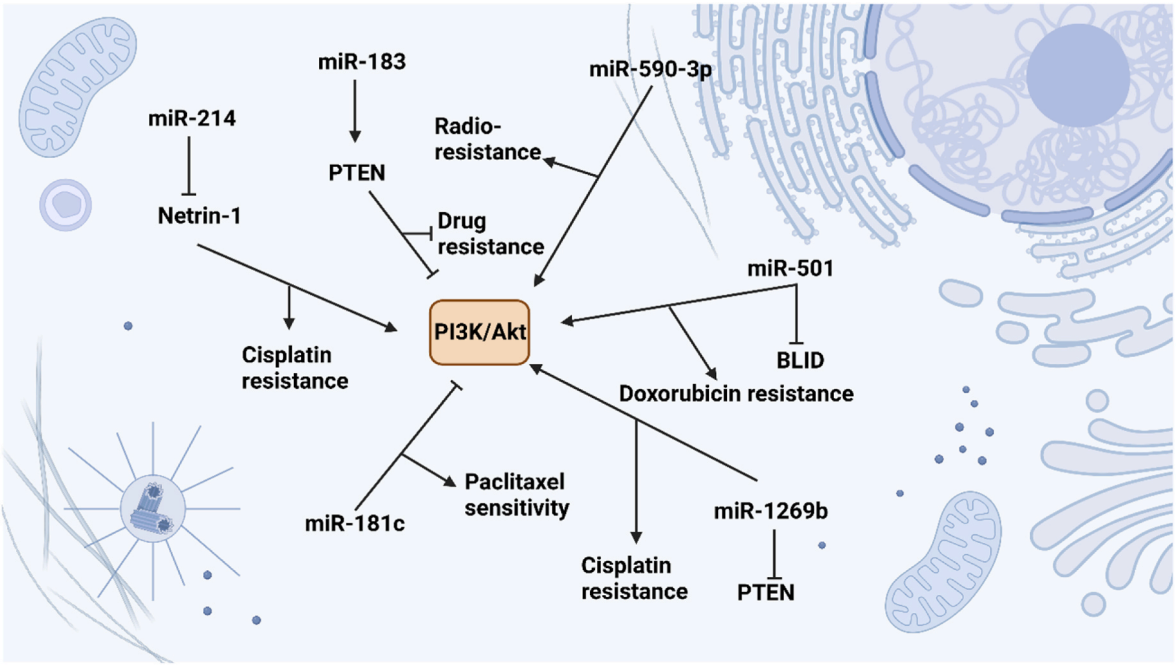

Fig. 2. The role of miRNAs in regulating the PI3K/Akt pathway: miR-214 downregulates Netrin-1, activating the PI3K/Akt axis to enhance cisplatin resistance; miR-183 induces PTEN, downregulating the PI3K/Akt pathway to overcome drug resistance; miR-590-3p activates the PI3K/Akt axis, mediating radio-resistance; miR-501 downregulates BLID, inducing the PI3K/Akt pathway to mediate doxorubicin resistance; miR-1269b downregulates PTEN, activating the PI3K/Akt axis and triggering cisplatin resistance; miR-181c downregulates the PI3K/Akt pathway, mediating paclitaxel sensitivity.

drug resistance in lung cancer by reducing PTEN expression and activating Akt signaling, thereby enhancing cancer progression and drug resistance. Additionally, miR-106a-5p is another RNA transcript enriched in extracellular vesicles and exosomes. Cancer cell-derived extracellular vesicles can contain high levels of miR-106a-5p, which reduces KLF6 expression, enhancing the invasive potential of ovarian tumor cells [141]. Furthermore, miR-106a-5p reduces AMPK phosphorylation, promoting autophagy and the progression of lung tumor cells [142]. In nasopharyngeal cancer, high levels of miR-106a-5p contribute to cisplatin resistance in tumor cells. The enrichment of miR-106a-5p in exosomes stimulates Akt signaling, mediating cisplatin resistance in these cells [143]. Table 1 and Fig. 2 provide an overview of the role of miRNA/PI3K/Akt axis in regulating the progression of human cancers.

3. LncRNAs and PI3K/Akt signaling

Less than 2 % of the genome encodes proteins, while up to 75 % is transcribed into RNAs that do not encode functional proteins [157,158]. LncRNAs, which are over 200 nucleotides in length, can be transcribed from up to 173,112 loci, resulting in up to 96,411 distinct lncRNAs [159]. These lncRNAs can modulate gene expression at epigenetic, transcriptional, and post-transcriptional levels [160,161]. LncRNAs are important biomarkers in cancer and can function as competing endogenous RNAs (ceRNAs) for miRNAs [162]. Recent studies have shed light on the role of lncRNAs in regulating tumor cell progression and their interactions with other molecular pathways [163]. For example, high levels of NEAT1 in medulloblastoma are associated with increased tumor progression and cisplatin resistance. NEAT1 induces cisplatin resistance by reducing miR-23a-3p expression, while silencing NEAT1 increases cisplatin sensitivity [164]. LINC01614, a cancer-associated fibroblast-related lncRNA, promotes glutamine uptake in lung tumors by interacting with p65 and ANXA2 to induce NF-κB signaling [165]. Additionally, NEAT1 downregulates miR-577 and miR-1224-5p expression, leading to upregulation of CCNT2 and increased progression of laryngeal papilloma [166].

3.1. Tumor progression

The previous section highlighted the role of miRNAs as crucial regulators of the PI3K/Akt axis in cancer progression. This section aims to explore the relationship between lncRNAs and the PI3K/Akt axis in regulating tumorigenesis. The lncRNA AK023391 acts as an inducer of gastric tumor progression. High levels of AK023391 are associated with poor survival rates in gastric cancer patients. Silencing AK023391 reduces tumor cell proliferation and metastasis, leading to apoptosis and cell cycle arrest, thereby decreasing malignancy both *in vitro* and *in vivo*. AK023391 promotes gastric tumor progression by stimulating the PI3K/Akt axis, which in turn enhances NF-κB levels and carcinogenesis [167]. However, lncRNAs often do not directly target the PI3K/Akt axis; instead, they frequently act by influencing other pathways and factors. For example, in thyroid cancer, miR-34a impairs the PI3K/Akt axis, reducing tumor progression. The lncRNA XIST is highly expressed in thyroid tumors and promotes carcinogenesis by reducing miR-34a expression and increasing MET levels, which subsequently activates the PI3K/Akt axis to enhance tumor cell proliferation [168]. Interestingly, a single lncRNA can exhibit both oncogenic and tumor-suppressive functions depending on the context. ADAMTS9-AS1 is one such example. Silencing ADAMTS9-AS1 suppresses the Wnt/β-catenin axis, reducing glioma cell growth and metastasis [169]. However, in other contexts, ADAMTS9-AS1 is beneficial in suppressing tumorigenesis by regulating miRNA expression [170,171]. In bladder tumors, ADAMTS9-AS1 directly interacts with the PI3K/Akt/mTOR axis, promoting tumorigenesis. It stimulates the PI3K/Akt/mTOR axis, thereby suppressing apoptosis and autophagy, and enhancing cancer cell invasion [172].

Understanding the regulation of lncRNAs in cancer cells and their impact on the Akt and PI3K pathways involves complex molecular interactions. The lncRNA THAP7-AS1 has been shown to promote tumorigenesis in gastric cancer, with its expression enhanced at the transcriptional level by SP1 and at the post-transcriptional level by METTL3, both of which facilitate the tumorigenesis process. THAP7-AS1 enhances the nuclear translocation of CUL4B, which reduces miR-22-3p

and miR-320a levels, thereby inducing the PI3K/Akt axis [173]. Most lncRNAs exert their effects on tumor progression by modulating miRNAs. LncRNA SNHG6, a newly discovered RNA transcript in cancer, is in the cytoplasm and can increase the proliferation and invasion of colorectal tumor cells [174]. SNHG6 also regulates miRNA expression and mediates cisplatin resistance in gastric tumors [175]. In breast cancer, upregulation of SNHG6 promotes tumorigenesis by reducing miR-543 levels, leading to the upregulation of LAMC1 and subsequent stimulation of the PI3K/Akt pathway [176]. Additionally, LAMC2 is influenced by lncRNAs in regulating PI3K/Akt signaling in tumor cells. LncRNA CASC9 interacts with CREB-binding protein in the cytoplasm to increase LAMC2 levels. LAMC2 then translocates to the cytoplasm, inducing FAK phosphorylation, which in turn activates the PI3K/Akt axis, leading to increased MMP levels and enhanced esophageal cancer invasion [177].

LINC00641 is considered an inhibitor of cancer progression, with reduced expression levels in ovarian tumor cells and tissues. LINC00641 decreases miR-320a expression, thereby reducing tumorigenesis [178]. LINC00641 also interacts with the PI3K/Akt axis in regulating bladder tumor progression [179]. It increases KLF10 expression by downregulating miR-197-3p, which subsequently leads to PTEN upregulation and suppression of the PI3K/Akt axis, thereby reducing bladder cancer progression [180]. In summary, lncRNAs and the PI3K/Akt axis interact in tumor cells. If a lncRNA has an oncogenic function, it stimulates the PI3K/Akt pathway. PTEN, an upstream regulator of the PI3K/Akt pathway, can be modulated by lncRNAs to influence carcinogenesis. The most well-known mechanism by which lncRNAs affect PI3K/Akt expression is by sponging and regulating miRNA expression, a process that occurs in various human cancers [181–184].

3.2. Therapy response

The previous section (3.2) focused on the role of the miRNA/PI3K/Akt axis in the development of chemoresistance in cancers. It is clear that the upregulation of the PI3K/Akt pathway can lead to drug resistance in tumors. Additionally, accumulating evidence highlights the role of lncRNAs in the development of drug resistance. For example, the overexpression of lncRNA ANRIL in breast cancer causes chemoresistance by accelerating the proliferation rate of tumor cells through the induction of aerobic glycolysis [185]. Moreover, the interaction of lncRNAs with miRNAs can influence the chemotherapy response of tumor cells [186,187]. This section aims to focus on the role of the lncRNA/PI3K/Akt axis in drug resistance. Cisplatin is commonly used in the treatment of gastric cancer, but dysregulation of lncRNA expression can lead to cisplatin resistance [188]. The use of cisplatin in cancer therapy has often been disappointing due to the development of chemoresistance, leading to therapy failure and patient death. The use of other anti-tumor compounds (especially natural products) and genetic tools such as siRNA has shown promise in enhancing the potential of cisplatin in cancer suppression [188]. Overexpression of lncRNA UCA1 enhances the progression of gastric tumor cells, while its silencing increases cisplatin-mediated apoptosis. UCA1 can recruit EZH2 to induce PI3K/Akt signaling, triggering cisplatin resistance in gastric tumors. It is important to note that the development of drug resistance in human tumors is not solely attributed to one cancer hallmark or molecular pathway; instead, it is the result of the coordination of various molecular pathways and mechanisms. For instance, increased expression of the lncRNA MALAT1 leads to enhanced metastasis of tumor cells via EMT induction and prevention of apoptosis through Bcl-2 upregulation and caspase-3 downregulation. Additionally, MALAT1 induces an inflammatory condition in the tumor microenvironment by increasing levels of TNF-α, IL-1, IL-6, and COX-2, among others. MALAT1 also stimulates the PI3K/Akt axis to increase the growth rate of tumor cells. These combined actions contribute to the development of drug resistance in tumor cells [189].

Glioblastoma is a malignant brain tumor with a median survival rate of 14.6 months and a 5-year survival rate of less than 3 %, despite advances in treatment [190,191]. The prognosis for glioblastoma patients can be improved with temozolomide chemotherapy [192,193]. However, the efficacy and therapeutic index of temozolomide can be hindered by the development of resistance [194]. Upregulation of the lncRNA CRNDE leads to temozolomide resistance in glioblastoma, while silencing CRNDE increases drug sensitivity. Silencing CRNDE stimulates the PI3K/Akt/mTOR pathway, reducing ATG5 and Beclin-1 levels, suppressing autophagy, and promoting temozolomide sensitivity in glioblastoma. Therefore, lncRNAs that induce the PI3K/Akt axis can mediate chemotherapy resistance [195]. High expression levels of UCA1 lead to daunorubicin resistance in leukemia. Upregulation of UCA1 suppresses miR-613 expression, inducing the PI3K/Akt axis and contributing to chemoresistance in tumor cells [196]. Hepatocellular

Table 2
The role of lncRNA/PI3K/Akt axis in regulating tumor progression.

Cancer type	Molecular pathway	Remark	Ref
Nasopharyngeal cancer	LncRNA MIR31HG/PI3K/Akt	Silencing MIR31HG impairs the PI3K/Akt axis in reducing growth and stimulating apoptosis	[206]
Non-small cell lung cancer	NORAD/miR-520a-3p/PI3K/Akt/mTOR	NORAD reduces miR-520a-3p expression Stimulation of PI3K signaling	[207]
Endometrial cancer	CCAT2/miR-216b	CCAT2 sponges miR-216b to induce PI3K/Akt axis	[208]
Colorectal cancer	LncRNA ST3Gal6-AS1/ST3Gal6/PI3K/Akt	LncRNA ST3Gal6-AS1 increases ST3Gal6 expression to suppress PI3K/Akt axis	[209]
Myeloma	LncRNA RP11-301G19.1/miR-582-5p/HMGB2/PI3K/Akt	RP11-301G19.1 increases HMGB2 expression via miR-582-5p sponging to induce Akt axis	[210]
Osteosarcoma	MALAT1/PI3K/Akt	Increased invasion by MALAT1 via inducing Akt	[211]
Hepatocellular carcinoma	RHPN1-AS1/miR-7-5p/PI3K/Akt	miR-7-5p inhibition by RHNP1-AS1 Stimulation of Pi3K/Akt signaling	[212]
Breast cancer	AC012213.3/RAD54B/PI3K/AKT	AC012213.3 stimulates PI3K/Akt in increasing tumorigenesis	[213]
Gastric cancer	SLC25A5-AS1/miR-19a-3p/PTEN/PI3K/Akt	SLC25A5-AS1 reduces miR-19a-3p expression PTEN upregulation Inhibition of PI3K/Akt axis	[214]
Gastric cancer	NORAD/miR-204-5p/KMT2D	NORAD increases KMT2D expression to induce PI3K/Akt axis via PTEN inhibition	[215]
Breast cancer	LINC00839/PI3K/Akt	Paclitaxel resistance and increased progression by LINC00839 through inducing PI3K/Akt axis	[216]
Luekemia	HOTAIR/Akt/Notch1	HOTAIR induces Akt/Notch1 axis to mediate doxorubicin resistance	[217]
Triple-negative breast cancer	H19/Akt	Silencing H19 reduces Akt expression to enhance paclitaxel sensitivity	[218]
Non-small cell lung cancer	AFAP1-AS1/miR-139-5p/RRM2	miR-139-5p inhibition by AFAP1-AS1 to increase RRM2 expression in inducing Akt signaling and triggering drug resistance	[219]
Colon cancer	CASC7/PI3K/Akt	CASC7 suppresses PI3K/Akt axis in suppressing growth and metastasis of tumor cells	[220]
Breast cancer	PCAT7/PI3K/Akt	PCAT7 stimulates PI3K/Akt axis via ErbB upregulation in increasing carcinogenesis	[221]

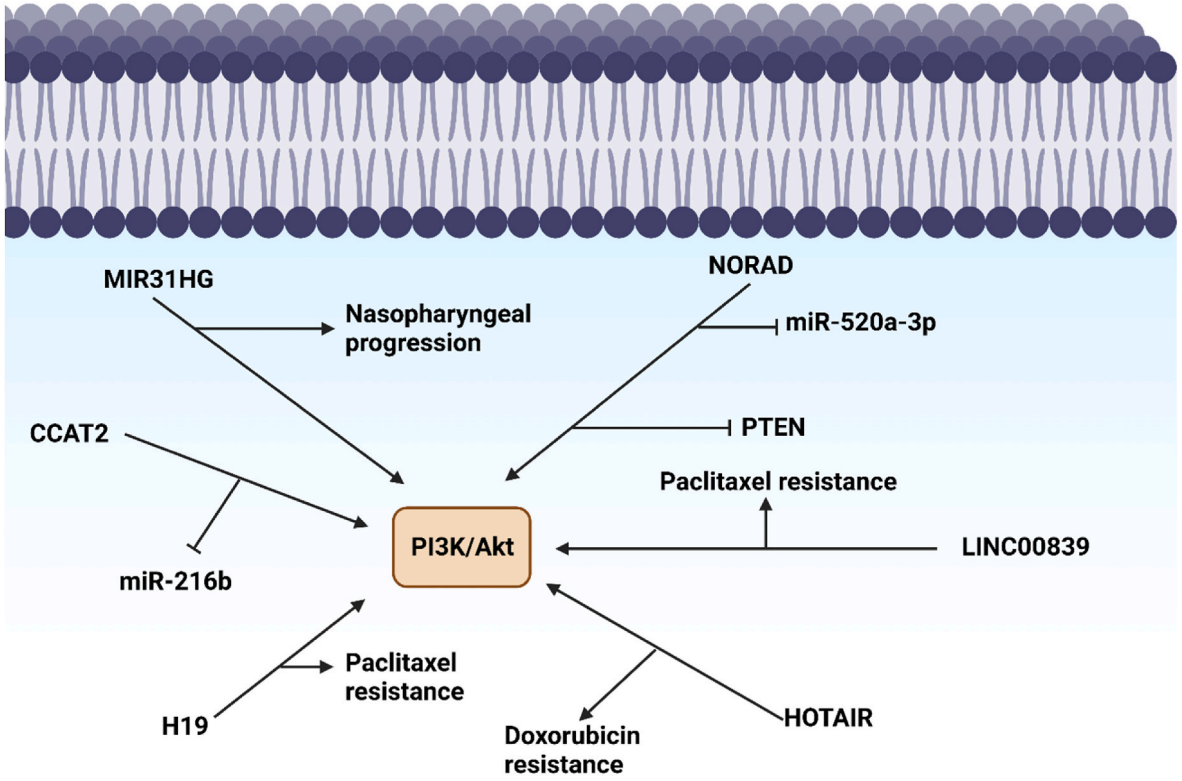

Fig. 3. The regulation of PI3K/Akt by lncRNAs: MIR31HG activates the PI3K/Akt axis to enhance the progression of nasopharyngeal cancer; CCAT2 induces the PI3K/Akt pathway by sponging miR-216b; H19 stimulates the PI3K/Akt axis to enhance paclitaxel resistance; NORAD sponges miR-520a-3p, mediating the PI3K/Akt axis through PTEN downregulation; LINC00839-mediated PI3K/Akt activation promotes paclitaxel resistance; HOTAIR induces doxorubicin resistance by upregulating the PI3K/Akt axis.

carcinoma, the most common type of liver cancer, poses a significant threat to human health [197]. Dysregulation of molecular pathways can drive the progression and development of chemoresistance in hepatocellular carcinoma. Stimulation of the PI3K/Akt axis can lead to sorafenib resistance. LncRNA HEIH mediates sorafenib resistance in hepatocellular carcinoma by triggering the PI3K/Akt axis through miR-98-5p inhibition [198].

Doxorubicin is a widely used chemotherapy agent in cancer treatment, but dysregulation of lncRNAs has led to resistance. New therapies, such as the use of nanostructures for targeted delivery, have been developed for doxorubicin chemotherapy. However, drug resistance remains a significant problem. The upregulation of lncRNA TRDMT1-5 is associated with poor prognosis in breast tumors and mediates doxorubicin resistance through interactions with pathways including Wnt and PI3K/Akt [199]. Anti-tumor compounds that regulate the lncRNA/Akt axis can help increase doxorubicin sensitivity in tumor cells. For example, polydatin reduces the expression level of lncRNA TUG1, thereby suppressing Akt signaling and reversing doxorubicin resistance in osteosarcoma [200]. These studies highlight the importance of the lncRNA/PI3K/Akt axis as a key regulator of cancer progression and therapy resistance (Table 2, Fig. 3) [201–205].

4. Circular RNAs and PI3K/Akt signaling

Circular RNAs (circRNAs) lack 5′ caps and 3’ poly(A) tails due to their closed-loop structure, and they do not encode proteins, categorizing them as ncRNAs [222,223]. CircRNAs are not easily degraded by RNase enzymes, making them more stable than linear ncRNAs [224]. The first circRNA was discovered in RNA viruses in the 1970s using electron microscopy [225]. Initially, circRNAs were believed to be non-functional by-products of splicing [226]. However, extensive research has shown that circRNAs are important regulators of tumor progression [227,228]. Additionally, some circRNAs have been found to encode proteins, meaning not all circRNAs are considered ncRNAs. For instance, circ-0003823 has been linked to increased malignancy in esophageal cancer by targeting the miR-607/CRISP3 axis to induce apatinib resistance [229]. Consequently, circRNAs significantly influence the biological behavior of tumor cells [93] and can also serve as prognostic factors [230].

4.1. Tumor progression

Aerobic glycolysis is a key metabolic feature of tumor cells, characterized by increased glucose uptake, elevated lactic acid production, and the generation of large amounts of energy to support cancer cell proliferation [231,232]. The stimulation of the PI3K/Akt axis is crucial for the glycolysis process in thyroid cancer. However, circ-100395 reduces PI3K/Akt/mTOR expression to suppress glycolysis and decrease cancer progression [233]. Gastric cancer is a prevalent malignancy, with 1,089,103 cases diagnosed and 768,793 deaths worldwide in 2020 [4]. The incidence rate of gastric cancer is particularly high in developing countries, with up to 70 % of global cases found in China [234]. Early diagnosis can improve treatment outcomes, but most cases are diagnosed at middle and advanced stages. Dysregulation of molecular pathways and ncRNAs contributes to the progression of gastric cancer [235]. For example, hsa_circ_0006282 impairs gastric cancer progression by increasing PTEN expression, which suppresses the PI3K/Akt axis [236]. The mechanism by which circRNAs increase PTEN expression to modulate the PI3K/Akt axis in gastric cancer is noteworthy. hsa_circ_0072309 promotes PPARγ levels, which in turn induces PTEN signaling. Overexpressed PTEN then inhibits the PI3K/Akt axis, reducing the growth and invasion of gastric tumor cells [237]. However, PTEN is not the only molecular pathway regulated by circRNAs affecting the PI3K/Akt axis. Circ-E-Cad is upregulated in gastric cancer through

Table 3
The role of circRNA/PI3K/Akt axis in regulating the progression of human cancers.

Cancer type	Molecular pathway	Remark	Ref
Esophageal cancer	Circ-NRIP1/miR-595/SEMAD4D/PI3K/Akt	Circ-NRIP1 reduces miR-595 expression to induce Akt signaling via SEMA4D upregulation	[249]
Colon cancer	Circ-0001313/miRNA-510-5p/AKT2	Circ-0001313 increases Akt2 expression via miR-510-5p sponging	[250]
Gastric cancer	Circ-0023409/IRS4/PI3K/Akt	Circ-0023409 increases IRS4 expression to induce PI3K/Akt axis	[251]
Colorectal cancer	Circ-0104631/PI3K/Akt	Circ-0104631 increases Akt expression via PTEN inhibition	[252]
Gastric cancer	Circ_0006089/miR-143-3p/PI3K/Akt	miR-143-3p sponging by circ_0006089 in inducing PI3K/Akt axis	[253]
Gastric cancer	Circ-0000520/PI3K/Akt	Circ-0000520 suppresses the PI3K/Akt axis in suppressing Herceptin resistance	[254]
Gastric cancer	Circ-0078607/ERK1/2/Akt	Silencing circ-0078607 suppresses ERK1/2/Akt axis in reducing tumorigenesis	[255]
Thyroid cancer	Circ_0079558/miR-26b-5p/MET/Akt	Circ-0079558 promotes MET expression by miR-26b-5p inhibition to induce Akt signaling	[256]
Breast cancer	Hsa_circ_0000199/miR-206/613/PI3K/Akt/mTOR	Hsa_circ_0000199 reduces miR-206/-613 levels PI3K/Akt induction in enhancing cancer progression	[257]
Breast cancer	Hsa_circ_001569/PI3K/Akt	Hsa_circ_001569 stimulates the PI3K/Akt axis in enhancing cancer progression	[258]
Esophageal cancer	Circ-0007022/miR-338-3p/Neuropilin-1	miR-338-3p reduction by circ-0007022 Increasing NRP1 expression to induce PI3K/Akt axis EMT induction Radio-resistance development	[259]
Lung cancer	Circ-0000317/miR-494-3p/PTEN	Circ-0000317 promotes PTEN expression via miR-494-3p inhibition to suppress PI3K/Akt signaling	[260]
Breast cancer	Hsa_circ_0000851/PDK1/Akt	PDK1 upregulation by hsa_circ_0000851 to induce Akt signaling	[261]

TGF-β/Smad signaling, leading to PI3K/Akt axis induction and increased tumor cell progression [238].

The strength of these studies lies in their focus on the role of the circRNA/PI3K/Akt axis in various tumors. For instance, circ_103809 accelerates the progression of breast tumors by stimulating the PI3K/Akt axis, thereby inhibiting apoptosis and promoting cell cycle progression [239]. Conversely, there is growing interest in using anti-tumor compounds that can regulate the circRNA/PI3K/Akt axis in breast tumors. In a recent experiment, eriodictyol was used to suppress breast cancer progression by reducing the levels of circ_0007503, which in turn suppressed the PI3K/Akt axis [240]. Two important points should be noted about the association between circRNAs and the PI3K/Akt axis in tumor cells: miRNAs can be regulated by circRNAs, and PI3K/Akt activation by circRNAs may lead to changes in the levels of other downstream targets. For example, hsa_circ_0023984 promotes proliferation and metastasis in esophageal cancer by sponging miR-1294, which induces PI3K/Akt levels to upregulate c-Myc expression, thereby accelerating tumorigenesis [241]. Lung cancer, particularly non-small cell lung cancer (NSCLC), which accounts for 85 % of cases, remains a significant malignancy with poor prognosis despite treatment advances [242,243]. The role of ncRNAs in lung cancer progression has been evaluated, and circ_0017639 has shown an oncogenic function by stimulating the PI3K/Akt axis [244]. Furthermore, overexpression of hsa_circ_0001666 accelerates NSCLC progression by sponging miR-1184/miR-5481 to increase AGO1 levels, leading to the induction of the PI3K/Akt axis [245]. These studies collectively highlight that the circRNA/PI3K/Akt axis is a crucial regulator of tumor progression.

4.2. *Therapy response*

The role of the circRNA/PI3K/Akt axis in the therapy response of tumor cells has received relatively little attention. However, studies have shown that this pathway plays a significant role in cancer therapy. In nasopharyngeal cancer, the development of cisplatin resistance is common due to the extensive use of this agent, and circRNAs are valuable regulators in this context. Circ_0008450 exhibits oncogenic functions in nasopharyngeal tumors, and its silencing decreases proliferation and invasion while enhancing apoptosis and cisplatin sensitivity. Downregulation of miR-338-3p by circ_0008450 leads to the induction of the PI3K/Akt axis, mediating cisplatin resistance in tumor cells [246]. Paclitaxel is another crucial chemotherapy agent, and high expression levels of Akt can lead to resistance in breast tumors. Circ-AMOTL1 interacts with PAX to increase Akt expression, enhancing the survival rate of tumor cells by upregulating Bcl-2 and downregulating Bax and BAK, thereby inducing paclitaxel resistance [247]. Circ CDR1-AS can induce the EGFR/PI3K axis, mediating resistance of lung tumor cells to cisplatin and pemetrexed [248]. While these studies highlight the role of circRNAs in drug resistance, more focus should be given to the PI3K/Akt axis (Table 3, Fig. 4).

5. Conclusion and remarks

The role of molecular pathways in cancer is crucial for regulating tumor hallmarks. During oncogenesis, the expression levels of certain proteins and genes change, influencing tumor progression based on their functions. One of the key players in carcinogenesis is the PI3K/Akt pathway, which is typically suppressed by PTEN. However, the loss of PTEN expression during tumorigenesis leads to enhanced PI3K/Akt expression.

This review emphasizes that the regulation of PI3K/Akt expression can be mediated by ncRNAs. There is a region on the promoter of PI3K or Akt known as the 3′-UTR, where miRNAs can bind to reduce their expression, thereby altering tumor cell progression. Additionally, lncRNAs and circRNAs can regulate the PI3K/Akt axis, often by affecting miRNAs. NcRNAs share similarities in regulating the PI3K/Akt axis, including both direct and indirect pathways. Since PTEN is a well-known regulator of PI3K/Akt, ncRNAs can also influence PTEN to modulate the PI3K/Akt axis in tumor cells.

The ncRNA/PI3K/Akt axis is not confined to a single molecular pathway; it has been shown to impact the progression of various human tumors. This effect can be either oncogenic or onco-suppressive, providing potential therapeutic targets in cancer treatment. The axis can regulate tumor cell proliferation, metastasis, EMT, apoptosis, and survival rates. Moreover, the regulation of PI3K/Akt by ncRNAs can alter the response of cancer cells to chemotherapy.

As studies continue to provide new insights into the role of the ncRNA/PI3K/Akt axis in human cancers, future research should focus on therapeutic targeting of this axis to improve cancer therapy and enhance the quality of life for cancer patients.

This paper discusses the various types of ncRNAs that regulate the PI3K/Akt pathway in cancer therapy. Among miRNAs, there are both tumor-suppressor and tumor-promoting miRNAs. Tumor-suppressor miRNAs include miR-30e-3p, miR-122-5p, and miR-760. For example, miR-30e-3p targets THOC2 to suppress the PI3K/Akt/mTOR axis, reducing gastric cancer progression. MiR-122-5p downregulates FUT8 to inhibit the PI3K/Akt axis, thereby reducing the growth and metastasis of cholangiocarcinoma. MiR-760 targets HM13 to downregulate the PI3K/Akt axis, reducing tumorigenesis in breast cancer. Conversely,

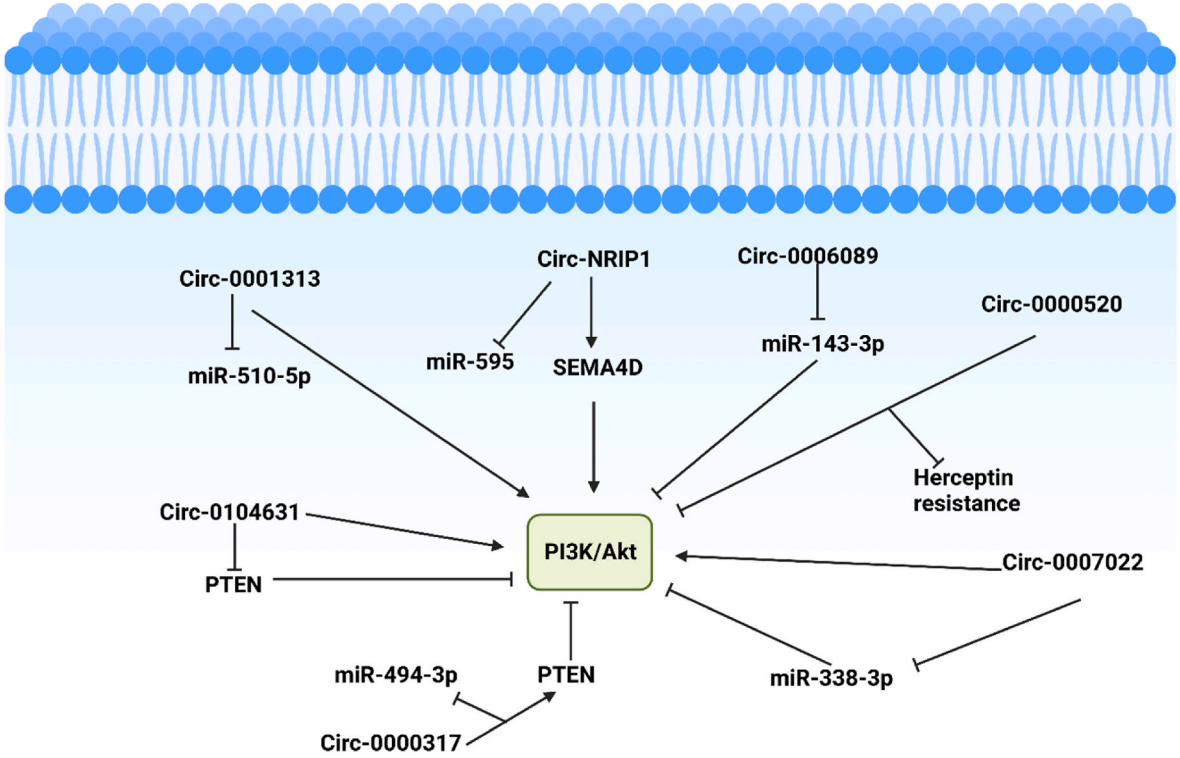

Fig. 4. The regulation of PI3K/Akt by circRNAs in human cancers: Circ-0001313 sponges miR-510-5p to activate the PI3K/Akt axis; Circ-NRIP1 sponges miR-595 to upregulate SEMA4D, thereby inducing the PI3K/Akt axis; Circ-0006089 sponges miR-143-3p to upregulate the PI3K/Akt pathway; Circ-0000520 suppresses the PI3K/Akt axis to overcome Herceptin resistance; Circ-0007022 sponges miR-338-3p to mediate the PI3K/Akt axis; Circ-0000317 downregulates miR-494-3p to induce PTEN, leading to the suppression of the PI3K/Akt pathway.

tumor-promoting miRNAs, such as miR-548k, downregulate PTEN to activate the PI3K/Akt axis and enhance breast cancer progression. MiR-762 stimulates the PI3K/Akt axis by downregulating LZTS1 in gastric cancer, while miR-421 decreases PTEN expression to mediate the PI3K/Akt axis in lung cancer.

In many cases, miRNAs regulate PTEN to influence the PI3K/Akt axis. MiRNAs, such as miR-129-5p, can affect glycolysis via PI3K/Akt regulation, highlighting their role in metabolic reprogramming. Additionally, apoptosis and cell cycle arrest are regulated by miR-137 and miR-22-3p through targeting COX-2 and KDM3A, respectively.

LncRNAs are also key regulators of the PI3K/Akt axis in human cancers, primarily by sponging miRNAs. LncRNAs can also mediate epigenetic and transcriptional regulation, as exemplified by lncRNA THAP7-AS1, which modulates miRNAs and the PI3K/Akt axis. Tumor-promoting lncRNAs such as AK02339, XIST, and SNHG6 induce the PI3K/Akt pathway through actions like sponging miR-34a and miR-543 or affecting LAMC1.

Similarly, circRNAs include both tumor-promoting and tumor-suppressor factors. Tumor-promoting circRNAs, such as circ-103809 and circ-0017639, can activate the PI3K/Akt axis, while tumor-suppressor circRNAs, such as circ-100395 and circ-0006282, can inhibit tumorigenesis by suppressing the PI3K/Akt/mTOR axis. Like lncRNAs, circRNAs primarily regulate the PI3K/Akt axis by sponging miRNAs, and they can also directly affect PI3K/Akt-related factors like PTEN.

Specific components of the PI3K/Akt axis can be regulated by ncRNAs in human cancers. Both miRNAs and lncRNAs have shown potential in regulating PI3K subunits, including the regulatory subunit (p85) and the catalytic subunit (p110α). Additionally, ncRNAs regulate mTOR, a downstream target of PI3K/Akt, affecting protein synthesis, cell growth, and metabolism. Akt phosphorylation can be influenced by miR-19a/b and circRNAs.

While studies have extensively evaluated the role of ncRNAs in regulating the PI3K/Akt axis, several challenges and limitations need to be addressed in future research:

1 Although dysregulation of PI3K/Akt has been observed in various human cancers, no studies have detailed how PI3K/Akt levels change across different stages of cancer. This aspect should be highlighted in both solid and hematological tumors.
2 The interaction between ncRNAs and the PI3K/Akt pathway has been studied in different cancers, but there is limited information on its impact on hematological tumors. Given the significant role of PI3K/Akt in the progression of these tumors, this area requires more focus [262–267].
3 While the interaction of ncRNAs and PI3K/Akt in regulating cancer drug resistance has been explored, there is insufficient information on the role of circRNAs. More studies are needed in this area.
4 The interaction of ncRNAs with the PI3K/Akt pathway in terms of radioresistance should be comprehensively evaluated to improve therapy response.
5 To enhance chemotherapy response, the regulation of autophagy [268,269], ferroptosis, and other cell death mechanisms is crucial [270,271]. However, the interaction between ncRNAs and the PI3K/Akt axis in influencing these cell death mechanisms has been largely ignored.
6 Nanoparticles have recently emerged as regulators of the PI3K/Akt pathway in cancer therapy. The potential of nanoparticles for targeting PI3K/Akt or ncRNAs to enhance tumor suppression should be thoroughly evaluated [272,273].

CRediT authorship contribution statement

Mehrdad Hashemi: Writing – original draft. **Elaheh Mohandesi Khosroshahi:** Writing – original draft. **Saba Asadi:** Writing – original draft, Investigation. **Mahsa Tanha:** Writing – original draft. **Forough**

Ghatei Mohseni: Writing – original draft. **Ramina Abdolmohammad Sagha:** Visualization. **Elham Taheri:** Visualization, Resources. **Paria Vazayefi:** Investigation, Writing – review & editing. **Helya Shekarriz:** Writing – review & editing. **Fatemeh Habibi:** Writing – review & editing. **Shaghayegh Mortazi:** Writing – review & editing. **Ramin Khorrami:** Writing – review & editing. **Noushin Nabavi:** Writing – review & editing. **Mohsen Rashidi:** Supervision, Conceptualization, Writing – review & editing. **Afshin Taheriazam:** Supervision, Conceptualization, Writing – review & editing. **Payman Rahimzadeh:** Supervision, Writing – review & editing. **Maliheh Entezari:** Supervision, Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The figures of this paper were prepared by Biorender (Biorender.com).

List of abbreviations

PI3K	Phosphatidylinositol-3-kinase
Akt	Protein Kinase B (PKB)
mTOR	Mammalian Target of Rapamycin
ncRNA	Non-coding RNA
miRNA	MicroRNA
lncRNA	Long Non-coding RNA
circRNA	Circular RNA
PTEN	Phosphatase and Tensin Homolog
RAS	Rat Sarcoma (a family of related proteins)
ERK	Extracellular Signal-Regulated Kinase
RTK	Receptor Tyrosine Kinase
GPCR	G Protein-Coupled Receptor
PIP2	Phosphatidylinositol 4,5-bisphosphate
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PDK1	3-Phosphoinositide Dependent Kinase-1
mTORC1	Mechanistic Target of Rapamycin Complex 1
mTORC2	Mechanistic Target of Rapamycin Complex 2
BAD	Bcl-2-associated death promoter
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
GLUT1	Glucose Transporter 1
HKII	Hexokinase II
NDRG2	N-Myc Downstream-Regulated Gene 2
SOX4	SRY-Box Transcription Factor 4
USP20	Ubiquitin Specific Peptidase 20
HM13	Histocompatibility (Minor) 13
COX-2	Cyclooxygenase-2
KDM3A	Lysine Demethylase 3A
LAMC1	Laminin Subunit Gamma 1
LAMC2	Laminin Subunit Gamma 2
FAK	Focal Adhesion Kinase
S6K1	Ribosomal Protein S6 Kinase Beta-1
4E-BP1	Eukaryotic Translation Initiation Factor 4E-Binding Protein 1
TGF-β	Transforming Growth Factor Beta
SP1	Specificity Protein 1
METTL3	Methyltransferase Like 3
UBE2C	Ubiquitin-Conjugating Enzyme E2 C
EGFR	Epidermal Growth Factor Receptor
Cx32	Connexin 32
RGS20	Regulator of G-Protein Signaling 20
STIL	SCL/TAL1 Interrupting Locus
ST3Gal6	ST3 Beta-Galactoside Alpha-2,3-Sialyltransferase 6
CXCL5	C-X-C Motif Chemokine Ligand 5
SLC2A3	Solute Carrier Family 2 Member 3
LAM	Laminin
SPP	Signal Peptide Peptidase
c-Myc	Myelocytomatosis Viral Oncogene Homolog
VEGF-A	Vascular Endothelial Growth Factor A
TIMPs	Tissue Inhibitors of Metalloproteinases
NANOG	Nanog Homeobox
SOX9	SRY-Box Transcription Factor 9
VPS33B	Vacuolar Protein Sorting 33 Homolog B
NESG1	Nasopharyngeal Epithelium Specific Gene 1
E-cadherin	Epithelial Cadherin
SEMA4D	Semaphorin 4D
AGO1	Argonaute RISC Catalytic Component 1
NRP1	Neuropilin 1
PDK1	Pyruvate Dehydrogenase Kinase, Isozyme 1

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