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PI3K/AKT pathway as a pivotal regulator of epithelial-mesenchymal transition in lung tumor cells

Meysam Moghbeli[1*]

Abstract

Lung cancer, as the leading cause of cancer related deaths, is one of the main global health challenges. Despite various progresses in diagnostic and therapeutic methods, there is still a high rate of mortality among lung cancer patients, which can be related to the lack of clinical symptoms to differentiate lung cancer from the other chronic respiratory disorders in the early tumor stages. Most lung cancer patients are identified in advanced and metastatic tumor stages, which is associated with a poor prognosis. Therefore, it is necessary to investigate the molecular mechanisms involved in lung tumor progression and metastasis in order to introduce early diagnostic markers as well as therapeutic targets. Epithelial-mesenchymal transition (EMT) is considered as one of the main cellular mechanisms involved in lung tumor metastasis, during which tumor cells gain the metastatic ability by acquiring mesenchymal characteristics. Since, majority of the oncogenic signaling pathways exert their role in tumor cell invasion by inducing the EMT process, in the present review we discussed the role of PI3K/AKT signaling pathway in regulation of EMT process during lung tumor metastasis. It has been reported that the PI3K/AKT acts as an inducer of EMT process through the activation of EMT-specific transcription factors in lung tumor cells. MicroRNAs also exerted their inhibitory effects during EMT process by inhibition of PI3K/AKT pathway. This review can be an effective step towards introducing the PI3K/AKT pathway as a suitable therapeutic target to inhibit the EMT process and tumor metastasis in lung cancer patients.

Keywords PI3K/AKT, EMT, Lung cancer, Metastasis

Background

Lung cancer is the leading cause of cancer-related mortality globally. Non–small cell lung carcinoma (NSCLC) accounts 80% of lung cancers. There is a low survival rate in metastatic NSCLC patients because of the aggressive behavior of these tumors [1]. There are various therapeutic strategies such as surgery, chemotherapy, radiotherapy, and targeted therapy for NSCLC patients. However, there is still a low 5-years survival rate in NSCLC patients that is associated with late diagnosis in regional or distant metastasis [2, 3]. Regarding the deep location of lung tumors without any clear clinical symptoms in the early tumor stage, more than half of NSCLC patients are diagnosed in advanced stages with distant metastases [4, 5]. Therefore, it is required to elucidate the molecular mechanisms of lung tumor progression to improve early detection and prognosis. Epithelial mesenchymal transition (EMT) is a pivotal cellular process during tumor metastasis that is characterized with down-regulation of epithelial marker (E-cadherin), while

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up-regulation of mesenchymal markers and EMT-specific transcription factors (N-cadherin, Twist, Zeb1, Snail, and Slug) [6, 7]. During EMT process, tumor cells lose their cell-cell adhesions to obtain a mesenchymal feature with a high ability for invasion [8, 9]. E-cadherin (CDH1) down regulation as a hallmark of EMT is associated with Twist, Snail, Slug, and ZEB1 up regulations [10]. Various signaling pathways such as Mitogen-activated protein kinases (MAPK), phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT), and Transforming growth factor-β (TGF-β) are also involved in regulation of EMT process [11–14]. Since, PI3K/AKT pathway has been reported to be activated in 90% of NSCLC cells; it can be introduced as a reliable target to inhibit the NSCLC progression [15]. Several inhibitors of PI3K/AKT/mTOR pathway have been introduced by preclinical and clinical trials in NSCLC patients [16]. GDC-0941 as a reversible inhibitor of PI3K was responsive to NSCLC cells with PIK3CA alteration and PTEN loss. A partial response was observed in a combination therapy by GDC-0941, paclitaxel, and carboplatin in NSCLC patients [17]. MK-2206 is an inhibitor of AKT that increases effect of RTK inhibitors and cytotoxic drugs in NSCLC cells [18]. Buparlisib (BKM120) is also an orally administered PI3K inhibitor that generates modest responses in lung cancer patients [19]. Temsirolimus inhibits NSCLC growth via reduced mTOR phosphorylation. It showed a partial response in NSCLC patients that lasted 12.7 months [20]. Therefore, in the present review we discussed the role of PI3K/AKT pathway in regulation of EMT process during lung tumor metastasis (Table 1).

PI3K/AKT axis

Receptor tyrosine kinases (RTKs) have a fundamental role in regulation of cell proliferation, metabolism, migration, and apoptosis through the PI3K/AKT pathway [21]. It has been shown that PI3K/AKT pathway has a key role in regulation of EMT process during lung tumor metastasis (Fig. 1). Ephrin (Eph) is considered as the largest RTK subfamily that can be activated by Ephrin ligands to regulate cell adhesion and proliferation [22, 23]. EphrinA3 inhibition reduced the LUAD cell proliferation and migration. It promoted PI3K/Akt to up regulate the CCND1. It also regulates the EMT process by MMP2/9 up regulations, which are the key factors during lung adenocarcinoma (LUAD) metastasis [24]. There was significant miR-448 down regulation in NSCLC tissues that was associated with poor prognosis. MiR-448 inhibited PI3K/Akt pathway and EMT process via EPHA7 targeting in NSCLC cells [25]. Brain Derived Neurotrophic Factor (BDNF) is an activator of the tropomyosin-related tyrosine kinase (Trk) receptors to promote MAPK and PI3K signaling pathways. PI3K/AKT can be promoted by BDNF/TRKB and p75NTR axes [26]. There was miR-147 down regulation in NSCLC tissues that was correlated with poor prognosis, lymph node invasion, and tumor stage. MiR-147 inhibited the EMT process by Vimentin (VIM) and CDH2 down regulations while CDH1 up regulation in NSCLC. MiR-147 also inhibited PI3K/AKT pathway via p-PI3K and p-AKT down regulations in NSCLC cells [27]. EGFR is a well-known RTK that promotes cell growth and metabolism via PI3K/AKT and MAPK pathways. There was miR-1299 down regulation in NSCLC tissues compared with normal margins. MiR-1299 reduced NSCLC cell migration and EMT process via EGFR targeting [28]. Phosphatase and tensin homolog (PTEN) is a negative regulator of PI3K/AKT pathway that has mainly a tumor suppressor function in tumor cells. MiR-92a increased NSCLC cell invasion and EMT process through PTEN targeting [29]. Tumor microenvironment (TME) induces the immune escape as a hallmark of tumor progression [30]. There is a continuous correlation between the immune cells of microenvironment and tumor cells during tumor initiation to metastasis [31]. Protein Tyrosine Phosphatase Receptor Type N (PTPRN) is involved in insulin secretion of pancreatic islet β-cells [32]. There was PTPRN up regulation in LUAD tissues that was contributed with poor prognosis and metastasis. PTPRN increased LUAD cell metastasis through the regulation of PI3K/AKT pathway. It up regulated the VIM, CDH2, and p-AKT in LUAD cells [33]. Small nucleolar RNAs (snoRNAs) are non-coding RNAs that are involved in chemical modifications of rRNAs, tRNAs, and snRNAs. It has been reported that Small Nucleolar RNA, H/ACA Box 47 (SNORA47) inhibition reduced NSCLC progression and EMT process through PI3K/AKT pathway. SNORA47 down regulated CDH1 while up regulated CDH2 in NSCLC cells [34].

EMT can be regulated by Snail and Twist transcription factors [35, 36]. AKT as the main effector of PI3K up regulates the Snail/Twist transcription factors to down regulate CDH1. Resistin is an inflammo-regulatory protein that is involved in tumor progression [37]. It induces the tumor cell proliferation through the promotion of PI3K/AKT pathway [38]. There was an inverse association between the levels of Resistin and miR-625 expressions that was significantly correlated with lymph node invasion and tumor stage in NSCLC patients. Resistin increased NSCLC progression and EMT process through PI3K/AKT/Snail axis. MiR-625 inhibited NSCLC cell migration and EMT by Resistin targeting [39]. MiR-126 reduced lung cancer cells invasion through targeting the PI3K/AKT/Snail axis [40]. Family With Sequence Similarity 83 Member A (FAM83A) functions in Epidermal Growth Factor Receptor (EGFR) pathway by promotion of the PI3K/AKT/TOR axis. There was significant FAM83A up regulation in NSCLC tissues which was associated with poor prognosis. FAM83A induced

Table 1 PI3K/AKT axis as a regulator of EMT process during lung tumor metastasis

Study	Year	Axis	Effect on the EMT	Samples	Clinical application
YIMIN-NIYAZE [24]	2023	EPHA3/PI3K/AKT	Induced	A549, H1299, H1975, and PC-9 cell lines	Diagnosis
LIU [25]	2020	miR-448/EPHA7/PI3K/AKT	Inhibited	51 NT* A549, H1299, H460, and SPC-A1 cell lines	Diagnosis and prognosis
LI [27]	2020	miR-147/BDNF/PI3K/AKT	Inhibited	79 patients A549 cell line	Diagnosis and prognosis
CAO [28]	2020	miR-1299/EGFR/PI3K/AKT	Inhibited	56 NT H1299, A549, H358, and H1975 cell lines	Diagnosis
LU [29]	2017	miR-92a/PTEN	Induced	50 NT A549, H358, SPC-A1, and H1299 cell lines	Diagnosis
SONG [33]	2021	PTPRN/PI3K/AKT	Induced	H1299 and A549 cell lines	Diagnosis and prognosis
YU [34]	2021	SNORA47/PI3K/AKT	Induced	A549 and NCI-H23 cell lines	Diagnosis
ZHAO [39]	2020	miR-625/RETN/PI3K/AKT/SNAIL	Inhibited	80 NT A549, H322, GLC-82, and H226 cell lines	Diagnosis and prognosis
JIA [40]	2018	miR-126/PI3K/AKT/SNAIL	Inhibited	SPC-A1 and LLC cell lines	Diagnosis
ZHOU [41]	2019	FAM83A/PI3K/AKT/SNAIL	Induced	101 patients PC-14, H661, A549, H827, PC-9, H1915, H2170, H460, and H1299 cell lines	Diagnosis and prognosis
WU [44]	2019	PAX6/ZEB2/PI3K/AKT	Induced	A549 and SPC-A1 cell lines	Diagnosis and prognosis
MA [48]	2019	miR-4458/AKT	Inhibited	A549, H1299, HCC827, PC-9, HBE, and 293T cell lines	Diagnosis
LIU [51]	2017	ING5/EGFR/PI3K/AKT	Inhibited	A549 and H1299 cell lines	Diagnosis
JIN [60]	2019	NETRIN1/PI3K/AKT	Induced	95 patients A549, H1299, H1975, SPC-A1, PC-9, and H522 cell lines	Diagnosis
XU [61]	2020	Circ-0018818/NID1/PI3K/AKT	Inhibited	30 NT A549, PC-9, H441, H1650, and 293T cell lines	Diagnosis
HU [64]	2021	CNTN1/PI3K/AKT	Induced	A549 cell line	Diagnosis
QIU [66]	2017	DAL-1/HSPA5/PI3K/AKT	Inhibited	A549, SPC-A1,HA579, H520, H460, and H1299 cell lines	Diagnosis
XUAN [69]	2019	miR-381/LMO/PI3K/AKT	Inhibited	54 NT A549, SPC-A1, H1299, and PC-9 cell lines	Diagnosis and prognosis
TANG [70]	2019	KIAA1199/PI3K/AKT	Induced	254 patients A549, H1299, H1975, and H1650 cell lines	Diagnosis
WANG [71]	2020	miR-874/AQP3/PI3K/AKT	Inhibited	49 NT A549 and H1299 cell lines	Diagnosis and prognosis
MA [74]	2019	ENKUR/PI3K/AKT	Inhibited	515T and 59 N A549, H322, PC-9, SPC-A1, and GLC-82 cell lines	Diagnosis
WANG [80]	2018	ELF3/PI3K/AKT	Induced	85T and 22 N SPC-A1 and A549 cell lines	Diagnosis and prognosis
LI [82]	2023	ZNF687/PI3K/AKT/GSK3β/SNAIL	Induced	98T and 82 N A549, PC-9, HCC827, and H1975 cell lines	Diagnosis and prognosis
LIN [85]	2021	ARHGAP10/PI3K/AKT/GSK3β	Inhibited	66 NT A549, H1299, H1975, and SKMES-1 cell lines	Diagnosis
KUANG [88]	2020	RNF8/PI3K/AKT/SLUG	Induced	1100 patients H1299, H1395, Calu-1, and A549 cell lines	Diagnosis and prognosis
LIU [90]	2017	TRIM22/PI3K/AKT/GSK3β/β-CATENIN	Induced	126 patients H460, A549, H358, LK2, H1299, and H3255 cell lines	Diagnosis and prognosis
JEON [94]	2017	PELI1/AKT/GSK3β	Induced	A549, CALU-3, CALU-6, H322, H358, H1650, H441, H460, H1299, H1264, PC-9, H827, H1833, H1838, H1975, H820, and H4006 cell lines	Diagnosis
LEE [97]	2017	APBB1/IGF1R/AKT/GSK3β	Induced	A549 and H460 cell lines	Diagnosis
YUAN [99]	2020	miR-410/PTEN/PI3K/AKT/Mtor	Induced	62 NT A549, H1299, PC-9, and SPC-A1 cell lines	Diagnosis

Table 1 (continued)

Study	Year	Axis	Effect on the EMT	Samples	Clinical application
KHEN-DELWAL [100]	2021	miR-320a/PI3K/AKT/mTOR	Inhibited	80 patients A549 cell line	Diagnosis and prognosis
CHEN [104]	2016	miR-206/C-MET/PI3K/AKT/mTOR	Inhibited	34 NT A549 and H1299 cell lines	Diagnosis
MOU [106]	2016	miR-485/FLOT2/PI3K/AKT/mTOR	Inhibited	25 NT A549,H1650, H332, and SPC-A1 cell lines	Diagnosis and prognosis
CHEN [113]	2016	miR-206/HGF/C-MET/PI3K/AKT/mTOR	Inhibited	35 NT A549, 95D, 95 C, and 801 C cell lines	Diagnosis
ZHAO [116]	2021	HRH3/PI3K/AKT/mTOR	Induced	H460, A549, H1703, PC-9, and H1975 cell lines	Diagnosis
PENG [120]	2023	GPX2/PI3K/AKT/mTOR	Induced	293 patients H520, H358, H1299, H460, and A549 cell lines	Diagnosis and prognosis

* Tumor (T) tissues, Normal (N) margins

NSCLC cell invasion by PI3K/ATK/Snail axis and EMT promotion [41].

Paired-box 6 (PAX6) is a developmental transcription factor that is involved in embryogenesis [42, 43]. There was significant PAX6 up regulation that was correlated with poor prognosis in NSCLC patients. It induced NSCLC cell migration via ZEB2 up regulation that reduced the levels of CDH1 expression through PI3K/AKT pathway. PAX6 up regulated the p-AKT, p-PI3K, CDH2, vimentin, while down regulated CDH1 [44]. High Mobility Group AT-Hook 1 (HMGA1) is a regulator of chromatin remodeling by binding to A/T-rich regions [45]. It has key roles in regulation of cell proliferation, invasion, and EMT process [46, 47]. It has been reported that miR-4458 inhibition up regulated p-AKT. miR-4458 reduced NSCLC cell migration and EMT via HMGA1 targeting [48]. Inhibitor of Growth (ING) protein family includes ING1-5 members that are involved in cell proliferation, apoptosis, and chromatin remodeling [49]. ING5 interacts with p300 and p53 via a zinc finger domain to promote apoptosis [50]. ING5 inhibition induced lung tumor cell invasion through promotion of the EGFR/PI3K/AKT mediated EMT process. ING5 had inhibitory role on EGFR/PI3K/AKT axis by p-AKT down regulation [51]. Sirtuin-1 (SIRT1) is a conserved histone deacetylase which has pivotal roles in epigenetic regulation through histones and non-histone modifications [52]. B7H3 (CD276) suppresses tumor associated T cell activation [53], while induces tumor cell invasion and drug resistance [54]. It was shown that B7H3 promoted the NSCLC cell invasion and EMT process. SIRT1 regulated the B7H3mediated EMT. Reciprocally, B7H3 also modulated SIRT1 through PI3K/AKT axis in NSCLC cells [55].

Hypoxia as a hallmark of fast-growing solid tumors has a pivotal role in metastasis that results in poor prognosis [56]. Since, Hypoxia promotes EMT in lung tumor cells, it is required to assess the molecular mechanisms of hypoxia mediated EMT to overcome the poor prognosis. Netrin-1 is a cell-secreted soluble protein that has key roles in tissue development and tumor cell migration [57, 58]. It promoted the PI3K/AKT mediated EMT via interaction with FAK. Therefore, Netrin-1 induces cell migration through activation of FAK/PI3K/AKT axis [59]. Hypoxia mediated Netrin-1 inhibition down regulated p-AKT that reduced NSCLC cell migration. Netrin-1 induced hypoxia-mediated EMT via PI3K/AKT pathway in NSCLC cells [60]. Nidogen 1 (NID1) is a sulfated glycoprotein associated with laminin that is involved in cellular interaction with extracellular matrix. Circ_0018818 inhibition reduced NSCLC tumor progression by miR-767-3p sponging that activated the NID1/PI3K/Akt/EMT axis [61]. Contactin-1 (CNTN1) is a neuronal adhesion protein involved in tumor progression [62, 63]. CNTN1 inhibition increased gefitinib sensitivity while inhibited EMT process through PI3K/AKT inactivation and cytoskeletal rearrangement in lung adenocarcinoma cells. CNTN1 inhibition down regulated the VIM and CDH2 while up regulated CDH1 [64].

Heat Shock Protein Family A Member 5 (HSPA5) is a member of the HSP70 protein family that is involved in regulation of EMT process and tumor metastasis [3, 65]. It was observed that DAL-1 suppressed EMT process and NSCLC cell proliferation via HSPA5 down regulation. DAL-1 mediated HSPA5 inhibition down regulated p-PI3K, p-Akt, and p-Mdm2 while up regulated p53 to attenuate EMT via suppressing the PI3K/AKT/Mdm2/p53 axis [66]. LIM-only protein 3 (LMO3) as a regulator of p53 is involved in cell growth and invasion [67, 68]. There was miR-381 down regulation in lung adenocarcinoma tissues that was correlated with poor prognosis. MiR-381 reduced lung adenocarcinoma cell proliferation and migration by LMO targeting and regulation of PI3K/Akt pathway and EMT process [69]. KIAA1199 as an endoplasmic reticulum (ER) protein has key roles in

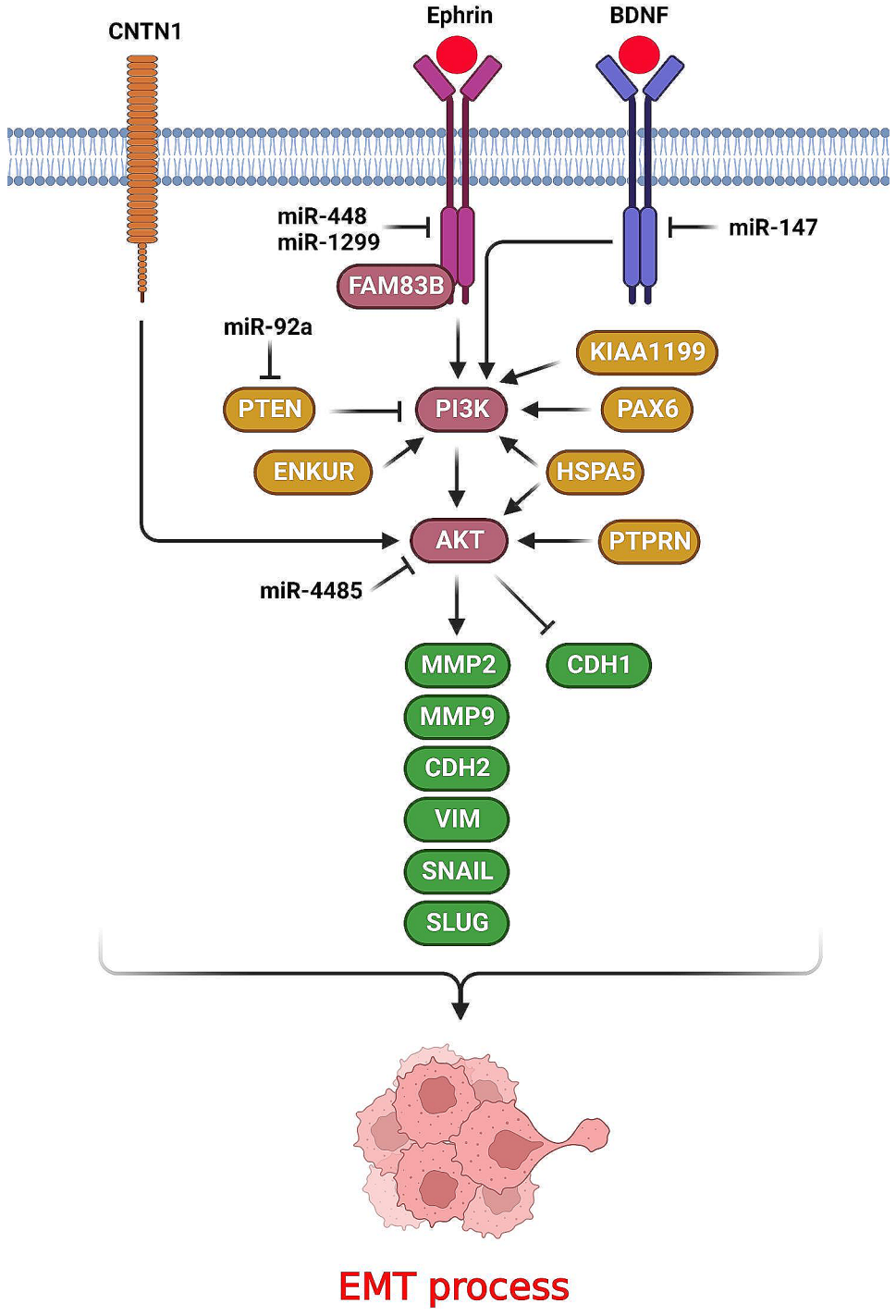

Fig. 1 Role of PI3K/AKT axis in regulation of EMT process during lung tumor metastasis. (Created with *BioRender.com*)

tumor invasion by Ca^{2+} release into the cytoplasm that activates protein kinase C to facilitate cell migration. It mediates hyaluronic acid (HA) depolymerization to regulate endocytosis. It regulates EMT by collaboration with HSPA5/BIP in a Ca^{2+} and PKC-related pathway. There was significant KIAA1199 up regulation in NSCLC tissues in comparison with normal controls. KIAA1199 promoted the EMT process during NSCLC progression and metastasis. KIAA1199 increased NSCLC invasion and EMT process via PI3K-Akt activation [70].

Aquaporins (AQPs) are a group of membrane channels that facilitate water transportation to regulate osmotic gradient. There was miR-874 down regulation in NSCLC tissues that was associated with poor prognosis.

MiR-874 suppressed NSCLC cell invasion and EMT process by AQP3 targeting via regulation of PI3K/AKT axis. AQP3 activated the PI3K/AKT pathway via PI3K and AKT phosphorylations. Therefore, miR-874 suppressed EMT process via AQP3 targeting and subsequent inhibition of PI3K/AKT in NSCLC [71]. Enkurin (ENKUR) is considered as a Calmodulin (CaM)-binding protein that links the signal proteins with TRPC channels [72]. It also binds to the p85 subunit of PI3K [73]. ENKUR inhibition resulted in CDH1 down regulation while VIM and CDH2 up regulations in lung tumor cells. ENKUR also significantly down regulated PI3K and reduced p-Akt levels [74].

PI3K/AKT/GSK3β axis

Glycogen Synthase Kinase 3 Beta (GSK-3β) is a downstream target of PI3K/AKT and Extracellular Signal-Regulated Kinase (ERK) signaling pathways that can be inhibited by AKT or ERK [75]. Both these signaling pathways phosphorylate and inhibit the GSK-3β, that results in Snail and Slug up-regulation and EMT induction [76, 77]. It has been shown that PI3K/AKT/GSK3β axis has a key role in regulation of EMT process during lung tumor metastasis (Fig. 2). E74 Like ETS Transcription Factor 3 (ELF3) has key roles in tumor progression and embryogenesis [78, 79]. There was ELF3 up regulation in NSCLC that induced cell proliferation and invasion via activation of PI3K/Akt pathway. ELF3 up regulation was correlated with distant metastasis and clinical stages in NSCLC patients. There was also a negative association between the levels of ELF3 and survival rate in NSCLC patients. ELF3 inhibition reduced NSCLC cell growth by Cyclin D1 (CCND1), E2F Transcription Factor 1 (E2F1), and c-Myc down regulations. ELF3 induced EMT via CDH2, vimentin, Slug, and snail up regulations while CDH1 down regulation. ELF3 silencing reduced the levels of p-PI3K, p-GSK-3β and p-Akt expressions. Therefore, ELF3 increased NSCLC cell proliferation and invasion by PI3K/AKT activation and its downstream EMT related targets [80]. Zinc finger protein 687 (ZNF687) is a C2H2 zinc finger protein that has key roles in transcriptional regulation via binding to the ZNF592 and ZNF532 complex. ZNF687 is involved in epigenetic modulation and also transcriptional inhibition in DNA damaged regions [81]. ZNF687 up regulation was observed in LUAD tissues that were associated with poor prognosis. ZNF687 promoted G1/S phase progression by CDK2/4/6 and CCND1 up regulations while p27, p53, and p21 down regulations. ZNF687 inhibition reduced the levels of CDH2, VIM, MMP2, MMP9, and Snail expressions while up regulated CDH1, suggesting the regulatory role of ZNF687 on LUAD invasion and EMT process. ZNF687 inhibition also decreased the p-AKT, p-PDK1, and pGSK-3β levels. Therefore, ZNF687 was suggested as an EMT modulator via regulation of PI3K/AKT/GSK-3β/Snail axis that affected the LUAD cell metastasis [82]. Rho GTPase activating protein 10 (ARHGAP10) is involved in regulation of cell migration, cytoskeletal organization, and EMT process [83, 84]. There was significant ARHGAP10 down regulation in NSCLC tissues. ARHGAP10 reduced EMT process by CDH1 up regulation while CDH2, snail, and VIM down regulations. ARHGAP10 also reduced the levels of components of PI3K/Akt/GSK3β axis that reduced EMT in lung tumor cells [85].

Ring Finger Protein 8 (RNF8) as an ubiquitin E3 ligase has pivotal roles in regulation of cell proliferation, spermatogenesis, and apoptosis [86]. It induces the EMT by GSK-3β inhibition that results in accumulation of β-catenin and subsequent tumor metastasis [87]. RNF8 induced lung tumorigenesis through stabilization of Slug and PI3K/AKT signaling. There was RNF8 up regulation in lung tumor tissues that was conversely associated with patient's survival [88]. Tripartite Motif Containing 22 (TRIM22) functions as a transcriptional regulator and E3 ubiquitin ligase [89]. There was significant TRIM22 up regulation in lung tumor tissues that was associated with poor prognosis. TRIM22 promoted the EMT process via Snail up regulation. It also increased the p-AKT levels. TRIM22 down regulated the CDH1 through snail following the AKT activation. Therefore, TRIM22 promoted EMT process via activation of PI3K/AKT/GSK3β/β-catenin axis in NSCLC cells [90]. Cancer stem cells (CSCs) are a small subpopulation of tumor cells that are involved in tumor recurrence via their self-renewal ability and drug resistance. EMT promotes tumor metastasis by generation of chemo resistant cancer stem cells [8, 91]. Pellino-1 as an E3 ubiquitin ligase is involved in immune response via regulation of T-cell receptor signaling and B and T cells activations [92, 93]. It also stabilizes the Snail and Slug through K63-mediated ubiquitination that induces the EMT process. Pellino-1 induced lung tumor cell proliferation by Akt activation that stabilized Slug and Snail. It also inhibited the GSK3β in lung tumor cells [94]. Amyloid Beta Precursor Protein Binding Family B Member 1 (APBB1) as an adaptor protein has critical role in cellular response toward genotoxic stress [95]. Insulin Like Growth Factor 1 (IGF1) binding to IGF1R activates insulin receptor substrates (IRS) to promote cell growth and migration [96]. APBB1 regulates EMT and radio resistance by activation of IGF1R/AKT/GSK3b axis in NSCLC cells [97].

PI3K/AKT/mTOR axis

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase that is one of the main effectors in PI3K/Akt pathway. mTOR refers to mTORC1 and mTORC2 complexes with different functions. mTORC1 promotes

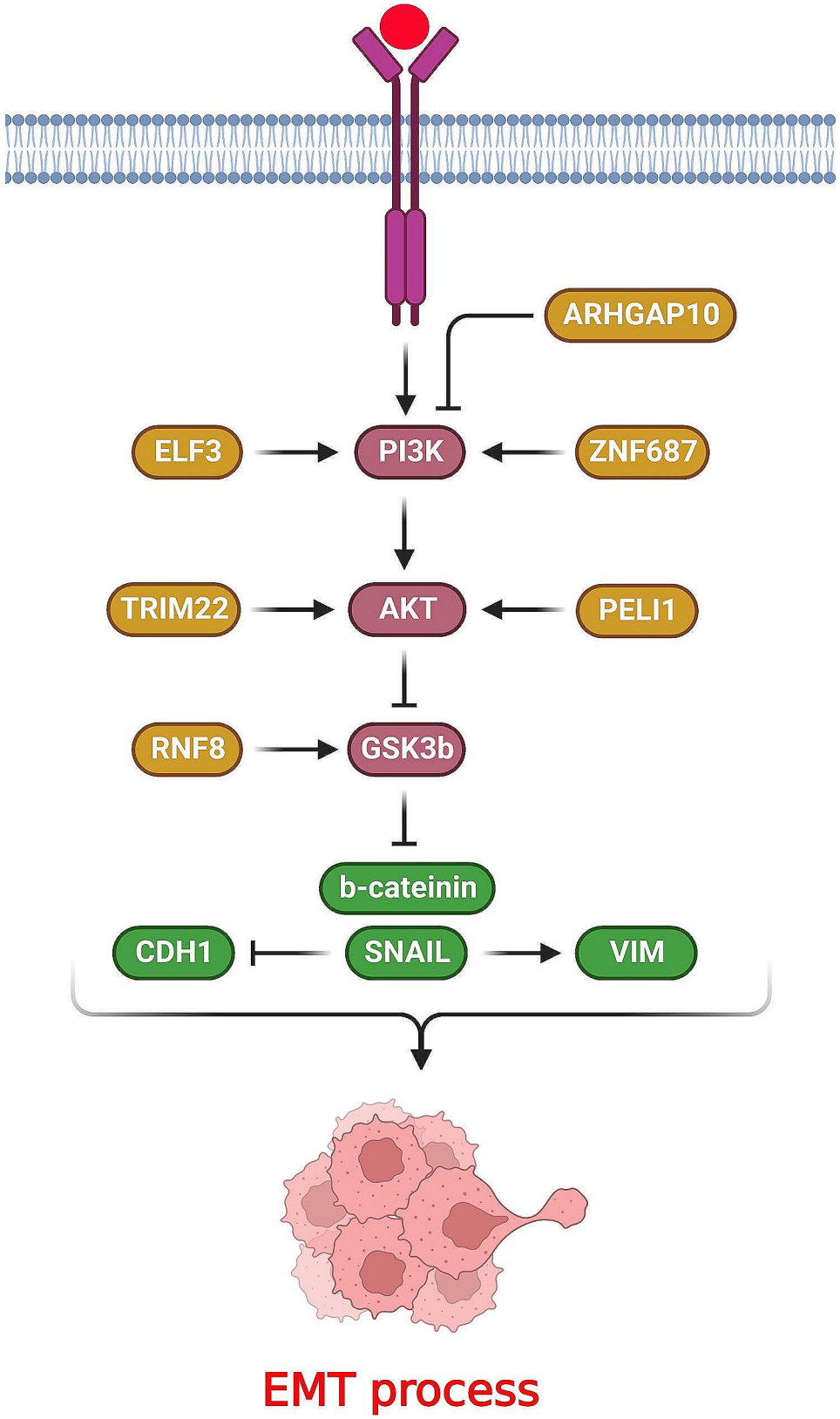

Fig. 2 Role of PI3K/AKT/GSK3β axis in regulation of EMT process during lung tumor metastasis. (Created with *BioRender.com*)

protein synthesis, cell metabolism, and growth by regulation of S6K1 and 4EBP1, while mTORC2 suppresses the Cyclin D1/E proteolysis via Akt activation [98]. Therefore, deregulation of PI3K/AKT/mTOR axis can be associated with neoplastic transformation [21]. It has been shown that PI3K/AKT/mTOR axis has a key role in regulation of EMT process during lung tumor metastasis (Fig. 3). MiR-410 promoted the EMT process and radio resistance by targeting the PTEN/PI3K/mTOR axis in NSCLC cells. MiR-410 up regulated the phosphorylated Akt and mTOR [99]. There was significant miR-320a down regulation in NSCLC samples that was correlated with TNM stage and poor prognosis. MiR-320a regulated the NSCLC progression via AKT3 targeting in PI3K/AKT/mTOR axis. MiR-320a inhibition up regulated CCND1, Matrix Metallopeptidase 9 (MMP9), Bcl-2, and β-catenin that increased cell proliferation and invasion in NSCLC [100]. Cisplatin (DDP) is one of the chemotherapeutic agents that are frequently used in lung cancer due to high efficiency and easy administration. However, there is a high rate of cisplatin resistance among patients [101]. It was observed that EMT process is involved in drug resistance of tumor cells [102, 103]. MiR-206 reduced EMT process and CDDP resistance via MET targeting that inhibited PI3K/AKT/mTOR axis in lung adenocarcinoma cells. EMT gene profile was significantly associated with MDR1 up regulation and CDDP resistance [104]. Flotillin 2 (FLOT2) is a caveolae-associated protein that is involved in vesicular trafficking and tumor progression [105]. There was miR-485 down regulation in lung adenocarcinoma tissues that was inversely associated with metastatic potential. MiR-485 inhibited the EMT process by FLOT2 targeting in lung adenocarcinoma cells. MiR-485 inhibited AKT and mTOR in lung adenocarcinoma that was reversed by FLOT2. Therefore, miR-485 promoted the PI3K/ AKT/mTOR axis by FLOT2 down regulation [106].

Angiogenesis has a key role in tumor progression and metastasis through preparing the required nutrients and oxygen for the tumor cells [107]. Angiogenic factors promote the endothelial cell proliferation to form the new vessels [108]. Both angiogenesis and EMT process can be stimulated by Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), and Platelet Derived Growth Factor (PDGF) growth factors [109]. Hepatocyte Growth Factor (HGF) promotes metastatic potential of the tumor cells to spread in blood circulation via activation of the c-Met pathway [110, 111]. It is considered as an angiogenic cytokine that modifies the microenvironment via c-Met activation to facilitate tumor progression [112]. MiR-206 reduced HGF-mediated EMT and angiogenesis in lung cancer by c-Met targeting that resulted in suppression of PI3k/Akt/mTOR axis. MiR-206 also inhibited lung tumor growth and angiogenesis in vivo that introduced miR-206 as an efficient therapeutic target in lung cancer [113]. Histamine has a significant role in regulation of tumor-associated processes that exerts its role by binding to G protein-coupled receptors (GPCRs) including H1-4 histamine receptors. Histamine receptor H3 (Hrh3) inhibition reduces the tumor cell proliferation while promotes caspase-mediated apoptosis [114]. Hrh3 activates PI3K/AKT and MAPK signaling pathways to exert pathophysiological functions [115]. Hrh3 inhibition reduced NSCLC cell proliferation and metastasis via suppression of EMT process that is related to inhibition of PI3K/AKT/mTOR pathway [116]. Glutathione peroxidase 2 (GPX2) has a critical role in protection of cells toward the oxidative damages by hydrogen peroxide and fatty acid hydroperoxides reductions [117–119]. It has been shown that GPX2 up regulation was correlated with poor survival of NSCLC patients with lymph node invasion and advanced TNM stage. GPX2 up regulated the Snail and VIM, while down regulated CDH1 that finally increased NSCLC cell invasion. GPX2 inhibition reduced the levels of p-PI3K, p-AKT, and p-mTOR in NSCLC cells [120].

Conclusions

A wide range of oncogenic signaling pathways can induce tumor cell invasion by promotion of the EMT process. In this study, we discussed the role of PI3K/AKT pathway in regulation of the EMT process during lung tumor metastasis. It has been shown that the PI3K/AKT pathway acts as an inducer of EMT process during lung tumor metastasis. Many tumor suppressors and miRNAs also exert their inhibitory effects on lung tumor metastasis and EMT through PI3K/AKT inhibition. This review can be an effective step in introducing the PI3K/AKT pathway as a suitable therapeutic target to inhibit the EMT process and tumor cell invasion in lung cancer patients. It has been shown that ncRNAs have a key role in regulation of the EMT process through PI3K/AKT pathway. Considering the inhibitory effect of miRNAs on the PI3K/AKT pathway as an inducer of the EMT process, miRNAs can be used as the reliable therapeutic targets via the miRNA mimics strategy. On the other hand, due to the inhibitory effects of lncRNAs and circRNAs on miRNAs, they can be also considered as the therapeutic targets to inhibit the PI3K/AKT mediated EMT process in the early stages of tumor metastasis. However, there is still not any clinical report about the application of ncRNAs to inhibit the EMT process through the PI3K/AKT pathway. Indeed, more animal studies and clinical trials are needed to use ncRNAs to inhibit PI3K/AKT mediated EMT process in lung cancer patients.

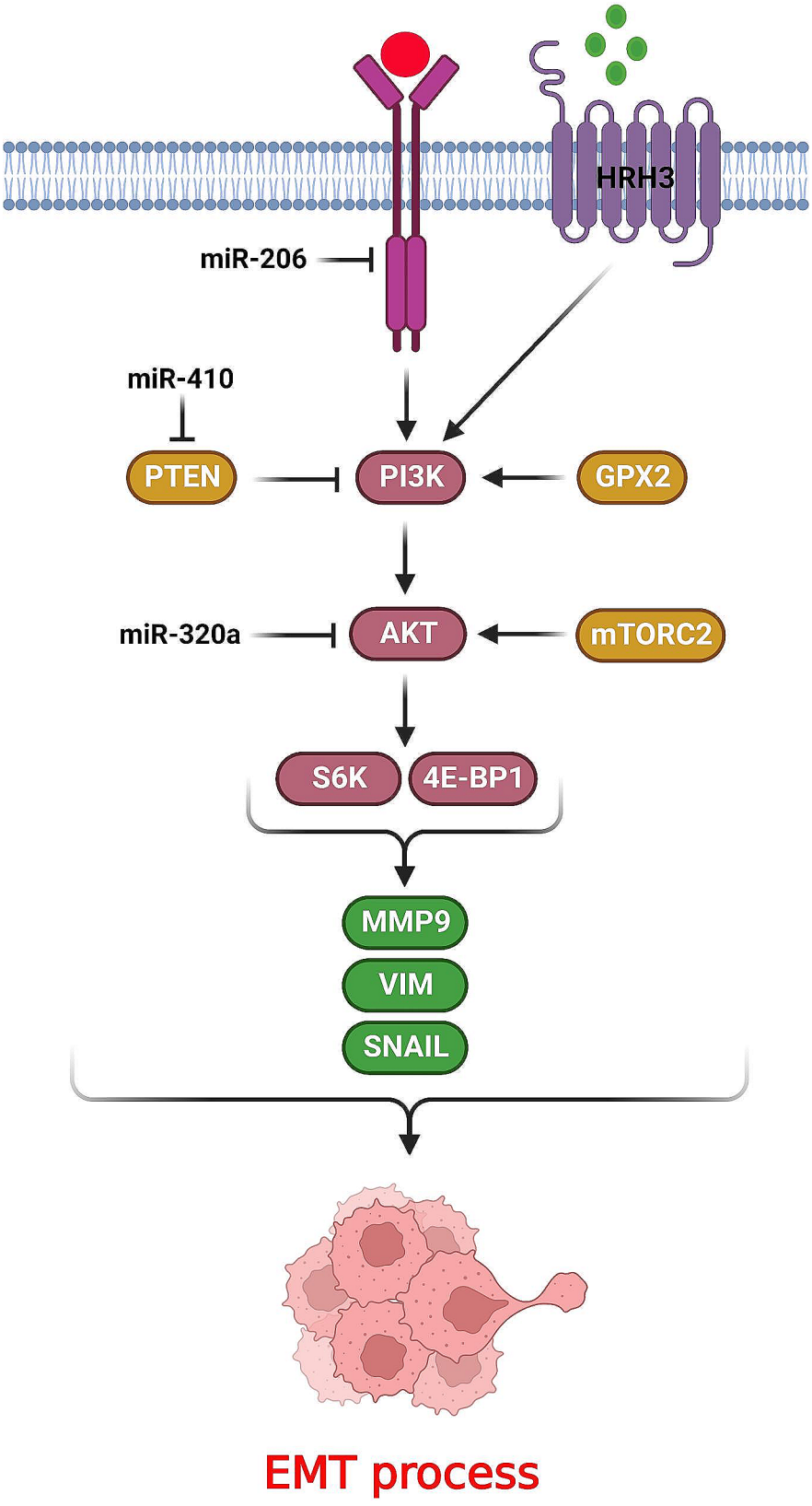

Fig. 3 Role of PI3K/AKT/mTOR axis in regulation of EMT process during lung tumor metastasis. (Created with *BioRender.com*)

Abbreviations

AQPs	Aquaporins
BDNF	Brain Derived Neurotrophic Factor
CaM	Calmodulin
CSCs	Cancer stem cells
DDP	Cisplatin
CNTN1	Contactin-1
CCND1	Cyclin D1
E2F1	E2F Transcription Factor 1
ELF3	E74 Like ETS Transcription Factor 3
CDH1	E-cadherin
ENKUR	Enkurin
EMT	Epithelial-mesenchymal transition
ERK	Extracellular Signal-Regulated Kinase
FAM83A	Family With Sequence Similarity 83 Member A
FGF	Fibroblast Growth Factor
FLOT2	Flotillin 2
GPCRs	G protein-coupled receptors
GPX2	Glutathione peroxidase 2
GSK-3β	Glycogen Synthase Kinase 3 Beta
HSPA5	Heat Shock Protein Family A Member 5
HGF	Hepatocyte Growth Factor
HMGA1	High Mobility Group AT-Hook 1
Hrh3	Histamine receptor H3
ING	Inhibitor of Growth
IRS	Insulin receptor substrates
LUAD	Lung adenocarcinoma
mTOR	Mammalian target of rapamycin
MMP9	Matrix Metallopeptidase 9
MAPK	Mitogen-activated protein kinases
NID1	Nidogen 1
NSCLC	Non–small cell lung carcinoma
PAX6	Paired-box 6
PTEN	Phosphatase and tensin homolog
AKT	Phosphoinositide 3-kinase (PI3K)/protein kinase B
PDGF	Platelet Derived Growth Factor
PTPRN	Protein Tyrosine Phosphatase Receptor Type N
RTKs	Receptor tyrosine kinases
ARHGAP10	Rho GTPase activating protein 10
RNF8	Ring Finger Protein 8
SIRT1	Sirtuin-1
SNORA47	Small Nucleolar RNA, H/ACA Box 47
snoRNAs	Small nucleolar RNAs
TGF-β	Transforming growth factor-β
TRIM22	Tripartite Motif Containing 22
Trk	Tropomyosin-related tyrosine kinase
TME	Tumor microenvironment
VEGF	Vascular Endothelial Growth Factor
VIM	Vimentin
ZNF687	Zinc finger protein 687

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Declarations

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The authors declare no competing interests.

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