PDLIM2 acts as a central regulator of ubiquitination, immune signaling, and mitochondrial metabolism in lung cancer suppression (Review)

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Abstract. Lung cancer is a leading cause of cancer-related mortality worldwide, which underscores the need to identify novel targets for improving early detection, therapeutic efficacy, and long-term patient outcomes. PDZ and LIM domain protein 2 (PDLIM2) is a multifunctional adaptor protein that plays a role in cancer biology, particularly in lung cancer. Although PDLIM2 exerts divergent functions across various cancer types, substantial clinical, genetic, and experimental evidence consistently supports its role as a tumor suppressor in lung cancer. PDLIM2 expression is markedly downregulated in the majority of lung tumors representing various histological subtypes and disease stages, and its loss is strongly associated with poor prognosis. Mechanistically, it functions as an E3 ubiquitin ligase or ubiquitin ligase enhancer to promote the degradation of key transcription factors, including NF-κB/RelA and STAT3, thereby restraining tumor-associated inflammation, proliferation, survival, immune evasion, and metabolic reprogramming. PDLIM2 downregulation in lung cancer occurs through coordinated genetic and epigenetic mechanisms, including loss of heterozygosity at chromosome 8p21, promoter hypermethylation, histone deacetylation, and oxidative stress-driven transcriptional repression. Functionally, the restoration of PDLIM2 suppresses lung tumor growth, enhances chemosensitivity, and promotes antitumor immunity, including response to immune checkpoint inhibitors. In addition, a protumoral mechanism of PDLIM2 downregulation involves mitochondrial dysfunction and accumulation of oncometabolites that lead to the activation of hypoxia inducible factor-1α signaling. Overall, PDLIM2 is emerging as a biomarker and therapeutic target for lung cancer management.

Contents

1. Introduction

Lung cancer is one of the most devastating malignancies worldwide, exerting a profound effect on patients, families, healthcare systems, and society. Lung cancer is often diagnosed at an advanced stage, when symptoms, such as persistent cough, dyspnea, weight loss, and chest pain, have already become evident. For patients, the disease causes not only physical discomfort but also emotional distress, fear,

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and uncertainty regarding prognosis and treatment outcomes. The burden extends far beyond the individual, as families frequently experience psychological strain while navigating caregiving responsibilities, financial challenges, and lifestyle disruption (1-4). Current treatment strategies for lung cancer rely on a multidisciplinary approach that includes surgery, radiotherapy, cytotoxic chemotherapy, targeted therapies, and immune checkpoint inhibitors. At the molecular level, the identification of actionable alterations, such as epidermal growth factor receptor mutations, anaplastic lymphoma kinase rearrangements, ROS proto-oncogene 1, receptor tyrosine kinase fusions, and Kirsten rat sarcoma viral oncogene homolog (KRAS) G12C mutations, has revolutionized the treatment of lung cancer, enabling precision therapies with significant clinical benefit (5-8). Immunotherapy, particularly programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) blockade, has further improved the treatment landscape for advanced disease and prolonged survival in subsets of patients. Nevertheless, major challenges remain. Numerous patients present with tumors lacking actionable driver mutations, and even among those who initially respond to targeted agents or immunotherapy, acquired resistance inevitably develops (9-12). Early-stage diagnosis remains insufficient due to limitations in current screening approaches, and tumor microenvironment heterogeneity further complicates therapeutic responses. Consequently, the overall 5-year survival rate for lung cancer remains significantly lower compared with other common malignancies, particularly for patients with metastatic disease. These limitations reflect the biological aggressiveness of lung cancer and the challenges associated with its early detection. Therefore, there is a compelling need to identify additional molecular pathways, biomarkers, and therapeutic targets to improve early diagnosis, overcome treatment resistance, and expand effective treatment options (6,13-15).

PDZ and LIM domain protein 2 (PDLIM2) is a cytoskeletal and nuclear regulatory protein that regulates diverse cellular functions through its ability to mediate ubiquitination-dependent protein turnover and control the stability and activity of key signaling molecules (16,17). It is significantly downregulated in lung cancer tissues and cell lines, and reduced expression is associated with tumor progression, enhanced NF-κB and STAT3-mediated inflammatory signaling, loss of epithelial identity, metastasis, reshaped antitumor immunity, and dysregulated mitochondrial metabolic function. Because of the substantial global burden of lung cancer, the limitations of current therapies, and the need for novel biomarkers and molecular targets, PDLIM2 has emerged as a compelling candidate for further study. Accordingly, the present review focuses on PDLIM2 structure, regulation, and function in lung cancer, and highlights its unique role as a tumor suppressor. Its potential as a biomarker and therapeutic target in lung cancer management is also discussed.

2. PDLIM protein family and structural features of PDLIM2

The PDZ-LIM (PDLIM) protein family consists of seven structurally related adaptor proteins: PDLIM1 (CLP-36), PDLIM2 (Mystique or SLIM), PDLIM3 (ALP), PDLIM4 (RIL), PDLIM5 (ENH), PDLIM6 (ZASP), and PDLIM7 (Enigma), which are characterized by the presence of an N-terminal PDZ domain and either one LIM domain (PDLIM1-PDLIM4) or three LIM domains (PDLIM5-PDLIM7) at the C-terminus (Fig. 1A) (18-20). The PDZ domain is comprised of 80-100 amino acids and is a well-characterized protein-protein interaction scaffold found in >150 proteins in the human genome. Minimal molecular alterations within PDZ-binding sites can markedly alter binding specificity, which suggests that structurally similar PDZ domains are capable of interacting with diverse ligands (21-24). The LIM domain contains 40-60 amino acids and adopts a zinc finger fold that facilitates protein-protein interactions. It is enriched in cysteine residues, and conserved cysteine and histidine residues coordinate two Zn^{2+} ions in a tetrahedral arrangement to stabilize the domain structure. Notably, ~70 LIM domain-containing proteins are encoded in the human genome, which highlights the importance of this domain in cellular signaling (25-28). The combination of PDZ and LIM domains endows PDLIM family members with exceptional scaffolding capacity, enabling them to interact with a wide range of binding partners and perform diverse cellular functions.

Among the PDLIM family members, PDLIM2 is unique in its cellular functions and prominent role in tumor regulation (16,17). PDLIM2 was initially identified from a rat eye iridocorneal angle cDNA library and shown to interact with α-actinin and filamin A (29). Early research reported PDLIM2 expression in insulin-like growth factor I receptor-expressing cells, where it localizes to cytoskeletal focal contacts and associates with α-actinin and β1-integrin. Under physiological conditions, PDLIM2 is ubiquitously expressed in tissues, with particularly high expression in the lung (30). The human PDLIM2 gene is located on chromosome 8p21.2. Its expression is more abundant than in non-transformed breast epithelial cells and breast carcinoma cells. Overexpression of PDLIM2 suppresses anchorage-independent growth, which requires both the PDZ and LIM domains (30). Subsequent studies identified SLIM/PDLIM2 as a STAT4-interacting protein in a yeast two-hybrid screen. Its nuclear localization enables interaction with activated STAT proteins, and PDLIM2 promotes the proteasome-mediated degradation and inactivation of STAT transcription factors. PDLIM2 deficiency results in increased STAT expression and enhanced IFN-γ production in activated $CD4^+$ T cells. These results established PDLIM2 as a novel regulator of immune responses through ubiquitin-mediated control of STAT signaling (31,32).

3. The role of PDLIM2 in ubiquitination

Ubiquitination is a highly conserved post-translational modification that is essential for maintaining cellular homeostasis. This process involves the covalent attachment of ubiquitin, a 76-amino acid polypeptide, to lysine residues on substrate proteins, thereby regulating their stability (33-35). Although ubiquitination is classically associated with targeting proteins for proteasomal degradation, it also regulates protein activity, localization, and protein-protein interactions in a wide array of biological processes, including DNA damage repair, innate and adaptive immune signaling, cell-cycle progression, autophagy, vesicle trafficking, and cellular stress responses (36-43). The functional versatility of ubiquitination arises from the ability of ubiquitin to

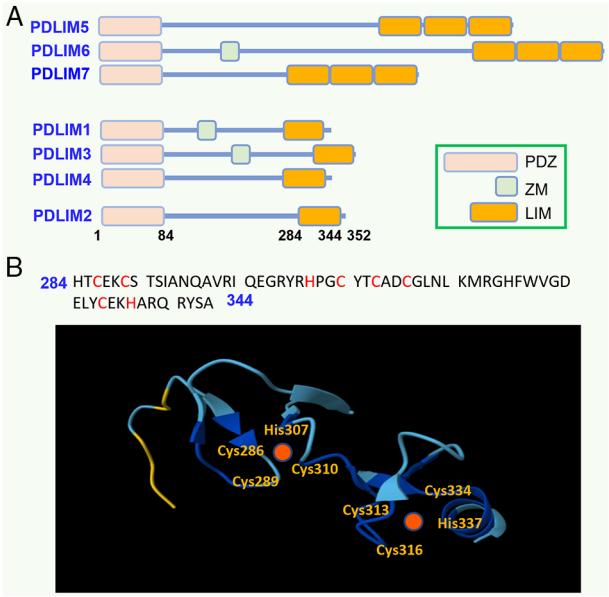

Figure 1. Protein structures of PDLIM family members and the LIM domain of PDLIM2. (A) Protein architecture of the PDLIM proteins. PDLIM proteins contain a PDZ domain at the N-terminus with or without a middle ZM domain and one or three LIM domains at the C-terminus. Of these members, PDLIM2 contains 352 amino acid (aa) residues with a PDZ domain and a LIM domain spanning from aa 1 to 84 and aa 284 to 344, respectively. (B) The LIM domain of PDLIM2. The protein sequence of the PDLIM2 LIM domain is shown at the top of the panel. Cysteine and histidine residues involved in the zinc-ion binding are highlighted in red. The architecture of this LIM domain was predicted using the AlphaFold program (https://alphafoldserver.com/). Orange round dots represent zinc ions. The locations of the cysteine- and histidine-binding residues are shown. PDLIM, PDZ and LIM domain-containing protein; PDZ, postsynaptic density protein 95/discs large/zonula occludens-1 domain; LIM, Lin-11, Isl-1, and Mec-3 domain; ZM, zinc-binding motif; aa, amino acid; LIM2, LIM domain-containing protein 2.

form distinct architectures, such as K48-, K63-, and M1-linked polyubiquitin chains, each encoding specific biochemical signals. Ubiquitination proceeds through a hierarchical enzymatic cascade that involves three core enzyme classes: E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases. E1 enzymes initiate the process by activating ubiquitin in an ATP-dependent manner to form a high-energy thioester bond with ubiquitin. Activated ubiquitin is subsequently transferred to an E2 enzyme, which serves as a carrier. The final and most selective step is mediated by E3 ubiquitin ligases, which simultaneously bind to the E2-ubiquitin complex and the substrate protein to catalyze the transfer of ubiquitin to the target (44-46). E3 ligases are the primary determinants of substrate specificity and exhibit extensive structural and functional diversity, including RING, HECT, and RBR domain-containing proteins (47-50). Besides this classical E1-E2-E3 paradigm, other regulatory layers have been identified. E4 ubiquitin chain-elongation factors facilitate the extension of pre-attached ubiquitin chains, which enables the formation of chain lengths or linkages required for proteasomal recognition (51-53).

The LIM domain of PDLIM2 shares structural similarity with the RING finger domains of numerous E3 ubiquitin ligases. Both domains contain conserved cysteine and histidine residues that coordinate zinc ions, suggesting that LIM domains are a subtype of RING-like structures (Fig. 1B) (28,54). Based on this structural resemblance, early research examined whether PDLIM2 exhibits intrinsic E3 ubiquitin ligase activity. PDLIM2 was shown to undergo self-ubiquitination *in vitro* in the presence of the E1 and E2 enzymes and to promote the proteasome-dependent degradation of STAT transcription factors, which supports its function as an E3 ubiquitin ligase. These results have established PDLIM2 as a negative regulator of STAT-mediated cytokine signaling (31). Subsequent research demonstrated that PDLIM2 also functions as a nuclear E3 ubiquitin ligase that targets NF-κB signaling. Specifically, PDLIM2 negatively regulates NF-κB activity by promoting the polyubiquitination and proteasomal degradation of the p65/RelA subunit. Structure-function analyses revealed that the LIM domain is required for E3 ligase activity, whereas the PDZ domain mediates intranuclear targeting and substrate engagement. By degrading p65/RelA, PDLIM2 serves as a key negative regulator of NF-κB-dependent immune and inflammatory responses (55).

The function of PDLIM2 in promoting the ubiquitination of p65/RelA has been further characterized. Multiple mechanistic models have been established to explain how PDLIM2 promotes RelA degradation (Fig. 2). Other than the monomeric E3 ligase activity identified for p65/RelA (55), mechanisms involving heterodimeric cooperation and participation in multiprotein ubiquitin ligase complexes were identified. In an example of the heterodimeric mechanism, the RING finger protein makorin ring finger protein 2 (MKRN2) was identified as a PDLIM2-interacting partner through yeast two-hybrid screening. MKRN2 binds directly to p65/RelA and promotes its polyubiquitination through its RING domain. PDLIM2 and MKRN2 act cooperatively to enhance RelA ubiquitination and proteasomal degradation. The evidence supports functional synergy between these two E3 ligases (56). In another example, PDLIM7, which is a closely related PDLIM family member, was shown to function as an E3 ubiquitin ligase that suppresses NF-κB-mediated inflammation. PDLIM7 directly ubiquitinates p65/RelA and forms a heterodimer with PDLIM2, thereby enhancing PDLIM2-mediated RelA turnover. Mechanistically, PDLIM7 promotes the K63-linked ubiquitination of PDLIM2, which facilitates recruitment of the autophagy and proteasome cargo adaptor p62/SQSTM1. This interaction promotes delivery of the PDLIM2-RelA complex to the proteasome. The combined knockdown of PDLIM2 and PDLIM7 or p62/SQSTM1 results in higher proinflammatory cytokine production compared with single knockdown, which supports their cooperative regulatory roles (57). In addition to proteasome-mediated degradation, selective autophagic pathways also contribute to PDLIM2-dependent RelA turnover. The planar cell polarity protein Van Gogh-like protein 2 recruits PDLIM2 to catalyze the K63-linked ubiquitination of p65/RelA, which is subsequently recognized by the autophagy cargo receptor nuclear dot protein 52 kDa (58). This mechanism promotes selective autophagic degradation of RelA, which further illustrates the versatility of PDLIM2 in regulating NF-κB signaling through distinct degradative pathways.

Beyond monomeric and heterodimeric mechanisms, PDLIM2 has been shown to function within the Cullin-RING ubiquitin ligase (CRL) complexes. CRLs are multi-subunit E3 ligases consisting of a Cullin scaffold to bridge a substrate-recognition module, such as the F-box proteins, and a RING finger protein that recruits E2 enzymes (59-61).

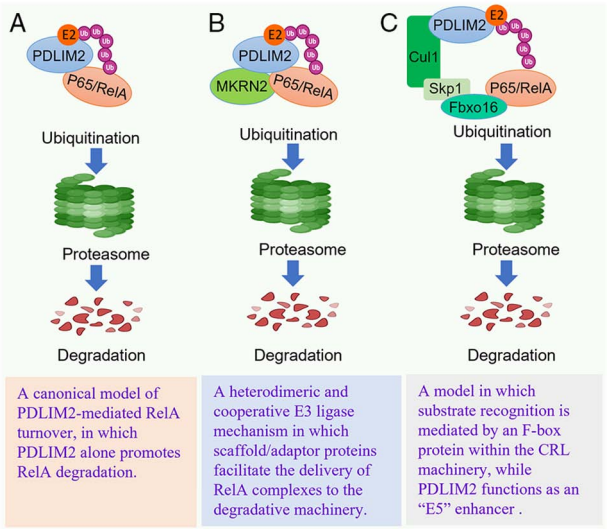

Figure 2. Mechanisms by which PDLIM2 promotes the ubiquitination and degradation of p65/RelA. Schematic illustration of the distinct molecular mechanisms by which PDLIM2 promotes the ubiquitination and degradation of the p65/RelA subunit. (A) Monomeric mechanism. PDLIM2 promotes the polyubiquitination of p65/RelA through its monomeric activity. (B) Heterodimeric mechanism. PDLIM2 forms functional complexes with other ubiquitin ligases, such as MKRN2, to enhance p65/RelA ubiquitination through cooperative E3 activity. (C) CRL complex-dependent mechanism. PDLIM2 acts within CRL complexes to enhance p65/RelA ubiquitination. Through stabilization of the ligase complex, PDLIM2 promotes efficient polyubiquitination and proteasomal degradation of p65/RelA. Taken together, these mechanisms highlight the multifaceted roles of PDLIM2 in regulating NF-κB signaling through proteasomal and adaptor-assisted ubiquitin pathways. PDLIM2, PDZ and LIM domain-containing protein 2; MKRN2, makorin ring finger protein 2; CRL, Cullin-RING ubiquitin ligase.

PDLIM2 facilitates RelA degradation by joining a CRL complex containing Cullin 1 and S-phase kinase-associated protein 1 (Skp1). siRNA screening identified F-box protein 16 (Fbxo16) as the substrate receptor responsible for recognizing p65/RelA. Fbxo16 binds RelA, and along with PDLIM2 in the CRL complex, promotes its polyubiquitination and proteasomal degradation, thereby suppressing NF-κB-dependent transcription (62). In addition to functioning as an E3 ligase, PDLIM2 acts as an E5 ubiquitin ligase enhancer within Skp1-Cullin-F-box (SCF) complexes. In this context, PDLIM2 stabilizes regulator of Cullins 1 (ROC1), the RING finger subunit of SCF ubiquitin ligases, and promotes the nuclear translocation of the SCF β-transducin repeat containing protein (β-TrCP) complex. By facilitating the association of ROC1 with β-TrCP, PDLIM2 enhances the ubiquitination of nuclear p65/RelA, leading to efficient proteasomal degradation. Knockdown of ROC1, Cullin 1, or β-TrCP markedly disrupts PDLIM2-mediated RelA ubiquitination, which confirms that PDLIM2 cooperates with canonical SCF components to promote NF-κB termination (63). Through these adaptor and stabilizing functions, PDLIM2 provides substrate engagement and structural support for the assembly of functional ubiquitin ligase complexes.

Despite the growing number of mechanistic studies, a definitive hierarchy or strict sequential prioritization has not been established among the monomeric, heterodimeric, and CRL-dependent models of PDLIM2-mediated RelA degradation. Instead, these mechanisms may function in a complementary or partially overlapping manner, which likely depends on the availability of interacting cofactors. Tanaka *et al* (55) established the intrinsic ability of PDLIM2 to terminate NF-κB signaling through RelA ubiquitination and nuclear degradation, thereby establishing the monomeric model as the foundational mechanism. Subsequent studies progressively expanded on this model by demonstrating that PDLIM2 cooperates with accessory E3 ligases, such as MKRN2 and PDLIM7, which indicates that heterodimeric mechanisms likely enhance substrate specificity, ubiquitination efficiency, or degradative routing under inflammatory conditions (56,57). Recent evidence suggests that PDLIM2 functions within canonical Cullin-RING ubiquitin ligase machinery, including SCF complexes containing Fbxo16, ROC1, and β-TrCP, in which PDLIM2 acts not only as a substrate adaptor, but also as an E5-like ligase enhancer that stabilizes CRL assembly (62,63). Thus, the monomeric mechanism represents the core intrinsic activity of PDLIM2, whereas heterodimeric and CRL-associated mechanisms represent additional regulatory layers that increase the efficiency, selectivity, and versatility of RelA degradation.

4. Tumor-suppressive and oncogenic roles of PDLIM2 in human cancers

PDLIM2 exhibits functionally divergent roles among various cancer types, acting either as a tumor suppressor or a tumor promoter through distinct patterns of expression, subcellular localization, and downstream signaling regulation (Table I). In breast cancer, it has a bidirectional role. PDLIM2 is frequently epigenetically repressed and functions predominantly as a tumor suppressor by restraining NF-κB signaling and limiting malignant transformation (64). By contrast, in triple-negative breast cancer (TNBC) and advanced metastatic disease, it has been shown to be highly expressed and aberrantly localized to the cytoplasm, where it promotes epithelial-mesenchymal transition (EMT), enhances cell survival, and facilitates invasion and metastasis (65). Similarly, PDLIM2 may have an oncogenic role in prostate and kidney cancers. It was revealed to be highly expressed in human castration-resistant prostate cancer (CRPC)-like cell lines. Its downregulated expression was reported to reduce cell proliferation and viability due to apoptotic cell death. In addition, PDLIM2 inhibition was revealed to significantly reduce tumor growth in a human CRPC xenograft model (66). In metastatic kidney cancer cell lines and cancer tissues, PDLIM2 expression was observed to be upregulated. Inhibition of PDLIM2 reduced cell proliferation and cell migration abilities of metastatic kidney cancer cells. PDLIM2 knockdown significantly reduced tumor growth and metastasis in a human kidney cancer xenograft model (67). Conversely, a tumor-suppressive role for PDLIM2 has been observed in multiple cancers. Reduced PDLIM2 expression occured in colorectal cancer cells and metastatic cancer. PDLIM2 suppressed tumor growth in a colorectal cancer animal model (68,69). PDLIM2 has been shown to be downregulated in hepatocellular carcinoma tissues and cells. Reduced expression of PDLIM2 was demonstrated to be associated with worse prognosis in patients with HCC. Ectopic expression of this protein was shown to inhibit the proliferation, invasion, and EMT of HCC cells and suppress the tumorigenesis and progression of HCC (70,71).

Table I. Dual and cancer-type-specific roles of PDLIM2 in tumorigenesis.

Cancer type	PDLIM2 expression	Functional role	Key downstream mechanism(s)	Experimental model	(Refs.)
Breast cancer	Downregulation (epigenetic repression)	Tumor suppressor	NF-κB signaling, reduced malignant transformation	Cell lines, xenograft model	(64)
Breast cancer (TNBC/ metastatic)	Upregulation, (cytoplasmic retention)	Tumor promoter	EMT induction, β-catenin activity, enhanced invasion/ metastasis	Cell lines, clinical samples, xenograft model	(65)
Prostate cancer (CRPC)	Upregulation	Tumor promoter	MAPK/ERK signaling, promotes proliferation and survival, inhibition induces apoptosis	CRPC cell lines, xenograft model	(66)
Kidney cancer (metastatic)	Upregulation	Tumor promoter	Promotes proliferation and migration, enhances metastasis	Cell lines, xenograft model	(67)
Colorectal cancer	Downregulation (DNA methylation, gene deletion)	Tumor suppressor	NF-κB-related signaling, limits tumor growth	Cell lines, animal model, sequencing	(68,69)
Hepatocellular carcinoma	Downregulation	Tumor suppressor	Inhibits β-catenin signaling, regulates TRIM27/STAT3, suppresses EMT and proliferation	Cell lines, clinical samples, animal model	(70,71)
Ovarian cancer	Downregulation (epigenetic repression)	Tumor suppressor	NOS2/NO signaling, TGF-β/Smad pathway inactivation, TME remodeling	Cell lines, clinical correlation, animal model	(72,73)
Esophageal squamous cell carcinoma	Downregulation	Tumor suppressor	Associated with cell migration and invasion	Clinical data,	(74)
Kaposi sarcoma (KSHV-associated)	Downregulation (DNA methylation)	Tumor suppressor	NF-κB, STAT3 inflammatory signaling	Viral models, cell systems	(75)
Lymphoid malignancies (Hodgkin, ALCL)	Downregulation (genomic alteration, promoter methylation)	Tumor suppressor	NF-κB and AP-1 activations	Cell lines, patient samples	(76)
Lung cancer	Downregulation (gene deletion, epigenetic, transcriptional and post transcriptional regulations)	Tumor suppressor	NF-κB and STAT3 regulation by ubiquitinayion, sharping anti-tumor immunity, mitochondrial metabolic regulation	Cell lines, clinical samples, patient data, animal model	(78-81)

ALCL, anaplastic large cell lymphoma; AP-1, activator protein 1; CRPC, castration-resistant prostate cancer; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; Kaposi sarcoma-associated herpesvirus; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NO, nitric oxide; NOS2, nitric oxide synthase 2; STAT3, signal transducer and activator of transcription 3; TME, tumor microenvironment; TGF-β, transforming growth factor-β; TNBC, triple-negative breast cancer; TRIM27, tripartite motif-containing 27.

PDLIM2 downregulation in ovarian cancer was demonstrated to be associated with malignant behavior of ovarian cancer cells, inflammatory tumor microenvironment remodeling, and poor clinical outcomes (72,73). Tumor-suppressive functions of PDLIM2 have also been reported in esophageal squamous cell carcinoma, Kaposi sarcoma, and lymphoid malignancies, where its loss was associated with enhanced inflammatory signaling, increased proliferation, and resistance to apoptosis (74-76). Analysis of RNA-sequencing data of multiple cancer types in The Cancer Genome Atlas (TCGA) revealed that PDLIM2 is more highly expressed in a few cancer types, but clearly repressed in most tumors (77). Of all cancer types examined to date, lung cancer represents one of the most consistent and well-supported examples of the tumor-suppressive role of PDLIM2 (78-81).

Although these findings show that PDLIM2 can function as either a tumor suppressor or a tumor promoter, the mechanisms underlying these opposing effects remain incompletely understood. Current evidence suggests that the biological outcome of PDLIM2 activity is likely to be context dependent. As a scaffold/adaptor protein involved in ubiquitin-mediated protein turnover and signaling regulation, PDLIM2 may exert distinct functions depending on the repertoire of interacting proteins, available substrates, and dominant signaling pathways present in different cancer types. In lung, colorectal, hepatocellular, Kaposi, and hematological malignancies, PDLIM2 was shown to suppress tumor progression by inhibiting pro-tumorigenic inflammatory signaling pathways, primarily through the proteolytic degradation of nuclear NF-κB and STAT proteins. Consequently, PDLIM2 was demonstrated to reduce oncogenic cellular processes, enhance immune surveillance, and maintain mitochondrial metabolic homeostasis (Table I) (68-71,75-81). By contrast, elevated PDLIM2 expression has been associated with enhanced cell survival, EMT, invasion, and metastatic potential in TNBC and CRPC through regulation of β-catenin- and MAPK/ERK-dependent signaling pathways (65,66). In addition, cancer type-specific subcellular localization and differential interactions with binding partners may redirect PDLIM2 toward distinct signaling pathways, thereby shifting its net biological effect from tumor suppression to tumor promotion. This concept is illustrated by the aberrant cytoplasmic and membrane localization of PDLIM2 in TNBC cells, where it regulates β-catenin activity (65). Such context-dependent behavior is commonly observed among ubiquitin-regulatory proteins and E3 ligase-associated factors, including HECT, UBA and WWE domain-containing E3 ubiquitin protein ligase 1, neural precursor cell expressed developmentally downregulated protein 4-like, speckle-type BTB/POZ protein, tripartite motif containing (TRIM)8, and ubiquitin-specific peptidase 11, whose tumor-suppressive or oncogenic functions are likewise dependent on cancer type and cellular context (82-86). However, the precise molecular mechanisms governing these dual functions remain poorly understood. Further studies are required to identify the molecular determinants that govern the switch between the tumor-suppressive and tumor-promoting functions of PDLIM2.

5. Downregulation of PDLIM2 in lung cancer and its clinical implications

Evidence from large-scale genomic analyses, patient-derived tumor specimens, and experimental models indicates that PDLIM2 is markedly downregulated in lung cancer, which highlights its particular relevance to pulmonary tumorigenesis. Analysis of the EMBL-EBI Expression Atlas revealed low PDLIM2 expression in 212 of 287 human lung cancer cell lines. These results were corroborated by studies of patient-derived tumor samples. At the mRNA level, PDLIM2 expression was reduced to <40% of matched normal lung tissue in 28 of 36 cases (~78%). At the protein level, immunoblotting and immunohistochemical analyses revealed decreased PDLIM2 expression in 51 of 69 lung tumor specimens (~74%) (78). Consistently, analysis of TCGA lung cancer cohort indicated significantly lower PDLIM2 expression in tumor tissues compared with that in normal lung tissues. Using matched normal samples as controls, PDLIM2 mRNA was reduced to <40% of normal expression in over 75% of tumors. When a 50% cut-off threshold was applied, repression was observed in ~94% of the cases, which suggests that PDLIM2 downregulation is a near-universal molecular feature of human lung cancer (79). Notably, PDLIM2 repression occurs across the major histological subtypes of non-small cell lung cancer (NSCLC). An analysis of the ENCORI Pan-Cancer Analysis Platform revealed significantly reduced PDLIM2 expression in lung adenocarcinoma and lung squamous cell carcinoma compared with normal lung tissue. These results were validated experimentally, as NSCLC cell lines consistently exhibited lower PDLIM2 mRNA and protein levels compared with non-transformed lung epithelial cells (80).

In addition to its prevalence, PDLIM2 downregulation has strong clinical and prognostic significance. Survival analyses integrating data from TCGA, the Gene Expression Omnibus (GEO), the European Genome-phenome Archive, and the Kaplan-Meier Plotter have consistently demonstrated that low PDLIM2 expression is associated with significantly worse overall survival, progression-free survival, first progression, and post-progression survival in patients with lung cancer. These associations were independently validated using lung cancer tissue microarrays and previously published gene expression datasets (78,79,81). Furthermore, an analysis of the UALCAN database revealed that PDLIM2 expression was significantly reduced across all clinical stages of lung cancer, from stage I to IV, compared with normal lung tissue. Consistently, analyses of TissueScan lung cancer cDNA arrays revealed the progressive downregulation of PDLIM2 expression from early-stage to advanced-stage tumors (81). These results suggest that PDLIM2 loss contributes to lung tumor initiation and progression rather than representing a late-stage event.

Large-scale public databases, such as TCGA, ENCORI, UALCAN, and GEO, provide valuable resources for evaluating the expression patterns and clinical significance of target molecules; however, findings derived from these databases should be interpreted with appropriate caution. Several limitations must be considered when interpreting these data. Potential sources of bias include differences in patient demographics and clinical characteristics, unequal sample sizes among cohorts, and batch effects associated with different sequencing platforms and experimental protocols. Nevertheless, despite these inherent limitations, analyses across multiple independent databases have consistently demonstrated significant

downregulation of PDLIM2 in lung cancer. Notably, evidence supporting PDLIM2 downregulation is not limited to bioinformatic analyses. *In vivo* genetic research has provided additional support for these observations. Mice with heterozygous or homozygous deletion of Pdlim2 were shown to spontaneously develop tumors, with lung tumors representing the most prevalent tumor type. Notably, Pdlim2 heterozygous mice developed tumors at frequencies comparable to those observed in homozygous knockout animals, indicating that PDLIM2 functions as a haploinsufficient tumor suppressor (79). The consistency of findings across multiple independent datasets, together with experimental validation in patient-derived tumor specimens, lung cancer cell lines, and animal models, strongly supports the conclusion that PDLIM2 downregulation is a common, biologically relevant, and clinically significant feature of lung cancer.

6. Mechanisms underlying PDLIM2 suppression in lung cancer

The frequent and profound downregulation of PDLIM2 observed in lung cancer raises important questions regarding the molecular mechanisms responsible for its suppression. Accumulating evidence indicates that PDLIM2 silencing in lung cancer is mediated by a combination of genetic, epigenetic, transcriptional, and post-transcriptional mechanisms (Fig. 3). At the genetic level, loss of heterozygosity at chromosome 8p21-p21.3, the genomic locus harboring the PDLIM2 gene, represents a key mechanism that contributes to reduced PDLIM2 expression. This chromosomal region is frequently deleted in lung cancer and is recognized as a hotspot for tumor suppressor gene loss (30,87-94). Copy number variation analyses from TCGA cohorts revealed that partial or complete deletion of the PDLIM2 locus occurs in a substantial proportion of lung tumors and is strongly associated with decreased PDLIM2 mRNA expression. Notably, because PDLIM2 functions as a haploinsufficient tumor suppressor, even monoallelic loss is sufficient to markedly impair its tumor-suppressive activity, thereby rendering lung epithelial cells more susceptible to oncogenic transformation (79). Epigenetic silencing represents another major mechanism underlying PDLIM2 repression in lung cancer as well as other cancers. Aberrant DNA methylation of CpG islands within the PDLIM2 promoter region has been consistently detected in lung tumor tissues and lung cancer cell lines. Promoter hypermethylation is associated with transcriptional silencing and reduced PDLIM2 mRNA expression. Moreover, repressive histone modifications, including increased trimethylation of histone H3 at lysine 27 (H3K27me3) and reduced histone acetylation, maintain a closed chromatin configuration at the PDLIM2 locus, thereby reinforcing transcriptional repression (64,68,72,78).

Chronic oxidative stress is a hallmark of lung carcinogenesis, particularly in the context of exposure to environmental carcinogens, such as tobacco smoke and persistent inflammation (95-98). PDLIM2 expression in lung epithelial cells and alveolar macrophages is downregulated by the reactive oxygen species (ROS)-activated transcriptional repressor BTB and CNC homology 1 (BACH1). In alveolar macrophages, increased ROS levels activate BACH1, which subsequently binds to the PDLIM2 promoter and suppresses its transcription. Chromatin immunoprecipitation assays have revealed BACH1 occupancy at a defined binding site upstream of the PDLIM2 transcription start site under oxidative stress conditions. BACH1 recruitment was shown to be inversely correlated with RNA polymerase II engagement at the PDLIM2 promoter, which supports a direct role for oxidative stress-induced BACH1 in transcriptional repression. Moreover, pharmacological inhibition of ROS was demonstrated to attenuate PDLIM2 suppression in macrophages exposed to tumor cell-derived stress, which further supports a mechanistic link between oxidative signaling and transcriptional downregulation of PDLIM2 (99).

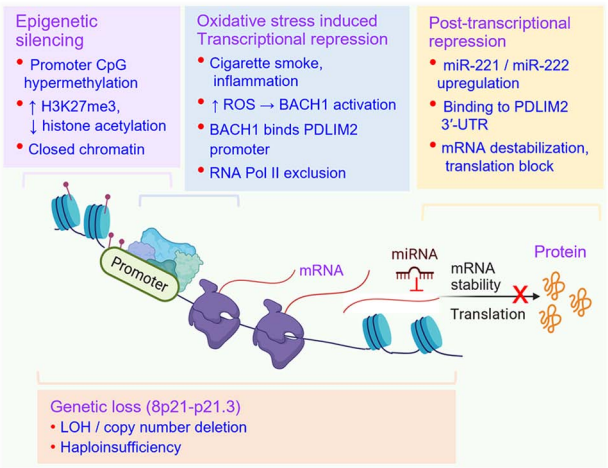

Figure 3. Molecular mechanisms underlying PDLIM2 suppression in lung cancer. PDLIM2 is downregulated in lung cancer through coordinated genetic, epigenetic, transcriptional, and post-transcriptional mechanisms. These mechanisms may converge to suppress PDLIM2 expression in lung cancer. PDLIM2, PDZ and LIM domain-containing protein 2.

Post-transcriptional mechanisms, particularly those mediated by non-coding RNAs, may also contribute to PDLIM2 downregulation in lung cancer. The 3'-untranslated region (3'-UTR) of PDLIM2 contains predicted binding sites for miR-221 and miR-222. In colorectal cancer cells, these microRNAs were shown to directly bind to the PDLIM2 3'-UTR, leading to reduced mRNA stability and altered RelA ubiquitination (100). Although the full repertoire of PDLIM2-targeting microRNAs in lung cancer remains to be defined, miR-221 and miR-222 are highly expressed in lung cancer (101-103). These results suggest that microRNA-mediated repression may constitute an additional regulatory layer that fine-tunes PDLIM2 expression and function in lung cancer cells.

Although these mechanisms contribute to PDLIM2 downregulation, current studies have not defined the relative contribution or hierarchical importance of each pathway during lung tumorigenesis. These regulatory mechanisms operate at distinct levels of gene expression control. Additional studies integrating genomic, epigenomic, transcriptomic, and functional analyses will be required to clarify how these distinct regulatory layers interact and which mechanisms predominate during different stages or subtypes of lung cancer.

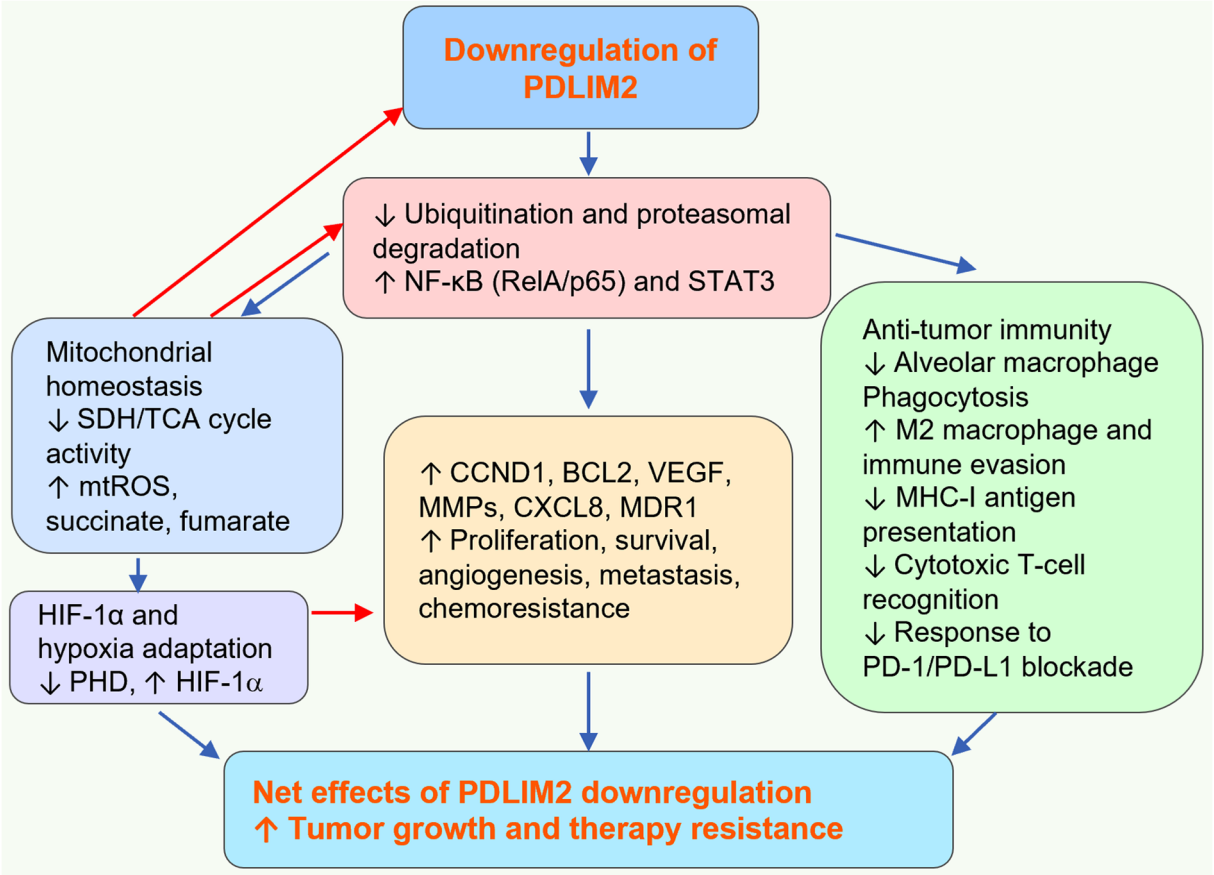

Figure 4. Proposed model illustrating how PDLIM2 downregulation promotes lung tumor progression through interconnected ubiquitination-, immunity-, mitochondria metabolic-, and hypoxia-associated feed-forward signaling networks. Loss of PDLIM2 disrupts the ubiquitination-mediated degradation of NF-κB and STAT3, resulting in persistent inflammatory and pro-survival signaling that induces the expression of CCND1, BCL2, VEGF, MMPs, CXCL8, and MDR1, thereby promoting proliferation, angiogenesis, metastasis, and chemoresistance. PDLIM2 deficiency also suppresses antitumor immunity by reducing macrophage phagocytosis, impairing MHC-I antigen presentation and cytotoxic T-cell recognition, and decreasing the response to PD-1/PD-L1 blockade. In parallel, disruption of mitochondrial homeostasis through reduced SDH/TCA cycle activity increases mtROS, succinate, and fumarate accumulation, leading to the stabilization of HIF-1α (blue arrow lines). Activated HIF-1α further enhances glycolytic metabolism, oxidative stress, inflammatory signaling, and NF-κB/STAT3 activation. Increased ROS production further suppresses PDLIM2 expression through BACH1 (red arrow lines). These events establish a self-reinforcing feed-forward loop that drives tumor growth, metabolic adaptation, therapeutic resistance, and malignant progression in lung cancer. PDLIM2, PDZ and LIM domain-containing protein 2; CCND1, cyclin D1; VEGF, vascular endothelial growth factor; CXCL8, C-X-C motif chemokine ligand 8; MDR1, multidrug resistance protein 1; MHC-I, major histocompatibility complex class I; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SDH, succinate dehydrogenase; TCA, tricarboxylic acid cycle; mtROS, mitochondrial reactive oxygen species; HIF-1α, hypoxia-inducible factor 1 alpha; BACH1, BTB and CNC homology 1.

7. Mechanisms of PDLIM2-mediated tumor suppression in lung cancer

PDLIM2 exerts multifaceted tumor-suppressive functions in lung cancer by regulating key ubiquitination, immunological, and metabolic processes that collectively restrain malignant progression (Fig. 4). Among its well-characterized tumor-suppressive activities, PDLIM2 negatively regulates the transcription factors NF-κB and STAT3 through ubiquitination and proteasomal degradation (31,32,54-58). NF-κB and STAT3 function as oncogenic hubs in cancers. They drive malignancy and contribute directly to therapeutic resistance. These pathways are activated by inflammatory cytokines, including TNF-α and IL-1β for NF-κB and IL-6 family cytokines for STAT3, as well as by oncogenic kinases in lung epithelial and stromal cells (104-108). Following activation, NF-κB and STAT3 translocate to the nucleus and induce transcriptional programs that promote cell-cycle progression via cyclin D1 (CCND1), inhibit apoptosis by upregulating anti-apoptotic genes, such as BCL2 and BCL2 like 1 (BCL2L1), and support angiogenic and metastatic processes mediated by VEGF, matrix metalloproteinases, and C-X-C chemokine ligand 8 (CXCL8). Constitutive NF-κB activation in lung tumors is sustained by chronic inflammation, tobacco-associated injury, and oncogenic KRAS mutations, whereas persistent STAT3 activation is frequently maintained through IL-6/Janus kinase (JAK) signaling loops. NF-κB and STAT3 further engage in cooperative crosstalk, forming a self-sustaining oncogenic circuit that amplifies inflammatory and survival signaling (109-111). Loss of PDLIM2 disrupts the suppression of these pathways, leading to sustained nuclear accumulation of RelA/p65 and STAT3, enhanced expression of growth and survival genes, and increased tumorigenesis. In preclinical models, lung epithelial-specific deletion of RelA or STAT3 was shown to attenuate tumor development driven by PDLIM2 loss, which indicates that unchecked NF-κB/STAT3 signaling is a principal mediator of the oncogenic consequences of PDLIM2 repression. PDLIM2

deficiency was also demonstrated to promote chemoresistance through RelA-dependent upregulation of multidrug resistance protein 1 (MDR1), a mediator of multidrug resistance, thus enhancing drug efflux and suppressing apoptosis in response to cytotoxic drug treatment. Consistently, enforced PDLIM2 expression was revealed to enhance the sensitivity of lung cancer cells to chemotherapeutic agents, such as carboplatin and paclitaxel (78,79). In addition to PDLIM2, several E3 ubiquitin ligases that regulate NF-κB and/or STAT3 pathways have also been identified as tumor suppressors. Among these, suppressor of cytokine signaling (SOCS)1 and SOCS3 are well-characterized negative regulators of inflammatory and oncogenic signaling. Through their SOCS-box-dependent E3 ubiquitin ligase activity, SOCS proteins promote ubiquitination-mediated suppression of JAK/STAT signaling while also restraining NF-κB activation. Loss or epigenetic silencing of SOCS1 and SOCS3 has been reported in multiple malignancies and is associated with enhanced proliferation, survival, and tumor progression (112-117). Additionally, the E3 ligases copper metabolism domain containing 1, STIP1 homology and U-box containing protein 1, TRIM7, TRIM21, TRIM22, and Kelch-like ECH-associated protein 1 (KEAP1) were shown to exhibit tumor-suppressive functions through inhibition of NF-κB- and/or STAT3-dependent oncogenic signaling networks (118-126). These findings support the concept that ubiquitination-dependent negative regulation of NF-κB and STAT3 signaling by tumor-suppressive E3 ligases represents an important mechanism for maintaining cellular homeostasis and preventing malignant transformation.

PDLIM2 also plays an important role in shaping antitumor immunity by regulating the adaptive and innate immune responses within the lung tumor microenvironment. In lung cancer cells, suppression of NF-κB and STAT3 signaling by PDLIM2 was revealed to enhance the expression of MHC class I molecules and antigen presentation-related genes, thereby improving tumor recognition by cytotoxic T lymphocytes and sensitizing tumors to immune checkpoint blockade. Conversely, STAT3 activation downstream of PDLIM2 loss was reported to suppress MHC class I expression, promote immune evasion, and decrease the response to anti-PD-1 and anti-PD-L1 therapies. Consistent with these results, epigenetic restoration or ectopic expression of PDLIM2 was demonstrated to synergize with PD-1 blockade to elicit robust antitumor immune responses and tumor regression in preclinical models (78,99,127). Beyond its tumor cell-intrinsic functions, PDLIM2 functions as an immune checkpoint in alveolar macrophages and monocytes, which are frontline sentinels that maintain immune and tissue homeostasis in the lung. PDLIM2 downregulation in alveolar macrophages was shown to result in constitutive STAT3 activation, reduced phagocytic capacity, and polarization toward a protumorigenic phenotype that suppresses cytotoxic T-cell activity and facilitates immune evasion. This process was accompanied by enhanced recruitment and differentiation of monocytes into tumor-associated macrophages, which further repressed innate and adaptive antitumor immunity. Mechanistically, PDLIM2 expression in myeloid cells was demonstrated to be suppressed by ROS-activated BACH1. This pathway may be amplified by high levels of tumor-derived ROS, thereby coordinately repressing PDLIM2 in tumor cells and tumor-associated immune cells. Restoration of PDLIM2 was reported to reverse these immunosuppressive programs, enhance antigen presentation, restore immune surveillance, and improve the response to immune checkpoint blockade (99).

In addition to its established role in terminating oncogenic transcription factor signaling and immunological regulation, PDLIM2 may regulate mitochondrial metabolism and cellular adaptation to hypoxic stress in lung cancer (81). Metabolic reprogramming is a hallmark of cancer, and lung tumors display marked alterations in mitochondrial metabolic function, including dysregulated oxidative phosphorylation, rewiring of the tricarboxylic acid (TCA) cycle, and increased production of ROS (128-131). These metabolic changes not only support the biosynthetic and energetic demands of rapidly proliferating tumor cells, but also shape the tumor microenvironment by promoting inflammation, angiogenesis, and immune evasion. Thus, mitochondria function as signaling hubs that integrate metabolic status with oncogenic and inflammatory pathways, and disruption of mitochondrial homeostasis is a driver of lung cancer initiation and progression (132-135). PDLIM2 loss in lung cancer cells was shown to disrupt mitochondrial metabolism by selectively suppressing the expression of genes involved in the TCA cycle, with a particularly strong effect on the succinate dehydrogenase (SDH) complex (81). SDH occupies a unique position at the interface between the TCA cycle and the mitochondrial electron transport chain (complex II). Its integrity is essential for maintaining efficient oxidative metabolism and redox balance. Mutations in SDH complex genes have been linked to various cancer types (136-139). PDLIM2 downregulation was revealed to inhibit SDH expression at the mRNA and protein level, resulting in defective mitochondrial respiration, reduced oxygen consumption, altered mitochondrial dynamics, and increased mitochondrial fission. These abnormalities were demonstrated to be accompanied by the accumulation of mitochondrial ROS (mtROS) and the accumulation of oncometabolites, such as succinate, fumarate, and 2-hydroxyglutarate, reflecting a blockade of normal TCA cycle flux. Notably, the suppression of SDH gene expression in PDLIM2-deficient cells was shown to be driven, in part, by increased NF-κB activity, which is consistent with previous studies showing that inflammatory signaling can epigenetically repress SDH subunits through NF-κB-dependent mechanisms (81,140-142). The accumulation of succinate and mtROS in PDLIM2-deficient lung cancer cells was reported to also affect hypoxia signaling. Succinate functions as a prototypical oncometabolite that inhibits prolyl hydroxylase domain (PHD) enzymes, thereby preventing the hydroxylation and proteasomal degradation of hypoxia-inducible factor-1α (HIF-1α). Elevated ROS production further enhances HIF-1α stability and transcriptional activity by inhibiting PHD expression and promoting HIF-1α gene transcription. As a result, the loss of PDLIM2 leads to robust stabilization and activation of HIF-1α, even under non-hypoxic conditions. Consistently, an analysis of TCGA datasets and human lung cancer specimens revealed increased HIF-1α expression across all stages of disease and a strong inverse correlation between PDLIM2 and HIF-1α expression (81).

Activated HIF-1α has been shown to induce the expression of genes that promote inflammation, angiogenesis, and glycolysis (143-147). These findings suggest a model in which

downregulation of PDLIM2 promotes lung tumor progression by establishing an interconnected feed-forward network (Fig. 4). Loss of PDLIM2 results in the persistent activation of NF-κB and STAT3, which not only drives inflammatory and pro-survival transcriptional programs, but also rewires antitumor immunity and mitochondrial function. Mitochondrial dysfunction subsequently enhances the accumulation of mtROS and oncometabolites, such as succinate, leading to the stabilization and activation of HIF-1α. In turn, HIF-1α further amplifies glycolytic metabolism, inflammatory cytokine production, angiogenesis, and oxidative stress, which reinforces NF-κB and STAT3 signaling through cytokine-mediated mechanisms. Increased ROS production may suppress PDLIM2 expression through activation of the BACH1 pathway, further sustaining the suppression of PDLIM2 and its function in antitumor immunity. Thus, PDLIM2 functions as a molecular brake that restrains reciprocal crosstalk among inflammatory signaling, mitochondrial dysfunction, oxidative stress, and hypoxia adaptation. Disruption of this regulatory axis establishes a self-reinforcing feed-forward loop that drives tumor growth, immune evasion, metabolic adaptation, therapeutic resistance, and malignant progression in lung cancer.

In addition to the PDLIM2-regulated SDH pathway, several other mitochondrial metabolic pathways play critical roles in regulating tumor growth, metastasis, and therapeutic resistance. These include pathways involving isocitrate dehydrogenase (IDH1/IDH2), glutaminolysis, fatty acid oxidation (FAO), glycolytic flux and anabolic metabolism. Mutant IDH enzymes generate the oncometabolite R-2-hydroxyglutarate, which competitively inhibits α-ketoglutarate-dependent dioxygenases, leading to widespread DNA and histone hypermethylation, impaired cellular differentiation, and tumorigenesis in gliomas and acute myeloid leukemia (148). In numerous cancers, tumor cells become highly dependent on the mitochondrial enzyme glutaminase, which converts glutamine to glutamate for entry into the TCA cycle, thereby replenishing carbon and nitrogen pools required for rapid macromolecular biosynthesis and tumor survival (149). Likewise, highly active FAO provides tumor cells with ATP and NADPH, enabling them to maintain energy homeostasis, counteract oxidative stress, and survive during chemotherapy or nutrient deprivation (150). In addition, activation of the oncogenic PI3K/AKT/mTOR pathway promotes glycolytic flux and anabolic metabolism, whereas dysregulation of the KEAP1/nuclear facotr erythroid 2-related factor 2 axis facilitates antioxidant adaptation and metabolic remodeling in cancer (151,152). Furthermore, E3 ubiquitin ligases such as Parkin, mitochondrial E3 ubiquitin protein ligase 1, F-box and WD repeat domain containing 7, and von-Hippel-Lindau tumor suppressor have been shown to suppress malignant progression through regulation of mitochondrial quality control, oxidative phosphorylation, metabolic homeostasis, ROS balance, and hypoxia adaptation (153-160). These observations indicate that multiple metabolic pathways converge on common biological processes that collectively contribute to tumor progression. Nevertheless, compared with these metabolic regulators, PDLIM2 appears distinctive because it occupies a strategic position at the intersection of ubiquitin-mediated inflammatory signaling, antitumor immunity, and mitochondrial metabolism through the coordinated regulation of NF-κB, STAT3, SDH expression, ROS production, and HIF-1α activation. Consequently, PDLIM2 may function as an integrative regulator that links inflammatory signaling with metabolic adaptation during lung cancer progression. Further studies are required to determine the relative contribution of the PDLIM2-SDH axis compared with other mitochondrial metabolic pathways in lung cancer.

8. Future directions and challenges in PDLIM2-targeted therapy

PDLIM2 represents an attractive therapeutic target and biomarker for lung cancer management. From a translational perspective, restoration of PDLIM2 function may constitute a promising therapeutic strategy. However, the druggability of PDLIM2 remains a significant challenge. Unlike kinases or cell-surface receptors that possess well-defined catalytic or ligand-binding domains amenable to pharmacological intervention, PDLIM2 primarily functions as a scaffold/adaptor protein and regulator of ubiquitin-mediated protein turnover. Consequently, direct targeting of PDLIM2 by conventional small-molecule agonists may be difficult. Current therapeutic strategies are therefore more likely to focus on restoring PDLIM2 expression, reversing upstream silencing mechanisms, enhancing its functional activity, or targeting downstream pathways dysregulated by PDLIM2 deficiency.

Epigenetic repression is considered a major mechanism underlying PDLIM2 silencing in multiple cancers, including lung, breast, ovarian, and colon cancers (64,68,72,78). DNA hypermethylation and chromatin-associated repression suppress endogenous PDLIM2 expression, suggesting that pharmacological reversal using DNA methyltransferase inhibitors (DNMTis), histone deacetylase inhibitors (HDACis), or next-generation epigenetic modulators may restore PDLIM2 expression and its tumor-suppressive activity. In fact, research using agents such as 5-aza-2'-deoxycytidine have demonstrated reactivation of PDLIM2 expression and suppression of the malignant phenotype in preclinical models (78). Nevertheless, the clinical application of epigenetic therapies faces important limitations. DNMTis and HDACis exert broad genome-wide effects and may alter the expression of numerous genes unrelated to PDLIM2, potentially resulting in off-target biological effects, toxicity, and unpredictable transcriptional responses. Furthermore, the extent of PDLIM2 reactivation may vary among tumors owing to differences in epigenetic landscapes and the coexistence of additional regulatory mechanisms. Therefore, although epigenetic therapies represent a promising approach to restore PDLIM2 expression, their specificity and long-term therapeutic benefit require further investigation.

Nanotechnology-based gene-delivery systems have emerged as an innovative therapeutic approach. Systemic administration of PDLIM2 expression plasmids encapsulated within nanoparticles (nanoPDLIM2) has demonstrated antitumor efficacy, high tumor specificity, and minimal systemic toxicity in refractory lung cancer models. Notably, nanoPDLIM2 not only suppresses tumor growth directly, but also enhances the response to conventional treatments. Preclinical studies have shown that restoration of PDLIM2 sensitizes

tumors to chemotherapy and prevents the activation of NF-κB signaling, which contributes to acquired drug resistance. Furthermore, PDLIM2 restoration was demonstrated to markedly enhance responsiveness to immune checkpoint blockade. Combination therapy involving PDLIM2 reactivation and anti-PD-1/PD-L1 treatment was revealed to convert immunologically 'cold' tumors into 'hot' tumors, characterized by increased T-cell infiltration and improved antitumor immune activity, thus markedly improving therapeutic efficacy (79,127). Despite these encouraging findings, several translational challenges remain. Efficient and selective delivery of PDLIM2 expression constructs to tumor tissues while minimizing uptake by normal organs remains difficult. Nanoparticle- and gene-based delivery systems may encounter barriers related to biodistribution, tumor penetration, intracellular trafficking, transgene expression efficiency, immune rejection, and the durability of therapeutic expression. Regulatory approval and long-term safety evaluation also represent important obstacles that must be addressed before PDLIM2 restoration strategies can be translated into clinical practice.

Targeting downstream pathways associated with PDLIM2 deficiency may provide additional therapeutic opportunities. PDLIM2 loss promotes mitochondrial dysfunction, excessive ROS production, and the accumulation of oncometabolites that activate HIF-1α signaling, collectively driving metabolic adaptation and tumor progression under hypoxic conditions. Consequently, HIF-1α inhibitors represent an indirect strategy to counteract the oncogenic consequences of PDLIM2 downregulation. The HIF-1α inhibitor PX-478 can suppress tumor progression associated with PDLIM2 deficiency, suggesting that targeting hypoxia-related pathways may complement PDLIM2 restoration therapies (81). Other HIF-1α inhibitors, including LBH589, SCH6636, 2ME2, and vorinostat, have been evaluated in clinical studies for cancer therapy (161,162). Nevertheless, the clinical translation of HIF-1α-targeted therapies remains challenging due to the pleiotropic physiological functions of HIF-1α, the complexity of hypoxia-regulated signaling networks, and the potential emergence of compensatory resistance mechanisms. Therefore, improved biomarkers and more selective therapeutic approaches will be required to maximize their clinical benefit in PDLIM2-deficient cancers.

PDLIM2 may also serve as a valuable biomarker for lung cancer diagnosis, prognosis, and therapeutic stratification as its downregulation has been observed across multiple histological subtypes and clinical stages of lung cancer, and reduced PDLIM2 expression is strongly associated with poor clinical outcomes. Furthermore, because PDLIM2 deficiency is linked to increased HIF-1α signaling and altered responsiveness to chemotherapy and immune checkpoint blockade, assessment of PDLIM2 expression may help identify patients who are most likely to benefit from specific targeted therapies or combination treatment strategies. Nevertheless, large-scale multicenter studies incorporating standardized analytical methodologies, comprehensive clinical annotation, and integrated multi-omics approaches will be required to establish the diagnostic, prognostic, and predictive value of PDLIM2 in lung cancer. Overall, continued elucidation of the molecular mechanisms regulating PDLIM2 expression and function, together with advances in biomarker development, gene-delivery technologies, and targeted therapeutic approaches, may ultimately facilitate the translation of PDLIM2-based strategies into clinical practice for lung cancer management.

9. Conclusion

PDLIM2 is a central regulator of lung cancer suppression through its coordinated control of the ubiquitination-dependent degradation of oncogenic transcription factors, antitumor immunity, and mitochondrial metabolism. The loss of PDLIM2 contributes to persistent activation of NF-κB and STAT3 signaling, immune evasion, metabolic reprogramming, ROS accumulation, and HIF-1α activation, which promotes tumor progression. The frequent and early downregulation of PDLIM2 in lung cancer, together with its strong association with poor clinical outcomes, highlights its importance as a biomarker and therapeutic target.

The restoration of PDLIM2 through epigenetic reactivation, nanoparticle-mediated delivery, or combination regimens with chemotherapy and immune checkpoint blockade has shown promise in preclinical studies. Moreover, targeting downstream metabolic, oxidative, and hypoxia-related pathways associated with PDLIM2 deficiency represents a complementary therapeutic approach. Nevertheless, significant challenges remain, including the complexity of PDLIM2 regulatory mechanisms, tumor heterogeneity, dataset limitations, and the distinct biological functions of PDLIM2 across different cancer types.

Overall, continued studies into the molecular regulation and functions of PDLIM2 will provide insight into lung cancer pathogenesis and therapeutic resistance. A deeper understanding of PDLIM2-centered signaling networks will facilitate the development of novel therapeutic strategies that improve clinical outcomes for lung cancer patients.

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Availability of data and materials

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Authors' contributions

THC, JHG, and CYL conceived and supervised the study. JXY, JCT, and HJW contributed equally to literature collection, review, interpretation, and writing the first draft of the manuscript and preparing the figures. THC, JHG, and CYL finalized the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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