

The role of Na,K-ATPase in lung diseases (Review)

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Abstract. Na,K-ATPase, commonly referred to as the sodium pump, is known for its essential function as an ion pump, which is key for transporting Na⁺ and K⁺ across plasma cell membranes. Additionally, Na,K-ATPase has multiple biological functions, independent of ion pumping, which are involved in regulating cell proliferation, apoptosis, differentiation and other processes associated with the development and progression of various diseases; particularly cancer, cardiovascular diseases, nervous system diseases, kidney diseases and lung diseases. As a potential therapeutic target, Na,K-ATPase may represent a novel strategy for treating these diseases in the future. The present review aims to summarize the role of Na,K-ATPase in lung diseases.

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1. Introduction

The Na,K-ATPase was first described by Skou (1) in 1957. It is classified as a member of the P-type ATPase class, in this class, the enzyme is phosphorylated by ATP in the presence of Mg²⁺ and Na⁺ and dephosphorylated in the presence of K⁺ (2,3). As a heteromeric transmembrane protein, Na,K-ATPase consists of three subunits: The α subunit, β subunit and γ subunit (FXD2). The α subunit, which serves as the catalytic unit, has four isoforms (α 1, α 2, α 3 and α 4). The β subunit, a highly glycosylated transmembrane protein, has three isoforms (β 1, β 2 and β 3). As a regulatory subunit, it carries out multiple functions, including enhancing the translation efficiency and stability of the α subunit, assisting in the folding of the α subunit and facilitating the transport of the α subunit from the endoplasmic reticulum to the plasma membrane. Additionally, it regulates the affinity of Na⁺ and K⁺ for the enzyme and acts as a cell adhesion molecule (4-8). The γ subunit, belongs to the FXD family, which has seven isoforms (FXD1-7), is present in different tissues, such as kidney tissues, cardiac tissues and skeletal muscle, carries out a regulatory role by modulating the affinity of Na⁺ and K⁺ for the enzyme, influencing pump kinetics and transport properties and stabilizing Na,K-ATPase (9-12).

The Na,K-ATPase functions primarily as an ion pump, importing two K⁺ ions and exporting three Na⁺ ions at the expense of one ATP molecule in eukaryotic cells. This process contributes to maintaining high intracellular K⁺ levels, preserving the osmotic balance, providing energy for active transport and regulating the membrane potential (2,13-15). In addition, Na,K-ATPase acts as a ligand for cardiac glycosides and regulates multiple signaling pathways, including non-receptor tyrosine kinase gene (Src), PI3K, caveolin-1, protein phosphatase 2, EGFR and MAPK, thereby modulating cell proliferation, motility and apoptosis (Fig. 1) (16-20).

Numerous studies have indicated that Na,K-ATPase is involved in various diseases (21-23). The present review discusses the relationship between Na,K-ATPase and lung diseases.

2. Lung cancer

Lung cancer is one of the most frequently diagnosed types of cancer and a leading cause of cancer-related mortalities worldwide with ~2.2 million new cases and 1.76 million

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mortalities per year (24). Patients have varying 5-year survival rates from 4 to 17% depending on stage and regional differences (25). There are two main types of lung cancer: Non-small and small cell lung carcinomas (SLCs). The most common is non-small cell lung cancer (NSCLC), which represents >80% of cases. NSCLC is commonly subdivided into three subtypes: Squamous cell carcinoma, large cell carcinoma and adenocarcinoma. Adenocarcinoma has become the most common subtype of lung cancer globally in 2022, with sex differences diminishing (26). NSCLC is a heterogeneous cancer with cellular and genetic diversity. Clinical treatment has been based on molecular genotyping in NSCLC tumors, such as in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase, *ros* proto-oncogene 1, receptor tyrosine kinase, rearranged during transfection and mesenchymal-epithelial transition factor (27).

Although new drugs for cancer are continuously being developed, the development of cancer therapies remains a considerable challenge due to chemoresistance. Na,K-ATPase has been studied as a target for cancer treatment, with cardiac steroids (CSs) binding to Na,K-ATPase and triggering several cell signaling pathways that result in anticancer effects by inhibiting proliferation and promoting autophagy or apoptosis (28-31). These effects vary depending on the cell type as well as the type and concentration of CS, and different cells frequently express different pump isoforms. At high concentrations, CSs were revealed to exhibit proapoptotic effects via Na,K-ATPase inhibition, which is not directly dependent on other intracellular cancer-specific pathways and kills cells by disrupting ionic homeostasis. However, at low concentrations, CSs are not selective for cancer cells and activate the Src-EGFR-Ras-Raf-kinase pathway through Na,K-ATPase, inhibiting the proliferation and survival of tumor cells (30,31). Src is a non-receptor tyrosine kinase that tightly associates with the Na,K-ATPase transmembrane complex in its activated form. Src activation contributes to MEK1/2 and ERK1/2 activation upon CG treatment and largely contributes to CG toxicity. Considering the well-described effects of CGs on endosomal trafficking, it is tempting to hypothesize that any activation of endosomal cycling by CGs modulates Src recruitment, signalosome assembly and subsequent cell survival mechanisms (32).

Smoking is a key risk factor for lung cancer and is usually associated with SCLC and squamous-cell carcinoma. Smoking impairs Na,K-ATPase activity through reactive oxygen species (ROS), although it does not notably alter protein expression of ROS. In patients with lung cancer who smoke, reduced expression levels of the Na,K-ATPase β 1 subunit are associated with poor survival (33). Furthermore, studies have reported the downregulation of the Na,K-ATPase β 1 subunit in other tumors, such as renal cell carcinoma and bladder cancer (34-36). The Na,K-ATPase β 1 subunit serves as a tumor suppressor, maintaining epithelial polarity, enhancing cell-cell aggregation, reducing cell motility and invasiveness, and inhibiting cancer cell proliferation *in vivo* (19,37-42).

Overactivation of the α 1-Na,K-ATPase/Src signalosome by oxidative stress during pathological states results in the phosphorylation of the Src kinase (pSrc), which activates the PI3K-Akt-mTOR pathway downstream. Activation of the PI3K-Akt pathway promotes the expression of the

anti-apoptotic protein survivin, driving abnormal cell growth, survival, proliferation, angiogenesis and metabolism. Signalosome normalization using an inhibitory peptide resets apoptotic activity in malignant cells, with a significant decrease in tumor burden *in vivo* (43). Furthermore, a reduction in Na,K-ATPase α 1 subunit expression can impair the proliferation and migration of A549 cells *in vitro* (44). Collectively, α 1-NKA may serve as a novel target for clinical therapy. Additionally, FXYP3, antigen-8 of mammary tumor, is known to exert protection of the β 1 subunit against glutathionylation, an oxidative modification that destabilizes the α - β heterodimer and inhibits Na,K-ATPase activity. The cellular expression of FXYP proteins that have the specific Cys residue is protective against oxidative stress-induced β 1 subunit glutathionylation and Na^+/K^+ -ATPase inhibition, while mutating the residue eliminates the protective effect of the expressed protein (45). FXYP3 proteins confer chemotherapy resistance when they are overexpressed in cancer cells. Chemotherapeutic compounds, such as doxorubicin, can induce oxidative stress and a study revealed that the suppression of FXYP3 with siRNA in pancreatic and breast cancer cells, which express FXYP3, increased doxorubicin-induced cytotoxicity (46). The point mutation in the cysteine residue of FXYP3 increases sensitivity to oxidative stress induced by the chemotherapeutic doxorubicin (47).

However, reduced expression of FXYP3 was reported in lung cancer cells, in which its inactivation was identified as a key mediator in lung cancer progression (48). In another study, the increasing levels of doublecortin-like kinase 1 in lung tumors, promotes the proliferation and metastasis of lung cancer cells through the downregulation of FXYP3 (49). FXYP3 regulates the activity of the Na,K-ATPase pump and may carry out a role in regulating cell proliferation, migration and invasion, key processes in cancer growth and metastasis (50).

The PI3K-Akt pathway has been reported to be constitutively activated in several types of malignancy (51). Factors that activate this pathway include loss of the tumor suppressor PTEN, activation/amplification of PI3K-Akt, activation of growth factor receptors including EGFR and exposure to carcinogenic agents (52). Digoxigenin, the aglycon of digoxin, binds to PI3K, could effectively treat breast cancer (53). Bufalin, an Na,K-ATPase ligand, exerts anti-cancer effects by inhibiting the proliferation of A549 cells and induces their apoptosis by suppressing the PI3K/Akt pathway and increasing BAX expression (54). Ouabain, another Na,K-ATPase ligand, promotes apoptosis in H292 cells by inducing the expression and activation of the apoptotic protein caspase 3 and degrading the anti-apoptotic protein Mcl-1 (55). Moreover, Na,K-ATPase α 1/ouabain signaling facilitates the fine control of PD-L1 expression and dampens tumoral immunity (56). Perillyl alcohol, an Na,K-ATPase inhibitor, reduces the growth of NSCLC cells by inducing G2/M arrest, causing DNA damage, decreasing the mitochondrial transmembrane potential, increasing the accumulation of ROS and activating MAP kinases (57). Coimmunoprecipitation and immunolocalization studies have demonstrated the interaction between Na,K-ATPase and Bcl-XL and Bak in lung cancer cell lines, specifically fibroblast carcinoma and A549 cells (58,59). Na,K-ATPase, in its intrinsic role or as a receptor for CS, may serve as a potential target for lung cancer treatment.

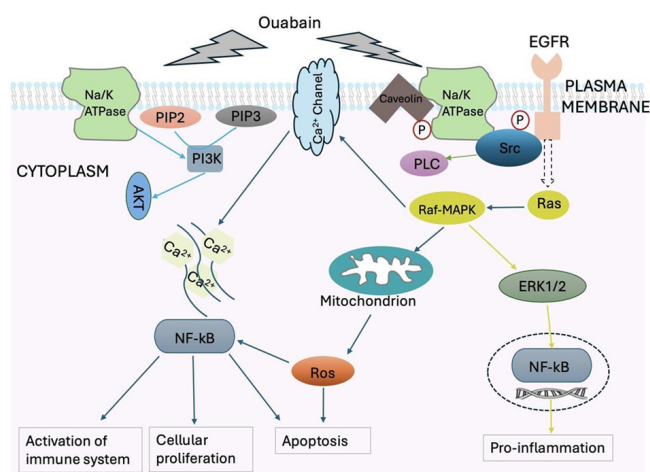


Figure 1. Schematic illustration of Na⁺/K⁺-ATPase signaling pathway. Na⁺/K⁺-ATPase acts as an ion pump and signal transducer, triggering lung inflammation. The binding of ouabain to Na⁺/K⁺-ATPase signalosome located in caveolae transduces signals to multiple pathways. Ouabain binding to the Na⁺/K⁺-ATPase activates Src and PLC which, in turn, evokes transactivation of EGFR and, together with the recruitment of adaptor proteins and Ras, leads to the activation of Ras-Raf-MAPK/ERK1/2 signaling pathway and intracellular Ca²⁺ waves. Ras-Raf-MAPK/ERK1/2 signaling pathway can activate NF-κB. NF-κB activation by ouabain induces the expression of pro-inflammatory genes. The activation of the Ras-Raf-MAPK cascade reaction triggers mitochondria to produce ROS. The activation of ROS and enhanced Ca²⁺ activates NF-κB, leading to the activation of the immune system, cell proliferation and apoptosis. Ouabain can also induce the physical interaction between Na⁺/K⁺-ATPase and inositol triphosphate receptor, triggering intracellular Ca²⁺ waves. Moreover, the binding of ouabain to Na⁺/K⁺-ATPase also stimulates PI3K. ROS release stimulates AKT and NF-κB activation. AKT can activate PI3K and NF-κB or be phosphorylated by PI3K, essential to inflammation. However, the type of reaction depends on the cell type, glycoside concentration and exposure time. Src, non-receptor tyrosine kinases; PLC, phospholipase C; ROS, reactive oxygen species; PIP, phosphatidylinositol (3,4,5)-trisphosphate.

3. COVID-19

Newly emerging viral diseases have become a major public health threat globally in recent years (60). During the last two decades, outbreaks of several viral diseases have been reported including the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, H1N1 influenza in 2009, the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, Ebola virus disease (EVD) in 2013 and Zika virus in 2015 (61). The outbreak of the novel coronavirus was initially reported to the World Health Organization (WHO) on December 31, 2019. On January 30, 2020, the WHO declared this viral outbreak as a public health emergency of international concern (62). As of December 21, 2022 >650 million individuals had coronavirus disease 2019 (COVID-19) and 6.6 million mortalities have been reported globally (63). COVID-19 is a potentially life-threatening condition caused by severe acute respiratory syndrome virus 2 (SARS-CoV-2), ~2% of infected patients and 15% of those who required hospitalization developed acute respiratory distress syndrome (ARDS), which is associated with poor outcomes (64,65).

Numerous SARS-CoV-2-mediated and COVID-19-related signals directly or indirectly impair the function of Na⁺/K⁺-ATPase, potentially contributing to alveolar epithelial barrier failure leading to further aggravation and persistence

of lung injury (66,67). Deregulation of the Na⁺/K⁺-ATPase may also lead to extrapulmonary manifestations of COVID-19. The evidence suggests that various molecular mechanisms that are key in the regulation of transcription, translation, maturation and trafficking of the Na⁺/K⁺-ATPase are negatively regulated by SARS-CoV-2, leading to decreased expression of the α1, α2, α3, β1 and β3 subunits. Thus, Na⁺/K⁺-ATPase carries out an important role in delaying disease progression (68,69). Moreover, SARS-CoV-2 affects alveolar type II epithelial cells, which markedly disturb surfactant homeostasis and deprives the Na⁺/K⁺-ATPase of ATP, which gradually decreases alveolar gaseous exchange, resulting in intracellular hypoxic conditions and increased ROS. This hypoxia/ROS activates AMP-activated kinase, which further inhibits Na⁺/K⁺-ATPase and exacerbates lung deterioration (70,71). Oxidation-induced carbonylation of the Na⁺/K⁺-ATPase α1 subunit desensitizes Na⁺/K⁺-ATPase signaling, and the subsequent increased activity of Src results in increased ROS and inflammation, which can further promote the inflammatory cytokine storm (72). Mechanistically, SARS-CoV-2 spike proteins inhibited the PI3K/AKT/mTOR pathway by upregulating intracellular ROS levels, thus promoting the autophagic response. ROS production leads to the activation of signaling cascades, including JAK/STATs, PI3K/AKT and MAPK/ERK. Alternatively, elevated ROS levels can also inhibit the PI3K/AKT/mTOR pathway, thus enhancing autophagy levels (73). Upregulated expression of this pathway has been observed in several diseases of neoplastic, autoimmune and viral origin and is considered to be implicated in the pathogenesis of the disease. This has led to the hypothesis that single or dual inhibitors of this pathway could ameliorate the course of SARS-CoV-2 infection (74).

Hypoxia-inducible factor 1α (HIF1α) is an important activator of glycolysis and the inflammatory response and enhances virus infection and proinflammatory responses (75). Digoxin has been reported to suppress the expression of HIF1α, which may provide a more effective therapeutic target for both cancer and SARS-CoV-2 infection (76). BiP, also referred to as 78-Kilodalton glucose-regulated protein (GRP78), is upregulated both intracellularly and at the cell surface during SARS-CoV-2 infection. Oleandrin, a unique lipid-soluble CG derived from *Nerium oleander*, has a strong affinity for the α3 isoform of Na⁺/K⁺-ATPase. Oleandrin suppresses GRP78 induction and viral production without affecting cell viability and enhances the activity of antiviral agent therapy (77,78). It also produces an anti-inflammatory response through the activation of Nrf-2 antioxidant genes, which may be beneficial for preventing hyperinflammatory responses to infection with SARS-CoV-2 (79). Increasing evidence has revealed that dexamethasone is beneficial in patients with severe and critical COVID-19 and is well known to increase the activity of Na⁺/K⁺-ATPase, which may contribute to the beneficial effects of corticosteroid therapy (80,81). Thus, the upregulation of Na⁺/K⁺-ATPase may help control the progression of COVID-19, providing a new option for treatment.

4. ARDS

ARDS is a clinical syndrome of acute hypoxemic respiratory failure due to lung inflammation, not caused by cardiogenic

pulmonary edema. It was first described in 1967 (82,83). Since then, the clinical definition of ARDS has been revised several times, first by an American-European consensus conference convened in 1992 by the American Thoracic Society and the European Society of Intensive Care Medicine (84) and subsequently by the ARDS Definition Task Force convened in Berlin in 2012 by the European Society of Intensive Care Medicine (85).

ARDS is characterized by an acute disruption of the alveolar-capillary barrier that leads to flooding of the alveolar space and thus, to marked impairment of gas exchange and ARDS is associated with a poor clinical outcome (86,87). Impairment of the enzyme Na,K-ATPase during ARDS not only prevents the resolution of lung oedema but also intensifies its formation (88). To clear pulmonary edema effectively, it is essential that a tight alveolar epithelial barrier is reestablished and that an Na⁺ gradient across the alveolar epithelium is created, which then drives the reabsorption of water from the alveolar space (89). Impaired alveolar fluid clearance (AFC) is one of the key mechanisms involved in this condition. AFC primarily depends on the basolaterally located Na,K-ATPase and the apically located epithelial sodium channel (ENaC) in epithelial alveolar cells. During the progression of ARDS, Na,K-ATPase is downregulated by various factors, including sepsis, hypoxia and influenza infection (90-92). Oleic acid (18:1 n-9), the most common and abundant fatty acid in the body of healthy individuals, is an Na,K-ATPase inhibitor and an Na⁺ channel inhibitor in the lung, resulting in notably increased endothelial permeability and inducing injury to lipid body formation in leukocytes and eicosanoid production (93,94). Consequently, Na,K-ATPase carries out a key role in the resolution of pulmonary edema (95).

Evidence demonstrated that the Src family kinase acted upstream of and was a required step (or trigger) for activation of both the PI3K/Akt and MAPK/ERK1/2 pathways, each of which is required for upregulation of alveolar epithelial cells, Na,K-ATPase activity and cell surface expression (96). MAPK is a key signal transduction system by which cells transduce extracellular signals into intracellular responses. Several reports suggest an important role of the MAPK signal transduction pathway in the regulation of Na,K-ATPase. β -Adrenergic agonists as well as dopamine stimulate MAPK activation that results in (long-term, >12 h) upregulation of Na,K-ATPase (97). Specialized proresolving mediators, as proinflammatory mediators, not only inhibit proinflammatory cytokine production and prevent leukocyte infiltration but also increase the ENaC, Na,K-ATPase and cystic fibrosis transmembrane conductance regulator (CFTR) levels to increase the AFC in patients with ARDS (98). Maresin1 is a newly described macrophage-derived mediator of inflammation resolution that stimulates AFC by upregulating Na,K-ATPase expression through the ALX/PI3K/Nedd4-2 pathway, suggesting that Maresin1 may constitute a novel therapeutic approach for the resolution of ARDS (99). Resolvin conjugates in tissue regeneration 1 (RCTR1) is an endogenous lipid mediator derived from docosahexaenoic acid that increases the protein levels of Na channels and Na,K-ATPase activity to improve AFC in acute lung injury (ALI) through the ALX/cAMP/PI3K/Nedd4-2 pathway, suggesting that RCTR1 may have potential as a therapeutic drug for ARDS/ALI (100). Ouabain has been reported to suppress the activation of the NF- κ B and

MAPK signaling pathways and attenuate lipopolysaccharide (LPS)-induced ALI (101). Additionally, lipoxin A4 activates alveolar epithelial Na,K-ATPase and enhances AFC (102). The electroporation-mediated transfer of Na,K-ATPase/ENaC plasmids has been revealed to improve lung function, reduce histopathological damage, decrease lung edema and increase survival in a translational porcine model of ARDS (103). Furthermore, pretreatment with cationic lipid-mediated transfer of Na,K-ATPase *in vivo* markedly reduces pulmonary edema by increasing Na,K-ATPase expression and activity (104).

Research suggests that the presence of the Na,K-ATPase α 1 subunit attenuates Lyn (a member of the Src family of kinases) activation by LPS, which subsequently restricts downstream ROS and NF- κ B signaling (105). Findings from β 1 subunit knockout mouse model experiments demonstrated that AFC was markedly decreased (106), indicating a key role for the Na⁺ pump β 1 subunit in alveolar ion and fluid transport. Claudin 18 is specifically expressed in lung epithelial cells and claudin 18 knockout mice present increased levels of AFC associated with elevated β -adrenergic receptor signaling, together with increased ENaC and Na,K-ATPase activity and increased Na,K-ATPase β 1 subunit expression (107). Na,K-ATPase β 1 subunit gene therapy not only upregulates tight junctions to ameliorate lung injury but also reduces lung permeability (108). Na,K-ATPase is a powerful target for ARDS/ALI treatment that is necessary for proper alveolar epithelial function because it promotes both barrier integrity and the resolution of excess alveolar fluid, thus enabling appropriate gas exchange.

5. CF

CF is an autosomal recessive disease caused by mutations in the gene encoding the CFTR, which leads to abnormal transport of ions and fluids across epithelial cell membranes, resulting in impaired mucociliary clearance (109-111). Respiratory failure is the most common cause of mortality in individuals with CF, leading to death in 90% of patients. Cystic fibrosis affects ~70,000 individuals worldwide. Although CF affects individuals of all ethnicities, it is most common in non-Hispanic White individuals (112). The majority of individuals with CF take inhaled medications daily to thin their mucus and use mechanical devices several times daily to dislodge mucus from the airways. Antibiotics may be prescribed to help control infection (113). Although there is an improvement in the management of CF for patients after the approval of CFTR modulators, this is still unsatisfactory, which includes a) non-significant response in F508del mutation heterozygotes to ivacaftor; b) requirement to continue other daily symptomatic treatment; c) interaction with CYP3A inducers and inhibitors and side effects such as elevated transaminases, cataract, oropharyngeal pain; d) negligible benefit in individuals aged <12 years old; and e) need of higher dose in case of lumacaftor and ivacaftor.

Multiple intra- and extracellular signaling pathways, such as HIF-1 α , NF- κ B, PI3K, AKT, and MAPKs, have been implicated in CF lung pathogenesis (114). Evidence indicates that inhibition of the PI3K/Akt/mTOR pathway improves CFTR stability and suggests that this pathway merits further study as a therapeutic target in CF (115). It has been reported that the activity of Na,K-ATPase in the lower airway epithelium is two-fold greater in patients with patients than in healthy

controls. The increase in Na,K-ATPase activity, which contributes to increased reabsorption in epithelial cells and a compensatory mechanism of Na homeostasis, may carry out an important role in the pathogenesis of CF (116,117). Research has revealed that increased FXYP5 expression increases Na,K-ATPase activity, leading to increased transepithelial Na⁺ absorption in CF airway epithelial cells, which may further promote the development of CF (118). Among patients with CF, female patients have worse survival compared with male patients (119). Estrogen carries out a key role in the pathogenesis of CF by increasing Na absorption through the activation of Na,K-ATPase (120). The activation of Na,K-ATPase, which increases transepithelial Na⁺ absorption, results in mucociliary clearance dysfunction and ultimately promotes the progression of CF. Inhibition of Na,K-ATPase may help control the development of CF (121).

6. Idiopathic pulmonary fibrosis (IPF)

IPF is a progressive and fatal lung disease with unknown causes, characterized by progressive lung scarring and excessive extracellular matrix deposition, with limited available effective therapies (122). It mainly occurs in elderly adults with a median survival time of 2-3 years (123). Chronic microlesions in the alveolar epithelium and the accumulation of activated fibroblasts are the main pathophysiological processes associated with IPF. A portion of injured alveolar epithelial cells express mesenchymal markers and secrete profibrotic cytokines.

The Na,K-ATPase β 1 subunit has been reported to be involved in organ fibrosis. Research has demonstrated the downregulation of Na,K-ATPase α 1 and β 1 subunits in the lung tissues of a bleomycin-induced lung fibrosis mouse model, as well as in TGF- β 1-treated A549 cells (124,125). In a further study, Na,K-ATPase β 1 subunit-deficient A549 cells exhibited increased expression of mesenchymal markers (126). Existing evidence suggested that overexpression of α -smooth muscle actin (α -SMA) in lung fibrosis was associated with the activation of PI3K/AKT12, and the interaction between TGF- β and PI3K/AKT promoted the formation of PF. Therefore, a potential approach to treating IPF may be inhibiting the PI3K/AKT/mTOR pathway (127).

In addition, ouabain has been revealed to have antifibrotic effects. *In vitro*, ouabain suppresses TGF- β 1 by blocking the TGF- β /Smad signaling pathway and downregulating TGF-R11 (128,129). It also ameliorates bleomycin-induced PF (130). An increase in the intracellular [Na⁺]/[K⁺] ratio drives the induction of cyclooxygenase-2 expression and PKA activation, which is accompanied by decreased Rho activation and myofibroblast differentiation in response to TGF- β (131,132). While ouabain may be a promising drug for the treatment of IPF, its narrow therapeutic window must be considered. Overall, Na,K-ATPase carries out an important role in IPF, with decreased expression in alveolar epithelial cells observed both *in vitro* and *in vivo*. Therefore, we hypothesize that ion dysfunction may be involved in the development of IPF.

7. Pulmonary hypertension (PH)

PH is a heterogeneous clinical disease characterized primarily by an abnormal increase in pulmonary artery pressure and

is associated with adverse vascular remodeling with obstruction, stiffening and vasoconstriction of the pulmonary vasculature (133,134). At least 1% of the world's population is affected, with a greater burden more likely in low-income and middle-income countries (135). Five main groups of pulmonary hypertension are recognized: Pulmonary arterial hypertension (rare), pulmonary hypertension associated with left-sided heart disease (very common), pulmonary hypertension associated with lung disease (common), pulmonary hypertension associated with thromboembolic disease (rare), and pulmonary hypertension with unclear and/or multifactorial mechanisms (rare) (136). The current therapy primarily targets the underlying cause (137).

Research has demonstrated that FXYP1 protects against vascular dysfunction by preventing glutathionylation-induced oxidative inhibition of endothelial nitric oxide synthase (eNOS) in isolated human endothelial cells and in vascular tissue from mice (138). eNOS also increases Na,K-ATPase activity in a FXYP1-dependent manner (139). In further studies, FXYP1 knockout mice displayed characteristics of PH, including marked increases in pulmonary arterial pressure and increased muscularization of small pulmonary arterioles (140). In addition, ouabain-induced inhibition of Na⁺/K⁺-ATPase increases both Na⁺ and Ca²⁺ levels in the caveolae of the pulmonary artery smooth muscle plasma membrane, which could be important for the manifestation of PH (141). In conclusion, Na⁺/K⁺-ATPase carries out an important role in modulating redox and inflammatory signaling pathways involved in the development of PH and may serve as a potential therapeutic target for PH treatment.

8. Conclusion

Na,K-ATPase is known to act as an ion pump to modulate ion metabolism, however its role in signal transduction is less well understood. The present review briefly described the structure and function of Na,K-ATPase and discussed its role in lung diseases. Na,K-ATPase is involved in the development of various diseases and carries out a key role in their pathogenesis. Targeting Na,K-ATPase for the treatment of lung diseases may provide a novel therapeutic strategy. We hypothesize that it holds potential in the treatment of patients with heart failure complicated by pulmonary edema. However, further clinical evidence is necessary to substantiate its efficacy. Ouabain, a natural compound belonging to the cardiac glycoside family, is a Na,K-ATPase specific inhibitor with a systemic bioavailability of 43-50% after oral administration, and has anti-aging, anti-tumor, anti-fibrosis and improved cardiac function (142,143). Na,K-ATPase is also a neuroendocrine hormone synthesized in the adrenal cortex and hypothalamus (122-132,144). Moreover, hypoxia is an important stimulus for the release of endogenous ouabain (145). This relationship may draw more attention to the connection between Na,K-ATPase and lung diseases.

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ZL and TD wrote the manuscript, BL and WZ edited and revised the manuscript, FL and CH interpreted the mechanism of action of Na, K-ATPase, prepared the figures and revised the manuscript. All authors read and approved the final manuscript. Data authentication 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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