# CD146: a promising target in respiratory diseases

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**CD146 is a cell adhesion molecule involved in angiogenesis and inflammation. Its role in respiratory disorders is increasingly demonstrated. CD146 and its soluble form may be investigated as a therapeutic target for lung diseases in the future.** https://bit.ly/4kpV44y

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## Abstract

Respiratory diseases are major causes of chronic disorders and death worldwide, involving inflammatory, tumoral or infectious processes. It has been proven that vascular mechanisms are key contributors to the pathogenesis of these diseases. For that purpose, it is essential to describe and validate new biomarkers and/or therapeutic targets responsible for lung vascularisation and/or angiogenesis. CD146 is an endothelial cell adhesion molecule also expressed on mesenchymal stem cells, epithelial cells and T-helper 17 lymphocytes. A soluble form of CD146 exists, sCD146, which can be detected in blood and biological samples, including the bronchoalveolar lavage fluid. CD146/sCD146 are involved in angiogenesis and inflammation and are associated with many inflammatory diseases. Recent studies have reported both protective and detrimental roles of CD146/sCD146 in lung diseases. In the present review, we will describe the potential role of CD146 and sCD146 in the pathogenesis of respiratory diseases in order to use them as key mechanistic biomarkers or new therapeutical targets to treat or even cure these pathologies.

## Introduction

Respiratory diseases, including lung cancer, chronic respiratory disorders and infectious diseases, are among the main causes of death worldwide [1]. Among the mechanisms involved in these diseases, lung vasculature is of central interest. The key role of the lung is to carry the air from outside to the alveoli and to perform gas exchange through the blood–air barrier. In this way, the lung displays two vascular systems, a low-pressure system responsible for gas exchange, which comes from the heart's right ventricle (pulmonary circulation), and a high-pressure system with high-level oxygen (bronchial circulation) to supply oxygen and nutrients to the lung cells. For these reasons, the lung is composed of a huge capillary network which represents 40% of all lung cells [2] and more than 80% of its surface area [3]. The importance of vascularisation has been documented in major pulmonary diseases, including bronchial, interstitial and neoplastic lung conditions [2], highlighting the need to improve our understanding of vascular remodelling and pulmonary angiogenesis for potential translation into diagnostic or therapeutic tools.

CD146 is a vascular adhesion molecule belonging to the immunoglobulin superfamily, also known as melanoma cell adhesion molecule (MCAM), mucin 18 (MUC18) and S-Endo1 antigen. It is a 113-kDa glycoprotein encoded by a gene located on chromosome 11 in humans. CD146 is mainly expressed by endothelial cells independently of vessel calibre and anatomic location, with a preferential localisation in endothelial junctions [4]. In addition, CD146 is expressed in other cell types, including T-helper (Th) 17 lymphocytes, mesenchymal stem cells and cancer cells such as melanoma cells or cancer-associated fibroblasts [5–7]. CD146 exists as two membrane isoforms, specifically short and long isoforms produced by alternative splicing of CD146 mRNA. In endothelial cells, the long isoform has a junctional localisation, whereas the short isoform is preferentially expressed on the apical pole. A CD146 soluble

form (sCD146) was also described, generated by shedding of the long and short membrane isoforms by ADAM-10 (a disintegrin and metalloproteinase domain-containing protein 10) and TACE (tumour necrosis factor-α (TNF-α)-converting enzyme) matrix metalloproteinases, respectively [8]. This soluble isoform can be detected in human blood, with concentrations ranging from 200 to 300 ng·mL$^{-1}$ in healthy humans. Concentrations may vary according to gender and age and may be affected by various pathological conditions [9, 10].

CD146 and sCD146 are involved in many physiological and abnormal processes and are especially implicated in angiogenesis and inflammatory processes [10–12] by acting as regulators for several signalling pathways. Wnt5a is one of the major partners of CD146. It binds to CD146 in order to activate the Wnt noncanonical pathway, which is implicated in differentiation, cell polarity, endothelial migration, reactive oxygen species (ROS) production and canonical pathway inhibition [13, 14]. In inflammatory processes, CD146 is implicated in endothelial permeability and mononuclear recruitment and participates in lymphocytic homing to foster trans-endothelial migration [15]. Moreover, CD146 is a co-receptor of the major angiogenic factor vascular endothelial growth factor (VEGF)-R2, which is necessary to activate its angiogenic function [16]. After the VEGF-A activation of endothelial cells, CD146 will directly interact with VEGF-R2 to enhance Akt/p38 mitogen-activated protein kinases/NF-κB activation, promote endothelial cell migration and increase microvascular formation [16]. Indeed, under physiological conditions, deletion of CD146 in zebrafish has been shown to inhibit the development of intersomitic vessels, reduce blood flow and narrow vessel lumen [17]. Within the blood–brain barrier, it has also been proved that CD146 is expressed on pericytes and is a regulator of platelet-derived growth factor receptor (PDGFR)-β signalling, leading to pericyte recruitment and vessel proliferation [18]. In pathological conditions, the use of a membrane CD146 blocking antibody reduced tumoral growth by decreasing tumoral angiogenesis [19]. sCD146 also plays a role in angiogenesis. It induces VEGF-R1 and VEGF-R2 phosphorylation and promotes angiogenic effects in endothelial progenitor cells through angiomotin, which regulates apoptosis, endothelial cell migration and tube formation [10]. sCD146 also mediates its effect through integrin αvβ3, which induces endothelial cell proliferation [20]. These mechanisms are summarised in figure 1.

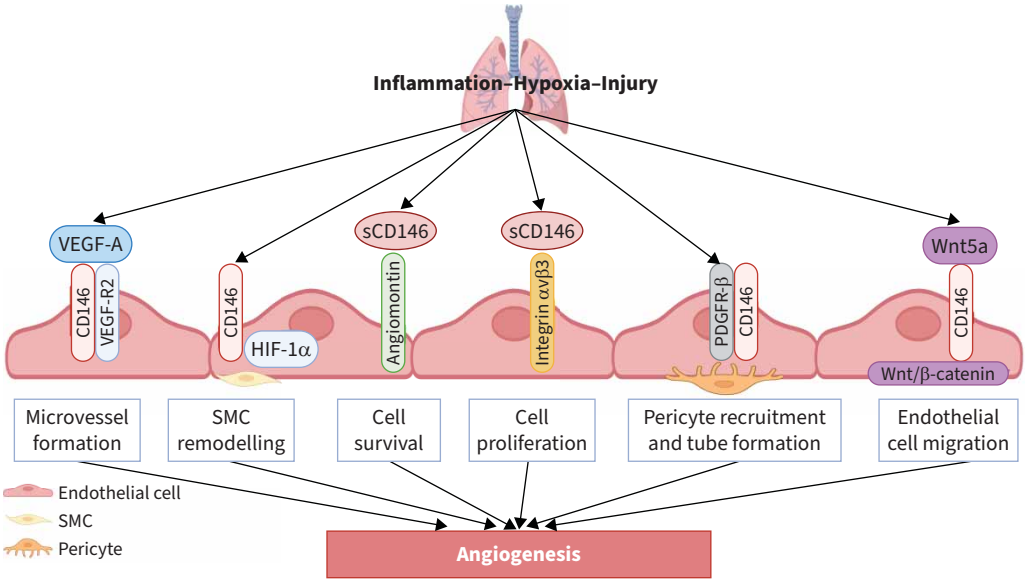


**FIGURE 1** Role of CD146 in angiogenesis translated to the lung. After an injury, inflammation or hypoxia, CD146 will be a key factor for angiogenesis. After vascular endothelial growth factor (VEGF)-A induction, CD146 will directly interact with VEGF-R2 enhancing Akt/p38 mitogen-activated protein kinases/NF-κB activation, promoting endothelial cell migration and microvascular formation. Under hypoxic conditions, CD146 will induce hypoxia-inducible transcription factor 1α transcription through NF-κB and favour smooth muscle cell (SMC) remodelling. Wnt5a is a major partner of CD146 implicated in endothelial migration and cell polarity. CD146 is also expressed on pericytes and is a regulator of platelet-derived growth factor receptor (PDGFR)-β signalling leading to pericyte recruitment and vessel proliferation. Soluble CD146 (sCD146) is able to activate angiomotin, which regulates cell apoptosis and cell migration. sCD146 also mediates its effect on integrin αvβ3 and induces endothelial cell proliferation. Figure created in BioRender.

Due to the huge vascular supply of the lungs, angiogenesis represents a key factor in respiratory diseases. Two main angiogenic mechanisms are involved, namely sprouting and intussusceptive angiogenesis [2]. Sprouting angiogenesis is characterised by the formation of blood vessels through endothelial migration from a pre-existing vessel. This is a slow process (2–5 days) and mainly involved in hypoxia, injury and oncologic signalling. It can be triggered by a localised overexpression of VEGF, fibroblast growth factor or Notch signalling [21, 22]. Intussusceptive angiogenesis is a fast and economic angiogenic process characterised by the splitting of an existing vessel into two vessels following the formation of a tissue pillar within the initial vessel. This mechanism appears a few minutes or hours after a change in shear stress or micromechanical forces mediated by a uniform and continuous overexpression of VEGF and is largely involved in inflammatory or tumoral process of lungs [2].

As CD146 and sCD146 are essential in angiogenesis, they may be crucial for respiratory diseases. Recently, the role of CD146 and its soluble form has been highlighted in lung disorders associated with auto-inflammatory diseases, such as systemic sclerosis (SSc). In SSc, CD146 regulates an interplay between Wnt and ROS signalling, which promotes the noncanonical Wnt pathway and prevents ROS signalling, paving the way for innovative therapeutic strategies [23]. Among the vascular molecules involved in angiogenesis and inflammation, CD146 represents an attractive molecular target in pulmonary diseases, considering that lungs represent the most extensive network of endothelial cells.

This review will report the recent findings and knowledge linking respiratory diseases and vascular mechanisms by focusing on a potential role for the sCD146–CD146 axis.

## Thoracic cancers

Thoracic cancers are the primary cause of cancer-related deaths worldwide. Risk factors include environmental exposure (tobacco smoking, occupational hazards and small particulates from various sources) and a susceptible genetic background. Thoracic cancer morbidity and mortality remain major concerns despite recent advances in treatment strategies and a vigorous research effort to better understand and initiate personalised treatments at an early stage. Angiogenesis is one of the most important mechanisms involved in this disease. It contributes to tumour growth, invasion and dissemination, which supports the rationale for targeting this pathway.

### *Nonsmall cell lung cancer*

CD146 was first described as a tumour antigen in melanoma and is associated with poor prognosis. It was then found to be involved in several cancers, including lung cancer. In 2003, Kristiansen *et al*. [24] reported CD146 expression in tumour cells in 51% of patients with nonsmall cell lung cancer (NSCLC), preferentially in squamous cell carcinoma. In adenocarcinoma, CD146 expression was significantly associated with poor survival. These results were confirmed in lung adenocarcinoma [25] and in NSCLC [26].

The role of CD146 in epithelial–mesenchymal transition (EMT) could explain the involvement of this molecule. EMT is a process associated with tumour cell invasion leading to cancer progression and metastasis. CD146 expression was correlated with vimentin expression and negatively correlated with E-cadherin expression on the tumour cells. In addition, CD146 expression has been shown in $CD4^+$ T-lymphocytes obtained from the tumours of patients with lung cancer, acting as a potential inhibitor for anti-tumour immune response [27], and so associated with a poorer prognosis.

sCD146 was also described to be a marker linked with a poor prognosis. In a cohort of patients with NSCLC undergoing surgery, the level of sCD146 was associated with tumour progression and poor survival. In this cohort, the authors analysed the level of sCD146 and the number of circulating endothelial cells (CECs) ($CD146^+$ $CD105^+$ $CD45^+$ $DAPI^+$) in patients with a COPD or NSCLC as compared to healthy volunteers. Levels of sCD146 and $CD146^+$ CECs were significantly higher in NSCLC and correlated with shorter progression-free and overall survival, illustrating that they could be markers of high angiogenesis tumours with a poor prognosis [28].

In the same way, $CD146^+$ CECs were evaluated in nonoperable NSCLC. Patients undergoing chemotherapy had higher pre- and post-treatment rates than healthy patients. Interestingly, the amount of baseline $CD146^+$ CECs was higher in patients with stable disease or responding to chemotherapy and decreased after chemotherapy, whereas it increased in progressive disease. In this way, $CD146^+$ CECs may be considered as a predictive factor for response because of their role in tumour angiogenesis and represent a target of antineoplastic agents [29].

In addition, it has been shown in epidermal growth factor receptor-mutated NSCLC resistant to tyrosine kinase inhibitor that CD146 induced an upregulation of stemness phenotype genes, while β-catenin decreased, resulting in an increased migration capability of resistant cancer cells. Conversely, CD146 downregulation with small interfering RNA (siRNA) suppressed the stemness phenotype [30]. Recently, the expression of CD146 in NSCLC has been compared to the levels of proteins related to EMT. CD146 silencing during cell invasion in NSCLC was associated with reduced levels of N-cadherin, vimentin, phosphoinositide 3-kinase (PI3K) and Akt phosphorylation, which are involved in EMT [31].

CD146 has been described as a target for immuno-PET (positron emission tomography) imaging in these patients. In a first study, a $^{64}$Cu-labeled CD146-specific antibody was used in immuno-PET imaging to quantify CD146 expression in subcutaneous lung cancer models on nude mice. The authors found a strong correlation between tumour uptake of the radiotracer and CD146 expression [32]. In another study, the same team proved in an NSCLC pulmonary metastasis model that this tracer had an excellent affinity for lung cancer cells expressing CD146 [33]. These results allow us to consider CD146 as a monitoring or therapeutic tool for such patients.

### *Small cell lung cancer*

In small cell lung cancer (SCLC), which has a high relapse rate and poor prognosis, CD146 is upregulated in chemoresistant cells and associated with a mesenchymal phenotype together with an increased proliferation through the PI3K/Akt/SRY-box transcription factor 2 pathway [34]. In pulmonary large-cell neuroendocrine carcinoma, CD146 is also involved in cell migration and influences EMT through Akt phosphorylation. Silencing CD146 with siRNA *in vitro* was associated with a decreased in cell migration and viability [35].

### *Malignant mesothelioma*

Malignant mesothelioma (MM) is another subtype of thoracic cancer with a poor prognosis, partly due to the difficulty in distinguishing malignant mesothelial proliferative cells from benign reactive mesothelial cells.

In a few studies, CD146 has been proposed as a highly sensitive and specific marker of MM, for both epithelioid and sarcomatoid types [36, 37]. Furthermore, CD146 has been evaluated as a therapeutical target when combined with gold nanoparticles and pemetrexed, and was found to be more effective than pemetrexed alone [38]. However, previous studies revealed that CD146 did not demonstrate optimal specificity and sensitivity in MM, a finding not confirmed in a recent study [39]. These data suggest that CD146 may be involved in MM, but may not the best target for these patients due to its heterogeneous expression.

Finally, all these data indicate that CD146 is associated with poor prognosis in thoracic cancer. By promoting angiogenesis and EMT, it is associated with the progression and metastasis of cancer, suggesting that CD146 and sCD146 could represent potential therapeutic targets in such patients.

## Chronic airway diseases

### *Asthma*

Asthma is a chronic airway disease characterised by inflammation and airway structural changes associated with bronchial hyperresponsiveness. Airway structural changes correspond to a change in the composition, thickness or volume of airway walls, including subepithelial fibrosis, goblet cell metaplasia and an overexpression of angiogenic factors [40]. Asthma is a heterogeneous disease and different phenotypes have been described based on clinical and functional features and mechanisms, including inflammation and/or remodelling, called endotypes. Two main endotypes have been described, namely type 2 (T2)-high, where production of T2 cytokines (interleukin (IL)-4, IL-5 and IL-13) and eosinophilic inflammation are involved, and T2-low, characterised by noneosinophilic inflammation and the potential involvement of type 1/T-helper (Th) 17 cells [41].

Few studies have investigated the role of CD146 in asthma. In particular, CD146 knockout mice (CD146KO) have been challenged with house dust mites (HDMs) as a classical asthma rodent model. Results showed that the CD146-deficient mice have a decreased ability to recruit inflammatory cells and a clearly decreased expression of EMT, which is involved in airway remodelling. *In vitro*, the exposure of alveolar epithelial cells to HDMs induced CD146 expression, which in turn activated the transforming growth factor-β/SMAD3 signalling pathway [42]. In asthma patients, the expression of CD146 is increased in the bronchial epithelium [43] and the level of sCD146 is increased in plasma [44]. *In vitro*, IL-13 has been shown to increase CD146 expression in tracheobronchial epithelial cells, which in turn induces eotaxin-3 secretion, an eosinophil chemoattractant, and mucin-5AC expression by IL-13, suggesting that

CD146 is involved in T2-high asthma [44]. Finally, CD146 was shown to be involved in bacterial adherence to epithelial cells (such as *Mycoplasma pneumoniae* and nontypeable *Haemophilus influenzae*) and thus CD146 may be implicated in exacerbating bacterial asthma [43]. Indeed, CD146 expression in alveolar macrophages was increased in asthma and COPD patients when compared with healthy individuals [45]. These findings highlight a role of CD146 in bronchial inflammation.

### *COPD*

COPD has emerged as a highly prevalent disease in developing countries, with high morbidity and mortality worldwide. COPD results from exposome risks (cigarette smoke, indoor and outdoor pollution) in susceptible individuals with a potential genetic factor (alpha-1 antitrypsin deficiency for instance). COPD is associated with chronic inflammation of the entire airway tree with some features of small airway and alveolar changes. Persistent inflammation is a source of many angiogenic factors that locally enhance angiogenesis, a phenomenon associated with COPD [46]. COPD is a heterogeneous disease with several phenotypes and endotypes leading to potential specific traits. The natural history is nonlinear and the patients' trajectories are crucial to better understand the disease and its treatments. Most treatments aim to reduce the burden of daily symptoms, avoid recurrent exacerbations and try to prevent the occurrence of respiratory insufficiency through the development of alveolar loss. Despite several advances in the understanding of COPD progression and mechanisms, the interventions are mostly symptomatic and do not interfere with the natural history of the disease in most cases [47].

In a murine model of COPD induced by lipopolysaccharide and porcine pancreatic elastase exposure, pulmonary CD146 expression is diminished. In addition, CD146 deficiency aggravates COPD through S100A9–matrix metalloproteinase-9 (MMP-9) pathway activation in macrophages. This signifies that CD146 negatively regulates MMP-9 production, therefore having a protective role in COPD [48]. In addition, in COPD, the expression of CD146 was found to be significantly higher in endobronchial biopsies of COPD patients as compared to healthy subjects [49], whereas it was found to be decreased in the lung vasculature of COPD patients [50]. Concomitant to this decrease, an increase in vascular permeability has been found, attesting for the contribution of CD146 to endothelial dysfunction in COPD. This was supported by another study which characterised $CD90^+$ $CD146^+$ mesenchymal cells in COPD and revealed that these cells failed to support micro-vessel formation in comparison to healthy control cells [51]. At transcriptional and protein levels, CD146 was found to be increased in primary bronchial epithelial cells from COPD patients as compared to those from smokers and ex-smokers [52]. As cigarette smoke is the most common risk factor for COPD, its effect has been studied on CD146 expression *in vitro*. Indeed, treatment of primary bronchial epithelial cells with cigarette smoke extract at an air–liquid interface led to a significant increase in CD146 expression at the protein level [49].

Moreover, circulating $CD146^+$ endothelial microparticles have been detected in COPD patients' blood, but no statistical difference from that of non-COPD patients was found. Also, the levels of these microparticles do not differentiate between controlled and exacerbated COPD patients [53]. In contrast, sCD146 was found to be increased in the serum and bronchoalveolar fluid of COPD patients and sCD146 plasma levels were lower in exacerbated COPD patients than in stable patients [54]. sCD146 expression has been shown to be elevated in frequent-exacerbator COPD patients in comparison to nonexacerbators [55]. In a model of second-hand smoke-exposed rats, plasma levels of sCD146 were found to be increased, suggesting shedding of membrane CD146, which contributes to pulmonary microvascular endothelial dysfunction and the development of emphysema [50]. Thus, detection of CD146 and sCD146 may be useful for anticipating the potential risk of COPD exacerbation.

### *Bronchopulmonary dysplasia*

Bronchopulmonary dysplasia (BPD) is associated with an abnormal lower respiratory tract development, resulting in a severe chronic disease, due to pre- and/or post-natal factors. BPD cases are frequently documented in neonates delivered before the 32nd week of gestation and in all preterm infants who still need oxygen supplementation at 28 days post-birth. Even though prematurity is already a risk factor for long-term lung pathologies, children with BPD have greater impairment of pulmonary structure and function [56].

The role of CD146 in BPD is not yet elucidated, but first the evidence for a possible contribution of CD146 in BPD came from a study revealing an increase in CD146 expression in newborn mice exposed to a cycle of hyperoxia. Increased expression of CD146 has been shown in two mice models of BPD in comparison to mice exposed to ambient air (21% oxygen). In the first mouse model, newborn pups were exposed to 65% of oxygen starting 24 h after birth until day 5, then returned to ambient air and sacrificed on day 14 [57]. In the second mouse model, newborn pups where directly exposed to 85% of oxygen for 14 days, then re-exposed to ambient air until sacrifice on day 56 [58]. In contrast, CD146KO BPD mice

(exposed to 65% oxygen 24 h after birth until their fifth day) exhibited less severe symptoms of BPD as compared to CD146 wild-type (WT) BPD mice, with better lung morphometry and respiratory parameters [57]. In humans, sCD146 is increased in the plasma of BPD infants [57]. Decreased expression of membrane CD146 in the lung mesenchymal stem cells of infants who died of fatal BPD was also observed in comparison to infants who died at similar ages from nonpulmonary diseases [58]. As sCD146 is the result of the shedding of the membrane form, we could hypothesise that the increase of sCD146 found in plasma is linked to and arises from the decrease of the membrane CD146. In an *in vitro* study of human fetal lung mesenchymal cells, it was found that they contain almost exclusively $CD146^+$ mesenchymal stromal cells. Upon exposure to hyperoxia, which mimics BPD, the expression of CD146 in mesenchymal stromal cells decreased, cell proliferation increased and the secretion of growth factors important for lung growth was impaired. An alteration of lung mesenchymal stromal cell function may contribute to the pathogenesis of BPD and raises the question of the involvement of CD146 [59].

### *Obstructive sleep apnoea*

Obstructive sleep apnoea (OSA) is a chronic disease affecting almost billion adults worldwide. It is the result of a temporary collapse of the muscular airway during sleep. This leads to sporadic hypoxia and hypercapnia, intrathoracic pressure swings, and sleep fragmentation. Untreated OSA can be the cause of organ dysfunction, especially in those within the thoracic cavity, due to intrathoracic pressure swings [60]. To date, no study has investigated the role of CD146 in OSA, except for one that indirectly extrapolates a possible role of CD146 as a biomarker in this disease. Indeed, an increased number of circulating apoptotic endothelial cells which are $CD146^+$ (and annexin $V^+$) were found in patients with OSA in comparison to healthy subjects. The number of cells was linked to the severity of sleep apnoea and correlated negatively with endothelial-dependent vasodilation. Decreased numbers of these cells were observed after continuous positive airway pressure therapy. In addition to being a biomarker of the severity of the disease, a high level of circulating $CD146^+$ annexin $V^+$ endothelial cells could also explain why patients with OSA are predisposed to premature vascular disease [61].

## Interstitial lung diseases

Interstitial lung diseases (ILDs) are a heterogeneous group of lung diseases characterised by infiltration of the pulmonary interstitium by an aberrant extracellular matrix, leading to respiratory insufficiency, comprising idiopathic pulmonary fibrosis (IPF) and ILDs associated with connective tissue disorders, including SSc and sarcoidosis.

SSc is a systemic disorder caused by vascular damage, leading to organ fibrosis, with the lungs being the primary site and the leading cause of death. The role of CD146 in SSc is becoming increasingly understood. Given that CD146 is involved in inflammation and angiogenesis, Kaspi *et al.* [62] highlighted its involvement in SSc, showing that levels of sCD146 in the blood were higher in patients with SSc compared with healthy individuals. Interestingly, among them, sCD146 was lower in patients with SSc associated with pulmonary fibrosis. In the same way, it has been shown that Th17 lymphocytes expressing CD146, which favour the recruitment of pro-inflammatory cytokines, are increased in SSc as compared with healthy subjects and inversely correlated with the diagnosis of pulmonary involvement [63]. This role of CD146 was confirmed in a murine model of skin fibrosis where CD146KO mice developed more fibrosis than WT mice but showed improvement when treated with sCD146 [62]. It was recently proven by Heim *et al.* [14] in dermal fibroblasts from patients with SSc that CD146 regulates the Wnt pathway and the production of reactive oxygen species (ROS). Indeed, when CD146 is missing, the Wnt canonical pathway and ROS production are activated, leading to inflammation and fibrosis in a skin model of SSc. It is very likely to be the same mechanism in lung fibrosis. However, this hypothesis is currently under investigation in a model of lung fibrosis by our team.

In another study including patients with SSc, additional isoforms of sCD146 were identified, I5-13-sCD146 and I10-sCD146, which are generated by alternative splicing in endothelial cells. Interestingly, I5-13-sCD146 was significantly increased in patients with SSc associated with pulmonary fibrosis and was associated with Krebs von den Lungen-6, the pulmonary fibrosis marker, whereas I10-sCD146 was not, suggesting a specific implication of I5-13-sCD146 in lung fibrosis. This can be explained by a reduced angiogenic effect of I5-13-sCD146 as compared to shed sCD146 or I10-sCD146, as has been shown by the authors. In agreement, in an *in vivo* murine model of cutaneous fibrosis, I10-sCD146 and sCD146 significantly reduced dermal thickness whereas there were no effects with I5-13-sCD146 [64]. Taken together, these data highlight the significant role of CD146 in SSc and lung impairment.

To our knowledge, there is no data about CD146 in IPF, which is the main cause of lung fibrosis. However, it is increasingly established that dysregulation of the endothelium and vascularisation is

involved in fibrogenesis because of its role in lung injury and repair. In response to inflammatory stimulation, increased endothelial barrier permeability allows cell transmigration to support tissue repair. In cases of lung fibrosis, increased alveolar-capillary permeability leads to vascular leakage and persistent recruitment of pro-inflammatory mediators, which results in fibrosis [3]. Because CD146 is located at the endothelial junction, it could be involved in such diseases.

## Pulmonary hypertension

Pulmonary hypertension (PH) is a severe disease of the pulmonary arteries characterised by endothelial dysfunction and vascular remodelling, leading to right ventricular enlargement, respiratory failure and death. It is divided into five groups depending on the disease environment and the mechanisms involved [65]. It is a challenging disease, with significant difficulties in early diagnosis and treatment. For this purpose, it has been shown that $CD146^+$ CECs were increased in PH [66, 67]. Moreover, in a prospective paediatric cohort of idiopathic and congenital heart disease PH, $CD146^+$ CECs decreased in responder patients and increased before worsening [68]. CD146 is expressed by vascular smooth muscle cells during embryonic development and in adulthood. It regulates the balance between proliferation and differentiation after injury, which explains its involvement. In addition, CD146 expression in pulmonary artery smooth muscle cells (PASMCs) correlates with PH severity [69, 70]. To better understand its role in vascular remodelling, it has been proved that CD146 expression in PASMCs is induced by hypoxia-inducible transcription factor 1α (HIF-1α) and promotes vascular remodelling. Conversely, specific ablation of CD146 in PASMCs in mice or targeting CD146 with anti-CD146 antibodies reduced vascular remodelling and improved cardiac function [70]. These results highlight a key role of CD146 in PH.

## Respiratory infections

Respiratory infections of the lower airways, associated with mycobacteria, bacteria or viruses, are frequent and may lead to death, even in nonimmunocompromised hosts. Despite its heterogeneity and complexity, it is one of the main triggers for acute exacerbation of chronic pulmonary diseases, underlining the need for a better understanding of the mechanisms involved. CD146 is expressed in airway epithelial cells in healthy patients and is overexpressed in patients with obstructive chronic lung disease. It is involved in bacterial adherence to epithelial cells through upregulation mediated by IL-13 in T2-high asthma [43, 44]. In normal human primary airway epithelial cells infected with human rhinovirus or polyinosinic: polycytidylic acid, CD146 was overexpressed and resulted in a proinflammatory response with IL-8

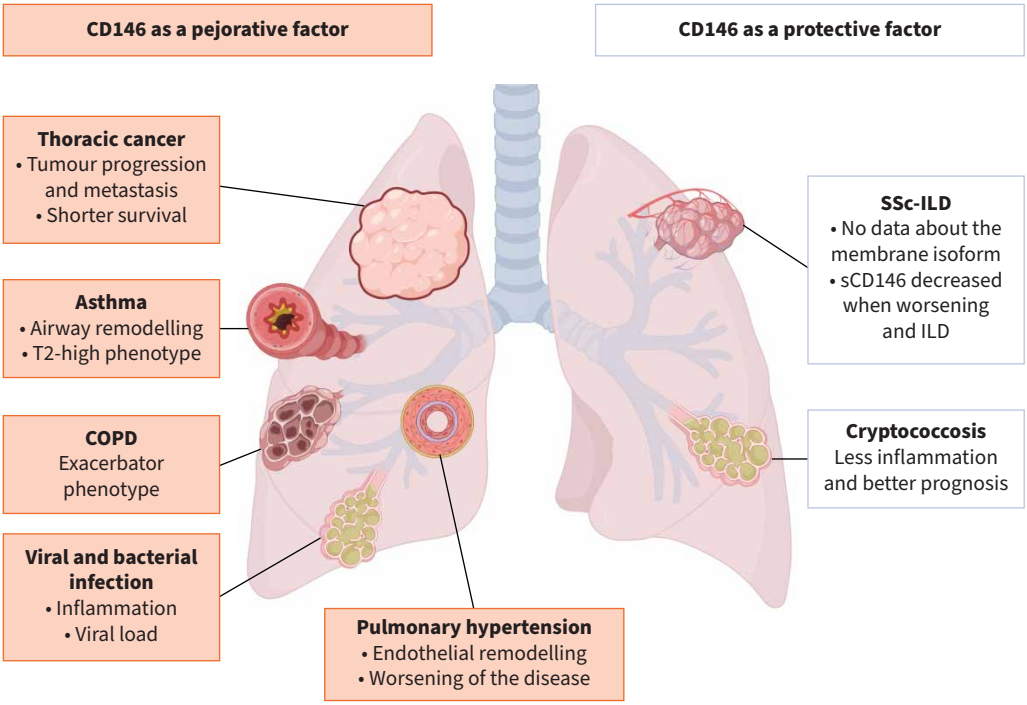


**FIGURE 2** Protective and pejorative role of CD146 in respiratory diseases. ILD: interstitial lung disease; SSc: systemic sclerosis; T2: type 2. Figure created in BioRender.

**TABLE 1** Role of CD146 in different respiratory diseases

| Pathology | Cell population expressing CD146 | Prognosis associated with CD146 expression | CD146 function | Reference |
|---|---|---|---|---|
| **NSCLC** | Tumour cells | Shorter survival, metastasis | Favours EMT | [24, 26, 32, 33] |
| | $CD4^+$ T-cells | Tumour progression | Favours tumour angiogenesis | [27] |
| | CECs | Short survival | Favours tumour angiogenesis | [28] |
| | | | Predictive factor for treatment response | [29] |
| **SCLC** | Tumour cells | Tumour progression | Chemoresistance, favours EMT | [34, 35] |
| **Mesothelioma** | Tumour cells | ND | Not enough sensitivity and specificity for diagnosis | [39] |
| **Asthma** | Epithelial cells | ND, increased expression | Favours inflammation, EMT and airway remodelling | [42] |
| | | | Regulate IL-13 inflammatory response and favours T2-high asthma | [43, 44] |
| **COPD** | Epithelial cells | Increased in exacerbator patients | Favours vascular permeability | [48, 50, 51] |
| **BPD** | CD146KO mice | Worst symptoms and respiratory parameters | KO has less symptoms and better respiratory parameters | [57] |
| **SSc** | Th17 | ND, increased in SSc but decreased in SSc-ILD | Favours inflammation and fibrosis | [63] |
| | CD146KO mice | Prone to develop more skin fibrosis | KO favours Wnt noncanonical pathway | [62] |
| **PH** | CECs | Increased in PH, decreased in responders to treatment and increased before worsening | Reflects accelerated endothelial remodelling/proliferation | [66–68] |
| | PASMCs | Increased with disease severity | Favours HIF-1α transcription through NF-κB | [70] |
| | CD146KO mice | KO is protective | KO disactivates CD146–HIF-1α axis and attenuates PH | |
| **Viral infection** | Epithelial cells | Proinflammatory function | Favours IL-8 and inhibit IFN-β expression | [71] |
| | CD146KO mice | KO is protective | KO decreases viral load and neutrophilic inflammation | [72] |
| **Bacterial infection** | Alveolar macrophages CD146KO mice | KO is protective | KO decreases lung proinflammatory cytokines KC and TNF-α and less neutrophil recruitment | [45] |
| **Cryptococcosis infection** | CD146KO mice | KO worsened infection | KO macrophages produced more neutrophil chemokine KC and TNF-α | [73] |

BPD: bronchopulmonary dysplasia; CEC: circulating endothelial cell; EMT: epithelial–mesenchymal transition; HIF-1α: hypoxia-inducible transcription factor 1α; IFN: interferon; IL: interleukin; ILD: interstitial lung disease; KC: keratinocyte-derived chemokine; KO: knockout; PH: pulmonary hypertension; ND: not determined; NSCLC: nonsmall cell lung cancer; PASMC: pulmonary artery smooth muscle cell; SCLC: small cell lung cancer; SSc: systemic sclerosis; T2: type 2; Th: T-helper; TNF-α: tumour necrosis factor-α.

overexpression, whereas interferon-β antiviral expression was suppressed [71]. These results were confirmed by the same team using a murine model treated with human rhinovirus where CD146KO mice had decreased viral load expression and neutrophilic inflammation compared with WT [72].

As mentioned above, CD146 is overexpressed in alveolar macrophages in bronchial diseases and can favour infectious exacerbation. In a murine model of *M. pneumoniae* infection, CD146KO mice had lower levels of proinflammatory cytokines KC and TNF-α and less neutrophil recruitment than WT. Interestingly, adenovirus-mediated MUC18 gene transfer in CD146KO mice increased proinflammatory cytokines production [45], highlighting the implication of CD146 in bacterial pneumonia.

The role of CD146 has also been proven in fungal pneumonia with *Cryptococcus neoformans*. In humans, CD146 alveolar epithelial cell expression is decreased in patients with pulmonary cryptococcosis. In a murine model infected with *C. neoformans*, CD146KO mice had lower survival rates, increased fungal burden and inflammatory type 2 cytokines such as IL-4, IL-5 and TNF-α [73].

Finally, sCD146 has also been evaluated in severe acute respiratory syndrome coronavirus 2 infection as a biomarker for endothelial damage with a high rate in infected patients compared with healthy individuals [74]. In the same way, increased levels of $CD146^+$ CECs were found in patients with a severe form of the disease [75, 76].

**TABLE 2** Role of soluble CD146 (sCD146) in different respiratory diseases

| Pathology | sCD146 sample | Function | Reference |
|---|---|---|---|
| **NSCLC** | Serum | Associated with short progression-free survival | [28] |
| **Asthma** | Serum | Increased compared to healthy subjects | [43] |
| **COPD** | Serum and BAL | Increased compared to healthy, lower in exacerbated patients than in patients with a controlled disease | [54] |
| **BPD** | Blood | Increased in infants compared to healthy individuals | [57] |
| **SSc** | Blood | Increased in SSc and decreased in worsened disease with ILD | [62] |
| | Blood (I5-13-sCD146) | Increased in SSc-ILD and correlated with KL-6 | [64] |

BAL: bronchoalveolar fluid; BPD: bronchopulmonary dysplasia; ILD: interstitial lung disease; KL-6: Krebs von den Lungen-6; NSCLC: nonsmall cell lung cancer; SSc: systemic sclerosis.

These findings support the potential involvement of the CD146 axis in respiratory infections, with its role varying according to the type of deleterious agent and the site of airway tree involvement.

## Conclusion

The lung vasculature is one of the most important elements in the pathophysiology of respiratory disorders. Due to its role in angiogenesis and inflammation in numerous lung diseases, CD146 may be a potential therapeutic target. As summarised in figure 2, CD146 can display different functions and effects depending on the respiratory disease. It is expressed in endothelial cells, but can also be found in epithelial or tumour cells, where it may have different functions.

In thoracic tumoral disease, CD146 expression on cancer cells seems to be associated with a poor prognosis, as well as plasmatic sCD146 levels. This is probably due to its involvement in angiogenesis, which is one of the mechanisms for cancer progression and involved in EMT, also characterising tumoral process. In bronchial disorders, the role of CD146 expressed in epithelial cells is similar and is correlated with lower control of the disease, favouring bronchial exacerbations and inflammation. Interestingly, CD146 can also have a protective role in SSc-ILD. Indeed, sCD146 is increased in SSc and decreased in severe impairments such as SSc-ILD. Moreover, a murine model of SSc highlights a protective role of CD146 and sCD146 in skin fibrosis suggesting a similar role in the lung. In PH, CD146 correlates with PH severity and is induced by HIF-1α. In fungal infection with *Cryptococcus*, CD146 expression on epithelial cells seems to be protective; indeed, CD146 knockdown favours a poor prognosis when compared with normal expression of CD146 on mice. Conversely, the prognosis of viral infections such as rhinovirus is better when CD146 is missing, suggesting an inverse role in these two infections. The roles of CD146 and sCD146 in different respiratory diseases have been summarised in tables 1 and 2, respectively.

All together, these data show that CD146 and its soluble form may have a Janus effect depending on the cell involved and the pathological context. CD146 and sCD146 may be used as a potential diagnostic or prognosis marker in many respiratory diseases. Furthermore, targeting CD146 or its soluble form with agonists or antagonists could be proposed as treatments depending on the clinical situation. However, more data are needed to better understand its real function and validate its use in clinical practice.

### Questions for future research

The vasculature of lung is essential for its physiological activity and is involved in its pathological processes. Given that lung disorders represent one of the main causes of death worldwide, it will be essential in the future to take account of vascularisation and angiogenesis in the development of new therapies and biomarkers. CD146 and its soluble form, sCD146, are widely involved in vascular processes and inflammation. They are involved in many respiratory disorders with different functions depending on the disease. A better understanding of these molecules will be a determining factor in the management of patients with respiratory disorders. It will be necessary to precisely determine the role of the membrane isoform of CD146 and sCD146 depending on the disease in order to develop new treatments that will be able to target CD146 or sCD146 with specific antibodies or replacement therapy.

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