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Review

Caveolin-1 as a critical component in the pathogenesis of lung fibrosis of different etiology: Evidences and mechanisms

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ABSTRACT

Caveolin is a structural protein of flask-shaped invaginations of the plasma membrane termed as caveolae and is widely expressed on the endothelial cells, smooth muscle cells and fibroblasts in the different parts of the body including the lung tissues. The expression of caveolin-1 in the lung tissues is important to prevent the fibrogenic actions of TGF-β1 in lung fibrosis of different etiology including idiopathic pulmonary fibrosis, systemic sclerosis-associated interstitial lung disease and allergen-induced airway remodeling. Caveolin-1-mediated internalization and degradation of TGF-β1 receptors may possibly account for the decreased actions of TGF-β1. Studies have shown that the deficiency of caveolin-1 is very important in inducing lung fibrosis and its upregulation is reported to prevent lung fibrosis. The biological actions of caveolin-1 involve signaling pathways including JNK signaling, IL-4, STAT-3, miR199a-5p, CXCR4$^+$ and CXCL12. The present review discusses the key role of caveolin and associated signaling pathways in the pathogenesis of lung fibrosis of different etiology.

1. Introduction

Caveolin is a 22-kDa, structural protein of flask-shaped invaginations of the plasma membrane termed as caveolae (Schwencke et al., 2006). There are three members of caveolin family including caveloin-1, 2 and 3. Amongst these, caveolin-1 is present in almost every cells of the respiratory system including type I epithelial cells, endothelial cells, smooth muscle cells, fibroblasts, macrophages and neutrophils (Jin et al., 2011). Caveolin-1 is known to perform a variety of biological functions including endocytosis, cell signaling, vesicular and cholesterol trafficking (Quest et al., 2008; Sun et al., 2010). Apart from it, it also participates in cell senescence (Feng et al., 2017), cell differentiation (Chen et al., 2017), aging (Wicher et al., 2019) and angiogenesis (Tu et al., 2017) *etc.*

Caveolin-1 is considered essential for maintaining the proper structural integrity of the lungs. Indeed in caveolin-1 deficient mice, a progressive reduction in the lung compliance and increase in airway resistance has been reported (Le Saux et al., 2008b). A progressive increase in deposition of collagen in respiratory airways and parenchyma has directly been correlated to increase in TGF-β1/Smad signaling pathway in the absence of caveolin-1 (Le Saux et al., 2008b; Pandey et al., 2017). Moreover, TGF- β1 has been shown to down-regulate caveolin-1 gene/protein in the fibroblasts (Sanders et al., 2015), resulting in development of hyperproliferative and apoptosis-resistant fibroblast phenotype (Xia et al., 2010). Another study in caveolin-1 deficient mice has shown the increase in the expression of α-smooth muscle actin and collagen in the lungs (Ryter et al., 2014). Moreover, studies have shown the protective role of caveolin-1 scaffolding domain peptide in preventing the pathological changes in the lungs (Chinnakkannu et al., 2018). Regarding the role of caveolin-1 in lung fibrosis, an earlier study of Kasper et al. demonstrated the down-regulation of caveolin-1 gene expression in the alveolar cell types I and II of rats and mini pigs during radiation injury, resulting in fibrosis (Kasper et al., 1998). Later, the role of caveolin-1 in lung fibrosis was further substantiated in other studies (Gvaramia et al., 2013) and loss of caveolin-1 was shown to be associated with the activation of TGF-β1 signaling to induce lung fibrosis (Tourkina and Hoffman, 2012). The present review discusses the key role of caveolin and associated signaling pathways in the pathogenesis of lung fibrosis of different etiology.

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2. Differential changes in caveolin-1 immunoreactivity in the alveolar epithelial cells and capillary endothelium in the lungs during fibrogenesis

The studies of Kasper et al. described the differential changes in the caveolin-1 expression in the lung tissues during fibrogenesis. Indeed, the authors showed the loss of caveolin-1 expression in the type I pneumocytes (alveolar epithelial cells) of rats in response to radiation injury. On the other hand, there was increase in the expression of caveolin-1 in the endothelial cells in this animal model of fibrosis (Kasper et al., 1998). Another study of same group of scientists described the increase in the caveolin-1 in the microvascular endothelial cells in an early stage of lung fibrosis. Indeed, the treatment of rat lung slices with $CdCl_2$ and TGF-β1 for three days led to changes as observed in early stages of lung fibrogenesis including deposition of extracellular matrix accumulation, myofibroblast transdifferentiation, loss of type I cells along with increased apoptosis of epithelial and non-epithelial cells of the lungs. Along with these changes, Western blot analysis confirmed the increase in caveolin-1 immunoreactivity in the pulmonary microvascular endothelial cells (Kasper et al., 2004). These differential changes in the expression of caveolin-1 may be due to different roles of epithelial and endothelial cells in lung fibrosis. The authors hypothesized that a decrease in caveolin-1 expression in the alveolar epithelial cells may interfere with cell signaling, pinocytic pathway and cell surface plasminogen activation, which may be critical in the development of lung fibrosis (Marshall et al., 1991; Kasper et al., 1998). On the contrary, an increase in caveolin-1in the capillary endothelium may possibly mimic the conditions of diabetic nephropathy and hyperlipidemia, in which an increase in caveolar transcytosis is associated with excessive deposition of extracellular matrix in the form of fibrosis (Guan et al., 2013; Van Krieken and Krepinsky, 2017). Nevertheless, the precise role of differential change in caveolin-1 in the epithelial and endothelial cells in lung fibrosis is not experimentally validated.

3. Diffuse lung parenchymal lung diseases associated with reduction in caveolin-1

3.1. Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis is an epithelial–fibroblastic disease with a mysterious pathogenesis in which unknown endogenous or exogenous factor disrupts the homeostasis of alveolar epithelial cells and triggers the epithelial-cell injury followed by aberrant epithelial repair. Histopathologically, this disease is characterized by diffuse interstitial fibrosis with mild inflammation (Khalil and O'Connor, 2004). There have been studies showing the key role of caveolin-1 in regulating the development of fibrosis in the patients as well as in the experimental models of idiopathic pulmonary fibrosis (Verma and Slutsky, 2007; Lino Cardenas et al., 2013). A significant reduction in the caveolin-1 expression has been documented in the lung tissues and in primary pulmonary fibroblasts isolated from patients of idiopathic pulmonary fibrosis (Sanders et al., 2015). In bleomycin-induced pulmonary fibrosis, there was a significant decrease in caveolin-1 expression along with an increase in lung fibrosis as indicated by increase in the hydroxyproline content (Wang et al., 2006). However, exogenous delivery of caveolin-1 through intrathecal route attenuated the extent of lung fibrosis in bleomycin-instilled mice and restored structural integrity of lungs (Wang et al., 2006). In an *in vitro* study, exogenous administration of TGF-β_1 was shown to decrease the expression of caveolin-1 in the human pulmonary fibroblasts. The exogenous addition of caveolin-1 prevented TGF-β1-induced increase in extracellular matrix deposition in the cultured human pulmonary fibroblasts (Wang et al., 2006). The *in vitro* study of Ding et al. describes that the treatment with TGF-β1 decreases the mRNA and protein expression of caveolin-1 in the human fetal lung fibroblasts in a dose- and time-dependent manner. Moreover, the authors showed an increase in the protein expressions of collagen-I and alpha-smooth muscle actin suggesting the inverse relationship between the caveolin-1 and the components of extracellular matrix (Ding et al., 2010). Apart from the direct profibrogenic effects of TGF-β1, it has been hypothesized that imbalance in TGF-β1 and caveolin-1 triggers poorly understood cascade of signaling pathways, which compromise the regenerative potential of parenchymal epithelial stem cells. This may eventually result in severe and irreversible functional impairment of lungs due to scarring, fibrosis, bronchiolar proliferation and abnormal remodeling (Chilosi et al., 2010).

Scientists have described the antifibrogenic actions of selected pharmacological agents in experimental models of idiopathic pulmonary fibrosis may be mediated through an increase in the caveolin-1 expression in the lungs. It has been shown that the beneficial effects of fluorofenidone, a novel pyridone agent, in attenuating levels of TGF-β1, collagen I, α-smooth muscle actin and fibronectin in bleomycin-induced pulmonary fibrosis in mice are secondary to the restoration of caveolin 1 levels (Meng et al., 2012). Moreover, it is also shown to attenuate TGF-β1-induced lung fibroblast activation *via* restoring the expression of caveolin-1 (Liu et al., 2015). On the similar lines, Yu et al. described the beneficial effects of pirfenidone and acetylcysteine in attenuating the levels of TGF-β1 and pulmonary fibrosis in bleomycin-instilled rats, secondary to enhancement in caveolin-1 expression (Yu et al., 2017). Ginsenoside Rg1, an active ingredient of *Panax Notoginseng*, exerts antifibrotic actions in bleomycin-instilled rats and prevents the development of pulmonary fibrosis in terms of decrease in the contents of alpha smooth muscle actin and hydroxyproline in a dose-dependent manner (Zhan et al., 2016). Moreover, it increases the mRNA and protein expression of caveolin-1 with a corresponding decrease in the expression of TGF-β1 in the lung tissues (Zhan et al., 2016).

3.2. Allergen-induced airway remodeling

Persistent exposure to allergens is known to trigger airway remodeling, which is characterized by TGF-β1 mediated-subepithelial airway fibrosis (Kenyon et al., 2003). In ovalbumin (OVA) sensitized mice (injection of OVA for 12 days), intranasal challenge with OVA led to significant development of lung fibrosis accompanied by increase in the levels of TGF-β1 (Yum et al., 2011). Importantly, there has been a significant decrease in the mRNA and protein expression of caveolin-1 in the lung tissues including on the lung fibroblasts in OVA-sensitized mice. The protective role of caveolin-1 against the development of lung fibrosis was further demonstrated by the results showing the enhancement in TGF-β1-mediated fibrosis in OVA challenged caveolin-1-deficient mice. It suggests that caveolin-1 mainly acts to inhibit the functioning of TGF-β1 and hence, it serves a negative regulator of TGF-β1. The exact mechanisms responsible for the decreased functioning of TGF-β1 in the presence of caveolin-1 are not clear. However, it may be possible that caveolin-1 acts as the scaffolding protein and it forms invaginations on the plasma membrane to enfold TGF-β1 receptors and inhibit the activity of TGF-β1 (Le Saux et al., 2008a).

3.3. Systemic sclerosis-associated lung fibrosis

Interstitial lung disease is a common complication of systemic sclerosis, an autoimmune disorder, which is characterized by interstitial pneumonia with a larger number of myofibroblasts and significant injury to epithelial and endothelial cells. The studies conducted in systemic sclerosis patients revealed a marked decrease in the caveolin-1 expression in their lungs (Del Galdo et al., 2008a; Yilmaz et al., 2014; Reese et al., 2014). These clinical results were substantiated by preclinical study in which caveolin-1 knockout mice showed greater degree of pulmonary fibrosis. However, restoration of caveolin-1 function by using a cell-permeable peptide corresponding to caveolin-1 scaffolding domain abrogated TGF-β1-mediated changes in the cultured fibroblasts of systemic sclerosis. This suggests that the downregulation

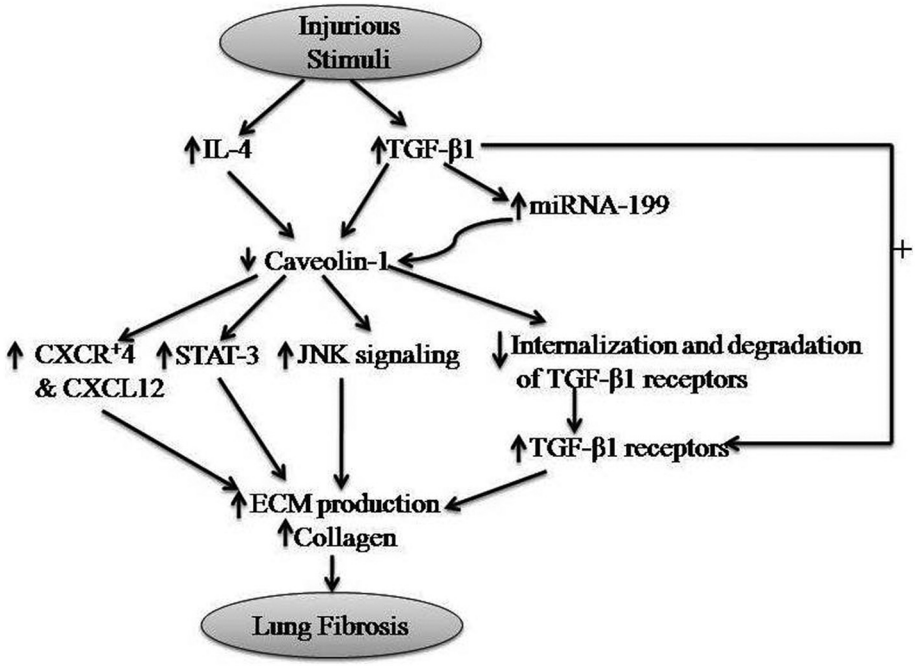

Fig. 1. Role of caveolin-1 and associated signaling pathway in the pathogenesis of lung fibrosis.

of caveolin-1 may potentiate the actions of TGF-β1 to promote lung fibrosis in systemic sclerosis (Del Galdo et al., 2008a). Moreover, restoration of caveolin-1 function by administering the caveolin scaffolding domain peptide reverses lung fibrosis in experimental model of systemic sclerosis-associated interstitial lung disease (Tourkina et al., 2011). Accordingly, it is suggested that caveolin-1-mediated inhibition of TGF-β/Smad signaling *via* caveolin-1 scaffolding domain may play an important role in the development of lung fibrosis in systemic sclerosis (Qian and Ueno, 2010). Another study has shown the reduced expression of caveolin-1 protein on the fibroblasts of systemic sclerosis-associated interstitial lung disease, which may activate the signaling pathways involved in increasing collagen production and overexpression of alpha-smooth muscle cell actin (Silver and Wells, 2008). A clinical study in patients suffering from systemic sclerosis-associated interstitial lung disease has shown a significant decrease in the levels of caveolin-1 in the serum and sputum in comparison to healthy volunteers again suggesting the key role of caveolin-1 in the development of lung fibrosis (Yilmaz et al., 2014).

Based on these studies, it is evident that increase in caveolin-1 down-regulates the actions of TGF-β1, however, the precise mechanisms responsible for caveolin-1-mediated downregulation of TGF-β1 function are not clear. It is proposed that in the presence of caevolin-1, the decrease in TGF-β1 signaling may be possibly due to internalization of TGF-β1 receptors through caveolin-1 lipid rafts followed by the degradation of these receptors (Del Galdo et al., 2008b). Another study has shown that human syndecan-2 protein helps in promoting caveolin-1-mediated internalization and degradation of TGF-β1 receptors. Indeed, transgenic mice constitutively over-expressing human syndecan-2 in the macrophages were resistant to lung fibrosis due to inhibition of TGF-β1-dependent signaling pathway. *In vitro* studies also showed that syndecan-2 promotes caveolin-1-dependent internalization and degradation of TGF-β1 receptors in the alveolar epithelial cells (Shi et al., 2013).

3.4. Other diseases

Scientists have also revealed the important contribution of caveolin-1 in the development of lung fibrosis in other disease models including animal model of rheumatoid arthritis-interstitial lung disease. Administration of freund's complete adjuvant to rats to induce adjuvant arthritis was associated with the development of pulmonary inflammation and fibrosis, which was closely related to a significant decrease in the protein expression of caveolin-1 and increase in the expression of TGF-β1 (Song et al., 2016). Chronic exposure to cleaning detergents limits the lung functions in humans, which may lead to decreased pulmonary functions (Vizcaya et al., 2015). In an *in vitro* study, Park et al. (2019) reported that exposure of ammonium lauryl sulfate to cultured alveolar macrophages producsd mitochondrial damage, increases free radical production and increased apoptotic cell death. Additionally, a decrease in the expression of caveolin-1 along with increase in TGF-β1 was also documented again projecting caveolin-1 as a key target in lung fibrosis (Park et al., 2019).

4. Possible mechanisms involved in caveolin-dependent lung fibrosis

4.1. c-Jun N-terminal kinase (JNK) signaling pathway

The loss of caveolin-1 results in the hyperactivation of signaling molecules including JNK, which in turn is associated with overexpression of collagen and tenascin-C (Tourkina and Hoffman, 2012). The study of Wang et al. (2006) described that caveolin-1 decreases the extracellular matrix production and fibrosis in idiopathic pulmonary fibrosis through regulation of the JNK signaling pathway. An increase in the components of JNK signaling along with a decrease in caveolin-1 was observed in the lung tissues and in primary pulmonary fibroblasts isolated from idiopathic pulmonary fibrosis. Similar changes were also documented in bleomycin-instilled lung tissues suggesting that the activation of JNK pathway and decrease in caveolin-1 are critical in the development of lung fibrosis. The interrelationship between caveolin-1 and JNK was further established by the results showing a dramatic suppression in the JNK signaling in response to treatment with caveolin-1. Furthermore, TGF-β1 failed to increase extracellular matrix production in JNK1-null fibroblasts and the results were very similar as observed after the treatment with caveolin-1. Accordingly, it may be suggested that a decrease in the expression of caveolin-1 may overactivate the JNK signaling to promote fibrosis in idiopathic pulmonary fibrosis (Fig. 1) and thus, exogenous treatment with caveolin-1 may

prevent lung fibrosis by inhibiting the JNK signaling pathway (Wang et al., 2006). The antifibrogenic effects of fluorofenidone in bleomycin-induced pulmonary fibrosis have also been attributed to increase in caveolin-1 and inhibition of JNK signaling pathway (Meng et al., 2012).

4.2. Inflammatory cytokines: Chemokine receptor type 4-positive ($CXCR4^+$) and its ligand CXCL12

Pulmonary fibrosis is characterized by an inflammatory phase during which inflammatory cells migrate from the peripheral blood into the damaged lung tissue and precede the collagen deposition. This transmigration is mediated by chemoattractant chemokines such as stromal cell–derived factor-1 (SDF-1/CXCL12) that bind and activate chemokine receptors on the inflammatory cells, monocytes and fibrocytes (Moore et al., 2006). The reduction in caveolin-1 plays a key role in neutrophil activation, transendothelial migration, and resultant lung inflammation (Hu et al., 2008). Therefore, it has been suggested that caveolin-1 negatively regulates the expression of $CXCR4^+$ and CXCL12 to prevent fibrosis in lungs. In bleomycin induced fibrosis, upregulation of the CXCL12/ CXCR4 axis was shown to increase the migration of monocytes and fibrocytes into the lungs (Phillips et al., 2004). In systemic sclerosis-associated interstitial lung disease, an increase in the expression of $CXCR4^+$ on the immune cells along with CXCL12 was reported in the lung tissues. Moreover, the expression of CXCR4 was increased manifold in caveolin-1 lacking monocytes, which was also associated with hyper-migration of monocytes and increase in fibrosis. The restoration of caveolin-1 function by administering caveolin scaffolding domain peptide was shown to reverse the hyper-migration of monocytes, inhibit the accumulation of inflammatory cells in the lung and lung fibrosis (Tourkina et al., 2011; Tourkina and Hoffman, 2012).

4.3. Inflammatory cytokines: IL-4

It has been shown that a decrease in the expression of caveolin-1 during the development of lung fibrosis is dependent on the presence of IL-4 (Le Saux et al., 2008a). Le Saux et al. demonstrated that the intratracheal instillation of IL-4 for 7 days led to the development of airway fibrosis similar to that observed following OVA-challenge. IL-4-induced lung fibrosis was characterized by a decrease in caveolin-1 and increase in the TGF-β1 levels in the lung tissue (Fig. 1). Furthermore, allergen-induced lung fibrosis and decrease in caveolin-1 was significantly abolished in IL-4-deficient mice suggesting that the presence of IL-4 is essential to induce caveolin-dependent lung fibrosis (Le Saux et al., 2008a).

4.4. Epigenetic regulation

Studies have shown that the epigenetic mechanisms may be involved in down-regulating the expression of caveolin-1 in idiopathic pulmonary fibrosis (Sanders et al., 2017; Lino Cardenas et al., 2013). miRNAs are non-protein coding RNA molecules interfere with the post-transcriptional process by inhibiting the target mRNA and miRNAs have been considered as important components of the epigenetic regulatory mechanisms (von Born et al., 2018). The study of Lino Cardenas et al. (2013) described that the pulmonary expression of miR-199a-5p was significantly increased, particularly in myofibroblasts in bleomycin-induced fibrosis model. Furthermore, the authors also showed that exposure to TGF-β1 increase the expression of miR-199a-5p in the cultured lung fibroblasts, which was sufficient to promote pathogenic activation of pulmonary fibroblasts including proliferation, migration, invasion, and differentiation to myofibroblasts. Not only this, an increase in the expression of miR-199a-5p was also correlated to the decrease in caveolin-1 expression (Fig. 1). It suggests that upregulation of miR-199a-5p during lung injury promotes fibrosis and mediates TGF-β-induced pathogenic activation of lung fibroblasts by inhibiting the expression of caveolin-1 (Lino Cardenas et al., 2013). The study of Sanders et al. has shown the involvement of another epigenetic mechanism *i.e.* histone modification in decreasing the expression of caveolin-1 in idiopathic pulmonary fibrosis. PCR-based analysis of lung fibroblasts of idiopathic pulmonary fibrosis patients revealed the correlation between downregulation of caveolin-1 and histone modification in the caveolin-1 promoter region. Indeed, a correlation was described between the active histone modification mark, H3 lysine 4 trimethylation, and downregulation of caveolin-1 in the activated/fibrotic lung fibroblasts. It suggests that the therapeutic strategies may be employed to prevent histone modifications and restore caveolin-1 expression in the fibroblasts to prevent pathogenic lung fibrosis (Sanders et al., 2017).

4.5. Signal transducers and activators of transcription (STAT) proteins

The key role of STAT in association with caveolin-1 in lung fibrosis has been described by employing caveolin-1-deficient lung fibroblasts (Ryter et al., 2014). These authors showed that the treatment of caveolin-1-deficient lung fibroblasts with TGF-β1 up-regulates the expression of STAT3, without any significant effect on STAT1 activation. The genetic ablation of STAT3 by siRNA failed to increase the expression of genes involved in cell proliferation and fibrogenesis. Accordingly, it may be proposed that the antiproliferative and antifibrogenic actions of caveolin-1 are mediated by inhibiting the excessive activation of STAT3 (Fig. 1) and dysregulation of STAT3 signaling in caveolin-1 deficiency is important to the development of tissue fibrosis (Ryter et al., 2014).

5. Discussion

Caveolin-1 is a key structural component of caveolae and plays a significant role in endocytosis, transcytosis and cell signaling (Quest et al., 2008; Sun et al., 2010). Studies have shown that there is a significant decrease in the caveolin-1 expression in the alveolar epithelial cells and fibroblasts along with increase in the expression in the capillary endothelium during the lung fibrogenesis (Kasper et al., 1998, 2004; Wang et al., 2006). In other words, lung fibrosis inducing agents/stimuli induce the reduction of caveolin-1 expression in the lung tissues and this decrease is expression is critical in inducing the development of lung fibrosis. It may be possible that the decrease in caveolin-1 expression during lung injury may be due to ubiquitination and lysosomal degradation. Indeed, it is well documented that the N-terminal domain of caveolin-1 is not required for formation of caveolae. Rather this domain has regulatory function and it is usually modified by mono-ubiquitin (mostly) and short ubiquitin chains (Kirchner et al., 2013; Mundy et al., 2012). Another protein, termed as valosin-containing protein (VAP) binds to the monoubiquitinated caveolin-1 and helps in its inward transportation to the late endosomes and lysosomes for degradation (Ritz et al., 2011). Accordingly, it may be hypothesized that the decrease in the caveolin-1 expression during the lung fibrosis may be secondary to increased ubiquitination and lysosomal degradation of caveolin-1. However, experimental studies are required to elucidate the role of ubiquitination and lysosomal degradation in reducing caveloin-1 expression in the lung tissues during lung fibrosis.

The anti-fibrotic functions of caveolin-1 are mainly mediated through inhibition of TGF-β-triggered proliferative actions. It is suggested that caveolin-1 may prevent TGF-β-mediated phosphorylation of Smad2 to prevent its signaling cascade (Razani et al., 2001). Moreover, it is also suggested that the internalization and degradation of TGF-β1 receptors through lipid rafts may also contribute in decreasing the proliferative actions of TGF-β1 (Del Galdo et al., 2008b). It has been proposed that membranous proteins like caveolin-1 are heterogeneously distributed and are clustered within cholesterol and glycophosphatidylinositol enriched microdomains, termed as lipid rafts (Levental and Veatch, 2016; Roh et al., 2014). Caveolae represent a

morphologically distinct subtype of lipid rafts and role of latter in regulating apoptosis of fibroblasts along with lung injury resolution has been described (Liu et al., 2017). Studies have shown that the alterations in lipid rafts-dependent endocytosis through caveolin-1 may be of pathological significance (Cha et al., 2015). Moreover, it is also shown that recruitment of TGF-β receptors from the lipid rafts (caveolae) to non-lipid raft microdomains enhances the functional activity of TGF-β (Huang et al., 2016). Accordingly, it is possible to hypothesize that lipid rafts-dependent internalization and non-functionality of TGF-β receptors may contribute in decreasing the fibrogenic actions of TGF-β in the presence of caveolin-1. The other signaling pathways involved in caveolin-1 mediated anti-fibrotic actions include JNK signaling, IL-4, STAT-3, miR199a-5p, $CXCR4^+$ and CXCL12 (Tourkina et al., 2011; Tourkina and Hoffman, 2012; Ryter et al., 2014; Sanders et al., 2017; Meng et al., 2012).

Although the role of caveolin-1 has been mainly highlighted in the development of lung fibrosis, yet the role of other caveolin has also been described. It has been described that the lung remodeling following acute myocardial infarction is associated with a significant decline in the expression of both caveolin-1 and -2 in the rat lungs (Jasmin et al., 2004). The decrease in the expression of both caveolins was also demonstrated in mice developing spontaneous lung dysfunction and fibrosis (Koval et al., 2011). Like caveolin-1, there is a key role of caveolin-2 in the normal lung functioning and its deficiency increases the cellularity in the lung parenchyma, thickens the alveolar septa and increases the number of endothelial cells (Razani et al., 2002). Moreover, caveolin-$2^{-/-}$ mice are also more prone to bleomycin-induced lung fibrosis. The decrease in the expression of caveolin-2 following treatment with pulmonary fibrosis-inducer bleomycin again highlights the role of caveolin-2 in the development of lung fibrosis (de Almeida et al., 2013). Mechanistically, caveolin-2 is reported as a negative regulator of TGF-β and the anti-proliferative effects of latter are diminished in the presence of caveolin-2. Indeed, caveolin-2 inhibits the anti-proliferative actions by suppressing TGF-β-induced Smad2/3 phosphorylation (Xie et al., 2011). Like caveolin-1, caveolin-2 is also reported to attenuate lung fibrosis by inhibiting STAT3 dependent signaling pathway (Jasmin et al., 2004). In relation to caveolin-3, its role in modulating airway response to cholinergic and serotonergic stimuli has been described (Keshavarz et al., 2018); however, its role in the development of lung fibrosis in not well defined.

6. Conclusion

The expression of caveolin-1 in the lung tissues is important to prevent the fibrogenic actions of TGF-β1 in the pathogenesis of lung fibrosis of different etiology including idiopathic pulmonary fibrosis, systemic sclerosis-associated interstitial lung disease and allergen-induced airway remodeling. Caveolin-1 mediated internalization and degradation of TGF-β1 receptors may possibly account for the decreased actions of TGF-β1 in inducing lung fibrosis. The biological actions of caveolin-1 involve signaling pathways including JNK signaling, IL-4, STAT-3, miR199a-5p, $CXCR4^+$ and CXCL12. Therefore, caveolin-1 and caveolin-1 triggered signaling pathway may be potentially employed to overcome lung fibrosis of diverse etiology.

Declaration of Competing Interest

None.

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