Review Article

Augmentation of Mast Cell Stability, a Therapeutic Strategy for Idiopathic Pulmonary Fibrosis

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Abdullah and Mazumder: Therapeutic Strategies for Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is a continuous deteriorating type of interstitial lung disease. In clinical practice, inhibition of fibrotic progression is essential. Currently available interventions for idiopathic pulmonary fibrosis are confined to prophylactic effects and also have limitations with dose-associated adverse effects. Progressive nature of idiopathic pulmonary fibrosis and unavailability of therapeutic drugs together is a huge setback for treating advanced stages of fibrotic conditions. Further, monotherapy with antifibrotic agents may not be adequate as various underlying mechanisms are involved in the development of idiopathic pulmonary fibrosis. The present article made an attempt to discuss potential targets that could impede fibrotic progression for developing mechanism-based strategies for the therapeutic control of idiopathic pulmonary fibrosis. A suitable combination therapy to potentiate antifibrotic effects with parallel augmentation of mast cell stability could be considered as a possible approach to stop disease progression as well as aid in the reversal of fibrotic condition in established idiopathic pulmonary fibrosis.

Key words: Antifibrotic agents, combination therapy, idiopathic pulmonary fibrosis, mast cell stability

Idiopathic pulmonary fibrosis (IPF) is a frequent type of interstitial lung disease, coupled with progressive tissue damage. It has unidentified etiology and imprecise pathogenesis. However, it is characterized by chronic inflammation and excess accumulation of extracellular matrix (ECM) components in lungs[1]. Globally, the incidence of IPF is found to be equivalent to stomach, liver, testicular and cervical cancer[2]. Prognosis of IPF is reported to be very poor with consistent progression of the disease[3,4]. The life expectancy in IPF is restricted to almost 3 y as median survival with 50% mortality after its confirmed diagnosis[4,5].

In the last few decades, considerable research efforts were applied to develop an effective antifibrotic agent. Unfortunately, despite various attempts except two drugs, pirfenidone and nintedanib, no other drug was approved by USFDA for the treatment of IPF[4]. The effects of these drugs are limited to slowing down the disease progression but not reversal of fibrotic severity in established IPF[6]. Recent clinical data on drugs revealed that these have dose-related adverse effects[3]. Moreover, pre-clinical studies indicated carcinogenic potential[7]. In the CAPACITY trial, the nintedanib-administered group reported diarrhea in >90 % of patients as the major adverse effect and also elevated levels of hepatic enzymes were seen[8]. Therapeutically safe and effective drug therapy is the ultimate requirement in the management of IPF. Sub-therapeutic action and associated adverse effects of conventional interventions usually impel the clinicians to look for the alternative treatments.

This review is an attempt to contribute to the knowledge of potential targets to impede disease progression and possible combination therapy to overcome the limitations of antifibrotic agents against IPF. In this article, an overview of the pathogenesis of IPF has been represented and subsequently the role of mast cells in the development of IPF has been discussed. Also, previous studies outcome of newly recognized antifibrotic agents have been summarized. Further,

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various mechanisms of antifibrotic agents involved in mast cell stabilization has been portrayed, which has been considered for the advancement of therapeutic control in IPF.

The data extracted included clinical, pre-clinical, systematic reviews and clinical practice guidelines published in PubMed and Google Scholar database using the keywords, idiopathic pulmonary fibrosis, mast cell, chronic inflammation and antifibrotic agents. Literature review included articles published during 1990 to 2019, which were used for the preparation of this manuscript. However, some relevant references from much older publications have also been included.

PATHOGENESIS OF IDIOPATHIC PULMONARY FIBROSIS

The actual reasons behind the onset of IPF are unknown and pathogenesis is also not clear. Broadly it has been suggested, that, IPF develops usually by repeated occurrence of microinjury to alveolar epithelial cells (AECs)[6,9]. It is essential to understand the cellular and molecular interactions in the development of IPF, mainly to derive effective therapeutic strategies. In general, fibrosis involves complicated inflammatory process, which occurs in association with several inflammatory mediators. During microinjury to AEC, inflammatory cells release various inflammatory mediators that can participate either to stimulate (profibrotic) or to inhibit (antifibrotic) the development of fibrosis. As per integrated views of several researches, chronic inflammation and disturbances in tissue healing process due to frequent microinjuries are the main concerns in the pathogenesis of IPF[1,9], where fibrosis may be developed under the influence of profibrotic mediators secreted from inflammatory cells[1,6]. Overall, it has been suggested that most important pathological factor responsible for onset of IPF is chronic inflammation[10].

Inflammation and fibrosis are interrelated with complicated signaling mechanisms[11]. Immediately after the incidence of microinjury, tissue repairing process initiate various types of cell interaction in which, the involvements of inflammatory cells are consider as the critical step[1]. Generally, microinjury to AECs and their subsequent response are associated directly to oxidative stress and inflammation. Persistent exposure of stimuli creates oxidative stress that leads to tissue damage, however, inflammation as a natural protective defense mechanism responses against the tissue injury[11], where mast cells play a chief function to initiate the process of inflammation[12,13] by releasing various inflammatory mediators as shown in fig. 1.

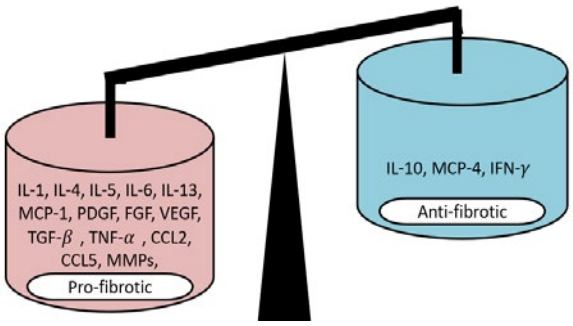

Fig. 1: Mast cell Inflammatory mediators involved profibrotic and antifibrotic effects[45,81-83]

CCL- chemokine ligand; FGF- fibroblast growth factor; IFN- interferon; IL- interleukin; MCP- monocyte chemoattractant protein; MMPs- matrix metalloproteinases; PDGF- platelet-derived growth factor; TNF- tumor necrosis factor; TGF- tumor growth factor; VEGF- vascular endothelial growth factor.

Inflammatory mediator release by mast cells can also occur as a consequence of other well-known factor such as allergens. Mast cell degranulation in allergic reactions involves FcεRI receptor activation. This receptor is vastly expressed on the surface of mast cells and correspondingly governed by increased concentrations of IgE[14]. The increased concentration of IgE in serum has been found to accompany pulmonary fibrosis[15]. Repeated degranulation of mast cells create imbalance between profibrotic and antifibrotic mediators, which finally provokes intense fibroblast activity and the activated fibroblast primarily participates in the pathogenesis of pulmonary fibrosis[16]. Moreover, epithelia mesenchymal transition, fibroblast differentiation into myofibroblast, over production of collagen, excess ECM deposition and subsequent cellular structural remodeling arises as characteristic of IPF[9,10].

ROLE OF MAST CELLS IN IDIOPATHIC PULMONARY FIBROSIS

Agents targeting the inflammatory cells like lymphocytes, macrophages and neutrophils could not inhibit the development of fibrosis. However, in the fibrotic condition it is reported that, concentration of mast cell increases and promotes fibrosis by the release of histamine, renin and growth factors[17]. Recently, histamine and renin have been identified as two fibrotic mediators primarily released from mast cells, which promote proliferation, Transforming growth factor-β (TGF-β) secretion and collagen synthesis by activating the fibroblasts in lungs of both human as well as rats[18]. Mast cell as the chief effector cell in inflammatory disease such as interstitial lung disease (ILD), is widely

expected to be accountable for the initiation of organ fibrosis[19], where, specifically Th2 cytokine (IL-9) initiates the mast cell recruitment and activation[20]. Chronic inflammation that occurs due to repeated lung injury causes frequent mast cell activation and recruitment in particular organ, which in turn leads to initiate fibroblast proliferation, differentiation and excess collagen production and ultimately assist in fibrotic disease progression[21]. Further, inflammatory damage can develop fibroblastic foci by continuous activity of TGF-β, platelet-derived growth factor (PDGF) and the basic fibroblast growth factor (bFGF) [22]. Chymase is the protease enzyme, primarily released from the mast cell, increases TGF-β activity and promotes establishment of pulmonary fibrosis[23] by activating fibroblast proliferation, excess production of collagen and matrix metalloproteinases (MMPs)[24]. Post allergen challenge, chymase may also participate in development of sub-epithelial fibrosis[25]. Among various mast cell mediators, chymase is considered as the main component responsible for the transformation of TGF-β from latent to active form[26] whereby, TGF-β play a key role in fibroblast activation, proliferation and fibroblast-myofibroblast differentiation[27]. Tryptase, is another protease enzyme, which is expressed by all kinds of mast cells and contributes to inflammation in many types of autoimmune diseases as well as in fibrosis[28,29]. Trans-differentiation of fibroblast into myofibroblast has a critical concern in the development of IPF related to overexpression of tumor necrosis factor α (TNF-α) and excess deposition of ECM that provides rigidity to the cells structure[30]. In addition, mast cells synthesize and store proteoglycans likes chondroitin sulphate and hyaluronic acid[31], which are released as matrix components in the lung interstitial space post degranulation and cause cellular structural remodeling either directly or by mitogenic effects on lung fibrotic cells[32].

In vivo study conducted in mice has showed that protease enzymes released from mast cells have direct contribution in bleomycin-induced interstitial lung injury[33]. Further, a comparative clinical study between fibrotic and non-fibrotic lungs, has demonstrated severity of fibrotic conditions had been increased with the increase in number of mast cells[34]. Additionally in IPF patients, the histamine level in bronchoalveolar fluid (BALF) has been reported 10 times higher in comparison to control individuals[35], which is also associated with elevated levels of tryptase and mast cells are considered the major source of both histamine and tryptase[36]. Furthermore, it has been reported that, human lung mast cell releases tryptase enzyme upon activation by co-culturing with lung fibroblasts obtained from IPF patients[36] and the presence of excess of inflammatory cells in the lungs tissue indicates continuous process of mast cell degranulation[34]. Moreover in IPF patients, infiltrations of inflammatory cells represented that, release of growth factors mainly TGF-β, is responsible for the onset of fibrosis[37], by deposition of collagen fibers, smooth muscle cells (SMC), fibroblasts and myofibroblast type cells[36,37]. In case of diffuse interstitial fibrotic patients, increased secretion of stem cell factor (SCF) from lung fibroblasts has been reported, which may also has an important contribution in the establishment of ILD[38]. Furthermore, in comparison to control subjects, the expression of SCF was found elevated in intact lung tissue as well as in isolated lung fibroblasts from IPF patients[36]. These interpretations advocate that interaction between mast cells and fibroblasts play a pivotal role in excess deposition of ECM and lead to develop lung fibrosis. Moreover, a previous study demonstrated, upon activation, mast cells release many of the profibrotic mediators locally that include chymase, tryptase, renin, histamine, leukotriene and TGF-β[39]. Hence, it appears clearly that mast cells are closely associated with fibrosis[36,40], where in, mast cell-derived TGF-β promotes fibroblast activation, proliferation and differentiation into myofibroblasts[41] and play a critical role in the development of pulmonary fibrosis as illustrated in fig. 2.

TARGETS TO IMPEDE FIBROTIC PROGRESSION

Mast cells are involved in immune reactions, usually facilitate allergic diseases such as anaphylaxis, allergic rhinitis and asthma[13,42], as well as inflammatory diseases such as chronic obstructive pulmonary disorder and ILD[21]. Mast cells commonly become activated through conjugation of IgE with FcεRI receptors, which are present in excess on the mast cell surface[43]. Activation of mast cell can also occur by means of cytokines and other micro-environmental stimuli[44]. Generally, mast cells release various kinds of vasoactive and inflammatory mediators stored in granules within cytoplasm after receiving activation threshold[45] where, intracellular calcium ion concentration plays a significant role in the degranulation process[46]. Also, control of actin cytoskeleton mechanics to be considered as a decisive step in preventing the mast cell degranulation[47] primarily depends on intracellular calcium ion concentration as shown in fig. 3.

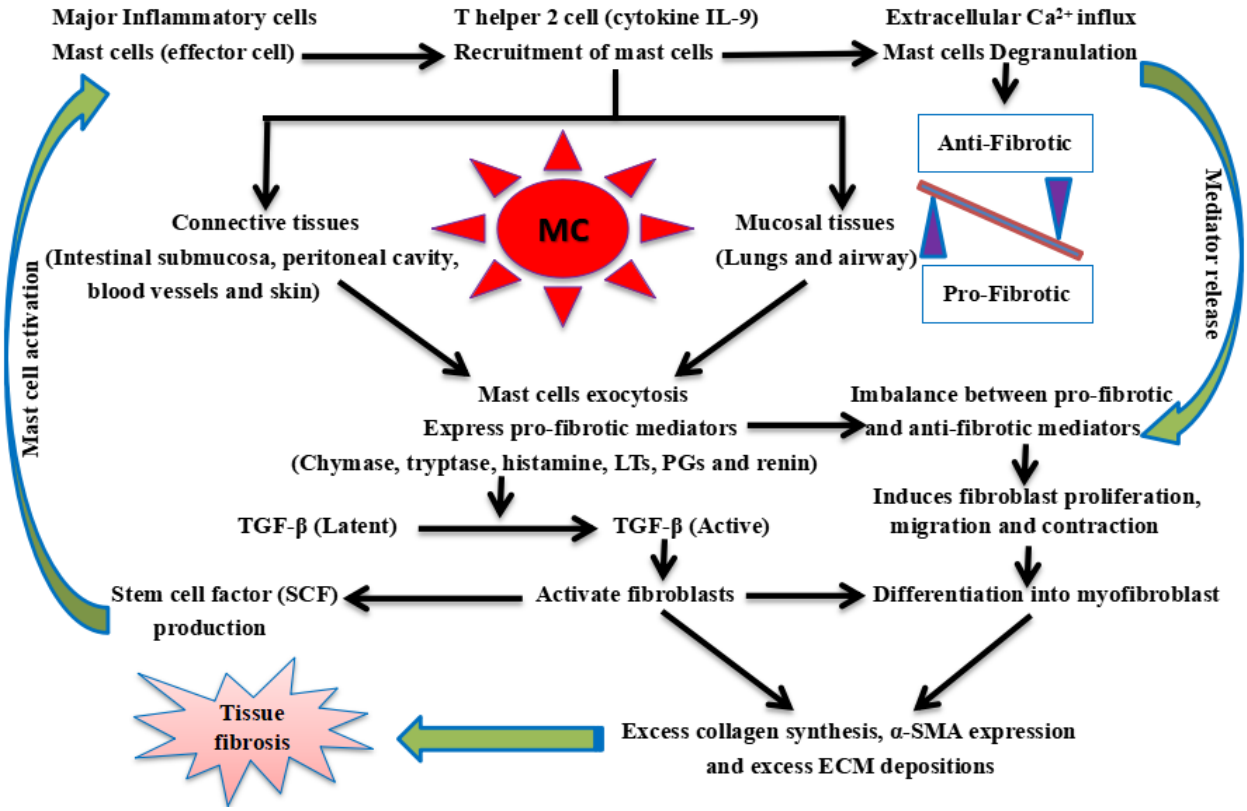

Fig. 2: Involvement of mast cells in activation, proliferation and differentiation of fibroblasts by means of various profibrotic mediators release after degranulation process that ultimately leads to development of tissue fibrosis

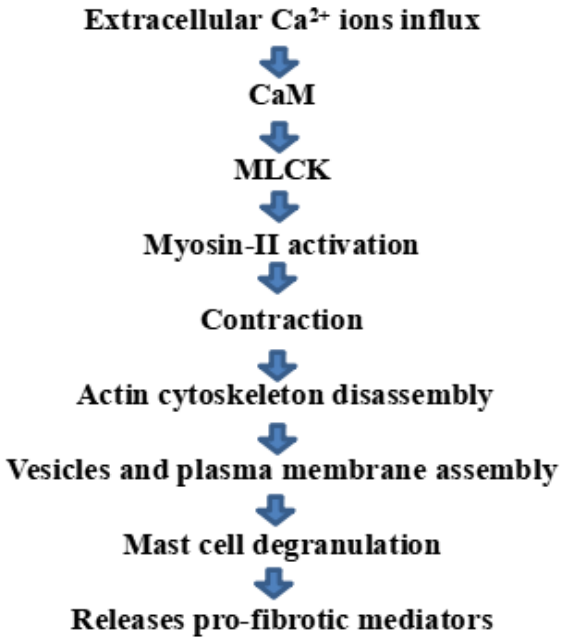

Fig. 3: Flow diagram of sequential steps involved in the mast cell degranulation

Sequential steps involved in the mast cell degranulation initiated by extracellular Ca^{2+} ions influx that finally leads to liberation of profibrotic mediators

Chronic inflammation as an important underlying mechanism of IPF[10], mast cell degranulation materializes frequently and creates imbalance between profibrotic and antifibrotic mediators[16]. These conditions lead to continuous disturbance in homeostasis[44]. In chronic inflammatory condition, degranulation of mast cells may take place in uncontrolled manner and releases excess of profibrotic mediators (cytokines, chemokines, growth factors and proteases) within target organ as represented in fig. 1, which provoke downstream mechanisms leading to progressive fibrosis[48] by involving different signaling pathways mainly PPAR-γ, NF-kB and TGF-β/Smad[49]. Thus, controlling excessive mast cell degranulation would provide potential therapeutic value in inhibition of fibrosis progression.

In view to inhibit mast cell degranulation, stabilizing agents can be used to prevent the activation of mast cell, where, it acts one step before the initiation of inflammatory cascade. But, the entire blockade of degranulation process practically might not be possible by using single mechanism based mast cell stabilizing

agent. Since, the major factor involved in mast cell degranulation process is usually intracellular calcium ion concentration, which is governed by various mechanisms as represented in fig. 4.

Targeting more than one mechanism to inhibit either direct or indirect entry of extracellular calcium ion would be wise enough and might produce profound inhibition of profibrotic mediator release by augmenting mast cell stability. Similarly, to get more control on the progression of IPF, optimum inhibition of mast cell degranulation is needed. This could be achievable by considering suitable combination of drugs acting by different mechanisms as potential tools to impede IPF progression.

ANTIFIBROTIC AGENTS WITH MAST CELL STABILIZATION PROPERTIES

Essentially, based on the outcome of recent pre-clinical studies, some active agents have been recognized that have preventive potential against animal models of IPF along with interesting facts related to ability to alter mast cell degranulation via different mechanisms. These antifibrotic agents included adenylyl cyclase activators, β-adenoreceptor agonists, flavonoids, mast cell stabilizers, phosphodiesterase inhibitors and procyanidins[50-69]. The antifibrotic actions of these agents have been reported at initial and pre-clinical stages as discussed below. However, their individual contributions in stabilizing the mast cell via different mechanisms are represented in fig. 4.

Adenylyl cyclase activators:

Forskolin, a diterpene from the roots of *Coleus forskohlii*, causes direct activation of adenylyl cyclase[50]. In a previous study, it had been observed that adenylate cyclase activity increased by 10-fold in rat cerebral cortical membranes after administration of forskolin. Activation of adenylyl cyclase enzyme leads to increase in the formation of cAMP. Forskolin mimics the effects of β-adrenoceptor agonists on fibroblast

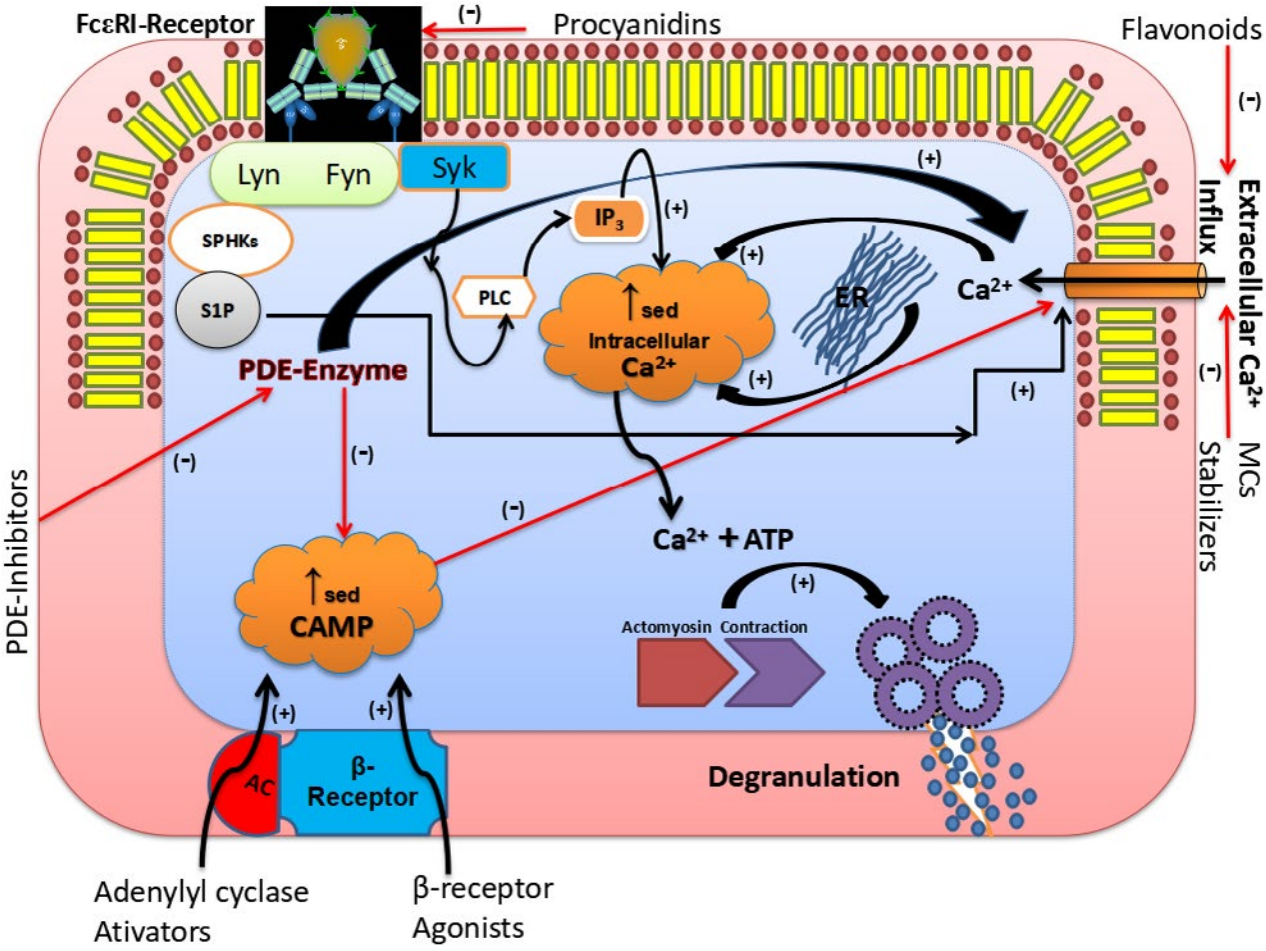

Fig. 4: Various mechanism of antifibrotic agents

Mechanisms of adenylyl cyclase activators, β-receptor agonists, flavonoids, mast cell stabilizers, phosphodiesterase inhibitors and Procyanidins involved in inhibition of mast cell degranulation acts through different specific targets including receptors, ions channels and enzymes and their favours in stabilization of mast cell. (+) promoting effect; (-) preventing effect

activation and proliferation. It also exhibited inhibitory effects on collagen synthesis, but diminished inhibition of fibroblast activity in fibrotic lungs due to insufficient phosphorylation of cAMP-response element binding (CREB) protein[51]. The role of cAMP in association with TGF-β had been investigated in the development of IPF[52]. Activation of cAMP exhibited reduction of myofibroblasts formation and deposition of ECM[53]. Therefore, agents such as forskolin that increase cAMP could be beneficial in mitigating IPF disease progression.

β-Adrenoceptors agonists:

β-adrenoceptor agonists inhibit many functions of lung fibroblasts. Non selective β-adrenoceptor agonist, isoprenaline as well as long-acting β2-adrenoceptor agonist formoterol and salmeterol inhibit cultured human lungs fibroblast proliferation. Isoprenaline, formoterol and salmeterol down regulated collagen synthesis[54-56]. Additionally, formoterol or salmeterol inhibited various cytokines including interleukin-1β (IL-1β), TNF-α or induced interferon-γ (IF-γ) expression[57,58]. Salmeterol decreased the basal and TNF-α related expression of α-smooth muscle actin (α-SMA) protein and fibroblast-myofibroblast differentiation[58].

Flavonoids:

There are different types of flavonoids, quercetin, luteolin and chrysin which were studied against bleomycin-induced pulmonary fibrosis in rodents. Effects of quercetin in bleomycin-induced pulmonary fibrosis revealed that bleomycin increased levels of BALF protein, hydroxyproline, malondialdehyde and total antioxidative capability of the lung tissue and the decreased levels of GSH/GSSG were almost reversed after treatment for 24 d[59]. Moreover, an *in vitro* study showed that quercetin could reverse the resistance to apoptosis of fibroblasts and modified the progression of firm pulmonary fibrosis in aged mice[60].

Similarly, chrysin exhibited protective effects on cell injury in lung fibrosis induced by bleomycin in rats. It was reported that chrysin has potential to significantly inhibit the bleomycin-induced lungs inflammation and fibrosis and also to reduce the activities of CAT, SOD, and levels of GSH[61].

Oral administration of luteolin (10 mg/kg) efficiently suppressed neutrophil infiltration, including elevated TNF-α and IL-6 levels in BALF, post bleomycin instillation in C57BL/6J mice. Luteolin demonstrated the ability to alleviate collagen deposition, TGF-β1 expression and lung fibrosis. However, these effects are mediated by inhibition of lungs inflammation and suppression of myofibroblast differentiation as well as epithelial mesenchymal cell transition[62].

Mast cell stabilizers:

In an experimental study to understand the contribution of mast cells in initiating pulmonary fibrosis, mast cell-deficient (MCD) mice were used to induce pulmonary fibrosis with bleomycin. It was observed that, MCD mice were protected against bleomycin-induced lung fibrosis, but protection was diminished upon incorporation of mast cells in the lung of MCD group. Additionally, mast cell mediators such as TGF-β, histamine and renin via angiotensin (ANG) II are identified as fibrotic agents[17]. Further, an *in vitro* study using both human and rat lung fibroblasts showed expression of H1 and AT1 receptor subtypes upon activation and they promote fibroblasts proliferation, TGF-β1 secretion and collagen synthesis[18]. It is evident that mast cell is a major source of TNF-α and act as an important inflammatory marker[17]. The effects of nedocromil was investigated on rat MC-derived TNF-α, whereby, it was reported that 2 h pre and 24 h post treatment with nedocromil inhibited TNF-α secretion by 20-37 and 59-83 %, respectively[63]. Moreover, fibroblasts and mast cells of fibrotic lungs showed presence of positive feedback effects through mast cell-derived protease enzymes, which stimulated the fibroblast growth in PAR-2/PKC-a/p44/42e dependent manner and also stimulated fibronectin and collagen production[36].

In vivo study of sodium cromolyn against the paraquat-induced pulmonary fibrosis was carried out in rodents, where sodium cromolyn showed significant reduction in the lung tissue damage and improved lung weight. It also decreased hydroxyproline content and collagen deposition in lung almost near to control. Further, it was reported that sodium cromolyn has the potential to decrease the fibrotic effects induced by paraquat via stabilizing the mast cell and inhibition of inflammatory mediators[64].

Phosphodiesterase (PDE) inhibitors:

PDE inhibitors cause indirect elevation of cAMP, which inhibits fibroblast proliferation. PDE inhibition also attenuated fibroblast chemotaxis, reduced α-SMA expression and enhanced the inhibitory effect of prostaglandin E_2 (PGE_2)[65]. In mice, PDE_4 inhibitor, roflumilast was evaluated under both preventive (day 0-21) and therapeutic (day 11-21) study protocol, against diphtheria toxin-induced lung fibrosis and was found to

have significantly improved the weight loss and lung collagen deposition that are the hallmarks of epithelial cell damage[66]. In bleomycin-induced lung injury model, roflumilast was reported to reduced hydroxyproline (primary pharmacodynamics marker of lung fibrosis) right ventricular hypertrophy, muscularization of pulmonary vessels and also diminished bleomycin-induced transcripts for TNF-α, TGF-β, collagen in lung tissues and growth factor. In addition, it reduced BALF containing TNF-α, interleukin-13, TGF-β levels and inflammatory cell counts in rats[67].

Procyanidins:

Procyanidins are natural constituents that belong to the proanthocyanidins class, which were also known as condensed tannins. Proanthocyanidins are a class of polyphenols available in a variety of plants. Chemically, these are oligomeric flavonoids and oligomers of catechin, epicatechin and their gallic acid esters. Recently, procyanidin C1 type has been identified as natural antiallergic agent, which has possibility to stabilize mast cell during allergic reaction by altering the binding affinity of IgE with FcεRI receptor[68]. *In vivo* study of proanthocyanidin indicated that, it could inhibit inflammatory cell infiltrations and fibrosis as well as decrease hydroxyproline content[69].

POSSIBILITY TO REVERSE ESTABLISHED IDIOPATHIC PULMONARY FIBROSIS

There are various possible mechanisms that might be targeted to inhibit different mediators and pathways in the development of antifibrotic drugs. These may be inhibitors of cytokine, chemokine, TGF-β, toll-like receptor and antihypertensive drugs, stem cell transplantation and other strategies[3,4]. In last few decades, several potential targets and strategies were suggested for the treatment of IPF. However, challenges to the clinicians to inhibit the disease progression including reversal of established IPF are still remain the same. Moreover, it has been reported that up to 45% of all deaths pertaining to respiratory disease are somehow related usually to fibrotic disorders in developed nations[70].

The treatment potential of antifibrotic agents in damaged tissues of lungs with no mark of histological evidence of fibrosis may be considered as an ideal treatment for IPF[71]. Also, inhibition of progression of lung fibrosis without disturbing the overall tissue healing process is primarily required in clinical management of IPF[72]. Currently, recovery from fibrosis appears unachievable even in most regenerating organ such as liver, when damaged tissue substituted with fibrous connective tissue, because persistent inflammation alters physiological changes of epithelial cell and leads to aberrant healing process[10,73]. In case of advanced IPF, degradation of ECM take place incompletely as endogenous antifibrotic mediators, MMPs are no more available in the target organ[74]. Further, up-regulation of tissue inhibitor of metalloproteinases-1 (TIMP-1) as profibrotic mediator contribute in collagen formation and inhibit ECM degradation[73]. Considering chronic inflammation as central mechanism liable for onset of IPF[10], causes continuous mast cell activation[75] and generates various profibrotic mediators, which leads activation and proliferation of fibroblast and enhances ECM deposition[16,39]. This may additionally contributes in opposing the reversal of fibrotic condition and constantly disturbing the homeostasis[44]. Moreover, targets with intention to treat the fibrotic conditions are primarily concentrating to inhibit cytokines (TGF-β1)[76], chemokines and inducers of angiogenesis, such as vascular endothelial growth factor (VEGF)[22]. However, many previous studies demonstrated these profibrotic mediators are primarily released from mast cell, which promoted proliferation, TGF-β secretion and collagen synthesis by activating the fibroblasts in lung tissues. Further, clinical study data of pirfenidone and nintedanib revealed that these are preventive in long-term disease progression[77]. However, these drugs claimed to enhance life expectancy to some extent by delaying disease progression in patients but were not able to prevent continued deterioration and failure to reverse fibrotic conditions in established IPF. Hence, till now no cure is available for IPF[78].

It is necessary to develop safe therapeutic strategies that halt disease progression and initiate reversal of established fibrosis in IPF. Overall, to obtain comprehensive recovery in established IPF, the principal prerequisites are to prevent mast cell degranulation and inhibit fibrosis simultaneously to the maximum extent. In view to enhance the therapeutic efficacy of antifibrotic agents, potentiation of antifibrotic effects with parallel augmentation of mast cell stability may be considered as a commendable approach.

An appropriate combination therapy of such antifibrotic agents, which have also an ability to impede mast cell degranulation by different mechanisms as shown in fig. 4, might advocate both retardation in disease progression and reversal of fibrotic conditions in established IPF. Because, such combination therapy

could maximize mast cell stabilization and minimize level of profibrotic mediators. Additionally, enhancement of antifibrotic effects may synergistically inhibit collagen production and increase ECM turnover from interstitial spaces. Elevated environment of profibrotic mediators due to frequent mast cell degranulation during chronic inflammation causes fibroblasts activation, play an important role in maintaining fibrotic structures and resists in ECM degradation[79-83], which may also effectively overcome by augmentation of mast cell stability.

Apart from these two approved drugs, pirfenidone and nintedanib, many other compounds such as adenylyl cyclase activators, β-adenoreceptor agonists, flavonoids, mast cell stabilizers, phosphodiesterase inhibitors and procyanidins have been identified. These have potential to inhibit fibrosis development as well as able to stabilize mast cell via different mechanisms. Treatment with suitable combination by using these antifibrotic agents might synergistically enhance both mast cell stability and antifibrotic effects. Therefore, such combination therapy could promise parallel potentiation of dual pharmacological effects, in retardation of disease progression as well as aid in the reversal of fibrotic condition in established IPF. Unfortunately, mainly due to lack of knowledge of benefits and risks of these combination therapies, result in loss of opportunities to enhance therapeutic control and possibility to improve patient condition in established IPF.

CONCLUSION

In conclusion, pharmacology based potentiation of mast cell stability by using different combinations of various proclaimed antifibrotic compounds reflected unique mechanistic approach in a dual manner. Firstly, it could extend the possibilities to inhibit disease progression. Secondly, these combinations might also improve quality of life by assisting the reversal of fibrotic condition of lungs, which is still challenging to the medical practitioners. Additionally, combination therapy could also lessen dose-associated adverse effects of antifibrotic agents. In future, the development of combined therapy with these compounds could effectively bring safe and novel therapeutic regimens to treat advanced stage IPF.

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