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Mast Cells Modulation: Potential Therapeutic Target for Anti-Fibrotic Activity

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ABSTRACT

Fibrosis is a severe pathological condition of most chronic inflammatory disorders. Excessive extracellular matrix component build-up is a characteristic of the disease. Organ dysfunction and death are the end results of the fibrotic progressive process. Fibrosis affects almost all the body's tissues. Chronic inflammatory conditions, infections, environmental factors and chronic secondary illness outcomes are some of the known causes of fibrosis. The two authorized and currently used fibrosis treatments are pirfenidone and nintedanib. The mechanism of pirfenidone is unclear however Nintedanib is a triple tyrosine kinase inhibitor. Therapeutic strategies that target inflammatory cells like macrophages, neutrophils, or lymphocytes have failed or had little success in changing the pathophysiology of fibrosis disease. Mast cells are attracting a lot of attention from fibrosis front research. The number of mast cells are increases in fibrosis condition and positively corelated with disease severity. Elevated expression of numerous mast cell mediators that may directly influence the excessive cellular matrix has been observed and various research suggests that regulating the activity of mast cell mediators might affect fibrotic tissue remodelling downstream. In this article, we look at how mast cells play a role in the aetiology of fibrosis and targeting mast cells might help with fibrosis disease management.

***Keywords**: fibrosis, mast cells, c-kit, kidney fibrosis, idiopathic pulmonary fibrosis, TGF-β*

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INTRODUCTION

Fibrosis is scarring of the tissue, which develops with continuous or repetitive exposure to stimuli. Fibrosis is characterised with a dysregulation in collagen synthesis, with I and II collagen deposition, and other extracellular matrix proteins, with the involvement of inflammatory cytokines, and dysfunction of the microvasculature and immunological parameters[1]. Fibrosis can affect nearly all types of tissues and organ systems, but majorly connected to lungs, kidney, liver, heart, skin, inflammatory vessels, eyes, scleroderma and atherosclerosis[2,3]. The fundamental mechanisms in normal wound healing response are same involved in fibrogenic responses and mechanisms become aggravated due to tissue injury. As fibrogenesis persists, over time it leads to a transformation in the tissue creating an environment where cells responsible, for producing the extracellular matrix (ECM) multiply excessively or become hyperactive. This excessive ECM production ultimately disrupts the architecture of organs [4]. Fibrosis initiated by parenchymal cell destruction, is driven by various detrimental agents and mechanisms. The ensuing tissue damage is accompanied by an inflammatory reaction, which results in the activation of dormant local immune cells such tissue macrophages, and the recruitment of additional relevant cells to the injured regions. A wide range of physiologically active cytokines and chemokines produced by recruited immune cells stimulate the local activation of mesenchymal cells, which can form ECM and boost the production of pro-inflammatory cytokines, chemokines, and angiogenic factors. These cells are distinguished by their ability to switch from a resting to an active state, during which time they express a lot of α-smooth muscle actin (α-SMA) and produce ECM components. The structure of the matrix changes and stiffens as too much ECM is deposited. The fraction of cells contributing to the formation of fibrillar collagens and non-structural

proteins with regulatory roles in ECM is significantly increased by other cell populations that can transit into potential myofibroblasts or matrix producing cells. This has been identified since last few years. In particular, tissue-resident fibroblasts, circulating bone marrow-derived fibrocytes, different epithelial and endothelial cell subsets that acquire a myofibroblast phenotype in a process termed epithelial-to-mesenchymal transition (EMT). Other mesenchymal cells such as pericytes and resident mesenchymal stem/progenitor cells are potential precursors for myofibroblast [5]. In earlier well documented reports it has been observed that increased numbers of mast cells are associated with pulmonary fibrosis [6], as they also contribute to the inflammatory phase but their role is unclear. Recent report [7] demonstrated involvement and pivotal role of mast cells in pathogenesis of fibrosis by conducting bleomycin induced pulmonary fibrosis in mast cell deficient mice. The study importantly showed mast cells play a critical role in initial inflammatory response and initiating pulmonary fibrosis. Other investigations have indicated increased mast cell counts in pulmonary fibrosis and clinical associations between mast cells and fibrosis [8,9]. Mast cells and tryptase showed increased fibroblast release of mediators that induced epithelial migration, this indicated a role of mast cells and tryptase in the interplay between fibroblasts and the alveolar extracellular matrix in health and lung disease [10]. Modulation of mast cell and their biological releases may reduce fibrosis as a therapeutic strategy, given the importance of mast cells in the aetiology of fibrosis.

MAST CELLS

Paul Ehrlich created the name mast cell in 1878 based on a function of granular histology staining with aniline dyes. Both human and rodent mast cells are innate immune cells in nature and develops from hematopoietic stem cells (HSCs) in the bone marrow, which give rise to common myeloid progenitors that can subsequently differentiate into mast cell precursors [11, 12]. Mast cells could also arise from a shared basophil/mast cell progenitor such as, mouse spleen [13], and in mouse bone marrow [14]. In humans, mast cells circulate as partly immature cells [15] and undergo final maturation upon entry into peripheral tissues. Most bodily tissues include mast cells, which are most noticeable at organs that serve as barriers to the outside world including the skin, lungs, and gut. There are two main subgroups of mast cells, which have a well-known phenotypic variability. The two subgroups have been distinguished in rats based on the differing anatomical localization and protease expression patterns. The peritoneal cavity and accompanying blood arteries, the skin, and the connective tissues of the intestinal submucosa are where most connective tissue mast cells (CTMCs) are found. The mucosal tissues of the lung and gut are often where one might find mucosal mast cells (MMCs). CTMCs express both chymase and tryptase and MMCs express chymase [16]. The two kinds of mast cells in humans are distinguished by the protease activity they express: MCT express only tryptase, whereas MCTC contain both tryptase and chymase. Mast cells possess well-characterized receptors, including the c-kit receptor essential for survival, proliferation, and differentiation via binding to its ligand, stem cell factor (SCF). Additionally, mast cell activation can occur through the aggregation of the FcεR1 receptor, the high-affinity IgE receptor [17], although stimulation of other receptors like TLRs and the IL-33 receptor ST2 can also trigger mast cell activation [18,19]. Mast cells can secret a broad variety of physiologically active mediators, which may be a sign of their adaptability and suggest multiple different effector activities. Pre-formed granules that can be exocytosed entirely or partially are among the mediators. Histamine, lipid mediators, proteoglycans, and proteases such as chymase, tryptases, and carboxypeptidases are all present in granules [20,21,22]. IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, GM-CSF, TNF, TGF, CCL2, CCL5, fibroblast growth factor (FGF), and platelet derived growth factors (PDGF) are just a few of the cytokines, chemokines, and growth factors that mast cells may produce and release [23,24,25,26,27,28].

MAST CELLS INVOLVEMENT IN FIBROSIS

Mast cells have been linked to the fibrosis pathogenesis. Previously, mast cell numbers are proven to be increased in patients with idiopathic pulmonary fibrosis and their products histamine was also proven in its role in pathogenesis of fibrosis [29]. Agents that target inflammatory cells such as lymphocytes, macrophages, and neutrophils were unable to stop the progression of fibrosis. However, it has been shown that in fibrotic conditions, mast cell numbers rises and promotes fibrosis through the production of histamine, renin, and growth factors [7]. Histamine and renin have been identified as two fibrotic mediators that activate fibroblasts in the lungs of both humans and rats by promoting fibroblast proliferation, TGF-β secretion, and collagen production [6]. The main profibrotic factor TGF-β has been activated by mast cell pro-fibrotic mediators. The latent TGF-β is converted to active TGF- β fibrotic factor by mast cell mediators [30] which eventually responsible for differentiation into myofibroblast and excess collagen synthesis, -SMA expression and deposition of extra cellular matrix converted into fibrosis condition. SCF known for mast cell ligand, expression was observed to be increased in both intact lung tissue and isolated lung

fibroblasts from IPF patients [31]. These theories contend that the excessive ECM deposition that results in lung fibrosis depends on the interaction between mast cells and fibroblasts. Additionally, earlier studies discovered that activated mast cells release a number of profibrotic mediators, including chymase, tryptase, renin, histamine, leukotriene, and TGF-β. Therefore, it seems that mast cells and fibrosis are closely related [32,33]. TGF-derived from mast cells increases the activation, proliferation, and differentiation of fibroblasts into myofibroblasts [30] and represented in Fig. 1.

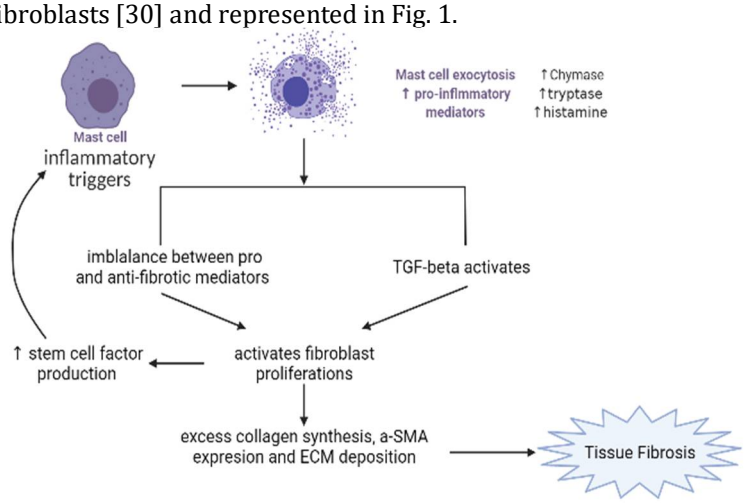

Fig: 1 Mast cells involvement in development of tissue fibrosis

Mast cell degranulation commonly occurs and unbalances profibrotic and antifibrotic mediators, making chronic inflammation a key underlying cause of fibrosis.[34] These circumstances cause ongoing disruptions in homeostasis [35]. Degranulation of mast cells may occur uncontrollably in chronic inflammatory conditions, releasing an excess of profibrotic mediators (cytokines, chemokines, growth factors, and proteases) within the target organ, triggering downstream processes that result in progressive fibrosis by involving various signalling pathways, primarily PPAR-γ, NF-κB, and TGF-β/Smad [36,37]. Therefore, limiting excessive mast cell degranulation may have therapeutic relevance in preventing the advancement of fibrosis.

Renal Fibrosis and Pulmonary Fibrosis

Fibrosis caused by an excessive build-up of extracellular matrix in response to chronic tissue damage has the potential to disrupt the organ's regular architecture and lead to organ failure. This is well known in chronic liver diseases, where cirrhosis is the end-stage with impaired liver function. The organ failures happen in portal hypertension, chronic kidney diseases and pulmonary diseases where severe glomerulosclerosis destroys glomerular filtration function and fibrosis reduces the lung's vital capacity.

To date, there has been evidence of a link between mast cell recruitment/infiltration and fibrotic disorders in a variety of tissues. Mast cells are absent in the normal kidney, but they are more prevalent and associated with fibrosis in renal fibrosis. Similar to this, mast cell infiltration is linked to renal fibrosis in kidney rejection following transplant [38,39]. It has been demonstrated that the frequency of infiltrating tryptase-positive mast cells in renal fibrosis is strongly correlated with the degree of renal interstitial fibrosis [40]. In experimental models, mast cells have been demonstrated to play a significant role in the development of renal fibrosis brought on by ureteral blockage [41]. corroborating the findings of Veerappan *et al*. [42] the study demonstrated mast cells are necessary for the development of renal fibrosis in the rodent unilateral ureteral obstruction model. These findings confirm clinical studies that indicate a link between mast cell count and the severity of fibrosis obstruction in experimental renal fibrosis [41]. Furthermore, the sodium cromoglycate induced remodelling of mast cell has been shown to reduce renal fibrosis [43]. Based on above indications that pro-fibrotic mediators generated by mast cells stimulate fibroblast activation and proliferation, making targeting mast cell type in renal fibrosis appealing. Mast cell-deficient strains derived from a c-kit genetic deficit have been utilised in a range of animal studies to investigate the mast cells importance in the lungs. Early studies found bleomycin-induced fibrosis was developed in WBB6F1- W/Wv mice, regardless of whether the mice had a mast cell deficiency.[44] Mast cells have a crucial role in the initiation of pulmonary fibrosis. The scientists administered bleomycin to mast-cell-deficient WBB6F1-W/Wv mice and their controls in this investigation, mast-cell-deficient WBB6F1-W/Wv mice showed a protection against bleomycin, but the protection was lost once the mast cell population was restored [7]. A recent study showed bleomycin raised histamine levels by causing mast cell build-up in the lungs. Berberine inhibited collagen accumulation via lowering hydroxyproline levels,

which was accompanied by lower histamine levels, suggesting a function for mast cells in the development of pulmonary disease [45]. The underlying mechanism for expanded mast cells in IPF is unclear; however, SCF may have a role. By binding to its receptor, c-kit, SCF enhances hematopoietic stem cell survival, proliferation, mobilisation from the bone marrow, and adherence of hematopoietic stem cells and other progenitor cells[46,47]. Increased production of SCF from alveolar fibroblasts from individuals with diffuse interstitial fibrosis suggests that this pathway is essential in fibrosis in the lung [48]. Blocking SCF has been found to reduce airway remodelling and lung collagen deposition in a murine model of cockroach-induced asthma [49]. Bleomycin-induced lung fibrosis can be prevented either SCF knock out genetically or using antibodies of SCF [50]. Recently scientist showed, Nintedanib reduces mast cells survival and activation, providing a unique mechanism that might have anti-fibrotic benefits in IPF condition both in vitro and in vivo via c-kit [51]. From these experiments, data showed the importance and vital function of mast cell involvement in pathophysiology of fibrosis. Several strategies might be used in the creation of antifibrotic medications to inhibit different mediators and pathways. Inhibitors of chemokines, cytokine, TGF-β, toll-like receptor, and antihypertensive medications, as well as stem cell transplantation and other methods, may be used [52,53].

MAST CELL MODULATION IN FIBROSIS

Several studies demonstrated that mast cells are increases significantly in fibrosis disease condition in lungs, kidney compared with normal condition [31]. Given the well-known deleterious roles of mast cells in fibrosis diseases, there is a pressing need to develop effective techniques for limiting mast cells negative effects in disease situations. There are several therapeutic strategies aiming with to modulate the mast cells activities, and are broadly categorised in three, 1. Inhibition or reduction of mast cell mediators and their effects, 2. cease of mast cell activation, and 3. reduction of mast cell numbers [54]. Imatinib mesylate is a potent and specific tyrosine kinase c-kit inhibitor, and demonstrated the antifibrotic effects in a bleomycin-induced lung fibrosis model in mice via inhibition of tyrosine kinase of platelet-derived growth factor receptors (PDGFRs) and mesenchymal cells [55]. Also Imatinib has shown suppression of various fibrotic illnesses, including human hypereosinophilic syndrome and myelofibrosis in chronic myeloid leukaemia [56,57]. In a recent research, the fibrosis medicine Nintedanib completely inhibited the phosphorylation of c-kit when compared to the impact of anti-SCF at biologically meaningful dosages[51]. Mast cell modulator could potentiate anti-fibrotic activity in combination with approved anti-fibrotic agents. Above research indicates that c-kit inhibitor which reduces mast cells activities has potential to inhibit the fibrosis pathology.

SUMMARY AND FUTURE PROSPECTUS

The use of diverse combinations of several declared antifibrotic agents to potentiate mast cell stability indicated a novel molecular approach in a twofold way. For starters, it might broaden the range of options for preventing disease progression. Second, by assisting in the reversal of the fibrosis illness, which is still a challenging work for specialists, may improve quality of life. The drug discovery industries have tried number of times to find viable medicines for fibrosis, but the condition has so far eluded all attempts at therapy. Clinical test failures can be caused by a number of factors, including illness heterogeneity, a lack of clinical endpoints that can be easily measured other than overall survival, and perhaps most importantly, a lack of knowledge about the underlying molecular mechanisms underlying the progression of fibrosis disease. On the bright side, fresh therapy options are emerging as a result of increased understandings of the mechanisms and cell types involved in fibrosis. Several previously unknown components of disease pathophysiology have already been discovered by molecular analysis of patient tissue samples. New cell types provide therapeutic opportunities that have never been investigated previously, such the myofibroblast and therefore the mast cell. But the only way to be certain that these cells are responsible for the pathophysiology of fibrosis is to use sufficiently effective medicines to target them and observe how the development of the illness is affected in phase 2 clinical trials. Based on our present understanding of disease mechanisms, therapeutic strategies that are effective in one kind of fibrotic disease are likely to be effective in other types of fibrotic disease. Mast cell-targeted therapy may be a better example of this. More research is needed to better understand to identify causes for mast cell degranulation so that new, more effective therapy options can be developed.

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DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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