Can Vorinostat be an Antifibrotic Drug for Pulmonary Fibrosis

Abstract

Pulmonary fibrosis is a condition defined as a recurrent and progressive interstitial fibrotic disease and is considered to be terminated by interstitial lung disease disorders.Accumulating evidence indicates that epigenetic alterations, including histone acetylation, play a pivotal role in this process. Histone acetylation is governed by histone acetyltransferases (HATs) and histone deacetylases (HDACs).Vorinostatis a member of a larger class of compounds that inhibit histone deacetylases. Even though the pathogenesis of lung fibrosis is complicated, hypotheses have been proposed in recent years that include inflammation, epithelial degradation, differentiated fibroblast, angiogenesis, and oxidative stress.Emerging evidence from several preclinical studies has shown that

Vorinostat has beneficial effects in preventing or reversing fibrogenesis.

In this review, we summarize the latest findings of the roles of HDACs in the pathogenesis of pulmonary fibrosis and highlight the potential antifibrotic mechanism of Vorinostat in this diseases.

Key word: Pulmonary fibrosis, Vorinostat, Histone deacetylase,Inflammation, cytokines

Introduction

Idiopathic pulmonary fibrosis (IPF) is especially a deadly disease with low-function lung parenchyma in consequent areas of normal lung function, inflammation of interstitial tissue, fibrous tissue accumulation with honeycomb appearance, and clinically specifics symptoms including dyspnea, wheezing, dry cough, respiratory failure, and death. More researches reported that 3-9 patients per 100,000 annually appear to increase the prevalence of IPF and the frequency, prevalence, and age-related death rate. The median period of survival after IPF is 2–6 years (Liu *et al.* 2019).

Even though the pathogenesis of lung fibrosis is complicated, hypotheses have been proposed in recent years that include constant inflammation, epithelial degradation, differentiated fibroblast, angiogenesis, and oxidative stress (Walter *et al.* 2011). IPF pathogenesis is not limited to alveolitis pathogenesis but is linked to a number of chemokines and cytokines that trigger active fibroblast recruitment and phenotype shift to myofibroblasts, causing excessive extracellular matrix (ECM) precipitation in alveolar and interstitial spaces. At this stage, the healed fibrous tissues undergo structural dysfunction and substitute the normal cells, resulting in fibroblast action, structural alveolar damage, accumulation of ECM, culminating in disturbances of gas exchange ended with the failure of the respiratory system (Hecker 2017). Increased collagen production replaces the normal parenchyma and ends with the failure of the respiratory system (Rao *et al.* 2016).

In almost all fibrotic processes, certain primary signal pathways, such as the transforming growth factor β1 (TGF-β1), are activated despite the different pathways in the different organ fibrosis procedures. TGF-β1 activates fibroblasts to be developed to myofibroblasts (Lyu *et al.* 2019).

Tuberculosis (TB) is now, in addition to the human immunodeficiency viruses (HIV), the world's leading cause of death. The pathology of TB is believed to be predominantly dangerous, as compared to the effect of the disease's direct cytopathic symptoms (Xu *et al.* 2017).

Bacillus Calmette-Guerin (BCG) vaccines are live Mycobacterium Bovis attenuated strains and are one of the most commonly used vaccines in the world. In newborns who expect to have severe meningitis and miliary tuberculosis, BCG has been shown to be effective. As the main human TB vaccine available, it is generally used as part of the Global Expanded Immunization Program of the World Health Organization (WHO) (Zheng *et al.* 2015).

Other than TB protection, BCG has other medical applications in two main areas of immunotherapy: cancer and autoimmune treatments, such as melanoma and type 1 diabetes, individually (Covián *et al.* 2019). BCG is utilized as a primary treatment to prevent bladder malignancy. There is also pre-clinical and clinical evidence that BCG can treat different kinds of malignancies (Song *et al.* 2019). BCG had been utilized as a bacterial carrier to establish applicants for vaccines against specific organisms (Palavecino *et al.* 2014).

However, BCG vaccination is a great model vaccine for studying tuberculosis defense mechanisms in models of small and large animals (Hawn *et al.* 2014). BALB/c shows greater susceptibility to Mycobacterium tuberculosis challenge. Contingent upon their susceptibility to Mycobacterium tuberculosis infection, mouse strains have been categorized as susceptible and non- susceptible. Other than Mycobacterium tuberculosis more prominent susceptibility profiles, these BALB/c models, additionally consider the most utilized mouse models for tuberculosis vaccine comparison, exhibit exact vaccine-induced protection. Males are most dominant and difficult to maintain only males in a group as they have a tendency to fight. On the other hand, compare to males, female mice are more responsive and immune sensitive because of variations in the hormonal physiology and immune defense mechanisms. So,

mostly young and adult female BALB/c of 4-6 weeks were preferred as a suitable model for immunology studies (Aguilo *et al.* 2016).

Until this point in time, no treatment has effectively stopped, considerably less turned around, the decrease in lung function that is a sign of IPF. Extra medications that might be utilized as in mix with existing treatments are critically required to improve results. Korfei *et al.* detailed the phenotypic expression-like malignancy of IPF-fibroblasts because of the unusual over-expression of histone deacetylase compounds (HDAC) (Korfei *et al.* 2015).

Suberanilohydroxamic acid (SAHA) (the trade name of Vorinostat) is a non-selective HDAC class I and II inhibitor (HDACi) and has been affirmed by the Food and Drug Administration (FDA) for the treatment of T-cell lymphoma. It is under evaluation for the treatment of non-small cell lung cancer in blend with DNA demethylating agents and chemotherapy (Pasini *et al.* 2015). In addition, this neoplastic drug is being studied in patients with HIV with the potential to influence latent HIV viral carriers, as it has been shown that HIV latency in these patients has been successfully disrupted (Rasmussen *et al.* 2014).

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Fibrosis

Definition of fibrosis:

The fibrosis is a pathological phenomenon of most chronic diseases. Fibrosis is also known as scars; it is known through the ECM accumulation components such as fibronectin and collagen in and around inflamed or damaged tissue, which can lead to permanent scarring and organ malfunction (Wynn and Ramalingam 2012; Herrera, Henke, and Bitterman 2018).

Inflammatory and immunological reactions underlie the process of fibrosis, affecting both elements of the innate and adaptive immune system (Figure 1) (Van Linthout, Miteva, and Tschöpe2014). One of the most vexing concerns in modern medicine remains progressive fibrosis. This apparent intractability is not due to a lack of scientific attention. If progressed significantly, the fibrous procedure eventually leads to dysfunction of the organs and death (Herrera, Henke, and Bitterman 2018).

Pathophysiology of fibrosis:

The most well-known type of connective tissue found throughout the body is fibroblasts. It is the main source of the normal ECM and is also the central mediator of pathological fibrotic accumulation and cell proliferation and differentiation in the ECM. The conversion of the fibroblast cell line includes several precursor cell types; myofibroblast is the apex of the fibrotic phenotype (Kendall and Feghali-Bostwick 2014).

Myofibroblasts are well characterized to differentiate from resident fibroblasts *in vivo* and *in vitro.* They were recognized as the critical manufacturers of ECM components after damage; however, it is now believed that fibroblasts could be extracted from different sources. Myofibroblasts display exaggerated ECM production and are hypersensitive to chemical

signals, for example, cytokines, chemokines, and growth factors. It produces matrix metalloproteinases (MMPs), which disturb the basement membrane, enabling inflammatory cells to be effectively selected to the site of damage and activated collagen secretion (Klingberg, Hinz, and White 2013; Darby *et al.* 2014).

Early respondents such as macrophages and neutrophils that engulf tissue waste, dead cells, and any pathogens that enter. These also develop cytokines and chemokines for endothelial cells that surround the damage site, which is mitogenic and chemotactic. These also help to create neovascularization as epithelial/ endothelial cells move to the wound core. It stimulates lymphocytes and other cells and begins to secrete pro-fibrotic cytokines and growth factors such as TGF-β, interleukin-13 (IL-13), and platelet-derived growth factor (PDGF) (Chen *et al.* 2018); it enhances macrophage and fibroblast activation. Activated fibroblasts transform into alpha-smooth muscle actin (α-SMA) that express myofibroblasts as they migrate within the wound through the fibrous network (Wynn and Ramalingam 2012).

Fibrotic Diseases:

Fibrotic diseases are responsible for 45% of deaths in the developed world; hence interventions targeting excessive fibrosis are a major therapeutic goal. The concept of 'core' and 'regulatory' pathways in focused on the fundamental regulatory pathways involved in multi-organ fibrosis, specifically for human fibrotic disease rather than mouse models, is still an enigma as recently reviewed in Nature Medicine (Wenzke *et al.* 2012).

The fibrosis is the common pathological outcome in some diseases, such as liver cirrhosis, cardiovascular fibrosis, systemic sclerosis and nephritis, extensive tissue remodeling, and fibrosis can ultimately lead to organ failure and death (Wynn 2008). Cirrhosis is also a pathological characteristic in many chronic autoimmune diseases like (systemic lupus erythematosus, scleroderma, spinal cord inflammation, ulcerative colitis, rheumatoid arthritis, and disease of Crohn) (Wynn and Ramalingam 2012).

In the lung parenchyma, interstitial lung diseases (ILDs) or diffuse parenchymal lung diseases are a heterogeneous group of disorders characterized by varying degrees of inflammation and fibrosis. The most prevalent pathological symptoms are pulmonary inflammation and fibrosis. There are over 150 different causes of ILDs, including sarcoidosis, silicosis, drug reactions, and infections, as well as vascular diseases of collagen, such as rheumatoid arthritis and systemic sclerosis (scleroderma). There is no known cause of IPF, the most common type of ILD (Dhooria *et al.* 2018).

Cytokines involved in fibrosis:

Cytokines are released from different immune cells, including monocytes, macrophages, and lymphocytes. Pro and anti-inflammatory cytokines, respectively, promote and suppress inflammation. Inflammatory cytokines are known as colony-stimulating factors (CSFs), tumor necrosis factors (TNFs), and chemokines. They are primarily developed by cells to recruit leukocytes at infection or injury sites (Turner *et al.* 2014). Cytokines modulate the immune response to infection or inflammation and regulate inflammation itself through a complex interaction network. However, excessive inflammatory cytokine development may result in tissue damage, hemodynamic changes, organ failure, and, eventually, death (Liu *et al.* 2016; Chen *et al.* 2018).

Tumor necrosis factor-alpha (TNF-α):

TNF-α is a pleiotropic cytokine with both pro-inflammatory and anti-inflammatory functions. TNF's biological functions are regulated by two receptors, TNF-α receptor type I (TNFR1) and type II (TNFR2). TNFR1 is widely expressed in almost all types of cells and has been extensively studied, whereas TNFR2 is primarily confined to immune cells and certain tumor cells (Ye *et al.* 2018).

TNF-α is predominantly secreted by hematopoietic cells, such as monocytes and macrophages, by stimulation of the Toll-like receptors (TLRs). The TLRs are involved in the

important first step of host response toward microorganisms and are widely expressed in immune cells and non-immune cells to identify a wide range of microorganism products (Takeuchi and Akira 2010; Yamamoto and Takeda 2010). Previous hypotheses demonstrated that TLRs are also activated by endogenous ligands, like those of highly mobile group box 1, hyaluronan, and heat shock proteins produced from damaged tissues, referred to as damage-associated molecular structures (Takeuchi and Akira, 2010).

Transforming growth factor-beta (TGF-β):

TGF-β is one of the most potent inducers of ECM production, including collagen and other matrix proteins. TGF-β expression is elevated in both animal models of lung fibrosis and fibrotic human lungs. There are three isoforms of TGF-β (TGF-β1–3) that all have the same biological processes, even though each isoform is expressed in a slight indentation under the direction of a peculiar promoter. Even though a wide range of cell types are developing and reacting to TGF-β, TGF-β1 is primarily associated with tissue fibrosis. TGF-β1 is released from cells in a residual complexity established by linking to latency-associated protein (LAP), which retains TGF-β1 inactive. To reach an active state, TGF-β1 must be dissociated from LAP, a mechanism that can be catalyzed by several agents, including cathepsins, plasmin, calpain, thrombospondin, MMPs, and integrins (Borthwick *et al.* 2013).

TGF-β synthesis associated with the progress of liver, lung, kidney, skin, and heart fibrosis and TGF-β1 signaling pathway inhibition has been shown to decrease fibrosis progression in many laboratory models. TGF-β1 is now commonly known as a multipurpose cytokine with wide-ranging modulatory actions that influence multiple essential biological mechanisms. This would include mechanisms to control embryogenesis, immunity, cancer, cell proliferation and migration, wound healing, inflammation, and fibrosis, among others (Wynn and Ramalingam, 2012).

In animal models of lung fibrosis, the elevation of TGF-β expression precedes collagen synthesis and deposition. The finding confirmed the pro-fibrotic role of TGF-β in lung fibrosis that adenoviral-mediated gene transfer of active TGF-β1 was sufficient to induce severe fibrosis in rodent lungs (Yue et al. 2010).

Interleukin-6:

Interleukin-6 (IL-6) is a cytokine that was established as a triggering factor for B-cells (Choy and Rose-John 2017). Although early observation provided initial clues of the pleiotropic role of IL-6, it is now understood that IL-6 has several roles in controlling and organizing the immune system, metabolism, and nervous system (Rothaug, Becker-Pauly, and Rose-John2016). It is not only implicated several autoimmune disorders, but it also plays an important role in protecting the body from infection, in several regenerative mechanisms, and in regulating body weight (Scheller *et al.* 2011).

IL-6 was involved in fibrotic disease pathogenesis, particularly lung and hepatic fibrosis (Sripa *et al.* 2012) and systemic sclerosis (Khan et al., 2012). IL-6 and TGF-β are produced by fibroblasts and macrophages, in particular by activated M2 macrophages (O'Reilly *et al.* 2014).

IL-6–deficient mice reversed this effect in a peritoneal model of inflammation-mediated fibrosis, indicating that IL-6 induced fibrosis by changing from chronic to acute inflammation by inducing T helper-1 (Th1) responses (Fielding *et al.* 2014). Dermal fibroblasts have high levels of cell surface gp130, and IL-6 trans-signaling results in fibroblast proliferation and excess ECM formation, especially procollagen and fibronectin, in hypertrophic scars (Ray *et al.* 2013).

Interleukin-12:

Through fostering inflammation and fibrotic responses, pulmonary macrophages play an important role in lung fibrosis pathogenesis (Desai *et al.* 2018). IL-12 is a significant Th1-

driving cytokine that establishes cell-mediated immunity and selectively expresses cells, including pulmonary macrophages, through antigen-presenting cell (APC). IL-12 is an important cytokine involved in the prototype's response Th1 and plays a key role in both innate and adaptive immunity (Bringardner *et al.* 2008).

IL-12, the prototype member of the cytokine heterodimeric family, comprises a subunit p40 and p35 covalently connected by two disulfide connections. All p35 and p40 are members of the IL-12 family of two heterodimeric cytokines (Tsuda *et al.* 2013).

IL-12 plays an important role in the tolerance of various autoimmune diseases to bacterial, viral, parasitic infections, and tumors. IL-12 p40 was found to be generated during the fibrotic reaction by activated pulmonary macrophages (Hamza *et al.* 2010).

Pulmonary fibrosis:

The fragile architecture of the lung is constantly under threat from both external and internal insults. Pulmonary fibrosis represents the end stage of several interstitial lung diseases (Hewlett, Kropski, and Blackwell 2018).

Definition:

Pulmonary fibrosis is a chronic interstitial lung disease distinguished by the lung's usually progressive deposition of fibrotic tissue and poor prognosis in general. IPF was the most severe and lethal disease with 3–5 years of median survival following diagnosis (Datta *et al.* 2011).

Etiology and Pathogenesis:

Numerous epidemiological risks were postulated as stimulating factors, but no unifying etiological agent or mechanism was established (Sgalla *et al.* 2018). Observations have closely linked the occurrence of IPF with cigarette smoking and metal particles, including pulmonary fibrosis in the population. It has also been shown that latent viral infections, like Epstein-Barr virus and Herpes virus, play a role (Kottmann *et al.* 2009). They have identified

more important correlations between IPF and agriculture, animals, wood dust, stone, sand, and silica (Taskar and Coultas 2008). The key mediators in the pathogenesis of IPF were discussed by Datta *et al.* (2011). They mentioned that the pathobiological processes influencing IPF's development are extremely complex. The disruption to the epithelial cells (possibly because of reactive oxygen species, endoplasmic reticulum stress, or viral infection) resulting in such an irregular wound healing process marked by myofibroblast aggregation (the main IPF fibrogenesis effector cells). The suggested myofibroblast cell source could be native fibroblasts, epithelial / endothelial-mesenchymal transition, or fibrocyte staffing. The pro-fibrotic reactions are mediated by several cytokines, growth factors, and signaling pathways.Figure (2) also shows the main pathogenetic actors in IPF.

Cells and mediators:

Research efforts have oriented on the pathobiology of IPF in the last few years. Historically IPF is known as an inflammatory disease. IPF has been regarded as an aging lung epithelial tissue subject to repeated micro-injuries results in defective trials of regeneration and an irregular distortion of epithelial-mesenchymal intermodulation. Create a discrepancy among pro-fibrotic and anti-fibrotic mediators, sustain an environment that promotes excessive fibroblast and myofibroblast development, and deprive chronic fibro-proliferation of natural curative processes. We will concentrate on the various types of cells and mediators involved in IPF pathogenesis in this section (Richeldi *et al.* 2017).

Alveolar epithelial cells (AECs, pneumocytes)

In normal lungs, loss of Alveolar epithelial type I cells (AECIs) after an injury is followed by proliferation and differentiation of AEC2s and stem cells that restore alveolar integrity involving several mechanisms: coagulation cascade, new vessel formation, fibroblast activation and migration, collagen synthesis and proper alignment. If the damage continues, or it disrupts normalization, the wound recovers over an inflammatory cycle with increased

levels of IL-1 and TNF-α, resulting in a chemical state that leads to sustained healing and tissue regeneration (Betensley, Sharif and Karamichos2017).

Apoptosis of AEC was involved in disease pathogenesis in areas next to aggressive renovating and strong myofibroblast activity with IPF lung biopsies showing influential AEC apoptosis. AEC apoptosis is a notable occurrence in the pulmonary fibrosis caused by the experimental bleomycin model, and apoptosis inhibition has been shown in this model to reduce fibrosis. However, it appears to be an important step in fibrosis production in other animal studies, particularly TGFβ1-induced lung fibrosis (Zoz *et al.* 2011).

Recently, Sisson *et al.* used a transgenic mouse model in which human diphtheria toxin receptor is expressed in type II AECs to show that induction of cell death by treatment with diphtheria toxin is sufficient to produce pulmonary fibrosis (Sisson et al., 2010).

Assimilating the currently available data suggests that the response of type II AECs to injury is a key determinant of the initiation and progression of lung fibrosis in IPF. Zoz and his colleagues' working model are based on the “vulnerable AEC” definition (Figure 3). In this scenario, the investigators hypothesized that in the existence of a genetic or gained corrupt and inefficient type II AEC phenotype, ongoing or repetitive injurious stimuli resulted in increased AEC injury/apoptosis, shortcomings in normal alveolar structure restoration, abnormal lung repair, and fibroblast modulation. Progressive lung fibrosis results from these pathobiological changes. Although this is an attractive model to consider, there are still many unanswered questions that need to be addressed by ongoing and future investigations(Zoz, Lawson, and Blackwell 2011).

Probably the most important mediator of IPF pathogenesis is TGF-β1. As a result of AECs may produce actin / myosin-mediated cytoskeletal contraction could be due to the stimulation of integrin. A basic biological method is the mechanism of the αβ6 integrin / TGF-β1: The compounds are formally bound so that harmful stimulation is recognized. Even

lysophosphatidic acid, which is dominated by autotoxin, can activate TGF-β1. TGFβ1 is an important fibrotic mediator: it promotes programmed cell death, mesenchymal stem cell stimulation, epithelial cell assimilation, the release of other pro-fibrotic facilitators, fibrocyte mobilization and fibroblast activation, proliferation to myofibroblast, tissue growth factor development, and other pro-angiogenic facilitators (Grimminger *et al.* 2015).

Fibroblast cell and myofibroblast cell

Numerous cell types are likely to be related to IPF pathogenesis; however, the lung fibroblast has been the most studied cell in lung fibrosis studies over the past two decades. Different hypotheses include fibroblast, particularly myofibroblast, as the main cell accounting for collagen accumulation and other ECM constituents throughout tissue fibrosis (Phan 2002).

Fibroblasts are mesenchymal tissue cells engaged in the process of wound healing to restore a natural and well-structured ECM. Lung and fibrocyte-derived fibroblasts are constantly exposed to pro-fibrotic facilitators excreted by stimulated fibroblasts during IPF pathogenesis, resulting in ECM formation and myofibroblasts trans-differentiation. The first and most crucial trans-differentiation activating factor is TGF-β1, but PDGF plays an important role as well. Stimulating such cells has significant effects on the intracellular and extracellular attitude: IPF lung fibroblasts express properties that improve genetic transcription as a hypermethylated DNA profile; these acts are similar to the biology of lung cancer (Sgalla *et al.* 2018).

Myofibroblasts synthesize more ECM than fibroblasts. The matrix produced by myofibroblasts is poorly organized but very dense. Moreover, they persist longer than fibroblasts in damaged tissue. Myofibroblasts have contractile properties due to αSMA. The mechanical characteristics of deposed ECM are probably the most important factor in the regulation of myofibroblasts activity: in fact, their synthesis activity is enhanced by contact

with a stiffer matrix, creating a positive feedback loop, whereas a healthy soft substrate strongly inhibits myofibroblasts and leads to the reduction of their number (Hinz 2012).

The function of the endothelium and the cascade of coagulation

Disruption of AEC's alveolar structure and deterioration, including basement membrane degradation, affects alveolar vessels and results in enhancement of permeability of the blood vessels. The initial stage of the healing of the wound is marked by the development of clots leading to the formation of new vessels and the proliferation of endothelial cells, including endothelial progenitor cells (EPCs). In 2013, Malli *et al.* showed that patients with IPF had dramatically decreased EPCs, with significant impacts as a loss of re-endothelization, which could contribute to a defective oxygen respiratory barrier, and a pro-fibrotic cytokine, which could then promote fibrotic processes and vessel function defects, leading to cardio-response. In addition, endothelial cells can experience a mesenchymal transformation with the same effects as epithelial-mesenchymal stem cell transition (Malli *et al.* 2013).

Endothelial and epithelial disruption in the early stages of the wound healing process contributes to the activation of the coagulation cascade. Coagulation proteinases have several effects on the cells participating in the healing wounds. The most important in IPF pathogenesis is the tissue-dependent pathway, resulting in a state of pro-coagulation induced by high levels of plasminogen activation-inhibitors, active fibrinolysis inhibitors, and C-inhibitors protein. Pro-coagulation factors released decrease ECM disruption resulting in a pro-fibrotic effect and help differentiate fibroblasts into myofibroblasts via proteinase-activated receptors (Betensley, Sharif, and Karamichos 2017).

Immune cells

The relationship between the immune system and IPF is still poorly understood. Although most researchers accept that IPF is not the product of an immunopathogenic mechanism,

animal model findings and human studies showed that immune pathways might prepare and perform current fibrotic reactions (Desai *et al.* 2018).

Innate Immune Cells

The first line of defense toward infections is the innate immune system. This identification of antigen mainly depends on the processing of information by innate immune receptors. Such cell groups are necessary for host defense and tissue homeostasis. One of the main inborn immune cells in IPF analysis is macrophages and neutrophils (Selman and Pardo 2006).

Macrophages

Macrophages are adaptive immune cells. Its function as antibacterial pulmonary phagocytes and plays an important role in the pathogenesis of the fibrotic pulmonary disease (Wynn and Vannella 2016). Macrophages may influence either injury or repair in different fibrosis models, and macrophage diversity has appeared as a significant study area in IPF (Blackwell *et al.* 2014). Prior classification schemes proposed the existence of two phenotypes, namely classically activated M1 macrophages that arise in response to interferon-gamma (INFγ) and TNFα, and alternatively activated M2 macrophages that arise in response to stimulation with IL-4, IL-10, IL-13, and TGFβ1 (Wynn and Vannella 2016).

After the alveolar epithelial injury, M1 macrophages are responsible for wound healing, whereas increased M2-associated and Th2-driven responses are essential components of many fibrotic diseases. For example, alveolar M2 macrophages, near sites of healed pulmonary injury, release chemokine C-C motif ligand-18 (CCL18) to stimulate collagen-producing fibroblasts. The nearby M2 macrophages connect to collagen type I via β2-integrin and trapper receptors, thus further growing their production of CCL18, creating a self-perpetuating vicious cycle of increased, continuous activation of M2 macrophages and excessive production of collagen by lung fibroblasts (Zhang *et al.* 2018).

Various regulatory cytokines, chemokines, mediators, and immune-regulatory cells influence lung macrophage's polarization and chemotaxis (Figure. 4). These mediators' interplay and influence disease duration and severity through altered polarization of M1 and M2 cells (Arango Duque and Descoteaux 2014).

Neutrophils

Neutrophils are innate immune cells correlated with cytokine and chemokine synthesis, injury existence, ECM breakdown modulation, and extracellular neutrophil traps (NETs) production. Most of these mechanisms are expected to lead to fibroblast stimulation and ECM aggregation (Mayadas, Cullere, and Lowell 2014).

The production of NETs is one of the recently identified fibrosis-promoting functions of neutrophils. Both chromatin and neutrophil pro-inflammatory collections control both the role of immune cells (Arango Duque and Descoteaux 2014) and fibroblast activation (Chrysanthopoulou *et al.* 2014). While there has been increased recognition of intrapulmonary NETs in both the bleomycin model and some varieties of fibrotic ILD, a particular IPF interaction has yet to be fully described (Chrysanthopoulou *et al.* 2014).

Through their ECM turnover regulation, neutrophils could also contribute to fibrosis. Neutrophil elastase (NE), the main alveolar proteolytic drug, is increased in the fluid of Broncho-alveolar lavage (BAL) in IPF patients (Obayashi 1997). Through the degradation of specific ECM elements like collagen, fibronectin, laminin and elastin, NE produces Damage-associated molecular patterns (Perona and Craik 1997; Chua *et al.* 2007). Ex vivo work suggests that NE can cause fibroblasts to proliferate and myofibroblasts to differentiate (Gregory *et al.* 2015). In both bleomycin and asbestos models, NE-deficient mice are free of fibrosis (Chua *et al.* 2007), and the NE inhibitor Sivelestat in the bleomycin model is protective (Takemasa, Ishii, and Fukuda 2012). Neutrophils also regulate ECM homeostasis

by regulating the net balance among MMPs and tissue inhibitors mineral proteins (Kruger *et al.* 2015), particularly the MMP-2, MMP-8, and MMP-9 pro-fibrotic.

Adaptive immune cells

T Lymphocyte cells

Samples from normal people, lung tissue and BAL fluid from patients with pulmonary fibrosis are enriched for several T lymphocyte populations. As shown in Figure (5), CD4 + T lymphocytes are divided up into multiple subgroups, with T-helper cells being the best studied in IPF. Maybe the most mentioned concept in T-helper biology is the contributions of Th1 and Th2 cells depending on their structure of cytokine expression as it relates to pulmonary fibrosis. The concepts of various T-helper populations in the context of IPF will be addressed in the following paragraphs. Furthermore, defining the balance between Th1 and Th2 as a key pulmonary fibrosis mediator may necessitate a re-evaluation of strategic growth to attack their secretory products better and more effectively. Th1 and 2 cells' theoretical role (Desai *et al.* 2018).

There is also an inadequate representation of the role of Th17 cells in IPF. IL-17 and IL-22 cytokines are generated by Th17 cells, which are host-defensive cytokines under many infectious conditions and promote inflammatory diseases like autoimmune diseases (Onishi and Gaffen 2010). IL-17's tasks involve activation of ECM development, collagen secretion and TGF-β signaling mediation (Wilson *et al.* 2010). While IL-22, a further component of Th17 cells, in the bleomycin model appears to be protective (Liang *et al.* 2006), BAL concentrations do not differ between pulmonary fibrosis and control. Because anti-IL-17 treatment has not been tested in pulmonary fibrosis, the efficacy of neutralizing Th17 cells and their secretory products as a therapeutic approach in pulmonary fibrosis is currently not known (Whittington *et al.* 2004). The majority of data obtained in animal data suggest that

the aberrant healing response of pulmonary fibrosis is initiated and regulated by molecules formed during the inflammatory response (Table 1) (Agostini, 2006).

Drug treatment of pulmonary fibrosis:

The French guidelines for IPF diagnosis and management recommend that, when a diagnosis of IPF is suspected in a patient, clinicians should ‘‘systematically’’ search for other causes of diffuse interstitial pneumonia in the family, together with the clinical signs suggestive of a genetic cause (Cottin *et al.* 2014).

Pulmonary fibrosis, therefore, represented a major unmet medical need for which novel therapeutic approaches are urgently required.

Corticosteroids

The 2011 guidelines don’t strongly recommend using corticosteroids in patients with AE-IPF, even though there are not enough randomized controlled clinical trials. They do not yet find the best treatment and period of treatment, but most times, the dose extended from 1 mg/kg of prednisone orally every day to 1 g of methylprednisolone per day intravenously for three days, accompanied by an incremental raising interest rate of the medical effect. There is still no clear role of high-dose corticosteroids in AE-IPF (Papiris *et al.* 2015).

For ILDs other than IPF, corticosteroids are widely used as first-line therapy, but there is very little data to support their effectiveness in ILD treatment. International guidelines for the treatment of IPF provide a strong recommendation against the use of corticosteroid monotherapy other than in the treatment of acute exacerbations (Raghu *et al.* 2011).

Maher & Wuyts reported that corticosteroid use is associated with significant morbidities, like weight gain, diabetes, cardiovascular events, cataracts, as well as osteoporosis (Maher and Wuyts 2019).

Antacid Therapy

There is a high proportion of symptomatic and asymptomatic gastroesophageal reflux (GER) in patients with IPF. Additionally, GER-secondary chronic micro-aspiration is known to be

involved in pathogenesis and disease progression. As a result, a few studies explored the possibility that antacid therapy could be effective by reducing disease progression and also rising health outcomes in IPF cases (Raghu *et al.* 2015).

Pirfenidone

Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone)is a treatment taken orally. It has anti-fibrotic, anti-inflammatory, and antioxidant activities. Although its exact mechanism of action is not very simple, the biological effects of pirfenidone are seen to occur mainly through the reduction of TNF-α, a key inflammation initiator. All these are primary targets of the TGF-β pathway and the Smad proteins, resulting in the distribution of fibroblast multiplication and differentiation of myofibroblast, as well as reduced collagen production (Kim and Keating 2015).

Nintedanib

Tyrosine kinases receptor vascular endothelial growth factor (VEGF) 1-3, receptor fibroblast growth factor (FGF) 1-3, and platelet-derived growth factor receptor (PDGFR) are now seen as an intracellular inhibitor. Nintedanib interferes with many of the processes involved in IPF pathogenesis by inhibiting VEGFR, FGFR, and PDGFR. The proliferation and migration of primary human lung fibroblasts, the transformation of fibroblasts into myofibroblasts, and primary human lung fibroblasts, in particular, are TGF-β-stimulated secretion and collagen deposition. It delays the excretion and deposition of the ECM (Richeldi *et al.* 2011).

In major clinical trials, neither Nintedanib nor pirfenidone has been shown to offer substantial relief from IPF-related dyspnea, cough, or quality of life loss. Whether this is because antifibrotic treatments do not have a meaningful effect on symptoms is unknown, or because these studies were performed in individuals with mild/moderate lung function deficiency at baseline and extended just one year. Clinical observational data indicate that antifibrotic medication can provide some relief of symptoms (van Manen *et al.* 2017).

To date, the deterioration in lung function, which is a hallmark of IPF, has not been successfully stopped, much less reversed. Thus, to improve patient outcomes, new medications that can single agents or with current therapies are urgently needed. Four HDACIs approved by the FDA for cancer treatment are currently available, but none for fibrotic diseases. Emerging data from preclinical studies in vitro and in vivo have shown beneficial effects of HDACIs in fibrogenesis prevention or reversal (Lyu *et al.* 2019).

Vorinostat

Vorinostat is a HDAC inhibitor, structurally belonging to the hydroxymate group. Other drugs in this group include Givinostat, Abexinostat, Panobinostat, Belinostat and Trichostatin A. These are an emerging class of drugs with potential antineoplastic activity. HDAC inhibitors have multiple effects in vivo and in vitro specific for cell types, like arresting growth, affecting cell differentiation and bringing about complete apoptosis of malignant cells. These drugs can be used both as monotherapy and in combination with other antineoplastic drugs. Vorinostat is an FDA-approved drug for cutaneous T-cell lymphoma (CTCL) (Lyu *et al.* 2019).

Chemistry:

Vorinostat, also knew as suberoylanilide hydroxamic acid (SAHA) is an orally bioavailable inhibitor of class I and II HDACs. It is a small-molecular-weight linear hydroxamic acid compound. Vorinostat is slightly soluble in water, alcohol, isopropanol and acetone soluble and is fully dimethyl sulfoxide soluble (Kavanaugh, White, and Kolesar 2010).

Mechanism of action:

Vorinostat is a broad inhibitor of HDAC activity and inhibits class I and class II HDAC enzymes (Marks and Dokmanovic 2005). However, Vorinostat does not inhibit HDACs belonging to class III. Based on crystallographic studies, it has been seen that Vorinostat binds to the zinc atom of the catalytic site of the HDAC enzyme with the phenyl ring of

Vorinostat projecting out of the catalytic domain onto the surface of the HDAC enzyme. On binding to the HDAC enzyme, there is the accumulation of acetylated proteins, including histones, which in turn manifests in multiple cellular effects (Secrist, Zhou, and Richon 2003). The effects seen include transcriptional and non-transcriptional (Marks and Dokmanovic 2005).

Pharmacokinetics:

Vorinostat has shown a relationship between plasma concentration and Vorinostat dose, administered orally in a dosage of 200-600 mg. Vorinostatt1/2 is about 60 to 100 minutes long. The absorption and bioavailability of Vorinostat in the absence or presence of food is not significantly different, while the administration of Vorinostat with food can avoid adverse effects of the gastrointestinal tract (Kelly *et al.* 2005).

Indications:

Vorinostat is an FDA-approved drug in the management of CTCL (Lyu *et al.* 2019).

Dosing:

The approved Vorinostat dose is 400 mg once daily given orally. A response rate of 31 % with very few life-threatening adverse effects is seen with this dose. Vorinostat is delivered as 100 mg orally approved capsules. However, for efficacy and safety, an intravenous (i.v) formulation was comparatively analyzed. Response to i.v Vorinostat 300-600 mg/m^2 given five days a week for three weeks was similar to the oral dosing of 400 mg/day (Mann *et al.* 2007)

Adverse effects:

Toxicities with Vorinostat were seen when the dosing exceeded 400 mg a day, rendering the clinical benefits of dose escalation very minimal. With the FDA-approved dosing, the most common side effects encountered include fatigue, diarrhea, and nausea. These side effects were usually mild to moderate, needing no intervention or non-invasive intervention. Other

side effects that were life-threatening and required hospitalization included thrombocytopenia, dehydration, pulmonary embolism, squamous cell carcinoma, and severe anemia. Vorinostat is a category D drug in pregnancy. An animal study concluded that Vorinostat could cross the placenta and harm the developing fetus. The most prominent developmental abnormalities were incomplete ossification of the skull, vertebrae, and other axial skeletal bones (Bubna 2015).

The preclinical studies of HDAC inhibitor and Vorinostat in pulmonary fibrosis:

Wang and colleagues evaluated SAHA (Zolina1or Vorinostat). In TGF-β1-treated fetal lung fibroblasts, adult lung fibroblasts, and IPF lung fibroblasts, the investigators investigated the antifibrotic capacity of SAHA and its possible anti-inflammatory function in mononuclear peripheral blood cells, lymphocytes, and peripheral monocytes. The researchers demonstrate combined antifibrotic and anti-inflammatory effects of SAHA, demonstrating the therapeutic benefits of pulmonary fibrosis (Wang *et al.* 2009).

In pulmonary fibrosis, Sanders and colleagues may show that the SAHA pan-HDAC hydroxamic acid inhibitor decreased pulmonary fibrosis and improved lung function in bleomycin-treated mice (Sanders *et al.* 2014). Conforti and its employees have also documented strong anti-proliferative and anti-fibrotic features of class I-HDAC romidepsin inhibitor on in vitro and in vivo fibroblasts (Conforti et al. 2017).

Korfei *et al.* contrasted with the pan-HDAC-inhibitor, the impact of pirfenidone on survival, fibrotic function, and primary in vitro IPF-fibroblast proliferation. They have incubated from six patients with IPF primary fibroblasts for 24 hours with vehicles, panobinostat or pirfenidone, followed by proliferation and analyzes the pro-fibrotic and genes for anti-apoptosis and apoptosis markers. The condition of the release of all HDAC enzymes has been investigated. Researchers reported that pirfenidone reduces pro-fibrotic signaling and weak epigenetic changes in IPF-fibroblasts in addition to other antifibrotic mechanisms and allows

the maintenance of altered fibroblasts. In IPF-fibroblast inactivation, the panobinostat pan-HDAC-inhibitor increases pro-fibrotic phenotypes, thereby inducing IPF-fibroblast cell cycle arrest and apoptosis. Therefore, they assume that HDACi, like panobinostat, will present a new strategy of treatment of IPF (Korfei *et al.* 2018).

Pasini *et al.* noted that TGF-β1 reduced cyclooxygenase-2 protein expression and prostaglandin E2 production and prevented this by the pan-histone deacetylase inhibitor SAHA and to a lesser degree by the DNA demethylating agent Decitabine, but not by the G9a histone methyltransferase. Chromatin immunoprecipitation assay showed that changes in the histone were unlikely to mediate the effect of SAHA (Pasini *et al.* 2018).

BCG induced pulmonary fibrosis:

TB is a widespread and severe contagious disease with an approximate worldwide death rate of 3 million per year. WHO reports that 10 million people worldwide fell ill with TB (5.7 million men, 3.2 million women, and 1.1 million children) (Ronald *et al.* 2019). BCG stays the most controversial of all vaccines used, as its protective efficacy has differed in various areas of the world. BCG vaccine stays the most controversial of all vaccinations used because its defensive effectiveness has differed in various regions of the world (Wang *et al.* 2015).

Nonetheless, traditional BCG vaccination triggers tissue pathology, including vaccine site induration and ulceration, and intradermal BCG is associated with a dose-dependent immune response that really can lead to scars (Barreto, Pereira, and Ferreira 2006).

BCG injection was found to induce granuloma in the liver and lung. BCG infection can induce the release of inflammatory cytokines, active free radicals and nitric oxide, triggering macrophages and T lymphocytes in granulomas to generate multiple forms of pro-inflammatory cytokines that are a form of cell-mediated immune response that may resemble chronic hepatitis fibrosis (Shkurupiy *et al.* 2013).

Garcia-Pelayo *et al.*tested the existence of the immune response and subsequent protection from the Mycobacterium Bovis vaccination challenge in two murine hosts with different genetic backgrounds: BALB/c and C57BL/6 (Garcia-Pelayo *et al.* .2015).

Conclusion:

Vorinostat could be considered a promising drug to target inflammation and fibrosis. It can be used not only in fibrotic lung diseases but also in systemic fibrotic diseases.Future studies are needed to evaluate and confirm the most effective dose of Vorinostat that produce better results with minimal side effects.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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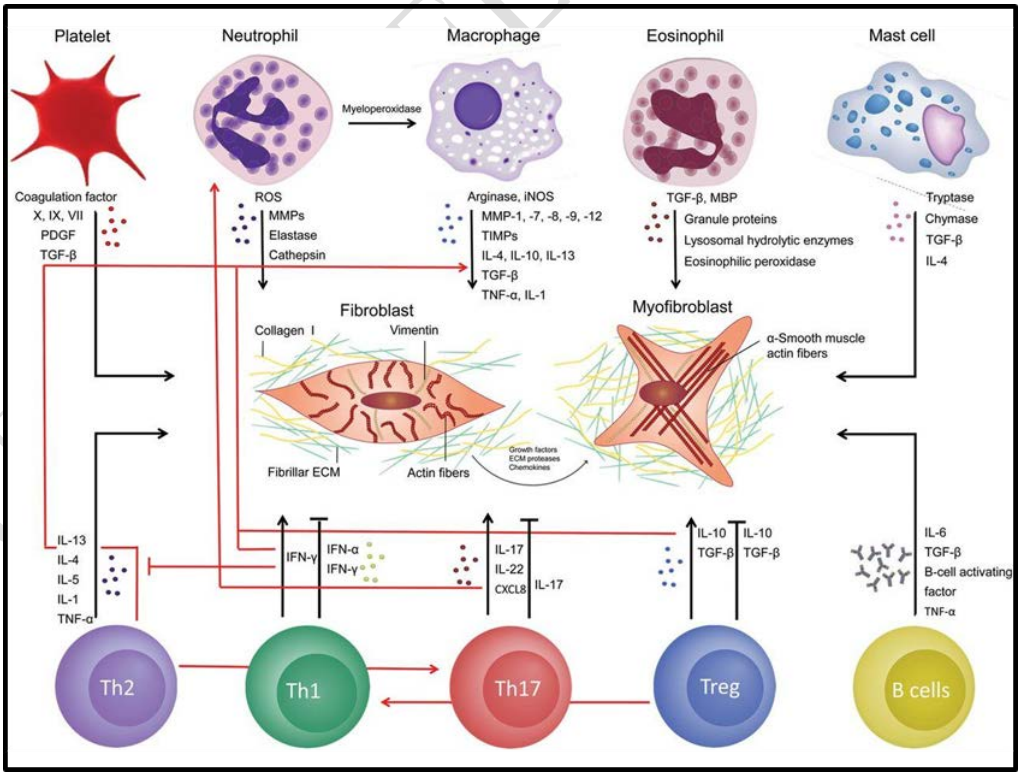

Figure 1: Impact of innate and adaptive immunity components on fibroblasts activation and mediator of inflammation (Van Linthout, Miteva, and Tschöpe, 2014).

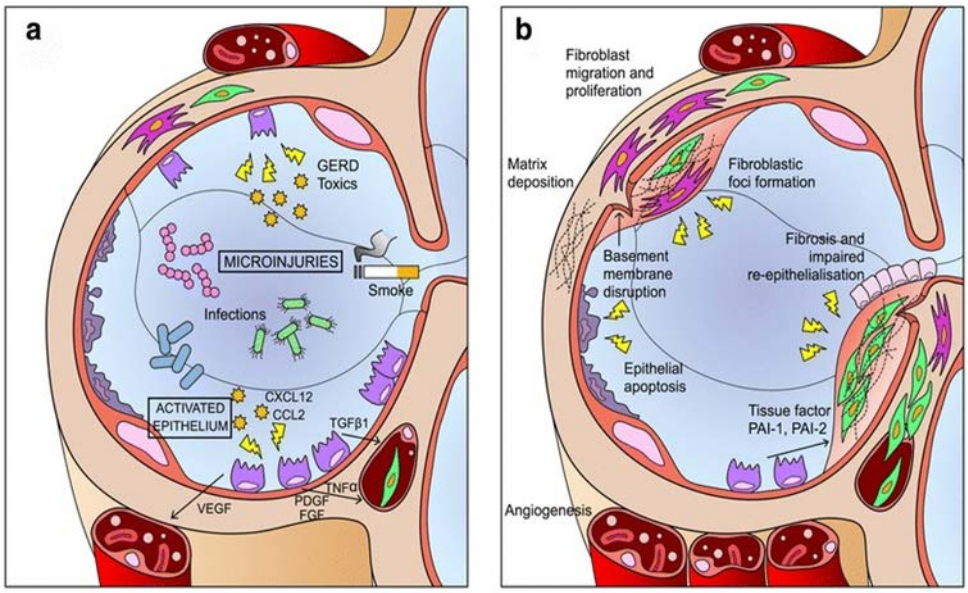

Figure 2: IPF pathogenesis schematic view. Repeated injuries over time (a) and fibroblasts, the proliferation of myofibroblasts, and ECM accumulation (b) (Sgalla et al., 2018).

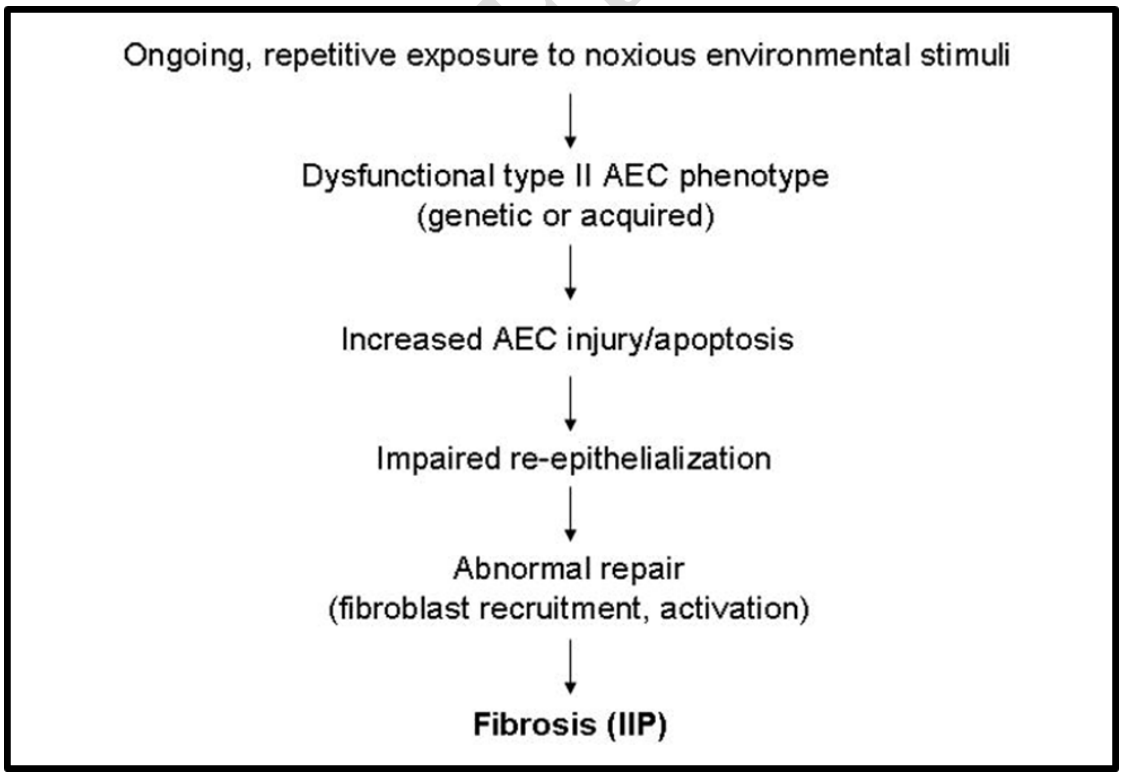

Figure 3: Diagram for dysfunctional (vulnerable) alveolar epithelial cell pathogenesis (Zoz, Lawson and Blackwell, 2011).

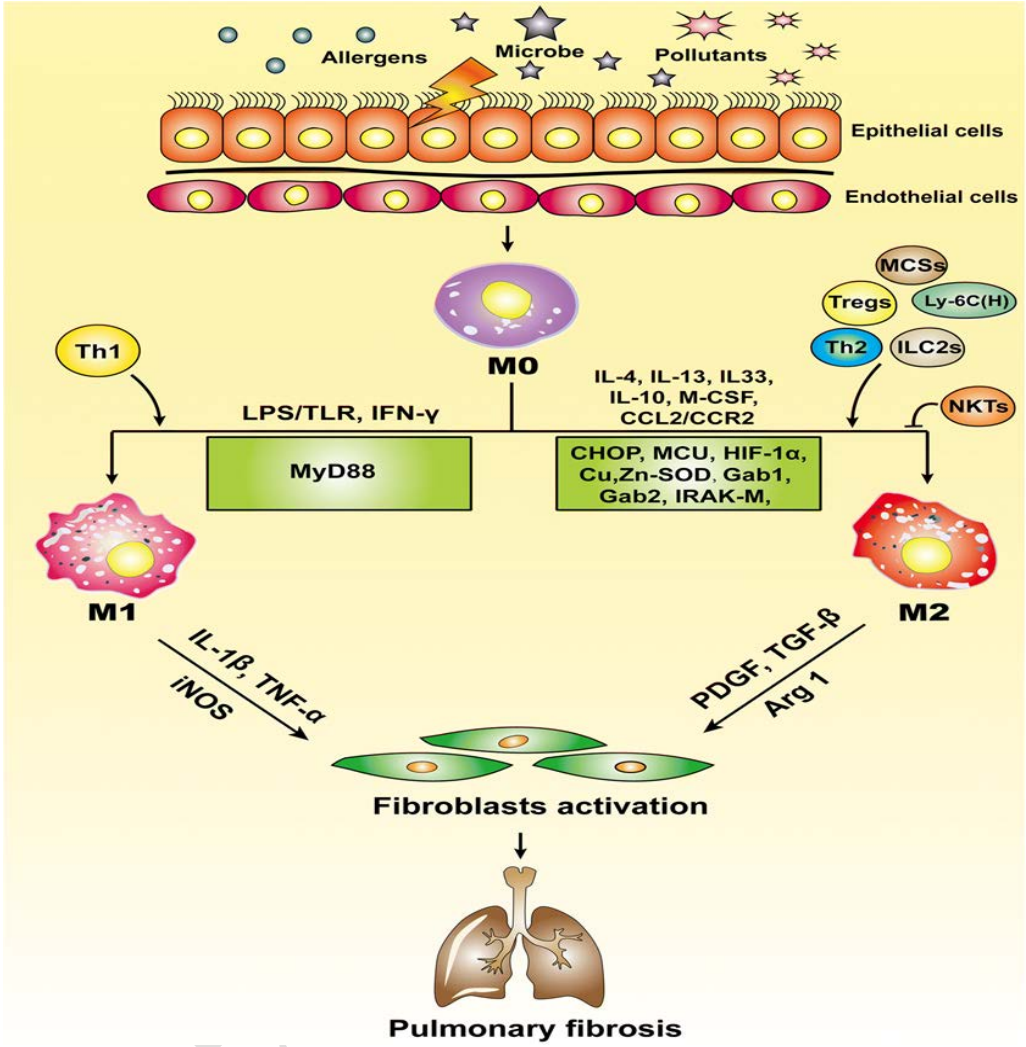

Figure 4: This diagram showing the pathogenesis of the macrophages in pulmonary fibrosis (Zhang et al., 2018).

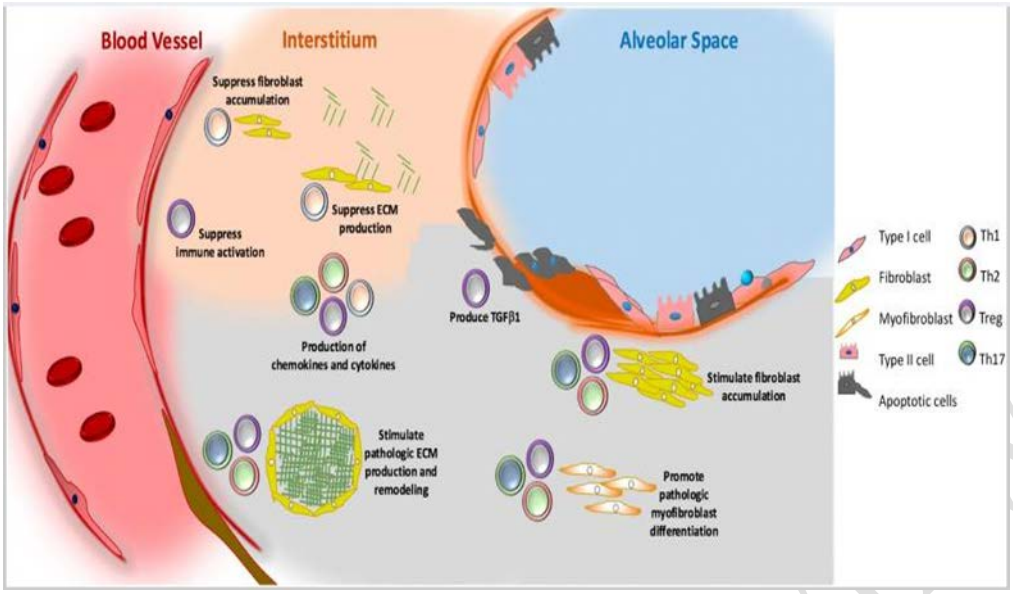

Figure 5: The function of adaptive immunity in IPF (Desai *et al.* 2018).

Table 1: Cytokines and chemokines found to have been involved in the Pathogenesis of pulmonary fibrosis (Agostini, 2006)

Chemokines	**Description**
CXCL12	Recruitment of fibroblastsmarking pathways is completed to advance CTGF articulation in fibroblasts and start AP-1 by CXCL12.
CCL17	CCL17 and alveolar macrophages enhance PF by recruiting CCR4 + Th2 cells.
CCL2	CCL2 increases fibroblast recruitment and differentiation in fibroblasts, resulting in excessive deposition of collagen. CCL2 increases the activation of M2 macrophages and promotes PF.
CCL18	CCL18 enhances collagen production in pulmonary fibroblasts through signal pathways PKCα, ERK1 / 2 and Sp1 / Smad3.
PDGF	PDGF activates fibroblasts. PDGF leads to an expansion in ECM quality expression in fibroblasts.
IL-13	Through a JNK-dependent pathway, IL-13 separates human pulmonary fibroblasts into myofibroma.

AP-1: activated protein 1, Tregs: administrative T cells, CTGF: a component of connective tissue development, CXCL, CXC: ligand chemokine, CCL, CC: ligand chemokine, MMP: metalloproteinase network, EMT: epithelial argument change, ERK: an extracellular marker administered kinase. IL-1R1, and IL-1 receptors 1, JNK, c-Jun N-terminal kinases, MAPK, protein kinase protein.