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Fibroblast-to-myofibroblast transition in bronchial asthma – A review

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Abstract
Bronchial asthma is a chronic inflammatory illness in which the bronchial wall remodels significantly. This phenomenon is linked to increased airway smooth muscle cell proliferation, increased extracellular matrix protein release, and an increase in myofibroblasts. One of the key ways through which myofibroblasts form in fibrotic lung tissue is phenotypic fibroblast-to-myofibroblast transition. The shift from fibroblast to myofibroblast necessitates a combination of numerous variables, the most essential of which are humoural and mechanical stimuli, as well as extracellular matrix proteins. Despite extensive investigation into the nature of this process, the mechanisms that underpin it during bronchial airway wall remodelling in asthma are still unknown. The purpose of this review is to summarise what is known about the fibroblast-to-myofibroblast transition in asthma. We want to think about potential processes and situations that may play a role in the fibroblast-to-myofibroblast transition but haven't been explored previously. Recent research has revealed that several intrinsic and previously unknown characteristics of fibroblasts might play an important role in the fibroblast-to-myofibroblast transition. Differences in bronchial fibroblast response to transforming growth factor, cell shape, elasticity, and protein expression profile between asthmatic and non-asthmatic bronchial fibroblasts may play a key role in these phenomena. An accurate knowledge and recognition of all aspects impacting the fibroblast-to-myofibroblast transition might lead to the development of effective techniques for combating this occurrence.

Keywords: Fibrosis, Lungs, TGF-β-signalling, Pro-fibrotic agents, Mechanical forces

I. Introduction
One of the most frequent chronic illnesses in the world is bronchial asthma. It affects more than ten percent of the world's population and is on the rise. Bronchial asthma is a clinically diverse chronic inflammatory condition of the airways characterised by airflow restriction and hyperresponsiveness to environmental stimuli. In asthma, the regulatory mechanisms and consequences of inflammation form a complex network of reciprocal influences, including a series of events in which structural and infiltrating cells, as well as their signalling molecules, play a role in the irreversible rebuilding of the bronchial wall (called remodelling) [1, 2]. Airway remodelling is characterised as a series of long-term structural changes in the airway wall that result in thickening, epithelium damage, subepithelial fibrosis, increased ECM deposition, smooth muscle hypertrophy, and enhanced vascularity [3–6]. The most strongly connected with remodelling is severe asthma, as defined by the clinical presentation. Inflammatory cell subtypes in asthma, on the other hand, are linked to bronchial wall thickening. The loss of lung function due to a drop in the FEV1/FVC ratio has been linked to eosinophilic inflammation of the airways [7]. Transgenic production of interleukin-8 in bronchial epithelium, on the other hand, caused the neutrophilic phenotype and gradual remodelling of the airways in mice in a recent work [8].

Despite extensive research, some critical questions concerning the pathogenesis of asthma

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remain unanswered. It's unclear if airway remodelling is a common response to chronic inflammation or if it's a critical event in asthma development that occurs independently of inflammation [6]. According to some evidence, airway remodelling is triggered by a variety of factors other than inflammation. First, bronchial wall changes can occur in early childhood, not necessarily as a result of inflammation, but rather prior to it [9–11]. Second, anti-inflammatory asthma medicines have shown to have little or no effect on bronchial wall remodelling [12–14]. Furthermore, several recent demographic and epidemiological studies have found that genetic factors have a significant role in the development of asthma and the remodelling of the bronchial wall [15–20]. Airway constriction and increased thickness of the airway wall (thickening of muscle bundles and subepithelial fibrosis) are well established in asthma patients' lungs, and these features are linked to the severity of bronchial asthma [21, 22]. The airway mucosa includes fibroblasts, myofibroblasts, inflammatory cells, vasculature, and ECM proteins, which causes subepithelial fibrosis [3, 5]. Airway smooth muscle cells (ASMC) hyperplasia and hypertrophy, as well as their specific hyper-reactive ('primed') phenotype, which is characterised by enhanced release of pro-inflammatory and immunomodulatory substances, cause muscle bundle thickening [6]. The critical significance of ASMC in remodelling has been thoroughly explored and elucidated [6, 23–29]. Exaggerated deposition of ECM proteins (primarily collagen I, III, and V and non-collagenous proteins such as elastin, tenascin, fibronectin, and laminin), which are predominantly produced by activated ASMC, fibroblasts, and myofibroblasts, causes the thickening of the asthmatic (AS) subepithelial layer [30–34]. Fibroblasts, myofibroblasts, and their interactions should be examined to complete the picture of activities occurring in AS bronchial walls. These amazing cells appear to be critical for the alterations that lead to airway lumen constriction. The function of myofibroblasts in the course of bronchial wall remodelling in asthma is undeniable, but the involvement of fibroblasts in the subepithelial layer in myofibroblast transition remains equivocal, despite the fact that it is frequently documented. The goal of this study is to compile the most up-to-date information on the components and processes that can lead to myofibroblast production, particularly as a result of the fibroblast-to-myofibroblast transition (FMT) in bronchial asthma.

Myofibroblasts in the bronchial wall

Myofibroblasts are mesenchymal cells that are typically described as a cross between fibroblasts and smooth muscle cells according to their nature. Myofibroblasts (like fibroblasts) may produce ECM proteins and the myocyte-specific isoform -smooth muscle actin ((α-SMA), which appears in cells as stress fibres. Myofibroblasts can contract because of these characteristics. It is generally accepted that myofibroblasts (including bronchial myofibroblasts from AS individuals), in addition to their expression of α-SMA, express transgelin (SM-22-α), smooth muscle myosin, osteopontin, and calponin-1 and are interconnected via gap junctions, highlighting their similarities with smooth muscle cells. As mesenchymal cells, myofibroblasts express vimentin and fibroblast surface protein (FSP) [35–41]. The contractile apparatus of myofibroblasts is composed of α-SMA-enriched bundles of microfilaments terminated with focal adhesions (FAs) positive for integrins (α1, α3, α4, α5, αV, β1), vinculin, paxillin, talin, and tensin [42–45]. Human bronchial myofibroblasts were found to have a larger mean surface area and less extension of cell shape when compared to fibroblasts [46]. Extension is a measure of how much a shape differs from a circle, taking a value of zero if the shape is circular and increasing without limit as the shape becomes less circular. Compared to mature myofibroblasts, human bronchial fibroblasts (HBFs) are smaller and less elongated [46–48].

Bronchial myofibroblasts are metabolically active as well as contractile. Collagens I, III, and V, fibronectin [49, 50], tenascin [51], and proteoglycans (lumican, versican biglycan, and decorin) [50, 52, 53] all show enhanced expression and secretion in AS myofibroblasts. Greater thickness of the lamina reticularis in AS patients' bronchi (between 4 and 12 µm, compared to 2–6 µm in non-asthmatic (NA) participants) is caused by increased collagen synthesis by fibroblasts and myofibroblasts [49, 54–56]. Although greater collagen deposition in the subepithelial basement membrane is a hallmark of asthma, Chu et al. propose that it may not explain the variations in asthma severity [57]. Matrix metalloproteinases (MMPs) and their inhibitors (tissue inhibitors of metalloproteinase, TIMP) are known to be found in myofibroblasts [33, 58, 59]. Increased MMP-9 and TIMP-1 expressions were seen in bronchoalveolar lavage fluid (BALF), sputum, and airway biopsies from AS patients [60–62]. AS sufferers, on the other hand, had a much lower MMP-9 to TIMP-1 ratio

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than control participants, which corresponds with the degree of airway blockage. The MMP-9/TIMP-3 ratio is reduced in both managed and uncontrolled asthma, according to Weitoft and colleagues [50]. Inflammatory mediators, cytokines, chemokines, and growth factors, such as granulocyte–macrophage colony-stimulating factor (GM-CSF), interleukins (IL-1, IL-6, IL-8), stem cell factor (SCF), transforming growth factor type (TGF-β), and vascular endothelial growth factor (VEGF), are abundant in myofibroblasts [63–66]. Thus, myofibroblast-derived factors may promote cell migration, hyperplasia, and hypertrophy not only in myofibroblasts but also in other airway and immune cells, such as smooth muscle cells [67, 68].

So far, several sources of myofibroblasts have been discovered. Both epithelial-to-mesenchymal transition (EMT) [69–72] and endothelial-to-mesenchymal transition (EndoMT) [73] can result in myofibroblasts. Myofibroblasts can also be produced from circulating fibroblasts and mesenchymal stem cells derived from bone marrow [74–81]. In chronic severe asthma [82], fibrocytes are a major source of myofibroblasts. Differentiated pericytes [83, 84] and smooth muscle cells [40] can also be used to make myofibroblasts. The population of fibroblasts located in the connective tissue of the bronchi is the most common source of myofibroblasts, as fibroblasts can alter their phenotype to that of myofibroblasts under the effect of numerous stimuli.

FMT

FMT is a phenomenon that happens in both healthy and pathological conditions in the human body. Impaired wound healing and chronic inflammation are linked to an increase in myofibroblast production in connective tissue as well as apoptotic abnormalities. As a result, aberrant myofibroblast production is frequently mentioned in fibrotic illness aetiology. Subepithelial remodelling in asthma has also been linked to increased myofibroblast production [85, 86].

In wound healing, the basic mechanism of FMT has been found and characterised [87]. According to several in vitro studies, the FMT process has two steps. Fibroblasts generate a transitory phenotype known as proto-myofibroblasts in the early stages, which are eventually transformed into fully differentiated (mature) myofibroblasts [42, 88]. The transition from fibroblast to proto-myofibroblast is aided by mechanical strain within the wound and is accompanied by the release of ED-A fibronectin [89] and platelet-derived growth factor (PDGF). PDGF has the ability to cause the production of stress fibres and promote cell motility [90]. The generated proto-myofibroblasts express both - and -actin isoforms (which are integrated into stress fibres) as well as N-cadherin, which has a lower adhesion force than OB-cadherin but allows proto-myofibroblasts to move more freely [91]. It's difficult to tell the difference between fibroblasts and proto-myofibroblasts in vitro since most fibroblasts in culture have a proto-myofibroblast phenotype [88]. Proto-myofibroblasts begin production of -SMA and gradually form -SMA-containing stress fibres in response to a protracted state of high stress and the presence of FMT-stimulating cytokines, growth factors, and ECM proteins. Fully differentiated myofibroblasts display OB-cadherin, have mature FAs (including de novo expression of focal adhesion kinase (FAK) and tensin), and have reduced motility, increased contractility, and lower proliferation rates [42, 64, 91].

FMT works in a similar way in asthma and other fibrotic lung diseases, but its effect on the bronchi microenvironment appears to be distinct. After performing their function, myofibroblasts usually join the apoptotic pathway. Normal lung myofibroblasts have been shown to be able to develop back into fibroblasts in vitro [92, 93]. Myofibroblasts appear to persist inside the tissue in asthma and play an active role in bronchial wall remodelling by producing a contractile force on the surrounding cells and ECM, as well as secreting growth factors and ECM components [94].

Stimuli affecting FMT in asthma

Previous research into the nature of FMT has led to the discovery of a number of elements that have a role in the production of this asthmatic symptom. Growth factors, cytokines, and chemokines are the most common humoural agents. Mechanical factors, which include intercellular contacts and cell interactions with various substrates and ECM proteins, comprise the second type of FMT-triggering agents. Many FMT triggers may interact with one another, leading to additional activation of FMT, due to the intricate pathophysiology of asthma.

Humoural factors

The involvement of growth factors in activating FMT is obvious and crucial, according to the present research. TGF-β is the most well-known of all the discovered pro-fibrotic factors. TGF-β1, TGF-β2, and TGF-β3 are three homologous TGF-

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β isoforms that have been found. Both bronchial structural cells (epithelial cells, fibroblasts, endothelial cells, vascular cells, and ASMC) and inflammatory cells infiltrating the bronchial wall (eosinophils, macrophages) produce TGF-β into the extracellular space [95–98]. According to the literature, all TGF-β isoforms are secreted in the AS lung, although the 1 and 2 isoforms appear to be the most important [99–103]. TGF-β levels have been shown to be higher in the bronchi [95, 104] and BALF of AS patients [105, 106]. It has also been hypothesised that there is a link between the amount of TGF-β present in the respiratory tract and the severity of asthma [106, 107]. Nonetheless, various investigations looking into the expression of TGF-β1 in asthma have come up with contradictory conclusions. There are no changes in the immunohistochemistry staining of TGF-β1 between AS and control participants in human bronchial biopsy tissues [56, 108, 109]. TGF-β , on the other hand, has been shown to play a key part in most cellular biological processes that contribute to asthmatic airway remodelling. TGF-β has pleiotropic and immunomodulatory effects on several cell types [95, 106, 110–115]. TGF- may have pro- or anti-apoptotic effects on epithelial cells depending on chemical and mechanical circumstances [116], and can promote EMT in AS airway epithelial cells [117]. TGF-β has been shown to cause FMT in AS patients in vitro [95, 97, 98, 118, 119] and in vivo [120–122]. TGF-β has also been found to contribute to fibrosis indirectly in AS patients by inducing the development of additional fibrosis mediators such as interleukin-6 (IL-6) [123]. TGF-β can also stimulate or increase the production of fibroblast growth factor-2 (FGF-2), connective tissue growth factor (CTGF), and VEGF by fibroblasts, myofibroblasts, and airway smooth muscle [124–128].

Another major growth factor involved in fibrotic processes in bronchial asthma is CTGF (also known as CCN2). CTGF is overexpressed in the lung tissue and plasma of AS patients [130] and is implicated in the progression of chronic inflammatory disorders [129]. Fibroblasts, epithelial cells, endothelial cells, and ASMC are the principal producers of this growth factor in the bronchi. Similar to FMT, CTGF's involvement in bronchial wall remodelling mostly entails modulating several of TGF-β's actions [126–128, 131]. TGF-β induced CTGF release, for example, has been shown to increase fibronectin, collagen I, and VEGF synthesis in ASMC [132–134] as well as induce FMT [126–128, 135].

Other growth factors, in addition to TGF-β and CTGF's well-coordinated actions, are undoubtedly involved in FMT induction in asthma, either directly or indirectly. For example, PDGF has been demonstrated to enhance the migratory and phenotypic alterations of lung fibroblasts from AS patients [90], as well as to stimulate procollagen I expression in lung fibroblasts from severe asthma patients [136] and to raise the lung fibroblast proliferation rate in AS participants [137]. In turn, nerve growth factor (NGF), which is high in AS airways [138], can cause pulmonary fibroblast activation, fibronectin-induced fibroblast migration, and α -SMA and matrix contraction [139–141].

Pro-inflammatory cytokines and chemokines are also important factors in the initiation of FMT. Inflammation is definitely important in the etiology of asthma [1, 143–145]. Increased vascular permeability has been linked to an increase in immune cell inflow, and cytokines and chemokines have been detected in AS airways during illness exacerbation. Interleukins, such as IL-4 and IL-13, are thought to be closely linked to inflammatory responses in asthma. The involvement of interleukins in FMT is also well established. Through downregulation of cyclooxygenase (COX) gene expression and decrease of prostaglandin E2 synthesis, IL-4 and IL-13 may directly act on lung fibroblasts and cause myofibroblastic transformation [146]. Furthermore, FMT can be induced by IL-4 and IL-13 via the c-Jun NH2-terminal kinase-dependent pathway [147]. Furthermore, both interleukins have a role in the development of the myofibroblast phenotype [148–159]. Although it is unclear how other interleukins influence FMT induction in asthma, various in vitro and in vivo investigations have revealed that several interleukins may boost FMT potential in a TGF-β dependent or TGF-β independent manner. IL-5 [150], IL-11 [160, 161], IL-17 [162], IL-17A [163–166], IL-25 [167–170], IL-33 [171, 172], tumour necrosis factor type (TNF-α) [118], interleukin-6 (IL-6) superfamily members, and oncostatin M (OSM) [173] are examples of cytokines that can both indirectly and directly trigger FMT. All of the cytokines listed above have been found to be over expressed in asthma patients [150, 174–180].

Eotaxins (eotaxin-1, eotaxin-2, and eotaxin-3) [181–184], osteopontin (OPN) [39, 185, 186], and periostin [154, 187–190] are three chemokines that should be studied in the context of FMT induction. First, in humans, OPN is increased in asthma and linked to bronchial remodelling. Furthermore, greater OPN subepithelial expression

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is linked to disease severity [39, 186]. OPN has been shown to stimulate the transformation of lung fibroblasts into myofibroblasts in mice [185]. Eotaxins, a different class of chemokines, can regulate lung and bronchial fibroblast activity by enhancing fibroblast proliferation and modulating MMP-2 activity, collagen formation, and cell migration [182, 183]. Periostin has recently attracted attention as a pro-fibrotic factor in asthma [154, 188–191]. Epithelial cells, fibroblasts, eosinophils, and fibrocytes are the major producers of this eosinophilia and type 2 inflammatory biomarker in asthma [103, 154, 192–196]. Periostin has been shown to have a role in the transformation of fibroblasts into myofibroblasts and the activation of fibroblast migration [187, 197]. It's also probable that periostin increases ECM formation and FMT as a cofactor of TGF-β [154, 187, 198].

Unclassified factors such as Fizz1 [199–201], cysteinyl leukotrienes [202, 203], bradykinin [204], and endothelin-1 (ET-1) [205, 206] should be included among the humoural factors that cause FMT. All of these elements can influence myofibroblast development directly.

Mechanical factors

Mechanical variables make up the second group of FMT-inducing factors. The condition of mechanical tension and changes in the tissue microenvironment are well established to be important for FMT efficiency. For more than a decade, researchers have investigated the physical changes involved in the production of myofibroblasts in a variety of tissues, including lung tissues [40, 45, 88, 207]. Mechanical stress has been proven to be one of the most significant elements affecting fibroblast phenotypic alterations and cell fate in both in vitro (with fibroblasts in 2D culture on different surfaces or in 3D collagen gels with varied stiffness) and in vivo (with animal models) investigations [208–212]. The stiffness threshold for myofibroblast development in vitro during wound healing was similarly discovered to be around 25–50 kPa [207]. Fibrotic lung tissue is up to 30 times stiffer than normal lung tissue, as assessed by atomic force microscopy (the Young's modulus varies between 20–100 and 1–5 kPa, respectively) [213–216].

Few researches on the direct influence of "mechanical forces" on the lung or bronchial FMT in asthma are worth mentioning. The exception is Shi and colleagues' work, which found that increasing substrate stiffness in culture, improved TGF-β1-induced bronchial FMT as well as cell stiffness and contractility [217]. In contrast, several studies have examined the impact of mechanical pressures on asthmatic airway remodelling [218, 219]. In AS fibroblasts under mechanical stress, several investigations have found an increase in ECM protein and proteoglycan content (versican, decorin, collagen I and III), MMP-2 and MMP-9 synthesis, and IL-6 and IL-8 production [218–222].

Patients with uncontrolled asthma had considerably more myofibroblasts (in central airways and alveolar parenchyma) and different compositions of ECM proteins than patients with controlled asthma, according to a study of bronchial and transbronchial biopsies from AS patients [50]. The mechanical qualities of lung tissue in people with uncontrolled asthma may be partly due to the features and subsequent changes in elasticity, as documented by Weitoft and others. Increased deposition of ECM proteins might explain the increased stiffness and decreased flexibility inside airways in asthma.

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completion [223]. Furthermore, Reeves et al. suggested that the contact between fibroblasts and epithelial cells may be important for the altered ECM production propensity in fibroblasts. Increased ECM and α-SMA production in fibroblasts co-cultured with epithelial cells from AS patients' bronchi might be a result of their reaction to the sick epithelial cell phenotype [34, 224]. The interactions outlined above are key in causing FMT. Although there are few findings demonstrating that mechanical variables have a direct role in asthma-related FMT, their presence is evident.

ECM proteins that trigger FMT in asthma

The fibronectin splice variant ectodomain A is a very essential element in the ECM protein group for promoting FMT (ED-A-FN). This protein's level has been discovered to be higher in asthma and other respiratory illnesses [37, 48, 225]. OVA-treated animals missing ED-A-FN had decreased proliferation, migration, α-SMA expression, and collagen deposition, as well as impaired TGF-β1 and IL-13 release [226]. Because it is well known that ED-A-FN binds TGF-β in the ECM and that it may interact directly with cells via integrins, no additional explanation of its peculiar involvement in asthmatic FMT is required. Although there is little evidence that additional ECM proteins have a direct effect on FMT, their potential indirect influence on myofibroblast formation cannot be overlooked. As a result, tenascin should be given extra attention. This myofibroblast marker is overexpressed in asthma [51, 227, 228], and its absence reduced airway inflammation and, in particular, eosinophilia, IL-5, and IL-13 levels in BALF [229]. Fibulin-1, a novel bronchial asthma marker, was recently discovered [230, 231]. Other ECM proteins are stabilised by this secreted glycoprotein. Increased ECM stability may enhance fibroblast sensitivity to FMT, given the indisputable effect of mechanical stress on FMT. Another indirect influence of ECM on myofibroblast production regulation is related to ECM proteins' capacity to bind certain growth factors. These growth factors, which may be generated in greater quantities by AS airways, interact with ECM proteins in a number of ways. Although the direct association of TGF-β binding to ECM in asthma has yet to be established, given that TGF-β regulation may be influenced by TGF-β binding to ECM proteins [94, 232], we believe that such an interaction may be relevant in asthma-related FMT.

Fibroblast features

The above-mentioned and discussed elements are widely acknowledged as being critical for FMT in asthma. However, some recent in vitro study results have revealed that innate fibroblast characteristics may possibly play a role in this process. Michalik et al. found that bronchial fibroblasts from AS patients have a higher TGF-β1-induced ability to develop into myofibroblasts than NA counterparts [46, 223], which might be due to the cells' underlying characteristics.

The differences between AS and NA HBFs that are linked to their proclivity for FMT have just recently been discovered. Several studies have found substantial changes in cell morphology (mostly cell shape) between AS and NA bronchial fibroblasts cultivated under the same standard conditions [44, 46]. Furthermore, Kotaru et al. [233] discovered significant variations in cell size across populations of fibroblasts isolated from the proximal and distal sections of AS lungs, which were associated to their proclivity for FMT. Furthermore, TGF-β1 or TGF-β2-induced FMT is associated with dramatic cell shape alterations, and this phenomenon was improved in HBFs generated from AS patients [46]. In comparison to NA HBF populations, these findings were connected with an increased number of cells with de novo expression of α-SMA and the integration of α-SMA into highly contractile microfilament bundles in AS HBF populations [36, 46, 204, 223, 234, 235]. Furthermore, AS human lung fibroblasts (HLFs) produced more SM22 (a protein that determines a cell's smooth muscle lineage) than NA fibroblasts [235].

Sarna et al. recently shown substantial changes in actin cytoskeleton architecture in HBFs obtained from AS patients and those derived from NA donors using a combination of cytofluorimetric and nanomechanical techniques [44]. AS HBFs, in contrast to NA HBFs, generated thick, aligned ventral stress fibres with larger FAs. The high elastic modulus and isometric tension of unstimulated (α-SMA-negative) AS HBFs, as well as their greater predisposition to TGF-β induced FMT, are linked to variations in cytoskeleton architecture between AS and NA fibroblasts [44].

Various ways of behaving of NA and AS HBFs are likewise seen after outer excitement. Many reports show that the supportive of fibrotic capability of HBFs got from AS subjects is increased because of humoural as well as mechanical elements. After feeling, AS HBFs displayed different articulation examples of certain

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proteins contrasted with NA HBFs. The most significant and prominent contrasts are enhanced degrees of α-SMA and connexin (Cx) 43 (protein engaged with the intercellular exchange of little metabolites and particles through hexameric channels named hole intersections) [236, 237] because of TGF-β organization in AS HBFs contrasted with NA HBFs [46, 223, 234, 238]. Cx43 levels in AS HBFs were shown to be associated with their FMT potential [234]. HBFs from AS donors had higher levels of bradykinin B2 receptor [204], leukotriene C4 synthase and CysLT1 receptors [239], PAI-1 [235], and MRTF-A [235], but lower levels of prostaglandin E2 [240].

TGF- receptor levels were also discovered to differ between AS and NA HBFs, which might affect FMT potential. Previous research clearly shows that, while the levels of TGF-RII in AS and NA cell populations are equal [238], considerably higher levels of TGF-βRI in HBFs from AS sufferers relative to healthy donors have been identified [203].

AS HBFs also alter the expression of ECM components and promote their secretion into the surrounding milieu (because to their greater tension). Collagens, particularly type I [158, 217, 235], proteoglycans [241], versican [221, 222], low-molecular-weight hyaluronan [242], fibronectin [235, 243], decorin [221], and tenascin C [229, 244], have shown significant changes in expression. Furthermore, whereas both sets of cells synthesise procollagens I and III [137], the balance between (pro) collagen production and breakdown in HBFs from AS patients is uncertain [245, 246]. This phenomenon has also been linked to an imbalanced TIMP/MMP ratio in AS HBFs [245]. These traits cause enhanced ECM component rearrangement and deposition, which supports HBF phenotypic change [49, 119, 158, 217], as previously demonstrated.

HBFs from AS donors also secrete considerably more CTGF, IL-6, IL-8, IL-11, IL-17, α-chemokines, and growth-related oncogene-α than their NA counterparts in response to the administration of humoural factors [106, 127, 163, 222, 247]. Similarly, both unstimulated HBFs from AS donors and HBFs under pro-inflammatory circumstances show enhanced production of an active type of TGF-β1 [106, 158, 203]. HBFs from AS donors show considerable elevation of IL-6, IL-8, MMP-2, MMP-9, collagen I and III expression in response to mechanical stress [158, 217, 219, 222, 244]. Increased production and release of these proteins may further auto-stimulate the transformation of HBFs from AS patients into myofibroblasts.

Because AS and NA HBFs are distinct, differences in intracellular signalling pathway activity might be detected. In comparison to their healthy counterparts, the acceleration of pro-fibrotic protein production in bronchial fibroblasts from AS donors is likely based on the activation of distinct signalling pathways. Different signalling pathways have been found to be activated by changes in ECM composition and rigidity. Mechanical strain enhanced the release of pro-fibrotic and pro-inflammatory cytokines in bronchial fibroblasts from AS patients, but no variations in cytokine secretion were identified in fibroblasts from healthy volunteers [222]. Furthermore, these researchers discovered a mechanical strain-induced increase in ECM protein expression in only AS fibroblasts, indicating that separate signalling pathways are involved in the transmission of mechanical stimuli in AS and NA fibroblast populations [222]. The substantial differential in the sensitivity of AS and NA fibroblasts to change into myofibroblasts in response to humoural factors (most notably TGF-β1) suggests that these factors might promote TGF-β1-induced signal transduction in HBFs from AS patients. The activity of the canonical TGF-β/Smad signalling pathway is primarily responsible for the difference in response of AS and NA HBFs to TGF-β1 [120, 238, 248]. Increased levels of Cx43 in AS HBFs relative to NA counterparts are tightly connected to enhanced TGF-1-induced Smad-dependent signalling [234]. Cx43 controls FMT by competing with Smad2 for binding sites on microtubules, acting as a'molecular switch' [234, 249–251].

Because of TGF-β1's pleiotropic features, the activation of several non-canonical TGF-β1-induced signalling pathways, such as the mitogen-activated protein kinase (MAPK) pathway, is frequently related with the development of FMT during airway fibrosis. FMT activation via the ERK1/2 MAPK pathway was also detected in AS fibroblasts following bradykinin [204], IL-4, and IL-13 [147] treatment. Furthermore, SB203580 inhibited the p38 MAPK signalling pathway, which reduced the bradykinin-induced myofibroblastic transition in both NA and AS HBFs [204], but there have been no findings on the influence of p38 MAPK signalling on TGF-β1-induced FMT in these cells. The stimulation of Rho-dependent signalling is also linked to the induction of the myofibroblastic transformation of NA HLFs by TGF-β [235, 252]. TGF-β-induced FMT in lung fibroblasts, on the

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other hand, has been linked to Wnt/GSK-3β/β-catenin signalling activation [238, 253]. Michalik et al. discovered that inhibiting GSK-3β with LiCl or TWS119 reduces TGF-β1-induced FMT in HBF populations obtained from AS patients, but not healthy donors. Furthermore, when TGF-β was combined with inhibitors of Wnt/GSK-3β/β-catenin signalling (LiCL, TWS119), the amount of β-catenin in NA HBFs was higher than in AS HBFs. TGF-β/LiCL activation of AS HBFs, on the other hand, reduced the Smad-dependent pathway. These findings imply that variations in sensitivity of AS and NA HBFs to TGF-β-induced FMT may be due to decreased intracellular trafficking of β-catenin via cross-talk with Smad-dependent signalling [238]. Differences in Smad- or GSK-3β/Wnt/β-catenin-dependent pathway activity in AS HBFs following TGF-β1 stimulation appear to be intimately linked to these cells' cellular and molecular characteristics. Different patterns of the above-mentioned proteins may also be a reaction to the various activities of signalling pathways, or they may control their activity. However, the most plausible hypothesis is that cells have inherent features that cause pro-fibrotic signals to be amplified, which is supported by HBFs' increased FMT capacity. The origin of airway myofibroblast precursors might be a source of phenotypic variability among HBFs.

Finally, the findings show that innate lung/bronchial fibroblast characteristics are just as important for the induction and efficacy of FMT during asthma development as growth factors and mechanical qualities of the milieu surrounding the cell.

Furthermore, it is critical to recognise that the bronchial wall of AS patients has many populations of fibroblasts. There have previously been reports that there are cells (up to 20%) in a single population of bronchial fibroblasts that are resistant to TGF-β-induced phenotypic change [46, 223, 238, 254]. Furthermore, compared to NA counterparts, unstimulated AS HBF populations have a higher percentage of α-SMA+ cells [46, 223, 238, 255, 256].

The origin of this TGF-β-insensitive population is unknown, although it might be linked to the infiltration of highly contractile myofibroblast precursors into the bronchial wall's pro-inflammatory niche, particularly CD34+ fibrocytes, mesenchymal stem cells, adipocytes, and pericytes. These characteristics may be connected to asthma heterogeneity, indicating that asthma's multidirectional pathways ultimately lead to myofibroblast growth and the formation of subepithelial fibrosis.

It's also vital to note the role of cellular contacts in fibroblast FMT potential. According to recent studies, AS epithelial cells promote myofibroblast formation and boost ECM creation in human lung fibroblast populations [34, 224]. However, little is known regarding the behaviour of bronchial fibroblasts co-cultured with epithelial cells, particularly because distinct FMT potentials have been found in human bronchial and lung parenchyma fibroblast populations [257, 258]. Finally, epigenetic or genetic variables may play a role in the impact of differentiated bronchial fibroblast characteristics. Although others [259–262] have discussed the impact of these (genetic and/or epigenetic) determinants on asthma development, little is known about the genetic and epigenetic factors that directly influence the differential response of bronchial fibroblasts to pro-inflammatory signals.

II. Conclusion

For the first time, the data reviewed in this paper show that the induction of FMT, a process that happens in AS bronchial walls, involves both extrinsic (humoural, mechanical, and ECM interactions) and intrinsic (bronchial fibroblast characteristics) elements. Despite the fact that the significance of these variables to the deterioration in lung function in AS patients is yet unknown, it appears reasonable to admit that the evidence supports a treatment based on topical suppression of bronchial remodelling pathways.

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