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# Pirfenidone –A Molecular Target for Oral Submucous Fibrosis?

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**ABSTRACT:** Oral submucous fibrosis is a potentially malignant disorder, which is characterized by a juxtaepithelial inflammatory reaction followed by a fibrotic change in the lamina propria along with epithelial atrophy and finally leading to oral carcinoma. Molecular pathogenesis of OSMF shows that it is a collagen metabolic disorder, caused by an imbalance between collagen formation and degradation pathway. The balance between synthesis and degradation of collagen is influenced by a variety of mediators, One such prominent mediator is transforming growth factor-beta especially TGF-β-1, which plays a major role in fibrotic diseases such as idiopathic pulmonary fibrosis, renal fibrosis, hepatic fibrosis, and cardiac fibrosis. Many studies also evidenced that the TGF- β signaling pathway involvement is a critical factor to develop OSMF. Since the pathogenesis of OSMF and other fibrotic diseases are analogous through the involvement of TGF- β, an antifibrotic agent pirfenidone, which targets TGF- β is currently in use for idiopathic pulmonary fibrosis, could be a promising agent for oral submucous fibrosis. Therefore, this paper hypothesizes that pirfenidone can be considered in the therapeutic approach for OSMF.

**Keywords** - Anti-fibrotic, Oral submucous fibrosis(OSMF), Pirfenidone, Transforming growth factor - β

## I. INTRODUCTION

Oral Submucous Fibrosis (OSMF) is a chronic, debilitating and potentially malignant condition which was first reported and described by J.Schwartz in 1952 and later, in 1966, Jens J. Pindborg et al had coined the term oral submucous fibrosis and defined it as "insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx, although occasionally preceded by and/or associated with vesicle formation, it is always associated with a juxta-epithelial inflammatory reaction followed by a fibroelastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat"(1). Prevalence of OSMF is predominantly seen in India and South East Asia and recent data suggest that the prevalence of OSMF in India has increased from 0.03% to 6.42% (2). Several etiological factors had been identified in OSMF including areca nut chewing, ingestion of chilies, genetic and immunologic processes, and nutritional deficiencies. Among this, chewing of betel quid has been recognized as one of the most important risk factors for OSMF as supported by the epidemiological evidence as well as from its histopathological effects on fibroblasts and keratinocytes(3). Though the causative factors of OSMF are multiple, the most accepted pathogenesis is an imbalance between the collagen synthesis and degradation pathway which is analogous to many other fibrosing conditions scrutinized in the medical literature (4). The synthesis of collagen is influenced by a variety of fibrogenic mediators. One such prominent mediator is transforming growth factor-beta (TGF- β), which has also been implicated in the development of many fibrotic diseases (4). Currently, the therapeutic approach for OSMF is focused on minimizing the inflammation, improving the mouth opening, and relieving the symptoms through medical and surgical intervention. But none of the approaches are targeted at the molecular level. So, the future research should be focused on drugs that target the molecular pathogenesis, especially anti TGF- β drugs such as pirfenidone, which is currently been approved for use in idiopathic pulmonary fibrosis and also various clinical trials underwent with pirfenidone for other fibrotic diseases like renal fibrosis, hepatic fibrosis, and radiation-induced fibrosis which showed promising results (4,5).

## II. ROLE OF TGF- β IN MOLECULAR PATHOGENESIS OF OSMF

Several studies on oral submucous fibrosis confirmed that an imbalance in collagen metabolism is a predominant mechanism in the development of fibrosis. The etiological factor, betel nut consists of alkaloids, flavonoids, and copper which alters the ECM homeostasis(collagen metabolism) in oral tissue and resulting in fibrosis (6). The constant irritation of betel quid results in chronic localized mucosal inflammation which recruits activated T cells and macrophages and increases the production of various cytokines and TGF-β. TGF-β

especially TGF-β-1 is a fibrogenic mediator involves in various pathways of collagen production and degradation and transforms the normal mucosa into fibrosis condition (6).

**a. Collagen production pathway**

TGF- β significantly increases collagen production by activating the procollagen genes in fibroblasts. These Procollagen genes are transcribed and translated to form procollagen monomeric chains (procollagen precursor) and contributing to increased collagen production (6,7). And, it also increases procollagen proteinase namely PNP and PCP (that cleave the N- and C-terminal, respectively) which plays an essential role in the processing of procollagen precursors into collagen fibrils, which are in soluble form. TGF- β also upregulates lysyl oxidase (LOX) which is an essential enzyme for final processing of collagen fibers into an insoluble, stabilized covalently cross-linked mature fibrillar form that is resistant to proteolysis. TGF- β robustly expresses the LOX both at the mRNA and protein levels in various culture models either directly or indirectly via the elevation of BMP1, which mediates the conversion of prolysyl oxidase to active LOX. All of these significantly increase collagen production and maintains it by preventing the lysis (6,7)(Fig.1)

**b. Collagen degradation pathway**

TGF- β decreases the collagen degradation by activation of the tissue inhibitor of matrix metalloproteinase gene (TIMP) and activation of plasminogen activator inhibitor(PAI). Matrix metalloproteinases are endopeptidases that play an important role in tissue remodeling by degrading ECM and they are simply referred to as collagenases. TIMPs are specific inhibitors of MMPs that prevent the degradation of collagen. An increase in TIMPs expression has been shown in OSMF (6–8). Another hindrance in the degradation pathway by TGF- β is stimulation of PAI gene which has been shown in various cell cultures and animal models. Plasminogen activator is necessary to cleave inactive plasminogen to active plasmin, which results in the proteolytic activation of pro- MMPs to active MMPs that can facilitate the degradation of collagen. Plasminogen activator inhibitor gene induced by TGF- β inhibits the plasminogen activator in OSMF. Thus TGF- β causes inhibition of the existing collagenase and decreased generation of active collagenase and thereby decreasing the collagen degradation (7,9) (Fig.1)

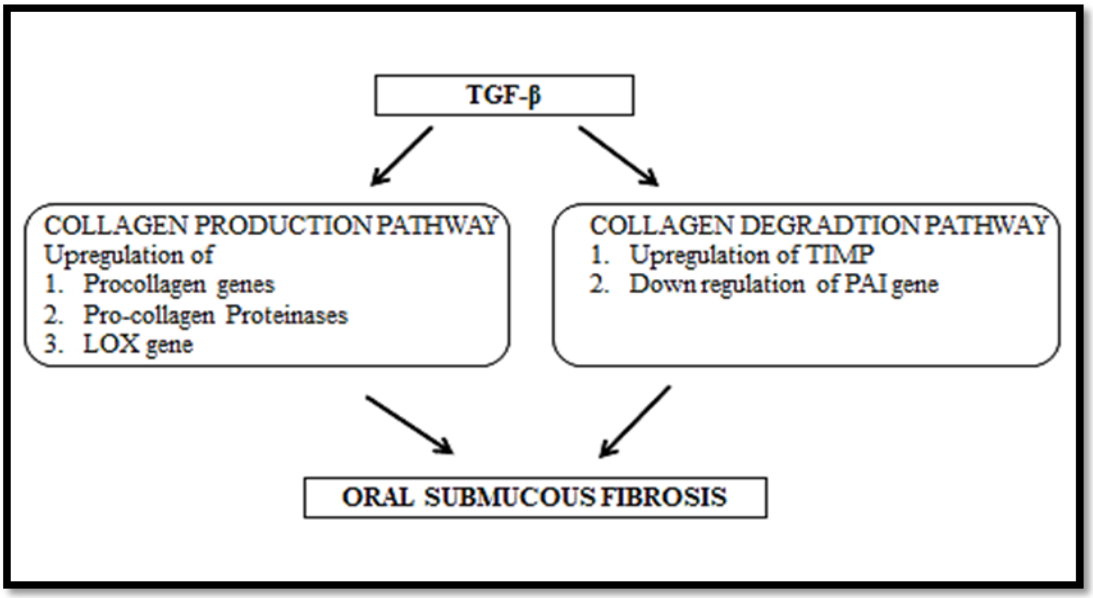


**Fig1. Overview of TGF- β in OSMF**

## III. TGF-β - ANALOGOUS LINK BETWEEN OSMF AND OTHER FIBROTIC DISEASES

Transforming Growth Factor (TGF)-β is the most scrutinized molecule in fibrotic diseases. Fibrosis is the result of chronic persistent inflammation and is considered as protective phenomena in contrast to acute inflammatory reactions. It is induced by a variety of stimuli and can manifest in different organs respective to chronic inflammation. Despite having distinct aetiological and clinical manifestations, most fibrotic disorders have in common is a persistent irritant that sets up a chronic inflammation and recruits macrophages and lymphocytes which play an essential regulatory role in fibrotic conditions by releasing mediators such as growth factors, proteolytic enzymes, angiogenic factors and fibrogenic cytokines (10,11). Among the mediators involved in tissue fibrosis, Transforming growth factor (TGF-β) is considered a key molecule in the activation

of the fibrotic program. Regardless of the origin of fibrosis, whether it is in the skin or fibrosis of internal organs, all fibrotic conditions are associated with the activation of TGF-β and its induction and activation are consistently observed in experimental models of tissue fibrosis(12). TGFβ signals through Smad proteins, that modulate the transcription of important target genes, including procollagen I and III. TGF- β also serves as a regulator of fibroblasts and differentiates them into myofibroblasts, the key effector cells in fibrotic diseases (10,11). TGF-β also preserves collagen degradation by suppressing the activity of MMPs and by inducing synthesis of protease inhibitors, such as Plasminogen Activator Inhibitor-1 (PAI-1) and Tissue Inhibitor of Metalloproteinase (10). Thus TGF- β plays a pivotal role in fibrosis by both increasing the collagen and decreasing its degradation (13). Studies done in fibrotic tissue models such as keloids, hypertrophic scars, idiopathic pulmonary fibrosis, renal fibrosis, hepatic fibrosis, myocardial fibrosis, and radiation-induced fibrosis shows upregulation of TGF-β and its promising responses towards anti-TGF-β antibodies and drugs (14–20). This evidence postulates that TGF-β involvement is an important link between fibrotic diseases and therapeutic strategies are required to antagonize TGF-β.

## IV. ROLE OF PIRFENIDONE IN ANTAGONISING TGF- β

Pirfenidone (5-methyl-phenylpyridin-2[H-1]-one), is a potent antifibrotic agent that has shown its antifibrotic efficacy in many organs, such as lung, liver, kidney, heart, and bladder. Currently, this agent has been approved by the FDA for clinical use in the treatment of idiopathic pulmonary fibrosis (21). Research suggests that Pirfenidone inhibits the progression of fibrotic lesions, and prevent the formation of new lesions following tissue injuries (22). Pirfenidone has been tested in many invivo and invitro fibrotic models which showed favorable results (Table 1). The main mechanism of pirfenidone based on several studies reveals that it can modulate TGF- β expression, which is the central molecule in fibrosis and significantly suppressing the TGF-β1-induced ECM synthesis by attenuating the differentiation of fibroblasts and collagen expression genes, therefore reducing collagen production and proliferation (21–24). TGF- β is the best-known inducer of fibrosis and is known to induce the expression of additional fibrogenic mediator. Since the pirfenidone can modulate and suppress TGF- β expression, it can downregulate the fibrosis (25). Besides anti-fibrotic activity, pirfenidone has also been shown to act as an anti-inflammatory and anti-oxidant agent. The anti-inflammatory effects of pirfenidone have been established in cell-based assays which reveals that pirfenidone downregulates certain inflammatory cytokines that have proposed roles in the initiation and maintenance of a fibrotic process. These include TNF-alpha , which promotes cell recruitment, fibroblast proliferation, epithelial cell hyperplasia and IL-1β, which induces fibroblasts to produce fibrogenic mediators such as PDGF and TGF- β (25). Fewer reports also suggested that pirfenidone reduces the production of ROS and lipid peroxidation and revealed its antioxidant property. Based on the data available in the literature it indicates that by targeting the TGF-β signaling pathway with pirfenidone represents a specific antifibrotic approach for OSMF(26–28).

**Table 1. Pirfenidone Tested In Invitro and Invivo Fibrotic Diseases**

| References | Study model | Invivo/invitro | Intervention | Inference |
|---|---|---|---|---|
| **Cui et al. (23)** | Human intestinal fibroblast | Invitro | HIF were treated with increasing concentrations of pirfenidone (0, 0.5, 1, and 2 mg/ml) for 72 h | Proliferation of intestinal fibroblasts is inhibited and collagen I production suppressed |
| **Enrico conte et al. (29)** | Human lung fibroblasts | Invitro | Pirfenidone (0.03– 0.3 mg/ml | Inhibition of fibroblast proliferation and TGF- β induced a-smooth muscle actin (SMA) and pro-collagen (col)-I mRNA and protein levels were attenuated |
| **Thomas Stahnke et al. (24)** | Human ocular fibroblasts | Invitro | Application of Pirfenidone [10−3 mmol/l] With and without TGF-β | Decreased cell proliferation and attenuated TGF-β |
| **Antonio di sario et al. (30)** | Hepatic stellate cells from rat liver | Invitro | Incubated with pirfenidone (0.1, 1, 100 and 1000 mmol/l | Pirfenidone 100 and 1000 mmol inhibited type I collagen-induced by TGF-β 1 |

| | | | | |
|---|---|---|---|---|
| **Yan wu sun et al. (21)** | Rat models-intestinal fibroblasts | Invivo | Pirfenidone (200, 400 md/kg/d) for 12 weeks | Proliferation and differentiation of intestinal fibroblasts is inhibited and TGF-β1/smad/CTGF signaling pathway is suppressed |
| **Liu Jian Duan et al. (31)** | Rat model | Invivo | Pirfenidone mixed with placebo was administered orally at 500 mg/kg body weight | mRNA levels of collagen subtypes and growth factors and protein levels of profibrotic growth factors and α-smooth muscle actin were reduced |
| **Marco rodríguez-Castellanos et al. (32)** | Localized scleroderma | Invivo | 8% pirfenidone gel three times daily for 6 months | Improvements in modified localized scleroderma skin severity index scores and cutaneous induration |
| **Paul W noble et al. (33)** | Idiopathic pulmonary fibrosis | Invivo | Pirfenidone 2403 mg/day, and pirfenidone 1197 mg/day | Pirfenidone reduced decline in FVC by 10% |
| **Nicole L simone et al.(34)** | Radiation-induced fibrosis | Invivo | Pirfenidone 800 mg three times/day | Improved function of at least 25% |

## V. CONCLUSION

A thorough understanding of molecular pathogenesis of OSMF and other fibrotic disorders along with the mechanism of pirfenidone can strengthen the idea of using pirfenidone in the clinical setting of OSMF. Despite the diverse and heterogeneous etiology for fibrotic diseases, the underlying pathogenesis of fibrotic conditions is similar and therefore therapeutic approach for fibrosis should involve the agents that targets TGF-β. Like any other fibrosing condition, OSMF also marches down the same pathway of fibrosis after activation of TGF- β by chronic inflammation following the ingestion of betel quid. Besides its antifibrotic property, pirfenidone also has anti-inflammatory and anti-oxidant which could synergize the effects in the treatment of OSMF. Although there are various invivo and invitro trials were done for other organs, no clinical trials of pirfenidone in OSMF were tried. Therefore, this paper suggests that pirfenidone might be a potential novel therapeutic drug for the treatment of oral submucous fibrosis and also encourages clinical trials to scrutinize the efficacy of drug pirfenidone in OSMF

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