5-HT2B Receptor in Fibrosing ILD

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Interstitial lung disease (ILD) encompasses a heterogeneous group of more than 200 conditions, of which primarily idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia, hypersensitivity pneumonitis, ILD associated with autoimmune diseases and sarcoidosis may present a progressive fibrosing (PF) phenotype. Despite different aetiology and histopathological patterns, the PF-ILDs have similarities regarding disease mechanisms with self-sustaining fibrosis, which suggests that the diseases may share common pathogenetic pathways. Previous studies show an enhanced activation of serotonergic signaling in pulmonary fibrosis, and the serotonin (5-HT)2 receptors have been implicated to have important roles in observed profibrotic actions.

Keywords: 5-HT ; 5-HT2B receptor antagonism ; fibrosis ; ILD

1. Introduction

The term interstitial lung disease (ILD) encompasses a large heterogeneous group of diffuse parenchymal lung disorders, of which primarily idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia, ILD associated with autoimmune diseases, hypersensitivity pneumonitis and sarcoidosis may present a progressive fibrosing (PF) phenotype [1]. Despite known or unknown causes and radiological patterns, the PF-ILDs have similarities regarding disease mechanisms with self-sustaining fibrosis [2], suggesting common pathogenetic pathways. In this review, we will address the potential role of serotonin (5-HT) and the 5-HT_{2B} receptor in three PF-ILDs: IPF, ILD associated with systemic sclerosis (SSc-ILD) and ILD associated with rheumatoid arthritis (RA-ILD).

2. Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is defined as usual interstitial pneumonia (UIP) based on high-resolution computed tomography (HRCT) and/or histopathological pattern after exclusion of other known causes of ILD [3]. IPF is the most common PF-ILD, and in a systematic review a conservative estimate of the incidence was 3–9 cases per 100,000 per year for Europe and North America with lower reports for East Asia and South America [4]. IPF is more prevalent in the older population, rarely diagnosed before the age of 70, and is more widely represented in males [5]. IPF patients demonstrate large heterogeneity in their pulmonary manifestation of fibrosis, and it is generally not regarded as an inflammatory disease, despite previous attempts to treat the disease with corticosteroids. Nonetheless, patients with a rapid progress or experiencing an acute exacerbation have reported severe innate and adaptive inflammatory infiltrates where the extent of inflammation was correlated with yearly forced vital capacity (FVC) decline [6].

It is now widely recognized that the aetiology of IPF is a gene-environment interaction involving a heterogeneous set of susceptibility genes such as *TERT, SFTPC*, *TOLLIP* and *MUC5B* [7]. Environmental factors that have been linked to the development of IPF in epidemiological studies include smoking, chronic viral infections and occupational exposures, such as agriculture and farming, livestock, wood dust, metal dust, stone dust and silica [8]. The clinical course of IPF is highly heterogeneous, but carries a poor prognosis with a mean survival of four years [9]. On a yearly basis 5–10% of IPF patients experience acute deteriorations in respiratory function, exacerbations, with a median survival of 3 to 4 months [10].

3. Systemic Sclerosis

Systemic sclerosis is an autoimmune disease characterized by vasculopathy of small vessels, immune dysregulation, chronic inflammation, and subsequent fibrosis of the skin and internal organs [11]. Skin fibrosis (scleroderma) is the distinguishing hallmark of SSc, and the extent of skin involvement and its rate of progression reflect the severity of visceral organ involvement. The reported prevalence of SSc varies between studies, but has been estimated to be 15–30

cases per 100,000 individuals worldwide [12], with a peak onset described at 55–69 years of age [13]. Although SSc, like other autoimmune diseases, is more common in women than in men, the male sex is a poor prognostic factor with more frequent and severe organ involvement [14].

ILD is a common and early manifestation of SSc, and most patients who develop severe restrictive lung disease do so in the first five years following the onset of SSc symptoms [15]. SSc-ILD often has a severe course, and was the leading cause of death (17%) in a large observational study in SSc [16]. The estimated prevalence of ILD has been reported at up to 84% on HRCT [17], and it has been suggested that pulmonary function tests should not be used for screening of ILD in SSc due to a lower sensitivity than HRCT [18]. The most common ILD pattern in SSc patients is nonspecific interstitial pneumonia (NSIP), although UIP can also be seen in 25–40% of cases [19].

Patients are grouped into limited cutaneous SSc (lcSSc), where the skin fibrosis is restricted to areas distal to the elbows and knees, and diffuse cutaneous SSc (dcSSc) with involvement also of the proximal extremities and trunk. The extent of skin involvement is a prognostic risk factor for ILD and patients with dcSSc have both a higher prevalence and mortality from ILD than those with lcSSc [20]. In addition, male sex, ethnicity and presence of anti-topoisomerase antibodies appear to be important determinants of ILD development.

4. Rheumatoid Arthritis

Rheumatoid arthritis is a systemic inflammatory autoimmune disorder estimated to affect 0.5–1% of the world's population. Although the predominant clinical feature is inflammation of the synovial lining of joints, RA has numerous extra-articular manifestations, and lung disease is a major contributor to the extra-articular morbidity and mortality. There are strong indications that lungs are involved in early pathogenesis of RA by citrullination of proteins triggered by environmental exposure of, e.g., tobacco smoke. Development of anti-citrullinated protein antibodies (ACPAs) in genetically susceptible individuals [21] may initiate inflammatory responses and autoimmune reactivity. ILD is one of the most common comorbidities associated with RA, significantly aggravating the patient's disease course, prognosis, and health-related quality of life [22]. The prevalence of RA-ILD has been reported to be as high as 76% in imaging studies, but clinically significant ILD occurs in less than 10%, albeit with increasing incidence [23].

The histopathology of RA-ILD is heterogeneous showing a highly variable mix of both fibrotic and inflammatory changes. Contrary to ILD associated with other connective tissue diseases, the most prevalent pattern in RA-ILD is UIP followed by NSIP, which can be further broken down into inflammatory and fibrotic subtypes [24]. Compared to RA patients with a non-UIP pattern, those with UIP confer a poorer prognosis with survival rates that are in parallel to those seen in IPF. The RA-ILD patients with UIP have been reported to have more respiratory-related hospitalizations than other ILD subtypes [25].

Risk factors for the development of RA-ILD have been identified in several studies and include older age, male sex, cigarette smoking, later onset RA, longer RA duration, RA disease activity, and elevated levels of rheumatoid factor or anti-ACPA [26].

5. Current Therapeutic Strategies

Treatment of PF-ILD has changed considerably during the last two decades. Corticosteroids were during many years widely used for the treatment of fibrotic lung diseases, but serious concerns have been raised due to increased mortality of IPF patients receiving prednisone, azathioprine and N-acetylcysteine in a clinical trial [27] and the risk for renal crisis in patients with SSc [28]. In patients with SSc and RA, the therapy for the underlying disease has formed the basis for treatment of the ILD component. In RA and SSc, immunosuppressive therapies including cyclophosphamide, azathioprine, and mycophenolate mofetil are widely used, and in SSc, haematopoietic stem cell transplantation has also been successful. The first targeted antifibrotic drug, pirfenidone, was introduced for the treatment of IPF in Japan 2008, and a couple of years later in the EU and the US. Another antifibrotic drug, nintedanib, was approved for treatment of IPF in the US 2014 and in the EU 2015. Since then, both drugs have been investigated in clinical studies enrolling a wide range of PF-ILDs, leading to approvals for use in SSc-ILD regarding nintedanib in both the US and in the EU, and for pirfenidone in the US. Nintedanib was further approved in 2020 in the EU for use in other chronic fibrosing ILDs with a progressive phenotype. Several antifibrotic drugs are currently investigated for IPF in clinical phase 2–3 trials, some of them also targeting a broader spectrum of PF-ILDs [29]. Today, there is no curative treatment available for ILDs where lung transplantation stands as the final therapeutic measure.

6. The Serotonergic Pathways in Tissue Repair and Fibrosis

Serotonin (5-hydroxytryptamine, 5-HT) is a multifunctional signaling molecule, mainly recognized for its role in the central nervous system (CNS), where it regulates several behavioral processes. Even now, over 70 years after its discovery, the functional role of 5-HT is still not fully clarified, with emerging studies showing new biological influences and disease associations. A mechanistic link between fibrosis and 5-HT was first reported in the 1960s for a condition called carcinoid syndrome which is caused by neuroendocrine carcinoid tumors that secrete vast quantities of 5-HT [30]. The syndrome was characterized by tissue fibrosis, particularly affecting cardiac valves but also impacting on other organs including lung and skin. More recently, agonistic activity on the 5-HT_{2B} receptor has been implicated in causing fibrosis, which led to the recall of fenfluramine used in the treatment of obesity, as well as pergolide, a drug used to treat Parkinson's disease [31] [32].

The 5-HT_{2B} receptor agonistic activity of these drugs has been suggested to lead to myofibroblast activation in a transforming growth factor (TGF)-β1 dependent manner, resulting in fibrosis [33][34]. Besides the 5-HT_{2B} receptor, the receptor subtypes 5-HT_{2A} and 5-HT_{2C}
have also been suggested to be involved in fibrosis. 5-HT has been described to play a role in alveolar macrophage function through 5-HT_{2C} receptors and thereby affect fibrosis development [35], while the 5-HT_{2A} receptor has been shown to induce a TGF-β dependent
fibrotic response in vivo [36]. Among the other classes of receptors, 5-HT_{7} was in a recent paper by Tawfik et al. suggested to mediate anti-inflammatory and anti-fibrotic effects in the bleomycin-induced lung fibrosis model in rats [37]. However, the cellular mechanisms
underlying PF-ILDs are still under investigation where the activation of specific 5-HT receptors remains an overlooked target in pulmonary fibrotic disorders. To understand the pathophysiological impact of 5-HT and the different 5-HT receptors, it is important to take into account the cellular context and the diversity in expression profile of the 5-HT receptors in different conditions. It is clear that activation of the 5-HT_{2B} receptor critically affects several profibrotic responses, whereby modulating its activity has been shown to attenuate fibrosis [38][39][40].

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