Viruses: Cofactors in Idiopathic Pulmonary Fibrosis

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Idiopathic Pulmonary Fibrosis (IPF) comes with the burden of its own name “Idiopathic”, meaning arising from an unknown cause [1]. IPF is a chronic and progressive interstitial lung disease characterized by lung tissue remodeling and a gradual loss of pulmonary function usually due to excess deposition of extracellular matrix components, mainly collagen [2]. There are few available therapeutic choices for treatment of IPF, the most common and severe form of pulmonary fibrosis. The average survival rate is roughly three years and lung transplantation remains the only feasible treatment [3]. Despite rigorous research, the etiology of IPF has remained unknown. One emerging hypothesis is that microscopic damage of alveolar epithelial cells and a dysregulated repair mechanism lead to lung fibrosis and in turn, IPF [4]. Since numerous factors have been suggested as initiators, IPF is now considered as more of a syndrome than a disease [5].

Viruses and Inflammation

The presence of a chronic inflammatory mediator, like a virus, can play a pivotal role as a co-factor in a genetically susceptible host. A virus can disrupt the normal healing process of the lungs and making them more vulnerable to other agents causing further damage. This makes the virus an appropriate causal candidate for IPF. Outstanding improvements in molecular detection technology helped to discover several viruses associated with IPF including Hepatitis C Virus (HCV), adenovirus, Cytomegalovirus (CMV), Epstein–Barr virus (EBV), herpes simplex virus, human herpes viruses 7 and 8 and parvovirus B19 [5]. Among these, few have been studied in humans to determine the link between viruses and IPF.

Hepatitis C Virus

Hepatitis C is a small (50 nm), single-stranded and enveloped RNA virus transmitted primarily by contact with contaminated blood products and is a common cause of chronic liver disease [6]. Conflicting results have been reported in human HCV studies. Studies conducted in Italy and Japan demonstrated a higher occurrence of anti-HCV antibody in patients with IPF compared to the patients without IPF [7,8]. To confirm the role of HCV in IPF, a similar study was conducted in the United Kingdom. However, Irving et al. [9] was unable to find any connection between HCV and IPF. Geographical differences could be one of the possible explanations for these controversial results. Genetic factors and racial differences may also play a role where people from Japan and Mediterranean countries are more susceptible to HCV than those from northern Europe [10]. Further cohort studies could be helpful to determine the relationship between HCV and IPF.

Adenovirus

Adenovirus is a double-stranded, 70-90 nm in diameter, non-enveloped DNA virus associated with many clinical conditions including interstitial lung disease [11,12]. Kuwano et al. [12] investigated the presence of adenovirus in IPF and interstitial pneumonia associated with collagen vascular disease (CVD-IP). In patients with both IPF and CVD-IP, adenoviral DNA in lung tissue was measured in 67% of patients treated with corticosteroids compared with 10% in those patients not treated with corticosteroids. Additional studies are required to determine whether corticosteroids, a common therapeutic for IPF, can make patients more prone to new adenovirus infection or reactivation of latent adenovirus infection.

Cytomegalovirus

Human cytomegalovirus (HCMV) is an enveloped, 150–200 nm in diameter, double-stranded DNA virus, belonging to the betaherpesvirinae subfamily [13]. HCMV is well known for causing asymptomatic and persistent infections in healthy people. However, HCMV can be life-threatening in immunocompromised individuals. One investigation was performed to evaluate the HCMV DNA copy number in Bronchoalveolar Lavage (BAL) cells, blood leukocytes and serum of patients with IPF. The patient groups consisted of 16 adults, newly diagnosed with IPF and never treated from pulmonary pathology or by any immunosuppressive agents whereas the 16 adult healthy volunteers represented as control group. There was not much difference in the prevalence of HCMV DNA positive subjects when comparing the patient group to the control group. Dworniczak et al. [14] also noticed a higher HCMV DNA copy number in blood serum in IPF patients than in controls. In both participating groups, the researchers measured a significantly higher HCMV DNA copy number in BAL cells than in blood leukocytes. These observations suggested the importance of the lungs in HCMV pathobiology. A higher HCMV DNA number in lung tissue of IPF patients compared to the control groups was measured in an earlier study [15]. Yonemaru et al. [16] also reported an elevation of HCMV IgG and complement fixation titers in patients with IPF and CVD-IP. These data suggest a connection between HCMV infection and IPF.

Epstein–Barr virus

The Epstein–Barr virus (EBV), also known as Human Herpesvirus 4 (HHV4), is a gammaherpesvirus, is an enveloped, 120–150 nm in diameter, double-stranded DNA virus. It is one of the most common human viruses present in all populations and latently infects nearly 95% of the people via saliva contact [17]. A number of studies have suggested a possible connection with EBV as a persistent antigenic stimulus in IPF. The association was first established in a serological study when increased levels of IgA and IgG against EBV antigens were found in patients with IPF. However, in other group, comprised of interstitial lung disease (ILD) of known cause, the EBV serological profiles were normal [18]. While previous study only proposed the association of EBV to IPF, Egan et al. [19] reported replicating EBV

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within type II alveolar cells of the lower respiratory tract in IPF patients. Furthermore, the authors proposed that EBV may be an immune trigger therefore potentially offering a novel opportunity for treatment of IPF by anti-viral therapy. Consistent with the previous research, lung tissue from 27 IPF patients and 28 control subjects was measured to confirm the presence of EBV DNA by immunohistochemistry and Polymerase Chain Reaction (PCR) analyses. They found that 44% IPF patients and 10% control subjects were EBV-positive analyzed by immunohistochemistry and 48% IPF patients and 14% control subjects were EBV-positive measured by PCR. The dual assay detected that 41% of IPF patients were lung tissue EBV-positive and further established the association between EBV and IPF [20]. However, a study by Wangoo et al. [21] did not support the hypothesis that EBV played a role in the pathogenesis of IPF. Lung tissue was obtained from three groups of patients: IPF only; IPF associated with other pulmonary disorders; and control (IPF-syndrome free). Immunohistochemical analysis showed positive staining in all three groups of patients and gene amplification did not detect any EBV DNA in the lungs of IPF patients. Thus the authors concluded that EBV infection was not associated with IPF.

Conclusion

Collectively, all of these studies on human viruses build a foundation to link IPF and viral infection. On the other hand, none of them suggest any causal relationship between IPF and viral infection. Beside the connection of these viruses with other interstitial lung diseases, the complex pathogenesis of IPF, the difficulties associated with studying association between these viruses with other interstitial lung diseases, the complex pathogenesis of IPF, the difficulties associated with studying the pathogenesis of IPF, the difficulties associated with studying the connection of these viruses with other interstitial lung diseases, the complex pathogenesis of IPF, the difficulties associated with studying the connection of these viruses with other interstitial lung diseases, the complex pathogenesis of IPF, the difficulties associated with studying the connection of these viruses with other interstitial lung diseases, the complex pathogenesis of IPF, the difficulties associated with studying the connection of these viruses with other interstitial lung diseases, the complex pathogenesis of IPF, the difficulties associated with studying

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