Editorial

Hot topics in IPF Pathogenesis: ERS and ATS highlights

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HOT TOPICS IN IPF

The recent official ATS/ERS/JRS/ALAT statement validated the progress in the field of idiopathic pulmonary fibrosis (IPF). The completion of three successful randomized controlled trials has led to the licensing of two novel drugs, namely pirfenidone and nintedanib in Europe, USA and Japan[1-4]. Moreover, recent studies focused on IPF pathogenetic mechanisms shed light to novel pathways, although the exact fibrotic mechanisms still remain unclear.

IPF is now considered a disease of premature aging[1]. Changes related with aging, such as oxidative stress, mitochondrial dysfunction, modifications of extracellular matrix, may be responsible for the fibrotic phenotype. PINK1 is considered as the major regulator of the mitophagy process and Bueno et al, in a series of in vitro studies and examinations of lung biopsies, demonstrated that PINK1 expression is reduced in type II alveolar epithelial cells in IPF lung biopsies and in aging mice[2]. Interestingly, PINK1 deletion in mice lead to defective mitophagy and accumulation of dysmorphic and dysfunctional mitochondria in alveolar epithelial cells, thus contributing to increased epithelial cell senescence and fibrosis in the aging lung[2]. PINK1 was also found downregulated in alveolar macrophages from IPF patients combined with an increase in mitochondria ROS levels in a BALF study[3]. Based on the idea that chronic accumulation of activated macrophages and leucocytes is a characteristic of IPF that could contribute to the microscopic injuries of the alveolar epithelium, mRNA from IPF and control BAL cells was analysed by NGS by Swaisgood C.M. et al[4]. This analysis revealed that among the top downregulated pathways in the IPF BAL cells was detoxification of ROS[4]. Direct analyses of mitochondria isolated from IPF BAL derived macrophages show increased levels of mitochondria membrane bound PINK1 which is driving the mitophagy process thereby protecting IPF alveolar macrophages from apoptosis[5].

Shortening of the telomeres is also a hallmark of IPF and aging. Telomeres are nucleotide repeats at the ends of chromosomes that provide chromosomal stability and shorten progressively during replication. Upon telomeres' shortening at a critical length, the cell undergoes cell cycle arrest,

senescence and apoptosis. A large study on telomere length (TL) among eight different ILD diagnoses and 532 subjects showed that TL in ILD patients is significantly shorter compared to healthy controls[6]. In addition, IPF and familial interstitial pneumonia (FIP) patients excluding familial forms of IPF with SFTP mutations showed significantly lower TL than other ILDs such as iNSIP and SR-ILD. Notably, Sarcoidosis patients had the smallest loss of TL than all other ILDs. Accumulation of shortened telomeres in PBMCs in the various ILDs excluding familial forms, although not driven by genetic predisposition of telomeropathy, demonstrate an acquired shortening of telomeres which is associated with pulmonary fibrosis and may be due to oxidative stress and/or increased proliferation of immune cells following immune system stimulation. Furthermore, the increased shortening of TL in familial IPF with uncharacterized mutations and sporadic IPF suggest a distinction between IPF and other ILDs suggesting an innate telomere defect in IPF as compared to a less severe stress-induced, acquired shortening of the telomeres. This notion is further supported by the discoveries of mutations in other genes involved in telomere maintenance in familial IPF cases that are associated with telomere capping such as the shelteringene TINF2[7], Dyskerin Dyskeratosis Congenita 1 (DKC1)[8], the regulator of telomere elongation helicase 1 (RTEL1)[9,10] and Poly(A)-specific Ribonuclease Deadenylation Nuclease (PARN)[10].

NAC antioxidant therapy is currently brought back in the spotlight following the recent findings of a post-hoc study in individuals of the PANTHER-IPF and the INSPIRE trials relative to IPF associated single nucleotide polymorphisms (SNPs) in *TOLLIP* and *MUC5B* genes[11]. The authors demonstrated differences in the composite endpoint-free survival between NAC and placebo groups after stratification by the rs3750920 (TOLLIP) genotype. The TT alleles of the rs3750920 polymorphism of *TOLLIP*, which correspond to approximately 25% of the IPF patients, were associated with increased survival in the NAC versus placebo arms of the trials. Conversely, individuals with CC alleles showed worse survival upon NAC treatment. TOLLIP is among the negative regulators of the TLR pathway and is involved in the induction of the anti-inflammatory cytokine IL-10 and the suppression of IL-6 and TNF-a following TLR2 and TLR4 stimulation. Monocytes from individuals with the minor TT alleles have previously been shown to express higher levels of the TOLLIP mRNA than those with the CC alleles[12] which may suggest that these individuals have a more tight regulation of TLR2/4 signaling. The rs35705950 polymorphism *in MUC5b* which is also linked with increased MUC5b mRNA levels and enhanced host responses showed evidence for potential interaction with NAC therapy[11]. Possible correlations between *MUC5B* genotype and BALF characteristics were analysed in a study by Van der Vis et al where the MUC5B minor allele was associated with significantly lower count of neutrophils and eosinophils[13]. However the possible mechanism for the observed association with NAC therapy is unknown. Acute exacerbations in IPF have been linked to *TERT* and *MUC1* gene polymorphisms which appear to be risk factors for AE-IPF among polymorphisms in various genes associated with IPF pathogenesis such as *MUC1, MUC5B, ELMOD2, HER2, IL8, TERT, Caveolin, EGF, HMOX1, ICAM1, VEGFA, DPP9, ATP11A, OBFC1, DSP, FAM13A1, TOLLIP*[14]. Additionally AE-IPF is associated with an increased BAL bacterial burden compared to stable disease[15].

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