IPF is a chronic, progressive and usually lethal lung disease of unknown cause, occurring primarily in older adults\(^1\). Aging is the strongest demographic risk factor for IPF, a disease that frequently occurs in smokers\(^2\).

Actually, almost all the proposed hallmarks that characterize the aging process/aging phenotype have been found in IPF patients, including genomic instability (e.g. microsatellite DNA instability and loss of heterozygosity), abnormal telomere shortening, loss of proteostasis, mitochondrial dysfunction, cellular/tissue senescence, stem cell exhaustion, and altered intercellular communication\(^2,3\). However, COPD is also an age-dependent disease, and in fact, these patients present similar features of accelerated lung aging as found in IPF\(^2,4\).

Therefore, the critical question is why does a current/former smoker of over 50-60 years old with accelerated aging features develop IPF and not COPD? In other words, what makes old “smoker” lungs distinctively susceptible to IPF? We propose that this is related to the convergence of specific gene architecture with a unique epigenomic behavior in an aging lung\(^5\).

### THE ROLE OF GENETIC SUSCEPTIBILITY

A recent genome-wide association study (GWAS) revealed that common genetic variants contribute to the risk of IPF. In this study, several previously described risk variants were corroborated (e.g. in the components of telomerase TERC [3q26], and TERT [5p15], as well as in MUC5B [11p15]). In addition, 7 novel genetic risk loci were identified (4q22, 6p24, 7q22, 10q24, 13q34, 15q14-15, and 19p13)\(^6\). These findings suggest that genetic susceptibility in IPF is related to alterations in epithelial cell behavior and defects in host defense. Another study confirmed most of these results but also found that novel variants in TOL-LIP at 11p15.5, an important regulator of innate immune response, but also an important inhibitor of TGF-b signaling risk factors for IPF\(^6,7\).

By contrast, GWAS studies in COPD have identified different loci including the 4q31 [hedgehog interacting protein (HHIP)], 15q25 [α-nicotinic receptor (CHRNA 3/5)], 19q13 [egl-9 family hypoxia-inducible factor 2 (EGLN2)]. Actually, the only shared risk loci is 4q22 [family with sequence similarity 13, member A (FAM13A)]\(^8\). More recently, these established associations were confirmed and novel associations were revealed, but in general these COPD risk gene/loci are not related with those found in IPF\(^9\).

### THE ROLE OF EPIGENOMIC CHANGES

The epigenome is a complex regulatory mechanism superimposed on the genome and includes nucleosome occupancy, positioning, composition, modification and dynamics, as well as DNA methylation, and among other factors, it is shaped by non-coding RNAs\(^10\).

A recent global DNA methylation study performed in IPF lungs identified 2130 differentially methylated regions (DMRs)\(^11\). Most of them were localized in the gene bodies with only a small proportion in the gene promoters. Forty three percent of these DMRs were hypomethylated. The analysis of the canonical pathways revealed, among others, enrichment of epithelial adherens junction signaling, sustaining a role of the epithelial cells in the pathogenesis of this disease. Likewise, the analysis of binding motifs in the gene promoters revealed several regulators of lung development, including β-catenin, the zinc finger transcription factor GLI1, and the forkhead box protein C2, supporting the putative role of the recapitulation of developmental pathways in IPF\(^12\).
In COPD, DNA methylation changes affecting hundreds of genes of the small airway epithelial cells have also been identified\(^1\). However, in contrast with IPF, most of them are hypermethylated. Also differing from IPF, the DMR of the COPD gene set was enriched for three pathways: G protein-coupled receptor signaling, Aryl hydrocarbon receptor signaling, and cAMP-mediated signaling.

Finally, a number of differences have been found in the deregulation of micro-RNAs, small non-coding ribonucleotides that play a key role in the regulation of gene transcription inhibiting the translation or degrading the mRNA\(^2\).

In summary, getting old, and accelerated lung aging are critical to the development of IPF or COPD, but sets of specific gene variants and epigenetic modifications contribute to the initiation of one or the other disease. Whether patients with combined pulmonary fibrosis and emphysema share some genetic epigenetic characteristics remains unknown.

### Bibliography


