

The pathogenesis of idiopathic pulmonary fibrosis: from “folies à deux” to “Culprit cell Trio”

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease with poor survival affecting aging people. Although the etiology of IPF is “officially” considered as unknown ¹, the pathogenesis of the disease has been substantially deciphered, revealing a complex scenario where different cellular and molecular mechanisms are involved. From the early seminal proposal of Selman et al. ^{2,3} a consistent amount of data have confirmed the occurrence of a deranged crosstalk of epithelial and mesenchymal cells, and this paradigm ³⁻⁵ replaced the previous mainstream “inflammatory” theory ^{6,7}. The role of intrinsic defects affecting type-II pneumocytes/alveolar epithelial cells (AECII) became more precisely defined when genetic studies on familial pulmonary fibrosis (and also sporadic cases) revealed specific gene mutations interfering with the control of either telomere length or genes specifically expressed by AECII (surfactant proteins, ABCA) ⁸⁻¹². Taken together these observations suggest that the initial (etiologic) mechanism is caused by a senescence-related progressive loss of stem/precursor reparative functions of AECII ¹³. In this pathogenic scheme, the concurrent contribution of a variety of risk and noxious factors (genetic defects/predisposition, “natural” replicative senescence, and toxic substances such as cigarette smoke and pollution) may determine cell senescence and stem-cell exhaustion in predisposed areas of lung parenchyma (where high levels of mechanical stress occur) ¹⁴⁻¹⁷.

Senescent AECII may be then considered as the “culprit” cells in triggering the activation of mesenchymal cells and eventual fibrosis ¹⁸. The senescence associated secretory phenotype (SASP) has been proposed as a plausible means to explain abnormal epithelial/mesenchymal crosstalk ^{14,17,19-22}. In IPF tissue samples, evidence of deranged mesenchymal differentiation (fibroblast foci, dense fibrosis, smooth muscle hyperplasia, ossification, fat metaplasia, dysregulated angiogenesis) is common, and these features are likely consequence of the abnormal epithelial/mesenchymal crosstalk affecting the physiological cell turnover ²³⁻²⁸. In IPF, intrinsically defective AECII and abnormally stimulated mesenchymal stem cells may then be considered as the “culprit couple” involved in a

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pathogenic “folies à deux”²⁹. A number of signaling pathways abnormalities occur in this scenario, including pathways regulating tissue development and repair, interconnected with mechanisms such as cell senescence, epithelial-mesenchymal transition, autophagy, mechanical stress, and others (WNT, NOTCH, TGF- β , Yap/Taz, cGAS/Sting, etc.)³⁰⁻³⁶.

This complexity has been recently widened by the emergence of a new “major character” in the pathogenic “stage” of IPF, a cell type characterized by an ambiguous phenotype and a robust profibrotic activity. This cell type, recognized by sophisticated methods (e.g. single cell analyses) has been mostly described as “*aberrant basaloid*”, and is characterized by a complex phenotype including basal epithelial, mesenchymal, senescence, and developmental markers³⁷⁻⁴⁴.

New experimental studies have demonstrated that these abnormal/senescent basal/oid cells in IPF can exert a robust profibrotic function, in part mediated by the activation of profibrotic macrophages, thus further modifying the pathogenic scenario^{34,40,43,45,46}. These pathogenic basal/oid cells and normal basal cells are not only different in phenotype, but may also exhibit opposite functions in regulating matrix homeostasis: basal/oid cells are profibrotic, whereas normal basal cells may possess anti-fibrotic properties via inhibition of TGF- β -WNT, as suggested by experimental studies with extracellular vesicles^{43,47}. Further studies are needed to better clarify the origin of aberrant basaloid cells (either modified airway basal cells or AEII derived transitional basaloid cells^{39,43,48}).

Interestingly, profibrotic basal/oid cells likely corre-

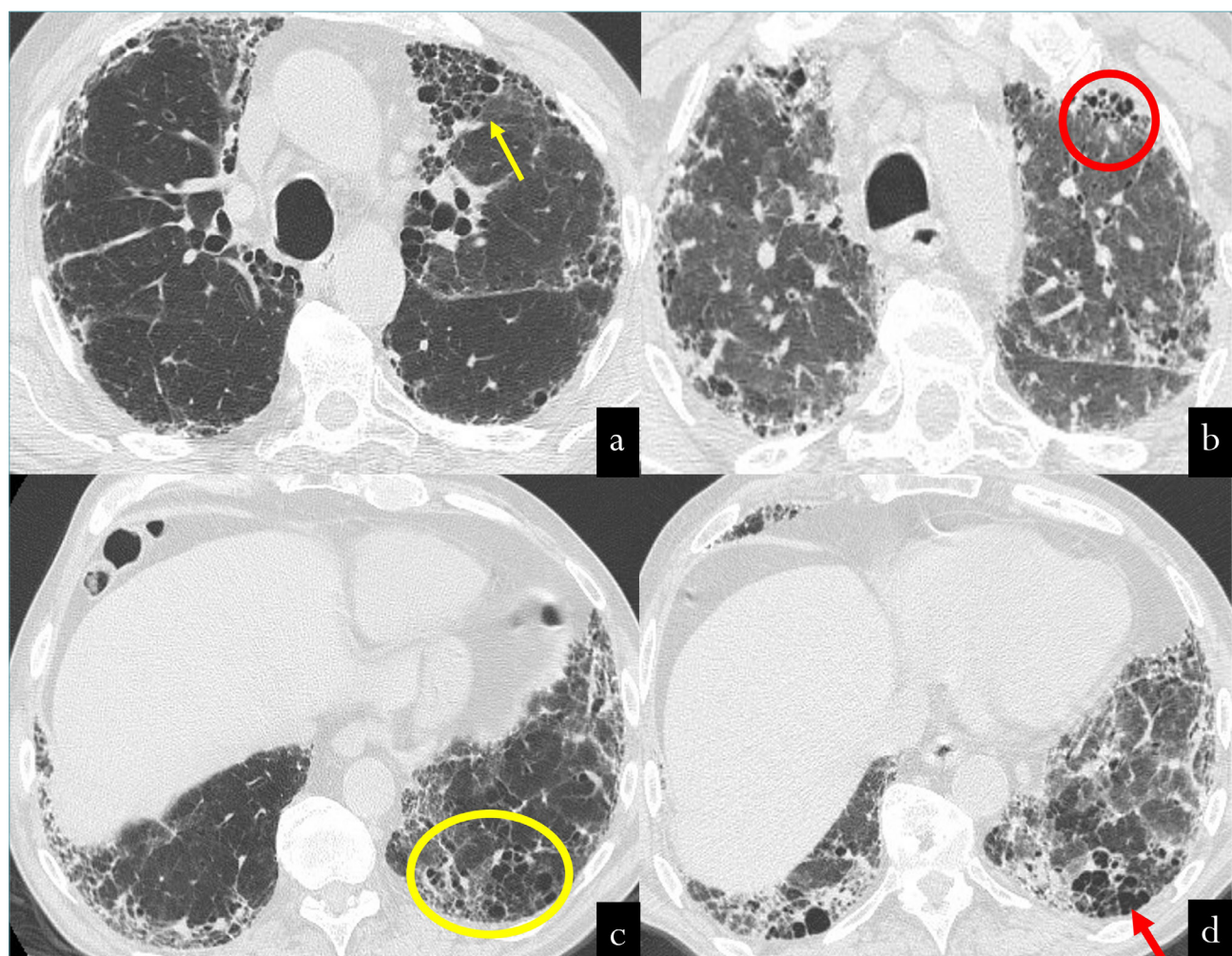


Figure 1. CT in inspiratory (a, c) and expiratory (b, d) scan. UIP pattern characterized by peripheral traction bronchiectasis and honeycombing (yellow arrow), mainly in the anterior segments of the upper lobes and in the costophrenic angles (yellow ellipse). In the expiratory scan, the lack of volume reduction in the portions of lung with honeycombing confirms the conducting airways proliferation and “bronchiolization” of the distal parenchyma (b, red circle; d, red arrow).

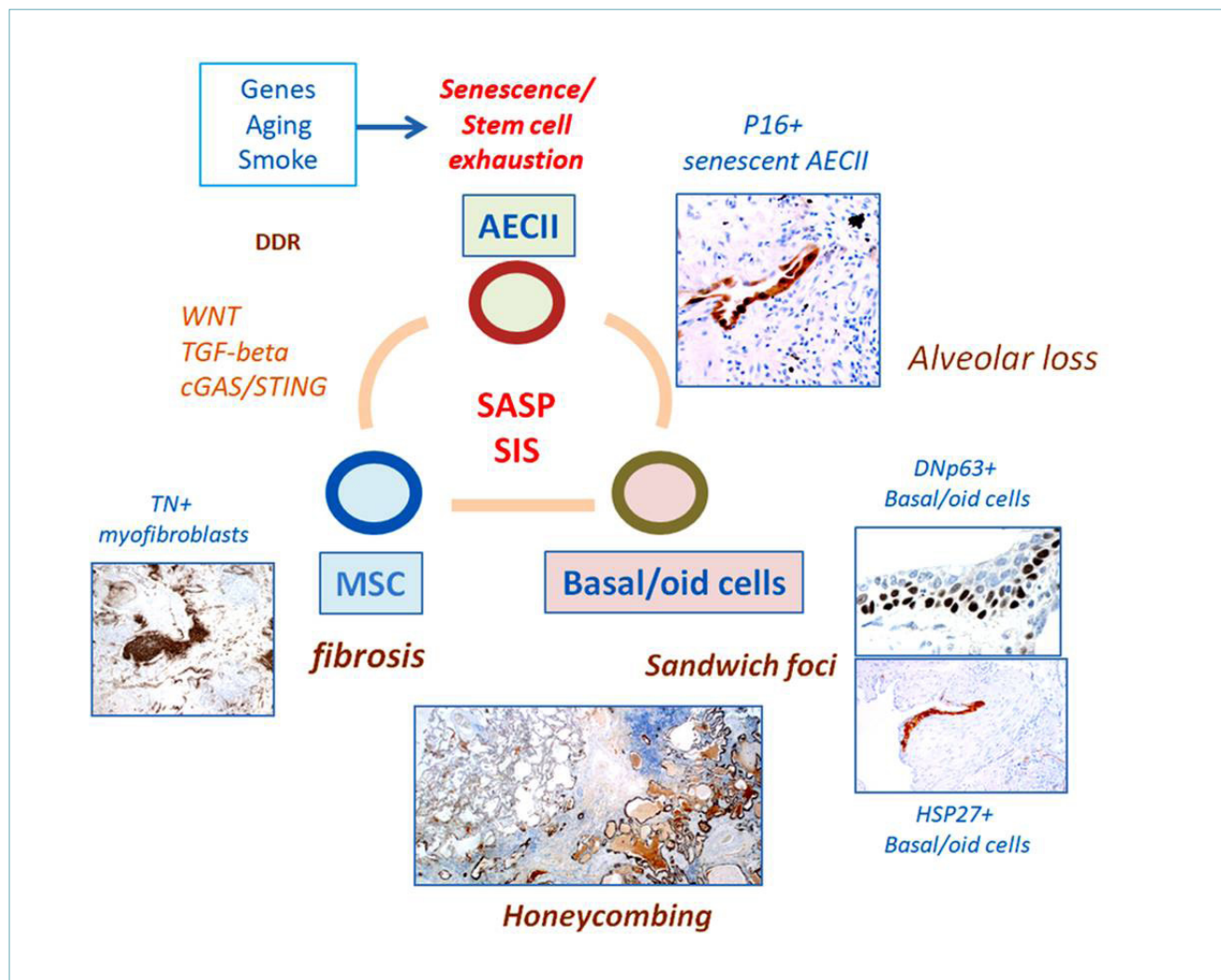


Figure 2. A simplified scheme of IPF pathogenesis. Different stem/progenitor cells are involved in the trio: alveolar epithelial cells type-II, mesenchymal stem cells and basal/oid airway's cells. The abnormal crosstalk between the trio induces deranged differentiation, abnormal remodeling of the bronchiole-alveolar units and eventual triggering of alveolar loss, fibrosis and honeycombing. DDR: DNA Damage Response; AECII: alveolar Epithelial Cells type-II; MSC: Mesenchymal Stem Cells; SASP: Senescence Associated Secretory Phenotype; SIS: Senescence Induced Senescence; TN: tenascin; HSP27: heat shock protein-27.

spond to the peculiar basal cells previously described at histology in bronchiolar proliferative lesions and honeycomb cysts of IPF using immunohistochemical markers^{40,49}. At variance with normal small airway basal cells, Δ Np63+ basal cells within honeycomb cysts express markers of epithelial mesenchymal transition (ZEB1), and molecules related to invasiveness (laminin-5 gamma-2, hsp27, MMP7)⁴⁹⁻⁵¹. These cells also show evidence of WNT-pathway activation as revealed in situ by the nuclear accumulation of beta-catenin, further supported by the expression of a variety of WNT-targets including cyclin-D1, metallo-

proteinase-7/matrilysin MMP7, and c-Myc^{19,30,52}. The relevance of these molecular mechanisms has been confirmed, and is likely central in IPF pathogenesis due to the tight interactions of the WNT-pathway with different mechanisms involved in IPF (EMT, cell senescence, apoptosis, fibrosis)^{34,53-61}. These observations strongly suggest that aberrant differentiation signaling at the bronchiolar-alveolar junctions may be implicated in the abnormal remodeling leading to honeycomb cyst formation.

Honeycombing is considered as a crucial feature of the UIP pattern, and has well known diagnostic and

prognostic relevance in IPF and other progressive ILDs^{62,63}. The abnormal cross-talk between AECII, mesenchymal precursors and the newly recognized basal/oid cells is likely involved in bronchiolar deranged proliferation, alveolar loss and fibrosis. This vicious circle may be further amplified by senescence-induced-senescence (SIS), a mechanism of bystander propagation of abnormal cell signaling and crosstalk^{64,65}.

Several data suggest that honeycomb cysts represent pre-neoplastic lesions, and the newly recognized abnormal basal cells likely contribute to the development of lung carcinomas characterized by a “small airway” phenotype⁶⁶⁻⁶⁹. These old and new data, taken together, significantly change the pathogenic paradigm of IPF, and also provide new possible lines of research. The distal airways acquire a new robust role⁷⁰⁻⁷², putting together apparently incoherent observations (e.g. the imaging evidence of small airway involvement in distal lung and the accumulation of MUC5B in honeycomb cysts)^{73,74}. The regenerative niche in distal lung has been demonstrated as more complex than expected^{75,76}, and is likely the site where the precise modulation of differentiation, proliferative and inhibitory signals is essential to avoid pathological derangement leading to pulmonary diseases^{49,77}. The “classic” incriminated cell couple, e.g. AECII and fibroblasts/myofibroblasts, should now include a third character, the abnormal “senescent basal/oid” cell. This peculiar cell type appears as crucial in honeycomb cyst formation and is a potential therapeutic target in IPF⁷⁸.

Conclusions

The “culprit trio” here described in IPF may alter the lung reparative processes by exchanging fake information within the regenerative niche, reciprocally inducing abnormal behaviors in a loop of “senescence-induced-senescence”^{5,79}. Accordingly, in IPF, senescence features have been demonstrated in all three members of the trio^{46,59,80-83}, and therapies addressing senescent cells appear as a promising rational tool for their removal, together with possible manipulation of other target mechanisms involved in its pathogenesis^{82,84-93}. This new paradigm may also represent a robust basis for new diagnostic criteria for classifying progressive pulmonary fibrosis⁹⁴.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTIONS

MC wrote the article, MC, CR, CD, SP, LS, VP reviewed the article.

ETHICAL CONSIDERATION

Not applicable.

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