

Idiopathic Pulmonary Fibrosis and Lung Cancer: Finding Similarities within Differences

Idiopathic pulmonary fibrosis (IPF) and non–small cell lung cancer (NSCLC) share important risk factors, including advanced age and cigarette smoking. Moreover, evidence of the efficacy of nintedanib, a small-molecule tyrosine kinase inhibitor, for slowing the progression of IPF (1) as well as for treating NSCLC has fueled hopes that similar epithelial “transformation” profiles in cancer and fibrosis might support the repurposing of other cancer therapies for treatment of IPF (2, 3). However, the potential usefulness of nintedanib for treating IPF and NSCLC belies critical differences in the pathobiology of these two disease processes. Although the development of NSCLC is characterized by the accumulation of characteristic somatic genetic alterations in lung epithelial cells, including in TP53, KRAS, and EGFR, leading to the expansion of malignant clones and ultimately metastasis (4), there is no evidence that somatic mutations, clonal epithelial cell expansion, or metastasis are relevant to the biology of IPF. Despite these differences, the growing array of small molecules available for the treatment of cancer is attractive as a potential source of therapies for IPF; however, how to best determine which ones might offer the most promise remains an open question.

In this issue of the Journal, Ulke and colleagues (pp. 713–726) tackle this question by performing a gene set enrichment analysis of publicly available NSCLC and IPF data sets (5). Starting with genes that were upregulated in patients with NSCLC compared with control subjects, the authors identified a set of 92 genes that were shared with IPF. These genes were more strongly enriched in alveolar epithelial type 2 (AT2) cells isolated from mouse lungs injured with bleomycin or from patients with IPF than fibroblasts isolated from the same patients, perhaps consistent with the epithelial component of IPF tissue, and the few positive cells were apparently nonepithelial (11). One wonders, therefore, about the degree to which AT2 cells in IPF are hyperplastic (i.e., dividing) versus hypertrophic (i.e., undergoing S-phase but not dividing). This distinction matters because polyploid cells are typically end-stage, ineffective at growing to new cells. Polyploid cells that do manage to segregate their chromosomes often make mistakes, leading to chromosome rearrangements that can drive carcinogenesis (12). In this way, polyploid AT2 cells might also contribute to the higher rates of lung cancer associated with IPF (Figure 1).

It is worth noting that Spek and Duitman recently undertook a similar analysis of differentially expressed genes in IPF and lung cancer, but also examined the downregulated genes as well as those oppositely regulated in IPF versus NSCLC (13). This broader analysis supports the view that IPF and NSCLC are largely transcriptionally divergent, although a similarly small group of upregulated genes were shared by IPF and NSCLC (n = 123). Although the gene set analysis by Spek and Duitman highlighted collagen organization, catabolism, and adhesion processes as commonly upregulated in IPF and NSCLCs, the study by Ulke and colleagues also identified a number of upregulated matrix metalloproteinases. Given longstanding evidence that integrin-based matrix adhesions are key upstream regulators of cell-cycle

---

This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/). For commercial usage and reprints, please contact Diane Gem (dgem@thoracic.org).
progression (14), it seems likely that the small number of upregulated genes shared by IPF and cancer will shed important light on the similarities and differences between these two diseases.

Ulke and colleagues show that the ECT2 Rho guanine nucleotide exchange factor (RhoGEF) is upregulated in both idiopathic pulmonary fibrosis (IPF)-associated hyperplastic AT2 cells and non–small cell lung cancer (NSCLC; solid arrows), suggesting a common proliferative mechanism that may be targeted for future therapy. Evidence that ECT2 positively contributes to DNA synthesis raises the possibility that it may also contribute to the formation of IPF-associated hypertrophic AT2 cells, which endoreplicate their DNA but do not divide (dashed arrow). Polyploid, hypertrophic AT2 cells that ultimately manage to divide may segregate their DNA imperfectly, leading to AT2 cell transformation and cancer. Graphics courtesy of BioRender.

Author disclosures are available with the text of this article at www.atsjournals.org.

Paul A. Reyfman, M.D.
Cara J. Gottardi, Ph.D.
Department of Medicine, Division of Pulmonary and Critical Care
Feinberg School of Medicine Northwestern University
Chicago, Illinois

ORCID IDs: 0000-0002-6435-6001 (P.A.R); 0000-0003-0912-7617 (C.J.G).

References

1. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al.; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014; 370:2071–2082.
2. Vancheri C. Idiopathic pulmonary fibrosis and cancer: do they really look similar? BMC Med 2015;13:220.
3. Yoon JH, Nouraie M, Chen X, Zou RH, Sellares J, Veraldi KL, et al. Characteristics of lung cancer among patients with idiopathic pulmonary fibrosis and interstitial lung disease: analysis of institutional and population data. Respir Res 2018;19:195.
4. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non–small cell lung cancer. Nature 2018;553:446–454.
5. Ulke HM, Mutze K, Lehmann M, Wagner DE, Heinzelmann K, Günther A, et al. The oncogene ECT2 contributes to a hyperplastic, proliferative lung epithelial cell phenotype in idiopathic pulmonary fibrosis. Am J Respir Cell Mol Biol 2019;61:713–726.
6. Fields AP, Justilien V. The guanine nucleotide exchange factor (GEF) Ect2 is an oncogene in human cancer. Adv Enzyme Regul 2010;50:190–200.
7. Disayabutr S, Kim EK, Cha SI, Green G, Naikawadi RP, Jones KD, et al. miR-34 miRNAs regulate cellular senescence in type II alveolar epithelial cells focusing on their commonalities may be fruitful.

Figure 1. Hypothetical model for ECT2 (epithelial cell transformation-2) upregulation and alveolar epithelial type 2 (AT2) cell transformation. Ulke and colleagues show that the ECT2 Rho guanine nucleotide exchange factor (RhoGEF) is upregulated in both idiopathic pulmonary fibrosis (IPF)-associated hyperplastic AT2 cells and non–small cell lung cancer (NSCLC; solid arrows), suggesting a common proliferative mechanism that may be targeted for future therapy. Evidence that ECT2 positively contributes to DNA synthesis raises the possibility that it may also contribute to the formation of IPF-associated hypertrophic AT2 cells, which endoreplicate their DNA but do not divide (dashed arrow). Polyploid, hypertrophic AT2 cells that ultimately manage to divide may segregate their DNA imperfectly, leading to AT2 cell transformation and cancer. Graphics courtesy of BioRender.