Comment on Iriguchi et al, page 370

A lymphocyte-mediated cause of secondary PAP

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In this issue of Blood, Iriguchi et al report that T-lymphocyte–restricted overexpression of T-bet causes a maturational arrest in mononuclear phagocyte lineage cells and severe secondary pulmonary alveolar proteinosis (PAP). PAP is a rare syndrome characterized by pulmonary surfactant accumulation and hypoxemic respiratory failure for which the current treatment is whole lung lavage, an invasive and inefficient procedure to physically remove the excess pulmonary surfactant. It occurs in a heterogeneous group of diseases usefully subdivided into primary PAP, secondary PAP, and disorders of surfactant production. Surfactant is normally comprised of a thin phospholipid/protein layer that stabilizes alveoli by reducing alveolar wall surface tension and is maintained by balanced secretion by alveolar epithelial cells, and clearance by these cells and alveolar macrophages. In PAP, however, progressive surfactant accumulation eventually fills alveoli, thus displacing inhaled air and compromising gas exchange.

While significant research advances have elucidated the pathogenesis of primary PAP and led to the development of novel diagnostics and therapeutics, other than its association with myelodysplastic syndromes, the pathogenesis of secondary PAP remains obscure, its prognosis is poor, and therapeutic options are limited. In primary PAP, the disruption of granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling causes alveolar macrophages to undergo maturational arrest, which impairs their ability to clear surfactant. From a mechanistic perspective, the disruption of the GM-CSF→PU.1→PPARγ signaling axis reduces the expression of a critical macrophage lipid exporter, ABCG1, which results in foamy, lipid-laden alveolar macrophages with impaired surfactant clearance capacity, intraalveolar surfactant accumulation, and PAP. The loss of GM-CSF signaling also increases pulmonary levels of monocyte chemotactant protein-1 (MCP-1), a biomarker of primary PAP. It is thought that secondary PAP is caused by a reduction in either the functional capacity or absolute numbers of alveolar macrophages, but data supporting this hypothesis are limited. Although expression of T-bet, a “master” transcription factor, is increased in inflammatory, autoimmune, and hematologic
Proposed mechanism by which constitutive, T-cell–restricted T-bet overexpression causes maturational arrest of mononuclear phagocyte lineage cells and secondary PAP. Transgenic mice overexpressing T-bet in T lymphocytes from the human CD2 promoter exhibit constitutive IFN-γ expression and multiple primary and secondary downstream biological consequences. A critical primary effect (black arrow) is activation of CD4+ T cells and promotion of TNF1 cell differentiation resulting in TNF1 cell accumulation and activation. Secondary consequences (gray arrows) include lymphocytic infiltration of the lungs and tissues, marked accumulation of pulmonary alveolar macrophages, maturational arrest of mononuclear phagocytic lineage cells, and time-dependent accumulation of pulmonary surfactant in alveolar macrophages/alveoli (secondary PAP). Characteristics of the alveolar macrophages (large, foamy-appearing, CD11b+CD11c−, reduced phagocytosis, reduced PPARγ, and ABCG1 messenger RNA [mRNA]) were similar to those of mice and humans with PAP caused by the disruption of GM-CSF signaling, yet GM-CSF mRNA was increased in the lungs of transgenic mice. Pulmonary MCP-1 was also increased (as it is in PAP, caused by the disruption of GM-CSF signaling) and likely contributed to mononuclear phagocyte recruitment (open arrows). Together, these results suggest that secondary PAP occurring in the context of increased expression of T-bet in T cells may be caused by an interruption of the GM-CSF-PU.1-PPARγ-ABCG1 axis, which is critical to surfactant clearance by alveolar macrophages but downstream of PU.1. However, the precise mechanism by which this signaling axis is disrupted in alveolar macrophages and the signaling molecule(s) responsible remain to be determined.

These findings are important because they provide a molecular explanation for the association between PAP and myelodysplastic syndromes, and confirm the leading hypothesis about the pathogenesis of secondary PAP (see figure). Nonetheless, the precise mechanism by which T-bet overexpression results in maturational arrest of myeloid lineage cells or the accumulation of functionally impaired alveolar macrophages remains to be determined. Future studies are needed to determine the pathogenic mechanism and to explore the clinical implications of these findings for myelodysplasia and secondary PAP.

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REFERENCES


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