and/or progenitor between the basophil and mast cell lineages.

IRF8 plays important roles in a number of other fate decisions within the myeloid compartment, including dendritic cell commitment, inflammatory monocyte development, and eosinophil production. Many of these mouse phenotypes have been elegantly reproduced through analysis of human patients with inherited IRF8 mutations.[7] One common thread throughout these pleiotropic effects is that IRF8 suppresses neutrophil potential,[8] yet it is clear that IRF8 also promotes lineage-specific programs, such as GATA2, as shown by Sasaki and colleagues.[1] How then does one transcription factor exert such diverse and cell-type–specific effects?

IRF8 and its closely related cousin, IRF4, possess relatively weak binding affinities for DNA.[9] Thus, their major modes of action come from cooperating with other transcription factors to modify their activities and/or DNA binding specificities. Two major groups of partners for IRF4 and IRF8 are the Ets and AP-1 families of transcription factors.[10] Using IRF8 point mutants, Sasaki and colleagues show that interaction with these partners is essential for promotion of the basophil lineage.[1] However, many members of the Ets and AP-1 families are expressed during hematopoietic differentiation. Thus, it remains an open question which of these factors partners with IRF8 to drive basophil differentiation, and whether distinct partners are used for other lineages. Moreover, it remains unknown how IRF8 synergizes with other transcription factors, such as C/EBPα, which are also important for basophil commitment.[4]

Although many such questions still remain, Sasaki and colleagues have made a major advance by demonstrating the functional requirement for IRF8 in basophil development. By marrying modern cellular and genetic approaches, the authors bring some clarity to the steps underlying the development of this intriguing lineage.

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Comment on Iriguchi et al, page 370

A lymphocyte-mediated cause of secondary PAP

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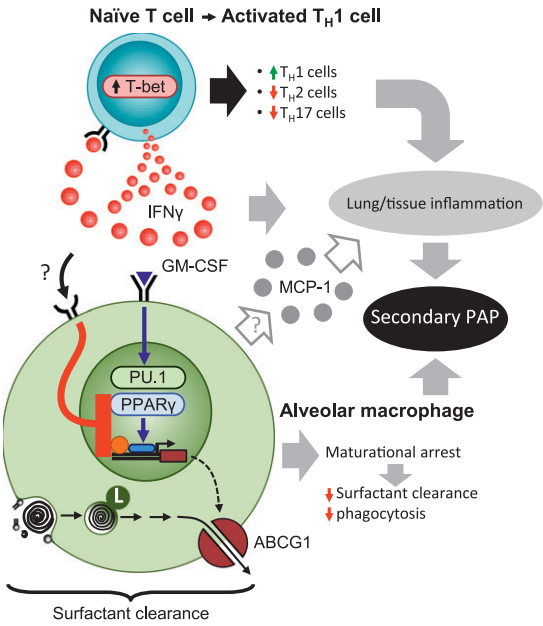
In this issue of *Blood*, Iriguchi et al report that T-lymphocyte–restricted overexpression of T-bet causes a maturational arrest in mononuclear phagocyte lineage cells and severe secondary pulmonary alveolar proteinosis (PAP).[1]

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.[2] 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,[3,4] other than its association with myelodysplastic syndromes, the pathogenesis of secondary PAP remains obscure, its prognosis is poor, and therapeutic options are limited.[5] 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.[6–9] The loss of GM-CSF signaling also increases pulmonary levels of monocyte chemoattractant 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.[2]

Although expression of T-bet, a "master" T_H1 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 IFNγ expression and multiple primary and secondary downstream biological consequences. A critical primary effect (black arrow) is activation of $CD4^+$ T cells and promotion of T_H1 cell differentiation resulting in T_H1 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, $CD11b^{Hi}CD11c^+$, 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.

disorders including myelodysplastic syndromes, its precise role in disease pathogenesis is unknown. To address this question and determine the contribution made by increased expression of T-bet to the pathogenesis of inflammatory diseases, Iriguchi et al studied wild-type (wt) and transgenic mice heterozygous or homozygous for a human CD2–T-bet transgene (tg) (wt/wt, tg/wt, or tg/tg mice, respectively). Unexpectedly, the results identified a novel mechanism by which increased expression of T-bet, exclusively in T lymphocytes, spontaneously drives the pathogenesis of both myelodysplasia and secondary PAP in a dose-dependent manner.[1]

Prior studies with these mice had shown that T-bet overexpression increased interferon-γ (IFNγ) production in $CD4^+$ cells, enhanced T_H1 and suppressed T_H2 antibody responses, and caused dermatitis.[10] The present report shows that compared with wt/wt mice, tg/wt mice spontaneously developed maturational arrest in the mononuclear phagocytic lineage, while tg/tg mice also spontaneously developed severe lung inflammation including perivascular/peribronchiolar lymphocytic infiltration, secondary PAP, and had increased mortality correlating with the presence and severity of the lung disease.

These results identify a previously unsuspected mechanism in which T-bet expression in T_H1 cells regulates myeloid lineage progression that, when activated constitutively, causes maturational arrest of mononuclear phagocytes, dose-dependent tissue inflammation, and secondary PAP. 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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