in erythroid/megakaryocyte progenitors (MEPs) or lymphoid cells. However, little was known about the precise cell type in which C/EBPα is first expressed within the hematopoietic hierarchy, and what the ultimate fate of the progeny of these C/EBPα-expressing cells would be.

Wölfler and colleagues make use of a model in which Cre recombinase is knocked-in in the Cebpa locus and Cre is therefore expressed under the control of the endogenous Cebpa promoter. These mice lack one Cebpa allele but this does not impair myeloid development or steady-state hematopoiesis. Next, these Cebpa+/Cre mice were crossed with ROSA26 EYFP reporter mice, in which EYFP is only expressed after Cre-mediated recombination of loxP sites within the locus. Thus, as soon as the Cebpa promoter becomes activated, expression of Cre will allow the expression of EYFP. Not only will cells in which the Cebpa promoter is activated become EYFP+, but also all progeny of these cells will be positive for EYFP since the loxP sites are irreversibly deleted, regardless of whether C/EBPα remains expressed (see figure).

Based on this mouse model several conclusions can be drawn: (1) only 4% of the most immature stem cells express C/EBPα, and the number of cells that express (or have expressed) C/EBPα increases to approximately 15% in multipotent progenitors; (2) upon differentiation along the myeloid lineage from CMP to GMPs an increasing number of cells express (or have expressed) C/EBPα, and practically all mature monocytes and granulocytes have expressed C/EBPα at least at some point during their development; and (3) despite the notion that erythroid and lymphoid cells do not express C/EBPα, it is clear from these tracing studies that at least some of these cells did express C/EBPα early in their development. In particular, this last point raises some important issues because it argues against a lineage-restrictive role for C/EBPα. Apparently, the expression of C/EBPα in immature progenitors does not prevent the differentiation toward a lymphoid or erythroid cell fate, even though the majority of C/EBPα–EYFP progenitor cells becomes myeloid cells. These findings are in line with the notion that the promiscuous expression of myeloid, erythroid, and lymphoid genes precedes the actual lineage commitment.

The Cebpa+/Cre-R26EYFP mouse model allows the identification of C/EBPα-expressing cells and particularly their progeny in an in vivo setting, but does not allow the quantification of C/EBPα expression at the protein level, which would for instance be possible in a transgenic mouse in which EYFP would be directly fused to C/EBPα. In addition, this C/EBPα–EYFP model would provide more insight into the kinetics of C/EBPα expression, and would allow the analysis of exact down-modulation of C/EBPα upon commitment along the lymphoid or erythroid lineage. Since the dosage and timing most likely matter, it will be interesting to develop those models as well.

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REFERENCES

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Comment on Peffault de Latour et al, page 4175

Abnormalities in Th17 T cells in aplastic anemia

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In this issue of Blood, Peffault de Latour et al demonstrate that interleukin-17 (IL-17)–producing Th17 T cells are increased in the peripheral blood and bone marrow of patients with aplastic anemia, compared with healthy controls. They also provide evidence that IL-17 contributes to the severity of marrow failure at an early stage. This work advances our overall understanding of the mechanisms of immune-mediated hematopoietic suppression and may ultimately have important clinical implications for the treatment of aplastic anemia.

Aplastic anemia is characterized by pancytopenia and bone marrow hypoplasia, resulting from immune-mediated suppression of hematopoiesis. Although the management of aplastic anemia is challenging and the outcome frequently fatal,
advances in our understanding of the immune pathophysiology of the disease over the years have led to improvements in the immunosuppressive regimens used for its treatment and, in some cases, improved outcomes and survival.1,2

Over the past 3 decades, extensive work has established that cytokines play key roles in the suppression of hematopoiesis seen in aplastic anemia.2 Observations made first in the 1980s suggested a disease model in which overproduction of myelosuppressive cytokines by activated cytotoxic T cells results in immune-mediated hematopoietic destruction.3,4 The principles established by such original observations remain essentially unchanged, but subsequent work has expanded on them and defined the mechanisms of immune deregulation seen in aplastic patients. An important observation in recent years was the demonstration that the T-bet transcription factor, which is known to activate the expression of several genes, is a target for decay by miR-144. NRF2 is a mediator of antioxidant response elements. Increased miR-144 levels (and consequently decreased NRF2 levels) therefore declare no competing financial interests.

REFERENCES

Micro-mismanaging sickle cell stress

Comment on Songokoya et al, page 4338

Micro-mismanaging sickle cell stress

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SCD (or “HbSS”) can vary markedly in its clinical manifestations:1 in HbSS cells, regulatory factors that skew in association with disease severity may present new prognostic and/or therapeutic opportunities. In this issue of Blood, Songokoya et al have applied unsupervised miRNA profiling to reveal elevated microRNA–144 levels in a severe anemia subset of SCD patients (despite an essential lack of mRNA transcripts, erythrocytes can retain miRNAs).2,3 Evidence further is provided that the CNC-bZip transcription factor NRF2 is a target for decay by miR-144. NRF2 is known to activate the expression of several antioxidant encoding genes (eg, SOD1, CAT, GCL2) in part via antioxidant response elements. Increased miR-144 levels (and consequently decreased NRF2 levels) therefore

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