blasts to create “field defects” and “niches” that allow for malignant growth and survival.

Several questions remain to be addressed to fully understand and harness the activity of myeloid blasts on the microenvironment, which could be the next frontier for molecularly targeted therapies in AML. What is the relationship between AML genotypes and the plasma arginase activity? Do high levels of arginase activity correlate with the presence of unfavorable AML cytogenetic and molecular features? Are residual blasts in patients receiving SCT still able to produce serum arginases, thereby inhibiting the host immune system and hematopoiesis, and in turn causing disease relapse? Are levels of arginase activity able to predict treatment failure, and can they be used as surrogate markers for minimal residual disease?

Ultimately, the answers to these questions will help us understand the clinical relevance of the findings by Mussai et al and whether determination of arginase levels at diagnosis and at regular follow-ups should be incorporated into the clinical evaluation of patients with AML. The development of novel treatment approaches for AML that include effective and nontoxic arginase inhibitors could eventually be pursued to improve the clinical outcome of patients with AML who have unfavorable clinical (ie, age, secondary disease) and genetic (cytogenetics, gene mutations, aberrant gene and microRNA expression) features.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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PHAGOCYTES, GRANULOCYTES, & MYELOPOIESIS

Comment on Doyle et al, page 781

To be, or not to be, an eosinophil: that is the ???

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In this issue of Blood, Doyle et al provide evidence that knockout of the genes encoding the two most abundant eosinophil secondary granule proteins disrupts the normal differentiation of eosinophils from progenitors in the bone marrow, providing a novel strain of mice with a highly specific deficiency in eosinophilopoiesis and, therefore, eosinophils. This strain is likely to be used by investigators to elaborate the normal vs pathogenic roles of eosinophils in health and disease.

In the more than 100 years following Paul Ehrlich’s 1879 identification of the eosinophil, the compendium of diseases and idiopathic syndromes characterized by blood or tissue eosinophilia grew by leaps and bounds, while our understanding of the functional roles of the eosinophil in innate immunity and host defense, allergic responses, tissue injury/repair, and remodeling/fibrosis lagged far behind, being addressed in only the past 30 or so years. Initial studies characterized the unique biologic characteristics of blood and tissue eosinophils, their preformed secondary granule proteins, and inducible lipid, oxidative, and cytokine products, focusing on the eosinophil’s proinflammatory and cytotoxic potential in the pathogenesis of allergic, parasitic, and a variety of idiopathic eosinophil-associated syndromes. Recognition of the eosinophil as an effector cell in asthma pathogenesis fueled an initial surge in eosinophil interest, while an “epidemic” of eosinophil myalgia syndrome from ingestion of tainted L-tryptophan, and more recent identification of the food-allergic disease eosinophilic esophagitis, markedly increased clinical interest and public awareness of this granulocyte.

The current paradigm—that eosinophils subserve proinflammatory tissue-damaging and tissue-remodeling roles in eosinophil-associated diseases—is supported by a growing number of definitive mouse model and human studies. A pivotal role for the eosinophil in the development of tissue remodeling and fibrosis, through elaboration of remodeling and fibrogenic factors (eg, transforming growth factor beta), is widely accepted. Studies using two strains of eosinophil-deficient mice (PHIL and ΔdblGATA)5,6 strongly support the concept that eosinophils contribute to the pathology of airway remodeling in asthma and are required for T-cell polarization for development of Th2 responses in the lung in response to allergen challenge. Clinical trials using anti-interleukin-5 (IL-5) antibody to ablate eosinophils in bone marrow, blood, and tissues of patients with eosinophilic, but not neutrophilic, asthma showed efficacy in reversing aspects of eosinophil-mediated tissue damage, remodeling, fibrosis, and airway dysfunction8 and pathologies associated with the hypereosinophilic syndrome. Thus, the availability of two strains of eosinophil-deficient mice, PHIL and ΔdblGATA, has been integral to understanding the contributions of eosinophils to disease pathogenesis and normal tissue homeostasis.

Expression of the major eosinophil granule cationic proteins, major basic protein 1 (MBP-1) and eosinophil peroxidase (EPX), is the consequence of normal hematopoietic development of eosinophil lineage-committed progenitors (EoPs) leading to terminal differentiation of the mature eosinophil or, under conditions of increased expression of IL-5 from Th2 T cells and other cell sources, expansion of the EoP population, which then leads to blood and tissue eosinophilia. The
study by Doyle et al reports the paradoxical finding that concurrent expression of MBP-1 and EPX appears to be required for and reinforces the development of the eosinophil lineage, or conversely, that the absence or loss of concurrent expression of MBP-1 and EPX may be a novel checkpoint for successful eosinophil differentiation, such that defective granulogenesis leads to impaired survival (apoptosis) of developing eosinophils, or that loss of expression of MBP-1 and EPX disrupts lineage-instructive gene regulatory mechanisms affecting continued EoP self-renewal and/or survival. Baso, basophil; EARs, eosinophil-associated ribonucleases; HSC, hematopoietic stem cell; Mac, monocyte/macrophage; MPP, multi-potential progenitor; PMN, polymorphonuclear neutrophil; RIP, rest in peace.

In summary, the study by Doyle et al characterizes a novel eosinophil-deficient mouse strain that lacks many of the problems and criticisms associated with the currently available eosinophil-deficient strains (PHIL and ΔdblGATA), since the defect is entirely eosinophil specific (affects only EoPs in a cell-autonomous manner) and does not involve the lineage-specific expression of a toxin (diphtheria toxin A chain) in developing EoPs (in PHIL) or have other collateral defects (eg, on red cell development in ΔdblGATA) due to dysregulation of GATA-1 transcriptional autoregulation. Although the specific mechanisms underlying the eosinophil deficiency in the MBP-1−/−/EPX−/− knockout mice remain to be determined, this novel strain is certain to be adopted by investigators for mouse model studies of the normal vs pathogenic roles of eosinophils in health and disease.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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A 2-hit model for chronic GVHD

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In this issue of Blood, Dertschnig and colleagues1 demonstrate in mice that acute graft–versus-host disease (GVHD) results in a marked reduction of autoimmune receptor–expressing medullary thymic epithelial cells (Aire+ mTEC) and a decrease in the diversity of Aire-dependent tissue-restricted self-antigens (TRAs) required for effective negative thymic selection. Both of these abnormalities are reversed by the peritransplant administration of the epithelial protectant drug, fibroblast growth factor 7 (Fgf7).

Chronic GVHD continues to be a major cause of both morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT).2 Chronic GVHD has been assumed to be caused by the continuation of the pathogenic mechanisms that cause acute GVHD, primarily donor-derived T lymphocytes specific for histocompatibility antigens uniquely expressed by recipient cells.3 As a consequence, therapy for chronic GVHD has traditionally been directed at suppressing the donor antirecipient immune response. However, during the last 25 years, a series of murine experiments have indicated that donor-derived, autoreactive T lymphocytes (ie, T lymphocytes specific for antigens expressed by both donor and recipient cells) are present in murine HSCT recipients with chronic GVHD and that the chronic GVHD could be transferred by the donor-derived T lymphocytes into both donor and recipient mice.4–6

More recently, a clinical trial of low-dose subcutaneous IL-2 in human HSCT recipients with established chronic GVHD demonstrated that an increase in circulating regulatory T lymphocytes (Treg) resulted in clinical improvement, suggesting that deficiencies in Treg lymphocytes play a role in the pathogenesis of human chronic GVHD.7 Dertschnig et al report that mice with acute GVHD have a profound decrease in the frequency of Aire+ mTEC, which are necessary for the thymic production of naturally occurring Treg lymphocytes. Other investigators have previously demonstrated that the diverse expression of TRA by Aire+ mTEC is required for the effective thymic elimination of autoreactive T lymphocytes by negative selection.8 Using microarray analyses of isolated Aire+ mTEC, the present investigators report the decreased expression and diversity of TRA with a selective decrease in the TRA associated with the tissues that are the target organs of human chronic GVHD (skin, liver, salivary glands, lung, eye, and gastrointestinal tract). The result of the restricted diversity of TRA expression would be the extrathymic presence of autoreactive T lymphocytes. Their present results suggest a 2-hit model for chronic GVHD, in which the presence of extrathymic autoreactive T lymphocytes (Hit 1) in the context of immune dysregulation (deficiencies in Treg lymphocytes, Hit 2) can result in the development of chronic GVHD.

The peri-HSCT administration of the epithelial protectant drug, Fgf7, does not affect the initial post-HSCT decrease in mTEC but does hasten the recovery of Aire+ mTEC and improves the diversity of TRA expression. Fgf7 acts by stimulating the proliferation and differentiation of TEC progenitors and the proliferation of residual mTEC.9 The relative contribution of the 2 populations to the recovery of Aire+ mTEC is unclear. The presence of normal numbers of Aire+ mTEC with normal TRA diversity during the recapitulation of immunologic ontogeny, which occurs after the engraftment of donor hematopoietic stem cells, may result in the presence of adequate numbers of circulating Treg lymphocytes and effective negative thymic selection, which would eliminate the peripheral presence of autoreactive T lymphocytes and an absence of chronic GVHD. As such, clinical trials to determine whether the peritransplant administration of Fgf7 results in a decreased incidence of chronic GVHD in human HSCT recipients are indicated.

The present murine experiments, however, do not address several potentially important clinical questions: (1) What would be the impact of the administration of Fgf7 to patients with established chronic GVHD? (2) Do HSCT recipients with established chronic GVHD have an adequate number of TEC progenitors and residual mTEC for the Fgf7 to be effective? (3) Do the TEC progenitors and mTEC in chronic GVHD patients become refractory to the action of Fgf7?; and (4) Is the loss of Aire+ mTEC during acute GVHD paralleled by a decrease in TRA diversity, or are they separable biological processes? If they differ, then some HSCT recipients may have a deficiency of Treg lymphocytes without the concomitant presence of peripheral autoreactive T lymphocytes, whereas other recipients may have adequate numbers of Treg lymphocytes with the presence of peripheral autoreactive T lymphocytes. Only HSCT recipients with both the presence of peripheral autoreactive T lymphocytes (Hit 1) and deficiencies in Treg lymphocytes (Hit 2) would be at risk of developing chronic GVHD. The immunophenotypic identification of functional human Treg lymphocytes will aid in the evaluation of