which are not used currently because of their high toxicity to the body.

The new strategy also provides hope for successfully treating CSCs by engineering bacteria to express antibodies targeting specific markers of these cells. Although there is an ongoing debate regarding the terminology and the exact nature of CSCs, it is commonly agreed that tumors have small subpopulations of special tumorigenic cells with the ability of renewal and differentiation into a variety of cell types and cause tumor relapse. These subpopulations pose a high risk because they are not detected by standard imaging methods, and since they can become dormant and thus successfully evade ordinary cancer treatments (chemotherapy, radiation therapy, and targeted/biological therapy). Development of specific therapies targeted at these transitional CSCs holds hope for improvement of survival and quality of life of cancer patients, especially for sufferers of metastatic disease. The advantage of the bacteria-based strategy is that the Trojan-horse bacteria engineered to express markers of both the tumor cells and the CSCs are expected to be able to find the dormant CSCs hiding within the tumor and attack them with newly discovered compounds effective against dormant cells.

An intriguing example of such a compound is salinomycin which is secreted by the Streptomyces albus bacteria. This widely used agricultural agent has recently been shown to be highly potent against CSCs. As promising as it is, salinomycin cannot be used currently because of its high general toxicity. The Trojan-horse bacteria may be able to deliver the compound to kill the CSCs while protecting the rest of the body from the drug toxicity.

To conclude, building on the results reported by Massa et al, we can envision recruiting engineered Trojan-horse bacteria to explore the body and find cancer cells. The engineered bacteria can then kill the cancer cells directly or expose them to the immune system and to other recruited bacteria engineered to kill them by acting together with the immune system. For example, it is now understood that most tumors at advanced stages are composed of several subclones. We can foresee the engineering of several Trojan-horse bacteria acting together, each able to better identify and target a specific clone. We may be seeing here the dawning of a new era of biological cyberwarfare on cancer, in which we will enlist bacteria to fight with the immune system and defeat cancer with minimal side effects to the patients.

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

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MYELOID NEOPLASIA

Arginase-mediated “field” defects in AML

Guido Marcucci1

Comment on Mussai et al, page 749

In this issue of Blood, Mussai et al report on the ability of acute myeloid leukemia (AML) blasts to inhibit the immune system and hematopoiesis through aberrantly high levels of arginase II activity. AML is a clinically, genetically, and epigenetically heterogeneous disease. Both epigenetic and genetic aberrations in AML blasts have been used to understand mechanisms of leukemia growth and predict patients’ outcomes, as well as assign them to different treatment approaches. However, the majority of patients treated with chemotherapy and/or molecular targeting agents continue to die of their disease. Stem cell transplantation (SCT) has been proven effective in curing AML by allowing for the administration of otherwise myeloablative and toxic doses of chemotherapy and for reconstitution of an effective immune system from the donor graft that, in turn, contributes to the eradication of resistant clonal cell subpopulations. These populations may include those with high self-renewal ability: the so-called leukemia stem (or initiating) cells. However, even following SCT, patients may relapse and die of their disease, underlining the complexity of AML biology and of the mechanisms of disease resistance.

The main focus of AML studies has been on the genetic and epigenetic features of the blasts and how these characteristics relate to mechanisms leading to the arrest of hematopoietic differentiation and the ability to proliferate and survive even after administration of cytotoxic compounds. However, an increasing number of studies now emphasize the biologic significance and potential clinical relevance of the microenvironment in AML. The findings by Mussai et al further support this view by showing that aberrant arginase II activity contributes to leukemogenesis via suppression of T lymphocyte activity through polarization of monocytes into a suppressive M2-like phenotype and direct inhibition of the hematopoietic activity, which in turn may contribute to pancytopenia and marrow failure observed in AML. The role of arginase I in mechanisms of immunosuppression through myeloid-derived suppressor cells has been previously recognized, whereas the activity of arginase II leading to an aberrant microenvironment is an original observation that reemphasizes the potential of myeloid...

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ARGINASE-MEDIATED “FIELD” DEFECTS IN AML

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In this issue of Blood, Mussai et al report on the ability of acute myeloid leukemia (AML) blasts to inhibit the immune system and hematopoiesis through aberrantly high levels of arginase II activity. AML is a clinically, genetically, and epigenetically heterogeneous disease. Both epigenetic and genetic aberrations in AML blasts have been used to understand mechanisms of leukemia growth and predict patients’ outcomes, as well as assign them to different treatment approaches. However, the majority of patients treated with chemotherapy and/or molecular targeting agents continue to die of their disease. Stem cell transplantation (SCT) has been proven effective in curing AML by allowing for the administration of otherwise myeloablative and toxic doses of chemotherapy and for reconstitution of an effective immune system from the donor graft that, in turn, contributes to the eradication of resistant clonal cell subpopulations. These populations may include those with high self-renewal ability: the so-called leukemia stem (or initiating) cells. However, even following SCT, patients may relapse and die of their disease, underlining the complexity of AML biology and of the mechanisms of disease resistance.

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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.

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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 ??

Steven J. Ackerman1

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 eosinophiloipoiesis 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.1

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.2 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,3 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.4 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.7 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.9 Thus, the availability of two strains of eosinophil-deficient mice (PHIL and ΔdblGATA),5,6 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
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