with plasminogen markedly stimulated uptake of prey, and plasmin activity and protein synthesis were required. Furthermore, clearance of apoptotic cells from the spleen and clearance of apoptotic thymocytes from the peritoneum were markedly reduced in plasminogen-deficient mice, as was phagocytosis by liver Kupffer cells in a hemolytic anemia model.1

Das and colleagues perform gene array studies and make the remarkable observation that plasminogen modulates expression of major genes involved in phagocytosis, including phagocytic receptors, recognition and engulfment molecules, phagosome maturation genes, phagosome processing genes, and signal transduction molecules. Thus, plasmin may regulate all of the steps in phagocytosis by stimulating cellular signaling. This study provides a strong rationale for future studies to investigate the role of specific molecules in plasminogen-dependent phagocytosis by macrophages. Das and colleagues demonstrate that the effects of plasminogen were modulated by a direct interaction of plasminogen with cells. As several distinct plasminogen receptors are present on the surfaces of macrophages,6 future studies are warranted to elucidate the roles of specific plasminogen receptors in plasmin–dependent signaling during the different steps in phagocytosis and whether these or other macrophage cell surface proteins are specific targets of plasmin. Subsequently, the specific signaling pathways induced by plasmin that lead to up-regulation of phagocytosis genes can be identified. There may also be additional mechanisms by which plasminogen plays a role in phagocytosis by mediating prey recognition. For example, certain plasminogen receptors that are tethered to cells by phosphatidyl serines7 may bind plasminogen on apoptotic prey cells that can then be recognized by a transmembrane plasminogen receptor8 on macrophages.

This novel function of plasminogen has important clinical implications. As pointed out by Das et al, deficiency of plasminogen or the presence of antibodies to plasminogen receptors is correlated with several disease states with an autoimmune and/or inflammatory component. Furthermore, Das et al demonstrate that the effects of plasminogen on phagocytosis are blocked by tranexamic acid, a lysine mimetic that interacts with plasminogen to block plasminogen binding to cells and to fibrin. Tranexamic acid is used therapeutically to inhibit fibrinolysis and hemorrhage in several conditions including surgery, angioedema, menorrhagia, and dental procedures in patients with genetic deficiencies of coagulation factors or of plasmin inhibitors. Thus, treatment with tranexamic acid and other fibrinolysis inhibitors may have important clinical effects that are yet to be elucidated. Finally, this novel study by Das et al points the way for consideration of plasminogen and plasminogen receptors as potential therapeutic targets in patients with defective innate immunity.

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MDSCs: the final frontier of the microenvironment in CLL?

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In this issue of Blood, Jitschin et al identify increased numbers of myeloid-derived suppressor cells (MDSCs) in untreated patients with chronic lymphocytic leukemia (CLL) suppressing T cells and inducing regulatory T cells (T\textsubscript{regs}), resulting in impaired immune responses.1

CLL is the most prominent B-cell malignancy among adults in the Western world, characterized by a clonal expansion of B cells. Early on, it coincides with a profound immunodeficiency, predisposing for infections and rendering the disease rather insensitive to conventional, and particularly immunotherapeutic strategies, leading to impaired antitumor immune responses. This resistance is largely mediated by the complex crosstalk between neoplastic B cells and the tissue microenvironment: Previous reports identified direct interaction of CLL cells with mesenchymal stromal cells and nurseslike cells (eg, via the CXCR4-CXCL12 axis), promoting survival of CLL cells.2 Similarly, expansion of T cells considerably contributes to microenvironment-mediated CLL protection. Although in many cancers, T cells are involved in antitumor immunity, T cells in CLL fail to mount an effective T cell–mediated immune response against CLL cells.3 In particular, T\textsubscript{regs} have been shown to increase in CLL, adding to the reduced immunosurveillance in CLL.4 Recently, a further major component of the microenvironment, the so-called “myeloid-derived suppressor cells” (MDSCs), has been identified in various malignancies including CLL and has been inversely linked with outcome.5 MDSCs represent a heterogeneous population of myeloid progenitors and precursors of granulocytes, macrophages, and dendritic cells. They can inhibit T-cell.

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IDOhi MDSCs represent central regulators of immune function in CLL and may critically dampen antitumor immunity. These data imply that antagonizing suppressive functions of CLL MDSCs (eg, by pharmacologic inhibition of IDO) could provide an attractive approach for enhancing immune responses.

Various studies implicated IDO with responses limiting immune therapeutic approaches and are induced by various factors expressed or secreted in states of cancer, inflammation, or trauma.6

In this issue of Blood, Jitschin et al characterize a subset of CD14+ HLA-DRlo MDSCs expressing high amounts of indoleamine-2,3-dioxygenase (IDO).1 These MDSCs are increased in untreated CLL patients at a rather early stage and suppress both T-cell activation and proliferation. In a series of carefully designed experiments, the authors discover that CLL cells directly induce IDOhi MDSCs capable of inducing suppressive Treg cells. At the same time, myeloid cells, with a catalytic function in the tryptophan pathway. Because tryptophan depletion results in the growth arrest of T cells, and degradation products of tryptophan may be toxic for CD8+ T cells and natural killer (NK) cells, IDO enforces various immunosuppressive effects. In fact, genetic deletion of IDO was recently shown to directly limit tumorigenesis.7 On the basis of these findings, inhibitors of IDO are currently being challenged in several clinical trials as potential treatment or combination treatment of recurrent or refractory solid tumors. However, thus far only one trial has been launched in a hematologic malignancy, namely in myelodysplastic syndrome. This trial is still recruiting (registered at clinicaltrials.gov as #NCT01822691).

A very promising step in a similar direction is the recent finding that the programmed death-1 (PD1) receptor, a negative regulator of T-cell effector mechanisms limiting immune responses against cancer, is strongly upregulated in CLL cells.8 A phase 1 dose-escalation study of the anti-PD1 antibody CT-011 (pidilizumab) showed evidence of response in 6 of 18 patients with advanced hematologic malignancies; of the 3 CLL patients who were enrolled, two showed evidence of stable disease.9 Given the preclinical data highlighting the significance of the PD1:PD-L1 axis in suppressing T-cell function in CLL, there is also a strong rationale that pharmacologic manipulation of the PD1:PD-L1 axis may contribute to restoring T-cell functions in the CLL microenvironment. The therapeutic approach of blocking the PD1:PD-L1 axis has also been pursued successfully in solid cancer: in patients with advanced melanoma, including those who had disease progression while they were receiving ipilimumab, treatment with the anti-PD1 antibody lambrolizumab (previously known as MK-3475) resulted in a high rate of sustained tumor regression.10

It will take time to validate the concept arising from the work of Jitschin et al in vivo. We will have to test whether antagonizing the suppressive function of MDSCs in CLL will ultimately limit this as yet incurable disease before this approach may be considered as a future therapeutic strategy for CLL and potentially incorporated into clinic rounds. In that context, the finding of the immunosuppressive network among CLL cells, MDSCs, and Tregs is highly intriguing and may be the final frontier of the microenvironment in CLL that we will have to overcome.

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Comment on Lu et al, page 771

**p53 at the crossroads of MPN treatment**

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In this issue of *Blood*, Lu et al describe the cooperation between an orally bioavailable mouse double minute 2 (MDM2) antagonist (RG7112) and the pegylated interferon α (Peg-IFNα 2a) to target JAK2V617F hematopoietic progenitors and stem cells. Their work provides a rationale for the treatment of patients suffering from myeloproliferative neoplasms (MPNs).1

**MPNs** are acquired clonal disorders of the hematopoietic stem cells (HSCs) characterized by the hyperplasia of one or several myeloid lineages. Non-BCR-ABL classical MPNs include essential thrombocytopenia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF). The JAK2V617F mutation of the protein kinase JAK2 is the most prevalent genetic abnormality in the 3 types of MPNs (95% in PV and ~50% in ET and PMF). JAK2V617F is a gain-of-function mutation, which leads to constitutive activation of signaling pathways downstream of cytokine receptors.

The discovery of JAK2V617F has rapidly led to the development of JAK2 inhibitors, but the efficiency of the current small molecule inhibitors to reduce the JAK2V617F malignant clone in patients remains disappointing despite major effects on splenomegaly and constitutional symptoms related to inflammation. In contrast, IFNα has been used for >20 years to treat MPN patients including chronic myeloid leukemia patients. It has been shown to efficiently control not only thrombocytosis and erythrocytosis in ET and PV patients but also hematopoiesis by restoring a polyclonal state.2 In contrast to JAK2 inhibitors, the majority of patients treated with IFNα display a partial or complete hematological response associated with a molecular response confirmed by a drop in JAK2V617F allelic burden. Using 2 Jak2V617F conditional knock-in mouse models, it was reported that IFNα specifically targets Jak2V617F stem cells, yet the mechanisms remain elusive.3,4 Some patients display a long-lasting complete molecular remission even after treatment discontinuation that suggests that IFNα may also impact Jak2V617F stem cells in humans, but further confirmation is needed.

IFNα is also able to stimulate both the transcription of the p53 tumor suppressor via the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway and the subsequent translocation to the nucleus of STAT1/2 and IFN regulatory factor (IRF)-9, which form a heterotrimeric complex triggering activation of the p53 promoter.5 Nevertheless, the basal expression of the MDM2 ubiquitin ligase induces the constant degradation of p53 protein that still remains poised for any stresses. Importantly, JAK2V617F strongly inhibits the stabilization of p53 after induction of DNA damages

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