Before the current study by Hay and Di-Michele, the main unresolved question was the influence of FVIII dosage regimens on the ITI success rate, particularly after a Dutch study obtained a high success rate (83%) using as little as 50 U/kg of FVIII 3 times weekly, instead of the 200-300 U/kg daily doses used by the acolytes of the Bonn regimen. This smaller dosage regimen, which achieved a high rate of ITI within a time frame similar to that of the high dosage (on average ~ 1 year from onset), was highly appealing due to decreased cost and patient acceptability.

Is there an answer to this question from Hay and DiMichele? Their study was designed to test the hypothesis of noninferiority, that is, that the ITI success rate is independent of the FVIII dosage. Even though equivalence between high and low dose was not formally established, my clinical interpretation of the results is that in good-risk patients (ie, those who were relatively likely to get rid of their anti-FVIII inhibitor), either regimen can be used successfully. Does this result imply that one should prefer the low FVIII dosage for reasons of cost and patient convenience? The low-dose regimen was associated with 2-fold more bleeding episodes than the high-dose regimen. Moreover, the cost of the FVIII bypassing products (recombinant activated factor VII, and anti-inhibitor plasma-derived complex) needed to treat the intercurrent bleeding episodes might nullify or substantially reduce any cost saving obtained in terms of less FVIII usage. Hence, one important piece of information still missing to make a meaningful therapeutic choice is a cost-effectiveness analysis. An answer to this question is particularly cogent at a time when the global economic crisis is mounting pressure on healthcare costs and austerity measures are imposed on drug spending, even for therapies as effective as those used in hemophilia that allow these patients to have a life expectancy similar to that of their peers without hemophilia (at least in high-income countries). On the other hand, it is obvious that more bleeding episodes may definitely impair the safety and quality of life of patients treated with low-dose FVIII. Hence, the risk/benefit ratio of the two regimens and a quality-of-life analysis are needed to evaluate the two regimens.

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When IFN interferes with cell fate

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In this issue of Blood, de Bruin and colleagues demonstrate the ability of IFN-γ to influence the binary cell fate choices of granulocytic-monocytic progenitors (GMPs) during viral infection, favoring monocytic over the granulocytic differentiation. This work provides mechanistic insights and a better understanding on how hematopoiesis can be remodeled during infections.

Infections are the most common stressors of the hematopoietic system. The ability of the BM to respond to infections by expanding the progenitor pool to produce more differentiated effector cells is a critical feature of the host’s defense, which translates into the difference between resolving an infection or succumbing to it.

For many years, studies have been focused on understanding the functions of critical effector cells of the innate and adaptive immunity, such as neutrophils, monocytes, macrophages, and lymphocytes. Recently, new conceptual and technical advances, including the availability of a wide range of genetic models, have led investigators to look at the immune response from a new angle, opening a window on the interface between stem cell biology and immunity. Recent studies have shown that hematopoietic stem cells (HSCs) and multipotential progenitors play a critical role in host defense and their behavior can determine the abundance of specific lineages by shaping, at the very origin, the hematopoietic response to infection.

This elegant work by de Bruin et al shows that IFN-γ can interfere with the binary cell fate decision of GMPs to differentiate into monocytes or granulocytes, compelling monocytic differentiation. Importantly, the authors show that loss of granulocytic differentiation does not occur by default, but by IFN-γ-mediated active suppression of G-CSF–triggered intracellular responses.

This finding stems from the initial observation that transgenic mice overexpressing CD70 (CD70TG) have an increased production of monocytes over granulocytes. In these mice, overexpression of CD70 in B cells causes a strong activation and expansion of Th1 effector T cells, via CD70-CD27 interaction, and results in the secretion of high levels of IFN-γ, pointing to a role for IFN-γ as inducer of monocytic differentiation in vivo. This hypothesis was confirmed using several complementary in vivo models. The authors show that normal monocyte levels can be restored in CD70TG in the absence of IFN-γ, and that monocytosis can be induced either by T-cell adoptive transfer in CD70TG/CD27−/− mice or by injection of a CD40 agonist in WT mice. As Th1 activation is an adaptive immune response occurring during viral infections, the authors tested the physiologic relevance of
IFN-γ redirects cell fate decisions in granulocytic-monocytic progenitors (GMPs) during infection. In homeostatic conditions, G-CSF and M-CSF regulate the monocytic and granulocytic output from GMPs. During viral infections, IFN-γ, produced by activated Th1 T cells, affects GMP differentiation by: (1) up-regulation of the expression of PU.1 and IRF-8, transcription factors driving monocytic differentiation, and (2) induction of SOCS3, which antagonizes G-CSF-dependent STAT3 phosphorylation. The overall result is a skewing of myelopoiesis toward monopoiesis at the expense of granulopoiesis.

their findings in a model of Lymphocytic Choriomeningitis Virus (LCMV) infection. Using this model in conjunction with IFN-γ−−/− mice, they confirmed that IFN-γ is required for induction of monopoiesis during infection. Strikingly, these experiments also revealed a requirement of IFN-γ for granulopoiesis suppression.

IFN-γ is a well-known critical mediator of immunity and inflammation and its activity has been investigated for more than 3 decades. IFN-γ plays a central role in macrophage and T-cell activation during inflammation and infection, and a few studies have reported that IFN-γ to enhance monocytic differentiation in vitro. Then why is the present work novel and relevant? Because it addresses for the first time the role of IFN-γ in monocytic differentiation in vivo. It also unveils a previously unrecognized role for IFN-γ in suppressing granulopoiesis during infection, providing novel information on the molecular mechanisms involved in this process and in the regulation of monocytic versus granulocytic differentiation.

Under homeostatic conditions, the balance between monocytes and granulocytes is regulated by M-CSF and G-CSF, respectively. Each of these cytokines has been shown to be required and sufficient to instruct lineage choice in GMPs in vitro. Here, de Bruin et al demonstrate that IFN-γ interferes with this balance and forces myelopoiesis toward monocytic lineage using 2 mechanisms, as shown in the figure: (1) increasing the levels of PU.1 and IRF-8, transcription factors required for GMPs to commit to the monocytic-macrophage lineage; and (2) inducing expression of SOCS3, which strongly antagonizes G-CSF signaling, required for steady-state and emergency granulopoiesis. Thus, this work provides a good example of how an inflammatory cytokine can override the physiologic regulation of binary cell fate decisions and re-direct hematopoietic differentiation, enhancing one cell fate while suppressing another.

The physiologic and clinical relevance of these findings is evident. During viral and intracellular pathogen infections, the ability of the hematopoietic system to coordinate a Th1 T-cell response, while simultaneously shifting myelopoiesis toward monopoiesis via IFN-γ, is critical for the resolution of the infection, as monocytes and activated macrophages are central for pathogen clearance and mycobacteria killing. However, suppression of granulopoiesis by IFN-γ can have negative implications. It is known that IFN-γ does not always favor the host immune response against bacterial pathogens and, indeed, its production is often suppressed by negative feedback loops (such as IL-10). In light of these novel findings, it is likely that the detrimental effect of IFN-γ during bacterial infection is because of its inhibitory effects on granulopoiesis. In fact, a key component of the host innate response to bacterial pathogens is represented by the neutrophil granulocytes defense system. Bacterial infection induces rapid mobilization of neutrophils to the site of infection and this reactive neutrophilia is maintained by accelerated production and differentiation of granulocytes in the bone marrow. Thus, in contrast to viral infection, the shift of myelopoiesis toward granulopoiesis is critical for resolution of bacterial infection.

Neutropenia is a poor prognostic factor in bacterial infections and often characteristic of severe sepsis with fatal outcome. Despite its clinical relevance, the causes of neutropenia in sepsis have been little investigated and, for a long time, depletion of neutrophils has been commonly accepted as the mere consequence of consumption during the antibacterial response. Pioneer work by Santangelo et al documented signs of myelosuppression and a shift toward monopoiesis at expense of granulopoiesis in murine models of severe sepsis. Recently, it is becoming increasingly evident that causes of neutropenia in sepsis include not only bacterial consumption and apoptosis, but also decreased neutrophil production by the bone marrow, such as defective generation of myeloid progenitors at the HSC level, as shown by our group.

The ability of IFN-γ to suppress G-CSF response by inducing the signal transduction antagonist SOCS3 can also explain why septic patients are neutropenic despite normal levels of G-CSF or are insensitive to G-CSF treatment. Similarly, this mechanism could also account for increased susceptibility of bacterial superinfection in patients after viral infections. On the bases of the findings of de Bruin et al, it will be clinically relevant to investigate whether patients with bacterial infection exhibiting neutropenia have high levels of IFN-γ and whether detection of high IFN-γ levels could be a negative prognostic factor in severe bacterial infection progressing to sepsis.
Although the clinical impact of this work remains to be seen, these observations have moved our understanding of how the hematopoietic system redirects lineage differentiation during infection a step forward and also open the possibility of targeting the IFN-γ pathway to restore neutrophil differentiation during bacterial infections.

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 Comment on Andersson et al, page 1555

High VWF, low ADAMTS13 puts women at risk

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In this issue of Blood, Andersson and colleagues reveal in a case-control study that high VWF and low ADAMTS13 plasma levels are each a risk factor for ischemic stroke and myocardial infarction, and that the combination of both results in a joint effect.1 At sites of vascular injury, platelet adhesion and aggregation on the exposed thrombogenic subendothelial matrix is crucial for normal hemostasis; however, under pathologic conditions it may lead to uncontrolled thrombotic events causing life-threatening disease states such as ischemic stroke and myocardial infarction.2 One major determinant of platelet adhesion to the injured vessel wall under conditions of elevated shear is the interaction between the platelet transmembrane receptor glycoprotein (GP) IIb and the multimeric plasma protein von Willebrand factor (VWF). VWF is synthesized by megakaryocytes and endothelial cells and stored in platelet α-granules and endothelial Weibel-Palade bodies from where it is released in response to stimulation. Released VWF is rapidly immobilized on the damaged vessel wall, which initiates platelet attachment via GPIb and provides a substrate for firm adhesion through integrin αIIbβ3 (GPIb/IIa), thereby starting the process of wound sealing by platelet aggregation and coagulation-dependent fibrin formation. Ultra-large VWF (> 20 million kDa) is the most thrombogenic form of VWF and is cleaved to smaller, less thrombogenic forms by the multidomain structured 185 kDa metalloprotease a disintegrin-like and metalloprotease with thrombospondin type I repeats-13 (ADAMTS13) in the plasma.3,4 In humans, qualitative or quantitative abnormalities of the VWF protein cause the VWF disease, an inherited common bleeding disorder, whereas lack of functional ADAMTS13 results in thrombotic thrombocytopenic purpura, which is characterized by the formation of thrombi in arterioles and capillaries.3,4 Studies in mice demonstrated that lack of VWF was highly protective in a model of ischemic stroke and improved the neurologic outcome,5,6 whereas ADAMTS13 deficiency aggravated the neurologic damage.6,7 Interestingly, these studies also revealed that alterations in the VWF-ADAMTS13 system not only affected thrombotic activity but also modulated immune cell recruitment to the affected brain territory, indicating that GPIb-VWF interactions contribute to inflammatory responses in this brain region by yet undefined mechanisms and lead to the concept of stroke being a “thrombo-inflammatory” disease.8

A number of clinical studies assessing the association between VWF or ADAMTS13 levels and the risk of cardiovascular diseases have produced partially contradictory results. Here, Andersson and colleagues report a case-control study in which they determined VWF and ADAMTS13 plasma levels in young women with a nonfatal first event of either ischemic stroke or myocardial infarction.9,10 The results of this study clearly show that either high VWF or low ADAMTS13 plasma levels—detected in the acute phase—represent risk factors for these diseases (see figure). Interestingly, high VWF levels had a greater impact on the risk to develop ischemic stroke or myocardial infarction than low ADAMTS13 levels but the reason is unknown. Another important finding of this study is that the combination of both high VWF and low ADAMTS13 plasma levels conferred a dramatically increased risk for the development of ischemic stroke (2- to 3-fold) and myocardial infarction (4- to 7-fold). This result strongly suggests that individuals with an unfavorable combination of expression levels of these 2 functionally linked proteins may be more prone to develop pathologic thrombotic and/or inflammatory events. Previously, it was reported in the RATIO case-control study that the intake of oral contraceptives by young women conferred an increased risk of ischemic stroke and myocardial infarction.9,10 In a second focus of the present study, Andersson et al made the interesting observation that the use of oral contraceptives considerably increased the risk of both myocardial infarction and ischemic stroke in individuals with high plasma VWF levels whereas it only moderately increased the risk of the latter disease in individuals with low ADAMTS13. How oral contraceptives increase the risk of thrombotic diseases and how this is linked to altered VWF-ADAMTS13 plasma levels is also unexplained. One reason could be...
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