Thrombopoiesis and Thrombopoietin: The Significance of "non-Tpo" Cytokines

To the Editor:

In the interesting review article "Thrombopoietin: The Primary Regulator of Platelet Production" by Kaushansky1 published in the July 15, 1995 issue of Blood, the author has ably summarized the already extensive new literature on the ligand for the mpl receptor, now commonly referred to as thrombopoietin or Tpo. Although the primary intent of the article was to review the rapidly emerging biology of this molecule, in his enthusiasm for showing the importance of the mpl ligand, Kaushansky has dismissed the importance of other cytokines that may contribute to platelet production. Therefore, the review leaves several misconceptions and false impressions for readers of Blood that we believe should be corrected regarding the biology of other cytokines, particularly interleukin-11 (IL-11).

In discussing the biology of three other cytokines, IL-6, leukemia inhibitory factor (LIF), and IL-11 under the heading of "The Would-Be Tpo's," Kaushansky essentially dismisses all of these molecules as irrelevant to megakaryocyte biology. The heading itself implies both that these molecules somehow have aspirations to be something that they are not and that the researchers who proposed that these molecules "function as thrombopoietins" were wrong (although there are no references to who actually made these proposals). However, as noted by Kaushansky, administration of IL-11, IL-6, or LIF to normal animals does result in significantly increased platelet production and platelet levels. Therefore, at some level, these molecules do "function as thrombopoietins." Furthermore, the mpl ligand itself has megakaryocyte colony-stimulating activity and animals receiving it have been observed to have three fold increases in the numbers of granulocyte macrophage progenitors.1 In addition, a recent report of the disruption of the NFE-2 transcription factor gene2 showed that, without this transcription factor, mice are extremely thrombocytopenic and yet surprisingly, they have normal levels of mpl ligand. Thus, it could be argued that technically, the mpl ligand does not meet all of the "commonly held assumptions" about Tpo in all situations. Does this mean that the mpl ligand is not the physiological regulator of platelet homeostasis? Certainly not; rather it means that some of the "commonly held assumptions" about "Tpo" were wrong. Similarly, that IL-11, IL-6, and LIF may not fulfill all of the criteria assumed for "Tpo" does not mean that these molecules are either unimportant or that they play no role in controlling platelet production. The use of "commonly held assumptions" to argue for or against mechanisms in biology is fallacious and circular, especially when selectively applied.

In the "Would-Be Tpo" section, Kaushansky also downplays the potential significance of the other cytokines by focusing largely on negative results. For example, we and others have shown many important effects of IL-11 on the growth and differentiation of stem3 and progenitor cells from very early in the megakaryocytic pathway, including the BFU-meg,4 all the way to and including promotion of megakaryocyte maturation, shifting ploidy to higher n values and increasing megakaryocyte size.5,6 This work is largely dismissed as unimportant in the "Would-Be Tpo's" section by ignoring it and by focusing on or putting a negative interpretation on other results. In Fig 4 of Kaushansky's review, the role of IL-11 is summarized by an arrow pointing at an "immature" megakaryocyte, thereby ignoring known effects of this cytokine on stem cells as well as early and late phases of megakaryocytogenesis. In contrast, the targets of "Tpo" are indicated to span all of megakaryocyte biology. The fact that the mpl deficient mice have sufficient levels of mature, functional, platelets (15% of normal)7 to allow apparently normal hemostasis indicates that other cytokines can replace all essential functions of Tpo. Clearly, there is significantly more redundancy and overlap among the functions of megakaryocytic growth factors than is illustrated in Fig 4.

An example of the negative focus with the other cytokines is the discussion of the modest effects of "very high doses" of IL-11 on the levels of circulating platelets in normal mice. These experiments were performed with human IL-11 in mice8 and we have never been overly concerned with just how high platelet counts could be driven. We would point out that platelet counts above 2 million per cubic mm have been reported for chimeric mice engrafted with bone marrow cells engineered to express IL-119 and, more recently, similar mice have been observed with platelet counts of 3 to 5 million (R. Hawley, S. Goldman, personal communication, March 1994). In addition, administration of IL-11 to nonhuman primates10 and non-myelosuppressed cancer patients has been reported to result in up to a four fold elevation in the levels of circulating platelets at much lower doses of IL-11 than used in the murine models. Most importantly, in preclinical models11,12 and patients,13,14 IL-11 has proven capable of significantly lessening the severity of platelet nadirs following various chemotherapy regimens. Although the purpose of the Kaushansky review was to focus on Tpo biology, the reader is left with the impression that IL-11 administration has minimal effects on megakaryocytogenesis and platelet production, a misconception that should be dispelled.

In evaluating the roles of the different cytokines in thrombopoiesis, Kaushansky points out that IL-6 levels in patients "do not vary inversely with platelet levels, the sine qua non for a physiologic regulator of platelet production." Interestingly, Cairo et al15 have recently reported that IL-11, which is generally undetectable in sera from normal patients is elevated in similar samples from thrombocytopenic bone marrow transplant or immune thrombocytopenic purpura patients. The activation of IL-11 expression in response to severe thrombocytopenia does not suggest to us that IL-11 is the physiological regulator of platelet homeostasis but rather that IL-11, along with other hematopoietic factors, plays an important role in responding to extreme insults to the hematopoietic system. Therefore, IL-11 may function as a factor whose production is upregulated during situations of extreme stress to the hematopoietic system to help restore hemostasis by stimulation of multiple phases of megakaryocytogenesis (directly or indirectly) and thrombopoiesis, as well as by activation of the expression of proteins important in coagulation including vWF and fibrinogen.16 This role is clearly different from the role of "daily regulator of platelet production" but is equally "physiological" and can be important, nonetheless.

Finally, the physiologic roles of these thrombopoietic cytokines may be very different from the effects observed when pharmacologic doses are administered in patients. From the clinical standpoint, the importance of a therapeutic is its relative efficacy versus possible toxicity. Our recently unblinded Phase II study of IL-11 in patients with chemotherapy-induced thrombocytopenia17 yielded very promising results which have led to the initiation of a Phase III study. This study and other ongoing controlled clinical trials will determine the level of effectiveness of IL-11 in treating thrombocytopenia.
REFERENCES


Response

In their letter taking issue with our recently published review on thrombopoietin, Turner et al from Genetics Institute, Inc, make several pointed comments. First, they state that by including interleukin-6 (IL-6), IL-11, and leukemia inhibitory factor (LIF) under a heading of "Would-be Thrombopoietins," the physiological relevance of these cytokines has been "dismissed." Although the choice of the terms in this heading could be debated, the review hardly "ignores" the literature pertaining to the physiology of these cytokines. Multiple references are devoted to the stimulatory role of IL-6, IL-11, and LIF in the thrombopoiesis of inflammation and paraneoplastic syndromes, and in various aspects of hematopoiesis. Moreover, it is clear from a brief consideration of the titles of several recent articles that many investigators felt that IL-6, IL-11, and LIF were candidate thrombopoietins (eg,2,3). But whether enough references to IL-6 and IL-11 exist in a review devoted to thrombopoietin, and whether previous investigators claimed that one or another cytokine was a candidate thrombopoietin are not the important issues. Rather, the physiology of thrombopoietin and hematopoietic cytokines in normal and accelerated thrombopoiesis and the potential role of these proteins to augment hematopoiesis in states of marrow failure will clearly occupy the interests of investigators and clinicians for many years to come. And these issues, not whether a single abstract indicates that IL-11 levels rise in the plasma of marrow transplant patients will be important long after these letters to the editor have been forgotten.

It was with this goal that the review on thrombopoietin was written. The report points out that the weight of available data indicates that thrombopoietin plays a critical role in platelet production. In the absence of thrombopoietin and in the absence of IL-6, IL-11, and LIF, megakaryocytes develop normally in vitro (ref 11 and V. Broudy et al, submitted for publication). Conversely, elimination of thrombopoietin significantly alters megakaryocyte maturation (and Zucker-Franklin and Kaushansky, submitted). Thus, although IL-6 and IL-11 could play a role to augment thrombopoiesis under certain conditions of accelerated platelet demand, or in genetically engineered mice (as stated in the review and ref 12), the current evidence suggests that they are dispensable. In contrast, megakaryocyte and platelet levels drop precipitously in the absence of thrombopoietin function.2 The data are very clear on this issue.

In closing, Turner et al pose a valid query, whether the physiologic roles of these cytokines may be very different from the effects observed when pharmacologic doses are administered to patients. I, too, add my voice to this question. Despite our best efforts at studying the physiology of hematopoietic growth factors, the pharmacologic effects of these same proteins continue to surprise us. The submitted abstract that Turner et al reference may show an important clinical effect on platelet recovery; in fact, I hope it does. Being a clinician who cares for such patients, I welcome any agent which can reduce the complications of
nyelosuppressive therapy. One could just as easily cite similar submitted abstracts attesting to the efficacy of thrombopoietin in thrombocytopenic patients. However, the review in the July 15, 1995 issue of *Blood* was not intended to discuss the relative clinical efficacy of thrombopoietin and IL-11, or the totality of megakaryopoiesis. Rather, the focus was on physiology of the primary regulator of megakaryocyte and platelet production, thrombopoietin. I hope that the review fulfilled this goal.

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REFERENCES


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cytokines [letter; comment]

KJ Turner, SJ Goldman, JA Kaye and SC Clark