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-6, 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 NF-E-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 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) 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 mice7 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-118 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 primates9 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 models10,11 and patients,12,13 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 physiological regulator of platelet production.” Interestingly, Cairo et al4 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.13 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 thrombocytopenia14 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.
Thrombocytopenia in c-mpl-deficient mice. Science 265: 1445, 1995
Takatsuki K: Synergistic effects of interleukin 3 and interleukin 11 responses are devoted to the stimulatory role of IL-6, IL-11, and LIF, megakaryocytes develop normally in vitro (ref 12, 1992). 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 suggested that they are dispensable. In contrast, megakaryocyte and platelet levels drop precipitously in the absence of thrombopoietin. Furthermore, 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 normal human subjects. Blood 84:276a, 1994 (abstr, suppl 1)

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. As a clinician who cares for such patients, I welcome any agent which can reduce the complications of...
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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

Thrombopoiesis and thrombopoietin: the significance of "non-Tpo" cytokines [letter; comment]

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