Thrombopoietin, Megakaryocytic Cytokines, and Reactive Versus Clonal Megakaryocytopoiesis: An Enigma Complex

To the Editor:

Megakaryocytopoiesis, which is a complex cellular developmental process that leads to platelet production, depends on both early and late-acting hematopoietic growth factors. The initial proliferative stages of this process are supported by megakaryocyte colony-stimulating factors. Further development is dependent on additional megakaryocytic cytokines. Once formed, committed megakaryocyte progenitors undergo final maturation in response to a lineage-specific cytokine, thrombopoietin (Tpo).1,2

We have read with great interest the excellent review by Kaushansky about Tpo and other regulators of platelet production that appeared in the July 15, 1995 issue of Blood.3 As Kaushansky states, “IL-6 is distinct from Tpo but that it may account for many cases of reactive thrombocytosis.” We would like to share our experience in this subject. We have recently reported two studies that showed that serum IL-6 concentrations increase in both reactive thrombocytosis associated with rheumatoid arthritis (RA) and secondary thrombocytosis due to iron-deficiency anemia.4 We have also shown that increments in serum IL-6 levels occur in patients with newly diagnosed autoimmune thrombocytopenic purpura (ITP), which suggests that this cytokine may promote megakaryocytopoiesis and therefore ineffective thrombocytopoiesis in ITP.5 The “would be Tpo,” IL-6, seems to be responsible for pathological megakaryocyte formation rather than physiologic megakaryocytopoiesis.

Several other megakaryocyte-related interleukins, including IL-1 and IL-4, should also be considered in megakaryocyte development, in addition to the major megakaryocytopoietic interleukins (IL-3, IL-6, and IL-11) on which the review focused.6 IL-1, which exists in two different molecular forms termed IL-1α and IL-1β, is a potent inducer of IL-6, and the combination of IL-1 and IL-6 can act as a megakaryocyte potentiator as well.6 IL-4 is a unique cytokine that may have multiple regulatory functions besides affecting the expression of other cytokines. IL-4 is one of the stimulators of IL-6, together with IL-1, and may increase IL-6 production.7 In contrast, it inhibits IL-6 synthesis and suppresses IL-6 production in vitro.8 IL-6 interacts with IL-4, which acts on an early stage of proliferation of megakaryocyte progenitors, to selectively enhance the growth of hematopoietic progenitor cells, including megakaryocytes.9 Conversely, IL-4 may also function directly as a negative regulator of megakaryocytopoiesis in vitro.10

Consequently, serum IL-1β concentrations, as well as IL-6, were found to be increased in the reactive thrombocytosis of the two different clinical circumstances and ITP in our three studies.5,11 IL-1α and IL-4 levels in ITP patients who had increased megakaryocytes in the bone marrow were not different from those of healthy control groups.11 IL-4, a dual regulatory factor in megakaryocytopoiesis, was also found to be increased in RA associated with thrombocytosis.12

The relation of IL-4 to inflammation and disease, together with diverse actions of this cytokine on megakaryocyte formation, interfere with the precise interpretation of increments of serum IL-4 levels in RA patients with reactive thrombocytosis in our study.7

On the other hand, the primary thrombocytosis (thrombocytopenia) associated with myeloproliferative disorders (MPD) is believed to be due to autonomous unregulated neoplastic platelet production. We found that megakaryocytic cytokines, including IL-1β, IL-6, IL-1α, and IL-4, were either suppressed or similar to normal subjects in patients with MPD and thrombocytopenia.3 Our observation supports the idea that thrombocytopenia associated with MPD is autonomous and independent of growth factors.

It is now evident that Tpo is the major regulator of platelet production, as Kaushansky did, and Tpo may also be operative in secondary thrombocytosis interacting with a family of cytokines. The thrombocytopenic response can be prolonged, amplified, and modulated in vivo by cytokine interactions. However, we agree that further experimental and clinical investigations are needed to determine the developing pattern in megakaryocytopoiesis that is one of the cell-cell interactions influenced in positive and negative ways by the release of various growth factors.

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REFERENCES

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