Thrombopoietin: Biology and Clinical Applications

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ABSTRACT

Thrombopoietin (also called e-Mpl ligand, megakaryocyte growth and development factor, megapoietin) has recently been purified and cloned. This molecule is indeed the long-sought-after hematopoietic factor that controls platelet production. Thrombopoietin levels increase within 24 h after the onset of thrombocytopenia and are inversely and exponentially proportional to the platelet count. Injection of thrombopoietin into animals stimulates the number, size and ploidy of bone marrow megakaryocytes and increases the platelet count up to ten-fold. Although human studies with several different forms of recombinant thrombopoietin have just begun, animal studies suggest a wide range of potential clinical applications. In animals, recombinant thrombopoietin reduced radiation- and chemotherapy-induced thrombocytopenia, enhanced platelet recovery after bone marrow transplantation and increased the number of megakaryocyte precursor cells in stem cell harvests. Active at very low concentrations, thrombopoietin appears to have few adverse effects in animals. At very high doses, reversible marrow fibrosis has occasionally been seen, but despite platelet counts up to ten times normal, there is no evidence that it increased the risk of thrombosis. There is little likelihood that thrombopoietin will stimulate tumor growth since receptors for thrombopoietin have not been detected on solid tumors. Therefore, thrombopoietin promises to be a specific and effective stimulator of platelet production and will soon join erythropoietin and G/GM-CSF in the clinical armamentarium. Although thrombocytopenia is uncommon in most chemotherapy protocols, ongoing clinical studies will determine the role of thrombopoietin in the prevention and treatment of thrombocytopenia in oncology patients. The Oncologist 1996;1:98-106

INTRODUCTION TO PLATELET BIOLOGY

The circulating blood platelet plays a crucial role in maintaining normal hemostasis [1]. It adheres to sites of tissue damage and recruits others to aggregate with it to form the "primary hemostatic plug." In addition, it serves as the surface upon which the coagulation factors are activated to produce a fibrin clot. In the absence of platelets, both of these functions are deficient and bleeding ensues. Although still subject to some debate, there is general agreement that hemostasis is normal at platelet counts above 50 × 10^9/l [2, 3], but is usually inadequate at platelet counts below 10 × 10^9/l [4]. The normal individual, however, maintains a platelet level many times greater than that required for adequate hemostasis.

It is the circulating platelet mass, not the platelet count, which is regulated by the body. Unless altered by disease, the platelet count in any one individual remains fixed [5], but among normal individuals in the population there is a wide range of values, from 150 × 10^9/l to 450 × 10^9/l [6-8]. This great difference in count is offset by the inverse relationship that exists between platelet volume and the platelet count [6-8] and has led to the calculation that platelet mass, like the hematocrit, is essentially constant in normal individuals [8, 9]. A practical demonstration of this principle is the effect of changes in the size of the spleen, which normally sequesters one third of the platelet mass [10], on the platelet count. With increasing splenomegaly, thrombocytopenia becomes progressively more severe, but the total body mass of platelets (circulating + splenic pools) remains constant [10].

How the body maintains this constant circulating platelet mass has been the subject of considerable investigation. The pluripotential stem cells in the bone marrow (Fig. 1) differentiate into precursor cells called colony-forming units-megakaryocyte (CFU-M). The CFU-M are initially mitotic cells but then stop cellular division (cytokinesis) while continuing to undergo DNA replication (endomitosis) to produce immature megakaryocytes that are polyploid and contain up to 64 times (128 N) the normal amount of DNA. The immature megakaryocytes then develop into larger, mature megakaryocytes that shed platelets into bone marrow sinusoids. In response to an increased demand for platelets,
as occurs in idiopathic thrombocytopenic purpura (ITP),
the number and size of megakaryocytes increase [11-13],
the average megakaryocyte ploidy increases (from 16N
to 32N) and platelet production rises up to a maximum
of 11-fold [11]. The hematopoietic factor regulating
this response has long been referred to as "thrombopoietin" [14].

THE PURIFICATION OF
THROMBOPOIETIN
(c-Mpl LIGAND)

After many decades of investigation, thrombopoietin
was finally purified by five independent groups in
1994 [15-21]. Two groups directly purified the molecule from large amounts of thrombocytopenic animal plasma [15-17], while the others used a novel approach based on the recent identification of the thrombopoietin receptor [22-25]. In 1990, a retroviral oncogene (v-mpl) in the murine myeloproliferative leukemia virus was described [22] that encoded the cytoplasmic portion of a membrane protein which had all the characteristics of a new hematopoietic receptor. When the full-length homolog (c-mpl) of this receptor was cloned [23], its mRNA was found to be present primarily in platelets and megakaryocytes and in a small percentage of CD34+ cells [24]. The identification of c-Mpl as the putative thrombopoietin receptor was further strengthened by the demonstration that the formation of CFU-M, but not CFU-GM or BFU-E, in bone marrow cultures was decreased when synthesis of the c-Mpl protein was inhibited by the addition of c-mpl antisense constructs [25]. Using the c-Mpl receptor, the protein that bound to it (c-Mpl ligand) was identified, purified, sequenced and cloned.

THE STRUCTURE OF THROMBOPOIETIN
(c-Mpl LIGAND)

The single gene for the human c-Mpl ligand is located on chromosome 3q26-27 [26-28] and produces a 353 amino acid precursor protein (Fig. 2) with a molecular weight of 36 kDa [18, 19, 27]. Following removal of the 21 amino acid signal peptide, the remaining 332 amino acids undergo glycosylation to produce a 60-70 kDa protein [19]. The first 153 amino acids of the mature protein are 23% homologous with human erythropoietin [28] and probably 50% homologous when conservative amino acid substitutions are taken into account. This region also contains four cysteine residues and is highly conserved among different species. Two arginine residues at 153-154 may serve as a site for cleavage of the molecule by dibasic proteases. Amino acids 154-332 comprise a novel sequence that contains six N-linked glycosylation sites [18, 28] and is less conserved among different species. Structure-function studies have demonstrated that while the first 153 amino acids of the c-Mpl ligand are all that

Figure 1. The differentiation and maturation of megakaryocytes. 1) The “commitment” of stem cells to the megakaryocyte differentiation pathway; 1) CFU-M stop mitoses and express platelet-specific features (as denoted by shading); 2) Megakaryocyte precursors undergo endomitosis; 3) Cytoplasmic maturation of megakaryocytes; 4) Shedding of platelets from megakaryocytes. Reprinted by permission of MIT Press [1].

Figure 2. The structure of human thrombopoietin. As described in the text, the signal peptide region (black), erythropoietin-like region (gray) and carbohydrate-rich region (white) are depicted. The numbers refer to the amino acid position. Conserved cysteine residues (arrows) are at positions 7, 29, 85 and 151. Glycosylation sites (arrowheads) are at positions 176, 185, 213, 254, 319 and 327.
are required for its thrombopoietic effect [18, 19] in vitro, this truncated molecule has a decreased circulatory half-life compared to the native protein [29]. Presumably, the glycosylated second half of the molecule confers stability and prolongs the circulatory half-life. Similar carbohydrate sequences regulate the stability of erythropoietin [30-32]. However, when the truncated, nonglycosylated c-Mpl ligand is coupled to polyethylene glycol (PEG), the modified c-Mpl ligand (PEG-thrombopoietin) has a normal circulatory half-life [29]. Currently, both the full-length, glycosylated molecule and the truncated, nonglycosylated, PEG-modified form are undergoing clinical trials.

**The In Vitro and In Vivo Properties of Thrombopoietin (c-Mpl Ligand)**

The c-Mpl ligand, also initially named megakaryocyte growth and development factor [19], megapoietin [15] and thrombopoietin [20], is indeed the long-sought-after regulator of platelet production. In vitro it stimulates both early megakaryocyte development such as CFU-M, as well as late megakaryocyte maturation (Fig. 3) such as the number, size and ploidy of megakaryocytes [15, 33, 34]. In culture, it can even stimulate megakaryocytes to produce intact platelets [35]. Except for some stimulation of BFU-E [36], its effect appears limited to megakaryocytes.

In vivo, after two days of treating rats with c-Mpl ligand, the ploidy and number of megakaryocytes increase and then after three to four days, a dose-dependent rise in the platelet count and platelet size begins [15]. In rhesus monkeys [37], bone marrow CFU-M increase up to seven-fold after three days and up to 11-fold after nine days of thrombopoietin treatment. Platelet counts in these same animals showed a dose-dependent increase that began on day 4 and rose rapidly to a maximum of eight-fold on day 12.

With the biological identification of the c-Mpl ligand and the c-Mpl receptor now clearly proven by these experiments, these molecules will hereafter be referred to simply as thrombopoietin and the thrombopoietin receptor, respectively.

**The Physiology of Thrombopoietin**

The primary site of thrombopoietin mRNA and protein synthesis is the liver [38, 39]. Lesser amounts are found in the kidney, brain and testes. Present data suggest that there is not a significant storage pool of thrombopoietin, but that thrombopoietin is synthesized and immediately released, like erythropoietin.

In response to an acute decline in the platelet mass, thrombopoietin levels rise half-maximally by eight hours and peak by 24 h [40]. With persistent thrombocytopenia, the steady-state thrombopoietin levels remain elevated and are increased exponentially and proportionally (Fig. 4) to the linear decrease in the platelet mass [41, 42]. An identical logarithmic relationship exists between erythropoietin levels and linear changes in the RBC mass [43]. Finally, upon transfusion of platelets into thrombocytopenic animals, the thrombopoietin levels return toward normal [41].

The almost one-hundred-fold rise in thrombopoietin concentration during thrombocytopenia is not due to changes in thrombopoietin mRNA production [38, 44]. Rather, platelets contain an avid thrombopoietin receptor that efficiently binds and removes thrombopoietin from the circulation [15, 38, 41]. As illustrated by Figure 5, thrombopoietin is released into the circulation at a constant rate. In the absence of platelets, there is little clearance of thrombopoietin by platelets, levels rise, bone marrow megakaryocytes are stimulated and platelet production increases. In
contrast, in the presence of platelets, thrombopoietin clearance increases, levels are low, megakaryocytes are not stimulated and basal platelet production ensues. Unlike the mechanism for red blood cells, there is no “sensor” of the platelet mass [45]; instead, as occurs in the regulation of neutrophils [46] and monocytes [47] where the regulated cells bind and clear their regulatory cytokine, the circulating platelet mass directly determines the circulating level of thrombopoietin.

There are several practical implications of this mechanism. First, there should be an “endogenous” rise in thrombopoietin levels which is inversely related to the degree of thrombocytopenia. Second, other cytokines or disorders may modify the constitutive hepatic production of thrombopoietin, analogous to the way interleukin 1 (IL-1) and infection reduce renal production of erythropoietin [48, 49]. Third, small molecules could be developed to decrease the platelet’s clearance of thrombopoietin and, in turn, stimulate platelet production. There is a suggestion that the thrombopoietic effect of low doses of vincristine may work in this fashion [50]. Finally, inherent, disease-related abnormalities in the platelet’s ability to clear thrombopoietin may alter thrombopoietin levels. For example, diminished clearance of thrombopoietin by abnormal platelets may account for the elevated platelet counts seen in myeloproliferative syndromes such as essential thrombocythemia.

**POTENTIAL CLINICAL USES OF THROMBOPOIETIN IN ONCOLOGY**

Thrombopoietin will soon join the clinical armamentarium of erythropoietin, G-CSF and GM-CSF, and allow the specific stimulation of platelet production just as the other growth factors already in clinical use can be used to stimulate RBC and neutrophil production. Human thrombopoietin studies in a wide range of areas have only recently been...
 started using both the full-length, glycosylated thrombopoietin and the truncated, PEG-thrombopoietin. None of these studies are sufficiently mature to have provided data for interpretation as of yet. However, recent animal studies with thrombopoietin, as well as the close parallels with clinical observations on the effects of G-CSF and erythropoietin, suggest potential clinical uses for thrombopoietin (Table 1).

Although significant (Grade 4) thrombocytopenia is uncommon in most solid tumor chemotherapy protocols, some such as MAID (mesna, adriamycin, ifosfamide, dacarbazine) and ICE (ifosfamide, carboplatin, etoposide) are associated with significant (~25%) thrombocytopenia, sometimes requiring transfusions and/or dose modifications. Mitomycin C, nitrosoureas and busulfan are also limited in their use by thrombocytopenia. The total national cost of treating such chemotherapy-induced thrombocytopenia in 1993 has been estimated as ranging from $146 million to $233 million [51]. Ulrich et al. [44] have recently shown that thrombopoietin given to mice after carboplatin chemotherapy reduced both the severity and the duration of thrombocytopenia, as well as minimized the decline in bone marrow megakaryocytes. Over the next several years, similar studies in humans can be expected to evaluate the ability of thrombopoietin to reduce the duration and possibly the severity of chemotherapy-associated thrombocytopenia.

However, administration of thrombopoietin should not be expected to play a significant role in the treatment of acute, symptomatic thrombocytopenia following chemotherapy. Platelet transfusions will usually be indicated in the acute setting since it will take four to five days for thrombopoietin to increase platelet production [37], about the average duration of such thrombocytopenias in any case [52].

The thrombocytopenia associated with the treatment of acute leukemia suggests another potential indication for thrombopoietin. There are no animal or human trials yet reported to address this issue, but thrombopoietin may decrease the duration of thrombocytopenia and possibly reduce the need for platelet transfusions.

Radiation or strontium 89 therapy commonly causes thrombocytopenia, but rarely is of enough severity to warrant transfusion. Administration of thrombopoietin to nonhuman primates [53] for 18 days following TBI produced higher nadir platelet counts and shortened thrombocytopenia from 40 to 19 days compared to control animals. Interestingly, administration of thrombopoietin from days 5-18 following TBI was much less effective. Thrombopoietin may therefore minimize the thrombocytopenia associated with TBI or aggressive radiation therapy in some patients.

While the use of peripheral progenitor cells has greatly reduced the duration of thrombocytopenia in autologous bone marrow transplantation, thrombocytopenia, often prolonged, is associated with allogeneic bone marrow transplantation. Using a murine autologous bone marrow transplant model, thrombopoietin has been shown to decrease the duration of thrombocytopenia post-transplant from four weeks to 10 days without affecting RBC or WBC recovery [54]. In humans, use of thrombopoietin in allogeneic transplantation might produce a similar shortening of the time to platelet engraftment, as well as some reduction in platelet transfusions. The small group of patients with very delayed platelet engraftment might be expected to benefit most from thrombopoietin.

This reviewer has little doubt that the many studies in humans that will be reported over the next several years will show that thrombopoietin will decrease the duration and, possibly, degree of thrombocytopenia after chemotherapy, irradiation and bone marrow transplantation. It may even allow chemotherapy protocols with significant dose-intensification. However, given the ability of platelet transfusions to prevent bleeding complications in most patients, the clinical endpoints of hemorrhage and survival will probably not show an advantage for thrombopoietin. Rather, the clinical utility of thrombopoietin in oncology will be determined by its impact on the following clinical endpoints: RBC and platelet transfusions, length of hospital stay, cost, maintenance of dose-intensity, infection risks or immune suppression (from exposure to platelet transfusions) and quality of life. The clinical impact of thrombopoietin will be markedly affected by whether the platelet “transfusion trigger” is set at $20 \times 10^9/l$ or $10 \times 10^9/l$ [4], as well as by the curative potential, dose-reduction scheme, frequency, intensity and the sequence of the chemotherapy used. This last point is of interest given the recent suggestion that thrombocytopenia was [55] ameliorated when paclitaxel was given prior to carboplatin chemotherapy, rather than after.

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**Other Potential Clinical Uses of Thrombopoietin**

Thrombopoietin may play an important role in the treatment of chronic thrombocytopenic states such as aplastic anemia, myelodysplastic syndromes, Gaucher’s Disease or HIV infection (Table 1). No studies are yet available but, by analogy with G-CSF in these disorders, some patients may...
show an improved platelet count and diminished transfusion requirements.

Thrombopoietin levels should be elevated and platelet production markedly increased in ITP. However, Ballem et al. [56] have suggested that some ITP patients may actually have reduced platelet production. A recent study [74] reported undetectable levels of thrombopoietin in patients with ITP. An interesting hypothesis is that such patients may have suboptimal thrombopoietin production and might benefit from administration of thrombopoietin. In contrast, the use of thrombopoietin in patients with thrombotic thrombocytopenic purpura/hemolytic uremic syndrome may be contraindicated. Increased platelet production might exacerbate clinical symptoms [57].

Thrombocytopenia is a major complication of cardiac surgery and is associated with increased mortality [58, 59]. The platelet count falls daily in patients on intra-aortic balloon counterpulsation and also drops after coronary artery bypass grafting, usually necessitating transfusion. Judicious use of thrombopoietin in these settings may minimize platelet transfusions and possibly improve outcomes. Similarly, preoperative administration of thrombopoietin to thrombocytopenic patients undergoing general surgical procedures may reduce bleeding complications.

Many hematopoietic growth factors increase the number of circulating peripheral blood progenitor cells and are used to enhance the harvest of these cells for bone marrow transplantation. Since some CD34+ cells express the thrombopoietin receptor [24], thrombopoietin may serve as an efficient means to increase the harvest of CD34+ cells. Alternatively, strategies might be developed to use thrombopoietin to increase the number of CFU-M harvested and thus shorten the time to platelet independence after transplantation. Indeed, treatment of donor mice with thrombopoietin prior to marrow harvesting accelerated the reconstitution of platelets in recipients after bone marrow transplantation [60].

Thrombopoietin may play a major role in transfusion medicine. Given its great effect on increasing platelet production, administration of thrombopoietin may provide a dramatic increase in the yield of platelet apheresis and allow daily donations. Furthermore, the addition of thrombopoietin to platelet units ex vivo may enhance their viability, minimize the "storage lesion" and provide a qualitatively better product for transfusion. Studies are currently under way to assess these possibilities. Finally, bioreactors may be developed to allow the continuous production of platelets in vitro.

**Potential Side Effects of Thrombopoietin**

On a molar basis, thrombopoietin is even more potent than erythropoietin. Therefore, the major clinical side effect to be expected will be thrombocytosis, especially in the less well-monitored outpatient setting (Table 2). Fortunately, the experience with "reactive thrombocytosis" suggests that platelet counts up to even 2000 x 10^9/l will be asymptomatic [1]. In mice chronically exposed to huge amounts of thrombopoietin, there was no evidence of ischemic damage to organs despite platelet counts five-fold above normal [54].

Some hematopoietic growth factors, like G-CSF, markedly enhance the function of the cells they stimulate. Early studies with thrombopoietin suggest that it stimulates the formation of platelets with only a subtle increase in platelet reactivity [61]. This increased reactivity is probably clinically irrelevant, but investigators need to be attentive to the possibility that thrombopoietin might increase the risk of thrombosis.

It has been suggested [62] that myelofibrosis might be due to an abnormal increase in megakaryocytes with release of platelet-derived growth factor or a similar substance. The marked stimulation of megakaryocytes by thrombopoietin might be expected to do the same. Recently, Yan et al. [54] described marked marrow fibrosis, osteosclerosis and splenomegaly in mice that had the thrombopoietin gene transfected into their bone marrow cells and thereby produced large amounts of thrombopoietin. When the excess thrombopoietin production was stopped [54], the fibrosis resolved. These complications may be unique to this animal model in which there is ectopic, locally very high thrombopoietin concentration within the bone marrow. In rhesus monkeys treated intravenously with thrombopoietin for 28 days, there was no fibrosis or splenomegaly despite an 8- to 10-fold increased platelet count [37, 54]. It is unlikely that such amounts or duration will be experienced in most clinical situations. Nevertheless, marrow fibrosis may need to be assessed during long-term administration of thrombopoietin.

Concern must be raised that thrombopoietin may stimulate endothelial cell growth or alter endothelial function and lead to an increase in veno-occlusive disease in the bone marrow transplant setting. Endothelial cells are reported to have receptors for thrombopoietin [25] and their response to thrombopoietin is currently being analyzed.

Possible interaction between thrombopoietin and other hematopoietic cytokines has recently been described [63]. The addition of some doses of G-CSF or GM-CSF to thrombopoietin dampened the expected platelet effect but not the WBC effect in mice following bone marrow transplantation. However, optimal ratios of G-CSF and thrombopoietin were found that permitted simultaneous accelerated recovery of both neutrophils and platelets. Whether this interaction will be seen in humans must await further studies.

**Table 2. Potential clinical risks of thrombopoietin administration**

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<td>Veno-occlusive disease</td>
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<tr>
<td>Interaction with other growth factors</td>
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Finally, the concern exists that thrombopoietin might stimulate the growth of solid tumors or leukemias. A wide range of nonhematopoietic solid tumors has been analyzed and none have receptors for thrombopoietin [64]. Thrombopoietin receptors were not increased in bone marrow cells of patients with acute lymphocytic leukemia, non-Hodgkin’s lymphoma or chronic myeloproliferative disorders (chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia), but were increased in the bone marrow cells in 26 of 51 patients with acute myeloid leukemia, and five of 11 patients with refractory anemia with excess blasts [65]. A similar concern was raised in initial work with G-CSF, and although many leukemia cells had G-CSF receptors, most were not stimulated to grow by G-CSF. It will therefore be important to assess leukemic blasts not only for the presence of the thrombopoietin receptor but also to determine whether its presence leads to a mitotic response.

**IS THROMBOPOIETIN THE ONLY RELEVANT THROMBOPOIETIC HORMONE?**

The data described above have clearly established thrombopoietin as the major physiological regulator of platelet production. Thrombopoietin accounts for all of the megakaryocyte “stimulatory activity” in thrombocytopenic plasma [41, 66]. Nevertheless, when the thrombopoietin receptor was “knocked out” in mice, megakaryocytes and platelets were produced at a level 15% of normal and hemostasis was adequate [67]. Other hematopoietic factors may therefore be responsible for this basal megakaryocyte and platelet production. IL-3, IL-6, IL-11 and stem cell factor have all been shown in vitro to enhance megakaryocyte growth [68, 69]. Recombinant forms of IL-3, IL-6 and IL-11 have been shown to stimulate platelet production in humans and reduce chemotherapy-associated thrombocytopenia [70-72]. None are lineage-specific and most have a broad spectrum of toxic side effects. The relatively greater thrombopoietic effect and apparent lack of toxicity seen in early animal studies suggest that thrombopoietin may be superior to these other factors.

**CONCLUSIONS**

With the discovery of thrombopoietin, the last of the lineage-specific cytokines has been identified and brought into the clinical arena. Thrombopoietin promises to be an exciting tool with which to understand megakaryocyte and platelet biology. Certainly, thrombopoietin will increase the platelet count in most clinical situations and is expected to have little associated toxicity. It may be highly effective in chronic thrombocytopenic disorders, cardiac surgery and transfusion medicine. Outside of allogeneic transplantation, its utility in oncology is unclear given the relative rarity of thrombocytopenic bleeding in most current protocols and the ready availability of platelet concentrates. The many studies that will appear over the next several years should help define the role of thrombopoietin in oncology. Practice guidelines such as those recently promulgated by the American Society of Clinical Oncology for G-CSF and GM-CSF [73] will be vital in assuring the rational use of thrombopoietin.

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