Chronic Idiopathic Thrombocytopenic Purpura: Mechanisms of Pathogenesis

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Key Words. Thrombocytopenia • Platelets • ITP • Thrombopoietin

ABSTRACT

The mechanism of idiopathic (autoimmune) thrombocytopenic purpura (ITP) has historically been attributed to platelet autoantibody production and the resultant platelet destruction. More recent evidence suggests a multifactorial pathogenesis. A complex picture of the immune processes involved in autoimmunity has emerged over the last decade with the identification and characterization of immunoregulatory elements (receptors, cytokines, and other signaling molecules) and cell trafficking patterns. An understanding of the interplay of cellular and humoral immune responses in the breakdown of self-tolerance has brought to light unrecognized mechanisms of the autoimmune destruction of platelets in ITP and potential targets for future therapeutic advances. The failure of the bone marrow to maximally increase platelet production also appears to play an important role in the thrombocytopenia of ITP. Treatment strategies targeting the thrombopoietin receptor to increase platelet production are a promising new approach to the management of ITP. The Oncologist 2009;14:12–21

INTRODUCTION

Idiopathic (or autoimmune) thrombocytopenic purpura (ITP) is an acquired disorder characterized by mild to severe thrombocytopenia, a relatively normal appearing bone marrow, and mucocutaneous bleeding. Characteristically, there is a rapid increase in the platelet count following treatment with corticosteroids or high-dose i.v. immunoglobulins. Chronic ITP, more common in adults, persists for at least 6 months and occurs in the absence of other abnormalities [1]. The triggering event for ITP is unknown [2, 3], but continued research is providing new insights into the underlying immunopathogenic processes as well as the cellular and molecular mechanisms involved in megakaryocytopenesis and platelet turnover.

Although historically ITP-associated thrombocytopenia was attributed solely to increased rates of destruction of antibody-coated platelets, it has become evident that suboptimal platelet production also plays a role [4–6]. This review...
examines the mechanisms, and their elements, underlying the pathogenesis and cellular kinetics of chronic ITP.

**AUTOIMMUNITY IN CHRONIC ITP**

In the early 1950s, Dr. William Harrington and several colleagues injected themselves with blood from patients with chronic ITP and within hours developed severe thrombocytopenia that persisted for several days [7, 8]. A factor in the globulin fraction of the blood was later identified as an important mediator of this effect. We now know that both humoral and cellular immunity are involved in the destruction of platelets in chronic ITP, and there is evidence that impaired T-cell expansion underlies the autoimmune response [9]. Indeed, a complex interplay involving components of multiple aspects of the immune system has been identified (Table 1).

**Autoreactive B Lymphocytes Secrete Antiplatelet Antibodies**

The most commonly occurring autoantibodies (~75%) in patients with ITP are directed against the platelet surface glycoprotein (gp) complexes gpIIb–IIIa and gpIIb–IX [10]. Antibodies against other glycoproteins (Ia–IIa, IV, and V) have been identified, and multiple platelet antigen specificities can be found in most patients [11–13].

Although antibodies are primarily of the IgG subtype, IgM and IgA may be found [13]. Platelets are targeted by the attachment of autoantibodies to their surface gp antigens, bound to Fcγ receptors expressed on tissue macrophages of the reticuloendothelial system and cleared from the circulation. Gamma camera imaging of ITP patients injected with 111In-labeled autologous platelets revealed that uptake occurs primarily in the spleen and liver [14]. Complement-induced lysis following antibody binding may also play a role [15]. After platelet internalization and degradation, macrophages express platelet epitopes on their surface and secrete cytokines that stimulate initiating CD4+ T-cell clones and clones with additional specificities [1, 16]. Unique to patients with ITP, autoreactive CD4+ T cells recognize several distinct epitopes on gpIIb–IIIa, leading to autoimmune response expansion and accelerated platelet destruction. The trigger for the initiating autoantibody response is unknown, although autoreactive T helper (Th) cells that interact with antibody-producing B cells are required [3].

Platelet-associated autoantibodies are detected in 50%–70% of patients with ITP [17–19], emphasizing the limitations of the currently available assays and/or suggesting that other or additional mechanisms are involved. A quantitative assay for nonspecific platelet-associated IgG had a positive predictive value of only 46% in patients with ITP and it could be detected in disease states other than ITP, including hematologic malignancy and infection [20]. Assays for antibodies targeting gpIIb–IIIa, gpIIb–IX, and gpIIa–IIIa may be more specific [17, 18, 21], but have limited sensitivity, and the diagnosis remains dependent on clinical presentation for the most part.

**Dysfunctional Cellular Immunity: The Role of Autoreactive T Cells**

Accumulating evidence indicates that CD4+ Th cells orchestrate the autoreactive B-cell response. B cells produce antibodies directed at normal platelet antigens in response to signaling from CD4+ Th cells [3]. CD4+ T cells autoreactive to platelet gpIIb–IIIa have been identified in patients with ITP. The trigger for T-cell dysregulation in ITP is unclear.

The native form of gpIIb–IIIa does not normally elicit a T-cell response; however, autoantibodies against gpIIb–IIIa are detected in patients with ITP, as are circulating memory B cells capable of producing autoantibodies [3]. Autoreactive T cells may be found in healthy individuals, but appear to be activated only in patients with autoimmune disease. This phenomenon could be explained by a cryptic epitope model in which self-antigens normally hidden from the immune system are presented at an increased concentration. In ITP patients, epitopes within gpIIb and gpIIIa molecules could in this way elicit a response.

The cytokine profile secreted by CD4+ cells in patients with ITP is consistent with Th-cell activation. A predominantly Th1 (proinflammatory) response is seen in ITP [22], a pattern seen in most organ-specific autoimmune diseases. An increased Th1–Th2 ratio has been observed in patients with active ITP [23], and an increase in interferon-γ and interleukin-2 receptor-β gene expression in patients with ITP has been detected [24]. Andersson et al. [25] found elevated levels of transforming growth factor β1, a potent immuno-

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**Table 1. Mechanisms underlying idiopathic thrombocytopenic purpura**

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<th>Mechanism</th>
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<td>Autoimmune mechanisms</td>
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suppressive cytokine, in patients with ITP in remission versus controls and patients with active disease.

**T Cell–Mediated Cytotoxicity**

Cytotoxic lymphocytes appear to be abnormally activated by autoreactive lymphocyte clones. CD3\(^+\) lymphocytes from patients with ITP show increased expression of cytotoxic genes such as tumor necrosis factor \(\alpha\), perforin, and granzyme A and granzyme B [24, 26]. Platelets from patients with active ITP displayed in vitro lysis when incubated with CD3\(^+\)CD8\(^+\) T effector cells but not with CD3\(^-\)CD16\(^+\)CD56\(^+\) natural killer (NK) cells. Killer cell immunoglobulin like receptor (KIR) genes showed increased expression, and CD3\(^+\) lymphocytes expressing KIRs were greater in number in ITP patients in remission than in patients with active ITP or normal controls [27]. The KIR family of genes downregulate cytotoxic T-lymphocyte and NK cell responses, preventing lysis of target cells. Megakaryocytes may also be damaged in ITP by autologous CD8\(^+\) T cells [28]. These findings suggest that cytotoxic T cells play a part in at least some patients with ITP, and downregulation of the auto-T-cell response is a potentially effective therapeutic strategy.

**NK Cell Activity**

An increase in the number of NK cells and expansion of the CD56\(^+\)CD3\(^-\) NK cell and CD56\(^+\)CD3\(^+\) cytotoxic T-cell subsets has been reported in patients with active ITP [29]. Patients with ITP requiring therapy (including a subgroup refractory to standard therapy) were compared with patients with stable disease and healthy controls. CD56\(^+\)CD3\(^-\) NK cells were substantially greater in number in patients with therapy-dependent ITP and in those with refractory disease versus patients with stable disease or controls. A high expression of major histocompatibility complex class II molecules was also observed in those patients refractory to standard therapy, suggesting in vivo activation. Although still speculative, these findings imply that the pathogenesis of ITP may include NK cells destroying the IgG-coated targets.

**MEGAKARYOPOIESIS AND THROMBOPOIESIS**

Platelet production, or thrombopoiesis, occurs in the bone marrow where committed stem cells differentiate into megakaryocytes. Megakaryocyte progenitors ultimately differentiate into mature megakaryocytes and release platelets into the bone marrow sinusoids. A stable platelet count occurs only when platelet production equals platelet consumption and destruction. In ITP, the increased demand for platelets, triggered by autoimmune-mediated platelet destruction, appears to result in an increased megakaryocyte mass with more and larger megakaryocytes and an increased mean ploidy [30]. However, there is evidence that platelet production is suboptimal in many patients with ITP.

**Platelet Kinetics in ITP**

Harker and Finch first described methodology for labeling platelets with radioactive \(^51\)Cr to measure platelet disappearance rates and, by implication, production (or “turnover”) [31]. By this method, at a stable platelet count:

\[
\text{turnover} = \frac{\text{platelet count} \times 10^9 \text{ per liter} \times 90\%}{\text{platelet survival (days)} \times \text{platelet recovery (\%)}},
\]

whereby platelet turnover (per \(\mu\)L per day) is calculated from the peripheral platelet count corrected for splenic sequestration, or “recovery,” by 90% based on studies in otherwise normal splenectomized individuals. Recovery in individual subjects is calculated from platelet activity (per ml) extrapolated to time zero, multiplied by the estimated blood volume and divided by the labeled platelet activity injected [31]. This calculation gives a fairly accurate measurement of effective platelet production, that is, the number of platelets that are released into the circulation by the bone marrow [6].

By these techniques, a shorter platelet life span (i.e., higher platelet turnover rate) is consistently seen in ITP patients compared with the 8- to 10-day platelet survival duration in healthy controls [4, 31–34]. Although early studies using allogeneic donor platelets suggested an extremely short platelet survival time, later studies using autologous platelets showed a shorter platelet survival time, but on the order of days as opposed to hours. Calculation of platelet turnover using longer platelet survival times results in destruction rates not as marked as previously thought and production rates that are modestly increased, if at all [35].

Ballem and colleagues compared \(^51\)Cr- or \(^111\)In-labeled autologous and homologous (normal donor) platelet survival in 13 patients with chronic ITP, showing that the survival duration of homologous platelets was significantly shorter than that of autologous platelets [32]. These findings suggest that platelets circulating in patients with ITP are relatively “protected” once leaving the bone marrow, compared with donor platelets from normal volunteers, and suggest that ineffective platelet production may be a significant factor in the pathogenesis of ITP. Some surface antigens are coexpressed on platelets, megakaryocytes, and megakaryocyte precursors (e.g., gpIIb–IIa and gpIb–IX) and recognized by autoantibodies, and may lead to impaired megakaryopoiesis [10, 19, 36], maturation, and platelet release. Newly formed platelets may be vulnerable to intramedullary reticuloendothelial removal, decreasing the numbers released into the circulation.
Our group measured survival of autologous $^{51}$Cr- and/or $^{111}$In-labeled platelets from 19 patients pre- and post-treatment with prednisone or splenectomy to determine how kinetics changed with increased platelet counts [6]. Whereas prednisone improved platelet counts by a mean factor of three, platelet survival was unchanged; therefore, effective platelet production had to have increased. Although this does not differentiate increased platelet production by the megakaryocytes from increased release of platelets by the bone marrow, this finding is consistent with the observation by Li and coworkers that abnormalities of megakaryocytopenesis observed in coculture of autologous bone marrow mononuclear cells and CD8\(^+\) T cells from patients with chronic ITP can be corrected by the addition of dexamethasone [28]. Following successful splenectomy, platelet survival improved, sometimes to normal, while platelet production appeared to remain unchanged.

Increased apoptosis or other forms of programmed cell death may play a role in the ineffective thrombopoiesis in the bone marrow of patients with ITP. An ultrastructural analysis of megakaryocytes of patients with ITP showed that 80% of mature megakaryocytes had features of apoptosis and para-apoptosis, suggesting that the low platelet production rate in ITP may be a result of greater apoptosis of platelet-producing megakaryocytes [37].

**Autoantibodies Suppress Megakaryopoiesis**

Chang and colleagues [38] showed that plasma from patients with ITP containing autoantibodies against gp1b and gpIIb–IIIa significantly suppressed megakaryopoiesis in vitro. They proposed that platelet autoantibodies may affect megakaryocyte maturation or survival, leading to decreased platelet production. McMillan et al. [18] studied the effects of plasma from 18 patients with chronic ITP on megakaryocyte production of CD34\(^+\) cell cultures from healthy volunteers. Cells were cultured in a medium containing pegylated recombinant human megakaryocyte growth and development factor (PEG-rhMGDF) and 10% plasma from either the ITP patients or healthy volunteers. In vitro megakaryocyte production was significantly lower when plasma from 12 of the 18 ITP patients containing either anti-gpIIb–IIIa antibodies, anti-gp1b–1X antibodies, or both was added to the medium.

**Thrombopoietin and ITP**

Thrombopoietin (TPO) is a lineage-specific cytokine and the major cytokine regulating platelet production in the body (Fig. 1). TPO, also referred to as cellular myeloproliferative leukemia proto-oncogene (c-Mpl) ligand and MGDF, is a 332-amino acid glycoprotein produced primarily in the liver, with smaller amounts produced in the kidney and bone marrow. It exerts biological effects on hematopoietic stem cells as well as megakaryocytes [39–41]. TPO is involved in nearly every step of megakaryocyte development, supporting cell survival and cell cycling and modulating apoptosis and cell cycle regulators [41]. In vitro, only the receptor-binding region of TPO is required for thrombopoietic activity [42, 43].

Binding of TPO to its receptor, c-Mpl, on hematopoietic stem cells and bone marrow megakaryocytes sets in motion a cascade of molecular signaling events that culminate in platelet production [40, 41] (Fig. 2). Intracellular Janus ki-
nase 2 is activated by binding of TPO to its receptor on megakaryocytes and their precursors leading to phosphorylation of signal transducer and activator of transcription, phosphatidylinositol 3\(^\prime\) kinase, and two mitogen-activated protein kinases. This results in induction of the transcription factor HoxB4 and translocation of the transcription factor HoxA9 from the cytoplasm to the nucleus, leading to hematopoietic stem cell expansion and proliferation and polyploidization of megakaryocytes by extracellular signal–related kinase (ERK)1 and ERK2.

TPO also affects mature platelets, reducing the level of agonists such as adenosine diphosphate, collagen, or thrombin needed to induce aggregation [44, 45]. TPO has been shown to enhance platelet adhesion in vitro in parallel-plate perfusion chamber assays [46].

Kuter et al. [47] have shown that, like megakaryocytes, platelets bear high-affinity TPO receptors (c-Mpl) that bind and internalize the hormone–receptor complex. Circulating platelet levels could therefore be mediated by an autoregulatory feedback loop. In thrombocytopenia, less TPO is bound to platelets and circulating levels increase, allowing binding to c-Mpl on megakaryocytes and hematopoietic stem cells, stimulating megakaryocyte development and platelet production [48]. The free TPO level decreases as the platelet count rises, and megakaryocytes are exposed to less TPO. Exceptions to this inverse relationship have been described. In patients with reactive thrombocytosis, TPO levels have been shown to be higher than expected [49]. Serum TPO levels in patients with ITP are much lower than in patients with amegakaryocytic thrombocytopenia [39], suggesting that the feedback mechanism between platelet count and TPO level is dysregulated in disease states such as ITP and reactive thrombocytosis (Fig. 3).

TPO levels have been repeatedly found to be within the normal range or only slightly elevated in patients with ITP [40, 50–53]. Under normal physiologic conditions, the megakaryocyte mass remains constant, but not the platelet count. The megakaryocyte mass, however, is increased in ITP [30]. Aledort et al. [52] found no relationship between TPO levels and platelet counts in patients with ITP. Levels of TPO could be lower than expected in ITP because of binding to c-Mpl on the increased megakaryocyte mass with subsequent internalization and degradation or secondary to TPO bound to platelets targeted for destruction.

**EMERGING THERAPIES TARGET PLATELET PRODUCTION**

The currently available treatment for ITP targets the autoimmune response and platelet destruction [1]. Various treatment options, such as corticosteroids, androgens, cytotoxic chemotherapy, rituximab, immunosuppressive agents, and immunoglobulin preparations, are directed against different steps and phases of the immune response (Table 2). Therapies targeting dysregulated T or B lymphocytes, including etanercept, anti-CD40 ligand, and mycophenolate mofetil, have shown activity in initial studies in patients with refractory ITP [54–56]. Decreased platelet production and TPO levels within the normal range despite
thrombocytopenia in patients with ITP suggest an opportunity to stimulate platelet production as a treatment approach [52, 57]. Several candidate molecules have been investigated including recombinant TPO preparations and TPO receptor agonists [58–60].

Two recombinant TPO preparations have been evaluated in the clinic—recombinant human (rh)TPO (Pharma- cia, Peapack, NJ) and PEG-rhMGDF (Amgen, Inc., Thousand Oaks, CA). Although they were active in raising the platelet count in ITP, the development of antibodies crossreactive with native TPO in a few normal individuals resulted in prolonged pancytopenia, limiting the usefulness of this class of drugs [61–63]. Newer TPO receptor agonists have no sequence homology with the native molecule and are not expected to provoke crossreactive antibodies. Results from recent trials with these agents provide in vivo evidence that boosting platelet production is an effective therapeutic strategy [59, 60, 64, 65]. Four TPO receptor agonists are currently being evaluated in patients with ITP—romiplostim (Amgen, Thousand Oaks, CA), eltrombopag or SB-497115 (GlaxoSmithKline, Collegeville, PA), AKR-501 (MGI Pharma, Bloomington, MN), and LGD–4665 (Ligand Pharmaceuticals, San Diego, CA).

Romiplostim consists of a novel compound, a “pepti- body,” consisting of two identical c-Mpl receptor-targeting peptides linked with an Fc carrier domain to increase the plasma half-life. Phase II trials in patients with ITP have shown that romiplostim is well tolerated and is associated with increased platelet production, with the target platelet range achieved in 63% (10 of 16) of patients treated with 1/2g/kg or 3/2g/kg of romiplostim [66]. Results of two randomized, placebo-controlled, double-blind phase III trials conducted in both splenectomized and nonsplenectomized patients demonstrated significantly higher response rates with romiplostim than with placebo. In both trials, romiplostim-treated patients had a significant decrease in rescue medication use while on study, and most were able to decrease or discontinue concurrent ITP therapy [67, 68].

Although most studies report an acceptable tolerability and safety profile, a treatment-related increase in bone marrow reticulin deposition has been reported [69, 70].

<table>
<thead>
<tr>
<th>Table 2. Idiopathic thrombocytopenic purpura treatment options and their mechanisms of action</th>
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<tr>
<td><strong>Mechanism</strong></td>
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<tr>
<td>Interfere with clearance of antibody-coated platelets</td>
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<tr>
<td>Clear antibody from circulation</td>
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<tr>
<td>Nonspecific T-cell immunosuppression</td>
</tr>
<tr>
<td>Interfere with B- or T-cell participation in antibody synthesis</td>
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<tr>
<td>Increase platelet supply</td>
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<td>Increase platelet production</td>
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*Transient benefit.

Abbreviations: PEG-rhMGDF, pegylated recombinant human megakaryocyte growth and development factor; rhTPO, recombinant human thrombopoietin.

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ITP, 59% of the patients receiving eltrombopag achieved a
cebo-controlled phase III trial of 114 patients with chronic
patients had reached this endpoint [60]. In a subsequent pla-
50,000/\mu\text{L} or 75 mg of eltrombopag achieved a platelet count
significantly higher proportion of patients receiving either 50 mg
alyzed eltrombopag in 118 adults with chronic ITP. A signif-
crease in platelet count was observed following sin-
volunteers in an early trial of AKR-501 [65]. Similarly, a sig-
crease in platelet count was observed following sin-
Abbreviations: AMT, amegakaryocytic thrombocytopenia; ITP, idiopathic thrombocytopenic purpura; TPO, thrombopoietin.

From Mukai HY, Kojima H, Todokoro K et al. Serum thrombopoietin (TPO) levels in patients with amegakaryocytic thrombocytopenia are much higher than those with immune thrombocytopenic purpura. Thromb Haemost 1996;76:675–678, with permission.


gabled doses of LGD-4665 in healthy male

50,000/\mu\text{L}, compared with those receiving placebo (p < .001), and by day 15, >80% of these eltrombopag-treated patients had reached this endpoint [60]. In a subsequent placebo-controlled phase III trial of 114 patients with chronic ITP, 59% of the patients receiving eltrombopag achieved a platelet count of ≥50,000/\mu\text{L}, compared with 16% of the patients receiving placebo, with a significantly lower incidence of bleeding reported in eltrombopag-treated patients (p = .029) [72]. The long-term safety of eltrombopag is being evaluated in an ongoing, open-label extension trial (Eltrombopag extended dosing study, EXTEND) [73]. Across all trials, headache was the most frequently observed adverse event in both the eltrombopag and placebo groups (placebo, 6%–11%; eltrombopag, 50 mg, 3%–20%), but overall tolerability was good, with most reported adverse events being mild in severity [60, 72–74]. Grade 4 elevations of hepatobiliary laboratory values were reported in one patient during eltrombopag therapy in clinical trials [60, 75]. Therefore, liver laboratory monitoring is recommended during treatment. An additional concern has been the observation of cataracts in young rats. Although cataract development and progression has been reported in eltrombopag-treated patients, there appears to be no excess risk for cataracts associated with eltrom-

Figure 3. Serum TPO levels (light bars) and platelet counts (dark bars) are represented in healthy volunteers, patients with ITP, and patients with AMT. Compared with healthy volunteers, serum TPO levels are markedly elevated in AMT patients. TPO levels in ITP patients are only slightly higher despite similar lower platelet counts.


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The author acknowledges the valuable editorial assistance of The Phillips Group in the preparation of the manuscript.

Financial and editorial support for this research was provided by GlaxoSmithKline, Collegeville, PA.

The author takes full responsibility for the content of the paper and would like to thank the Phillips Group Oncology Communications Company and Donna Capozzi, Pharm.D., supported by GlaxoSmithKline, for their assistance in organizing the published literature, collating author comments, and preparing the manuscript for submission.
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