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Piecing Together the Humoral and Cellular Mechanisms of Immune Thrombocytopenia

Lisa J. Toltl, Ph.D.[1], **Ishac Nazi, Ph.D.**[2], **Reza Jafari, M.L.T., M.L.S. (ASCP)**[2], and **Donald M. Arnold, M.D.C.M., M.Sc.**[1,3]

[1]Department of Medicine, McMaster University

[2]Department of Biochemistry and Biomedical Sciences, McMaster University

[3]Canadian Blood Services, Hamilton, Ontario, Canada

Abstract

The precise mechanisms leading to platelet-targeted autoimmunity in immune thrombocytopenia (ITP) are not known. Cellular checkpoints normally regulate immunological self-reactivity during the development of B and T cells through cell deletion, receptor editing, induction of anergy, and extrinsic cellular suppression. When these checkpoints fail, tolerance to self-antigens may be lost. In this review, we summarize the various immune mechanisms contributing to the development of ITP and relate them back to the checkpoint model of autoimmunity. These mechanisms, including increased levels of lymphocyte growth factors, resistance to death signals, and loss of T-regulatory function, result in an environment permissive to the development of platelet-reactive B and T cells. The mechanisms that lead to thrombocytopenia once tolerance for platelet antigens is lost are examined, including complement-dependent and apoptotic pathways. An improved understanding of ITP pathogenesis will ultimately guide the development of better therapies.

Keywords

Immune thrombocytopenia; self-tolerance; platelets; megakaryocytes; autoantibody

Primary immune thrombocytopenia (ITP) is an autoimmune disorder characterized by platelet autoantibodies, low platelet counts, and an increased risk of bleeding. ITP is a clinically and pathologically heterogeneous syndrome, implying that its physical signs and symptoms as well as responses to treatments are variable. Furthermore, the results of immunological tests including platelet autoantibodies are inconsistent across patients.[1,2] This diversity suggests that there might be multiple underlying mechanisms and supports the notion that ITP is an overarching designation that includes subtypes of patients with different immune causes of thrombocytopenia and different treatment requirements.[3]

Loss of self-tolerance for platelet autoantigens is fundamental to the pathogenesis of ITP. Cellular safeguards normally regulate self-reactive receptors during Band T-cell

Address for correspondence and reprint requests: Donald M. Arnold, M.D.C.M., M.Sc., Department of Medicine, McMaster University, 1280 Main Street West, HSC 3V50, Hamilton, ON L8S 4K1 Canada (arnold@mcmaster.ca).

differentiation; however, when these regulatory mechanisms fail, tolerance to self-antigens is lost.[4] In ITP the end result is an antibody-mediated attack on platelets and megakaryocytes causing severe thrombocytopenia. Many aspects of immune dysregulation in ITP have been investigated, but the findings often seem disconnected. This review attempts to piece together current knowledge of ITP immune pathogenesis relating it to an established model of autoimmunity. The first part of this review summarizes the immunological failures that may contribute to the loss of tolerance for host platelet antigens. The second part focuses on the mechanisms of thrombocytopenia as they affect both platelets and megakaryocytes.

LOSS OF SELF-TOLERANCE IN ITP

The human immune system is designed to detect and neutralize almost any invading pathogen, yet at the same time recognize and “tolerate” self-antigens. During B-cell differentiation in the bone marrow and T-cell differentiation in the thymus, immune effector cells are exposed to innumerable antigenic targets creating a vast repertoire of B- and T-cell receptors. In the process, some receptors will inadvertently recognize self antigens, including platelet glycoproteins in the case of ITP, and the cells bearing those receptors will become autoreactive. Several regulatory strategies prevent the propagation of autoreactive cells including cell deletion, receptor editing, induction of anergy, and extrinsic cellular suppression.[4] Failure at any of these steps may lead to the development of ITP (Table 1).

Cell Deletion

In the bone marrow, immunoglobulin (Ig) chain gene rearrangements construct the diversity of B-cell receptors. During differentiation, B cells with immunoglobulin G (IgG) molecules that bind strongly to marrow stromal cells (an indicator of self-reactivity) are destroyed.[5] This process of clonal deletion is facilitated by the depletion of growth factors such as B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) and increased expression of Bcl-2 interacting mediator of cell death. BAFF plays a crucial role in B-cell development, survival, and Ig production.[6] Excess BAFF protects self-reactive B cells from anergy[7] and has been documented in humans with systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome.[8–10] A study of 53 patients with chronic ITP found that BAFF levels were elevated in untreated patients with active disease ($n = 26$) and reduced following immunosuppressive treatment.[11] Other studies have supported the association between ITP and high levels of BAFF.[12–14] Similarly, levels of APRIL, a ligand that promotes B-cell maturation and survival, were found to be higher in patients with active ITP compared with patients in remission following corticosteroids or splenectomy.[15]

T cells with self-reactivity are negatively regulated by complex processes. T cells that react with self-peptides coexpressed with major histocompatibility complex I molecules are typically destroyed in the thymus.[16] Deletion of self-reactive T cells requires cellular proteins such as the tyrosine kinase ZAP70,[17] growth factor receptor-bound protein 2 (GRB2),[18] misshapen Nck interacting kinase-related kinase (MINK),[19] and proapoptotic signaling pathways. Altered expression of genes involved in apoptosis signaling, including Fas, interferon-gamma (IFN-γ), and interleukin-2 receptor β (IL2RB), Bcl-2-associated X

protein (Bax), caspase 8 and A20[20,21] have been demonstrated in patients with active ITP, suggesting that autoreactive T cells may be resistant to apoptosis.

The pathogenesis of ITP may also involve dys-regulated expansion of specific T-cell subsets, identified by their cytokine profiles. $CD4^+$ T helper (Th) cells and $CD8^+$ cytotoxic T cells can be categorized as type 1 (producing IFN-γ, interleukin-2 [IL-2], tumor necrosis factor-β [TNF-β]) and type 2 (producing IL-4, IL-5, IL-6, IL-10, IL-13).[22] Th1 cytokines tend to promote a proinflammatory response to facilitate macrophage activation, proliferation of cytotoxic T cells and production of opsonizing antibodies.[23,24] Th2 responses facilitate B-cell activation and proliferation and promotes antibody production.[24] The production of cytokines from both Th1 and Th2 subsets has been termed a Th0 response.[25] The balance of Th1 and Th2 subsets regulates the immune response under normal conditions, and this balance is skewed in many auto-immune diseases.[26,27] Cytokine profiles in ITP patients tend to show Th0/Th1 polarization,[28,29] with increased Th1/Th2 ratios in untreated patients.[30] Levels of the Th1 chemokine CXCL10 have been shown to be higher in patients with active ITP compared with patients in remission,[31] further suggesting a type 1-mediated response and an association with disease severity. Th17 cells, characterized by the production of the proinflammatory cytokine IL-17, may also be overrepresented in ITP[32,33] and may correlate with the levels of Th1 cells.[32]

Receptor Editing

Self-reactive B cells, which escape destruction in the bone marrow, are induced to continue editing their receptor so that the chances of reactivity with self-antigens is diminished. The normal antibody repertoire shows restriction of V, D, and J gene recombinations[34] and somatic mutations in the variable regions of the heavy (VH) and the light (VL) chain lead to diversity in the Ig receptor.[35,36] Disruption in the machinery leading to a restricted repertoire has been implicated in ITP. As in other autoimmune diseases, certain VH loci have been shown to be over-represented.[37,38] In two studies, patients with ITP had a higher restriction to VH6 gene family usage associated with a high level of somatic mutation in the VH6 genes.[39,40] Thus, defects in the selection of the B-cell repertoire may be an important mechanism in the development of ITP.

As with B cells, oligoclonal T-cell expansion is a feature of several autoimmune diseases.[41–43] In ITP, biased expression and clonal expansion of the T-cell receptor Vβ repertoire has been demonstrated[44–46] and correlated with disease activity.[47]

Induction of Anergy

Another way of controlling self-reactive lymphocytes is to inhibit their function, that is, render them anergic. Self-reactive B cells may be inhibited by the down-regulation of their receptors, continued expression of death-promoting signaling pathways or prevention of differentiation into long-lived antibody-producing plasma cells via Toll-like receptor-9 (TLR9).[48] Normally, T-cell responses can be inhibited by cytotoxic T-lymphocyte antigen 4 (CTLA4) to avoid overreactivity with self-antigens.[49] In ITP, the induction of T-cell anergy by CTLA4-Ig, a recombinant fusion protein consisting of the extracellular domain of CTLA4 fused to the constant region of mouse or human Ig, resulted in tolerogenic dendritic

cells incapable of stimulating platelet glycoprotein-specific T-cell responses.[50,51] These data suggest that the loss of antigen-specific anergy, possibly through defects in CTLA4, may contribute to overreactive T cells in ITP.

Extrinsic Cellular Suppression

T-regulatory cells (T regs), identified by their expression of CD25 and Foxp3, are critical for maintaining immune tolerance by suppressing self-reactive lymphocytes.[52] T regs suppress the production of cytokines by $CD4^+$ and $CD8^+$ T cells and limit $CD8^+$ T-cell cytotoxicity.[53] Impairment of T regs may contribute to the development of ITP because of decreased number or function.[54,55] The number of T regs has been shown to increase in patients with ITP following treatment with coriticosteroids,[56] rituximab (monoclonal anti-CD20),[57] or both.[58] Platelet count responses following rituximab treatment were associated with a normalization of defective T-cell responses,[47] suggesting that the depletion of B cells may have important downstream effects on cellular immunity. Chronic ITP patients, treated with a thrombopoietin-receptor agonist (either romiplostim or eltrombopag), have demonstrated improvement in T-reg activity and increased transforming growth factor (TGF)-β1 levels, which were associated with platelet count responses.[59]

$CD4^+$ Th cells facilitate B-cell activity and auto-antibody production. In chronic ITP, $CD4^+$ Th cells may become stimulated by platelets themselves to secrete IL-2 and facilitate the differentiation of autoreactive B cells.[60] $CD4^+$ T cells from patients with ITP recognize and proliferate in response to several distinct epitopes on GPαIIbβ3,[61,62] but not the native form of GPαIIbβ3.

PLATELET CROSS-REACTIVITY

Besides cellular mechanisms that may allow self-reactive cells to go unchecked, cross-reactive, cryptic, or altered antigens may deceive the immune system into thinking a self-protein is foreign.[63] This process of molecular mimicry is exemplified by secondary ITP due to infection with *Helicobacter pylori* (*H. pylori*), human immunodeficiency virus (HIV), or hepatitis C virus (HCV).

In some patients with ITP and concomitant *H. pylori* infection, eradication of *H. pylori* can improve platelet counts[64] independent of the effect of the antibiotics themselves.[65] Antibodies eluted from platelets have specificity for *H. Pylori* cytotoxin-associated gene A (CagA) protein in some patients, suggesting antigenic mimicry with CagA.[66] Platelet count responses to *H. pylori* eradication are more common in Japan, where infection rates are high and the CagA serotype is prevalent,[67] than in North America and Europe, where *H. pylori* infection rates are low and the CagA serotype is infrequent.[64]

ITP associated with HIV may be due to cross-reactive antibodies or immune complex formation. Anti-HIV antibodies can cross-react with epitopes on GPβ3, causing platelet lysis.[68,69] In addition, anti-HIV-1 gp120 immune complexes can cause accelerated platelet destruction[70] and complement-independent platelet lysis.[71] Ineffective platelet production may result from HIV infection of megakaryocytes, leading to apoptosis and defective platelet formation.[72,73]

Molecular mimicry has also been implicated as a mechanism for HCV-induced ITP as antibodies to HCV core envelope 1 have been shown to cross-react with platelet GPβ3.[74]

MECHANISMS OF THROMBOCYTOPENIA IN ITP

While accelerated platelet clearance is a hallmark of ITP pathogenesis, platelet production does not compensate adequately, suggesting that megakaryocytes are in-jured.[75] Impaired platelet production in ITP is supported by evidence from radiolabeled autologous platelet studies showing normal or reduced platelet production in the context of thrombocytopenia,[75] and by the remarkable success of thrombopoietin-receptor agonists in improving platelet counts in persons with ITP.[76,77] The binding of pathogenic autoantibodies to platelet and megakaryocytes may cause thrombocytopenia by opsonization, the direct activation of complement or apoptotic pathways. Alternatively, cytotoxic T cells may have a direct lytic effect on platelets and/or mega-karyocytes (Fig. 1).

Pathogenic Autoantibodies

Not all autoantibodies are pathological.[78,79] Naturally occurring autoantibodies can be of the IgM, IgG, or IgA class, and tend to be low affinity, polyreactive and germ-line encoded; whereas pathogenic autoantibodies are mainly of the IgG class, exhibit high affinity binding to self-antigens and are genetically mutated.[80] In ITP, autoantibodies are most often directed against platelet GPIIbIIIa and GPIbIX, and mapping studies suggest that they target specific and distinct epitopes.[81] Using direct glycoprotein-specific assays, antiplatelet autoantibodies are detectable in 60 to 70% of ITP patients.[1]

The autoantibody theory of ITP was conceived from experiments demonstrating that a transferable plasma factor caused thrombocytopenia in healthy volunteers.[82] The plasma factor was first identified as platelet-associated IgG and later as platelet glycoprotein-specific IgG.[2] Current evidence suggests that platelet autoantibodies may contribute to peripheral platelet destruction by Fc-mediated platelet clearance in the spleen,[83] complement activation,[84] and/or apoptosis.[85,86] In addition, autoantibodies may target megakaryocytes and interfere with their growth and function.[87–89]

OPSONIZATION OF PLATELETS—Platelet destruction and clearance by the reticuloendothelial system (RES) is the primary pathogenic mechanism for the development of ITP.[90–92] This mechanism at least partially explains the rapid and robust platelet-count responses observed following treatment with intravenous immunoglobulin (IVIg) and Rh-immunoglobulin (for Rh^+ individuals).[93] Studies using IgG-sensitized red cells, as an in vivo measure of RES function, demonstrated reduced clearance of these cells with increased concentration of plasma monomeric IgG.[94] Elevation in the concentration of IgG in the plasma progressively impaired RES function, with a dramatically impairment at concentrations seen after administration of high-dose IVIg. The spleen is the major site of clearance of antibody-coated platelets in ITP and splenectomy leads to a durable remission in up to 66% of patients.[95] There is renewed interest in indium-labeled autologous platelet sequestration studies, which have shown a correlation between splenic sequestration patterns and response following splenectomy.[96]

DIRECT EFFECTS OF PLATELET AUTOANTIBODIES—In addition to targeting platelets for opsonization in the spleen, ITP autoantibodies may have direct effects on platelets as a result of complement activation[84,97] or apoptosis.[85] Decreased complement components in plasma, and deposition of complement on platelets, have been demonstrated in ITP, suggesting complement deposition may contribute to platelet clearance by complement receptors on macrophages in the spleen or direct platelet lysis.[84] ITP plasma has been shown to contain higher complement activation capacity compared with plasma from thrombocytopenic and nonthrombocytopenic controls.[97] The effects of ITP autoantibodies on megakaryocyte function are not fully known; however, IgG fractions from ITP sera can induce complement-dependent cytotoxicity to bone marrow megakaryocyte progenitor cells[87] and antiglycoprotein antibodies may inhibit proplatelet and megakaryocyte colony formation.[88] Some effects of anti-GPIb antibodies may be due to agglutination of megakaryocytes and proplatelet formation rather than a direct effect on megakaryocyte maturation.[89]

APOPTOSIS—Apoptosis is a noninflammatory form of programmed cell death characterized by cell shrinkage, phosphatidylserine exposure, disruption of mitochondrial membrane potential, DNA fragmentation, cell surface blebbing, and the formation of apoptotic bodies.[98] Extrinsic apoptosis pathways involve ligand engagement to death receptors, and intrinsic apoptosis pathways involve members of the Bcl-2 family of proteins. Both require the activation of caspases to mediate intracellular apoptotic signaling ultimately cell death.[98] Platelet autoantibodies that induce thrombocytopenia in mice trigger caspase activation in platelets, an effect preventable by the injection of a general caspase inhibitor.[85] Anti-GPαIIb can trigger caspase-3 activation, phosphatidylserine exposure, and disruption in the mitochondrial transmembrane potential.[86] IVIg may inhibit caspase-3 activation and phosphatidylserine exposure on platelets.[86]

Apoptotic processes may be more important at the level of the megakaryocyte, as platelet release from mature megakaryocytes in culture requires the induction of apoptotic pathways.[99] Indeed, mice that lack proa-poptotic proteins or overexpress antiapoptotic proteins display a mild thrombocytopenic phenotype[100,101] and proplatelet formation from megakaryocytes can be attenuated by caspase inhibition.[102] Furthermore, in a study investigating familial thrombocytopenia, an apoptosis-enhancing mutation in cytochrome *c* (G41S) was found to cause premature platelet release and early platelet formation.[103] Experimental evidence supports both increased and decreased megakaryocyte apoptosis in ITP. In megakaryocytes cultured with plasma from ITP patients, there was suppression of megakaryocyte growth and maturation.[104,105] In ultrastructural studies, most bone marrow megakaryocytes in patients with ITP were extensively damaged and demonstrated structural abnormalities indicative of apoptosis.[106]

Thrombopoietin, an important factor mediating the growth, development, and ploidy of megakaryocytes,[107] has been shown to have antiapoptotic properties[108] and thus normally rescues megakaryocytes from early cell death. This may explain the remarkable success of thrombopoietin-receptor agonists in improving platelet counts in patients with ITP. On the other hand, inhibition of megakaryocyte apoptosis has also been shown to lead to thrombocytopenia.[109] Reducing apoptosis through reduced levels of TNF-related apoptosis-

inducing ligand (TRAIL) was shown to cause impaired platelet production even though megakaryocyte mass was increased.[110] Thus, controlled apoptosis appears to be important for proper platelet release, yet dysregulated apoptosis may lead to megakaryocyte injury or death.

Direct Cytotoxic Effect of T Cells

In vitro data suggest that cytotoxic T cells from ITP patients may have direct lytic effects on platelets. $CD8^+$ T cells from patients with active ITP but undetectable platelet autoantibodies bound to platelets in vitro and this causes direct platelet lysis, while $CD8^+$ T cells from patients in remission did not have significant platelet reactivity.[21] Furthermore, $CD3^+$ cells from ITP patients showed increased expression of genes involved in cell-mediated cytotoxicity relative to controls, such as TNF-α, perforin, granzyme A, and granzyme B.[21,111] Similarly, the expression of FasL and TNFα were increased in $CD8^+$ T cells obtained from patients with chronic ITP.[111] Additionally, severe ITP could be induced in a mouse model by antibodies and by $CD8^+$ T cells.[112] Although cytotoxic T cells may also target megakaryocytes in chronic ITP, activated $CD8^+$ T cells in the bone marrow of chronic ITP patients have not been shown to cause megakaryocyte lysis ex vivo.[113] Rather, $CD8^+$ T cells may prevent megakaryocyte apoptosis, leading to impaired platelet production.[113] Taken together, these studies suggest that T-cell dysfunction may be an important feature of chronic ITP and that in some patients, platelets and/or megakaryocytes may be targeted and destroyed by direct T-cell mediated mechanisms.

Summary

The pathogenesis of ITP involves the loss of immune regulation at various levels. In vitro and ex vivo studies suggest that the pathogenesis involves increased levels of lymphocyte growth factors, resistance to death signals, and loss of T-regulatory function, due to development and expansion of self-reactive B and T cells. Platelet antigens may be prone to autoimmune attack due to their structural similarities with antigens of infectious pathogens or their ability to form cryptic or altered epitopes. The final common pathway is the development of autoantibodies and/or cytotoxic T cells that targets platelets and megakaryocytes. Thrombocytopenia occurs because of Fc-dependent platelet clearance in the spleen and megakaryocyte apoptosis. New treatments such as the thrombopoietin-receptor agonists and rituximab have shed light on the mechanistic pathways in ITP. By furthering our understanding of disease pathogenesis, treatments will continue to be refined and tailored to individual patients.

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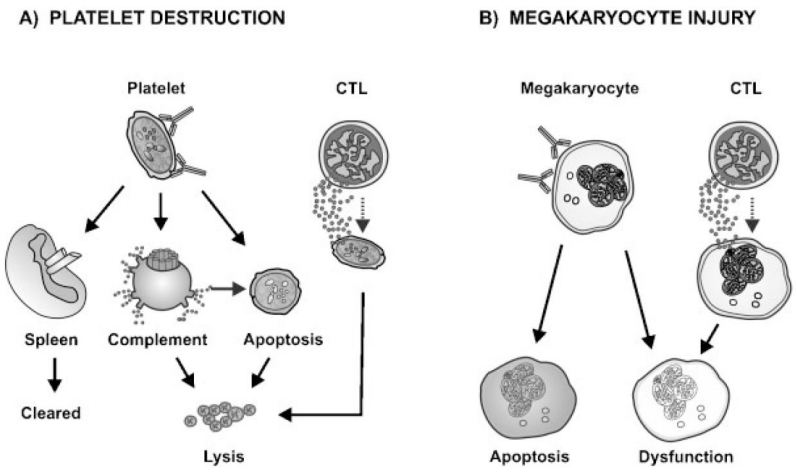

Figure 1.

Mechanisms leading to thrombocytopenia in immune thrombocytopenia (ITP). (A) Autoantibody-mediated platelet destruction: Autoantibodies bind to platelets causing Fc-dependent clearance in the spleen, lysis by complement or apoptosis via caspase activation. Cytotoxic T cells (CTL) can also directly mediate platelet lysis. (B) Megakaryocyte injury: Autoantibodies can bind directly to megakaryocytes leading to agglutination, apoptosis, or dysfunction which can result in impaired platelet production. CTL can also impact megakaryocyte function by inhibiting platelet formation.

Table 1

Normal Immune Checkpoints Preventing the Development of Autoreactivity and the Failure of These Checkpoints in the Development of ITP

Self-Tolerance Checkpoint	Cytokine or Cellular Dysfunction in ITP	Downstream Effects Contributing to the Development of ITP
Cell deletion (apoptosis)	↑ BAFF	Survival and maturation of platelet-reactive B-cells
	↑ APRIL	
	↑ Caspase 8	T-cell resistance to apoptosis in active ITP
	↓ Bax	
	↑ Calpastatin	
	↑ A20	
Receptor editing (somatic hypermutation V(D)J recombination)	Biased expression and clonal expansion of BCR V(H) repertoire	Expansion of platelet-autoreactive B-cell subsets
	Biased expression and clonal expansion of TCR Vβ repertoire	Expansion of platelet-autoreactive T-cell subsets
Intrinsic regulation (Induction of inhibitory receptors)	↓ Antigen-specific anergy (CTLA4 defect?)	Overreactive T cells
Extrinsic regulation	↓ T regs	Activation and proliferation of platelet-reactive T-helper and cytotoxic T cells

ITP, immune thrombocytopenia; Bax, Bcl-2-associated X protein (see text for specific references; BCR, B-cell receptor; TCR, T-cell receptor; CTLA4, cytotoxic T-lymphocyte antigen 4; BAFF, B-cell activating factor; APRIL, a proliferation-inducing ligand; T regs, T-regulatory cells.