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Innate and adaptive immunity in ITP

Alan H. Lazarus^{a,b,c,d,e}, John W. Semple^{a,b,c,e,f}, and Douglas B. Cines^g

^aThe Canadian Blood Services, Canada

^bThe Keenan Research Centre in the Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada.

^cThe Toronto Platelet Immunobiology Group, Toronto, ON, Canada.

^dDepartment of Medicine, University of Toronto, Toronto, ON, Canada.

^eDepartment of Laboratory Medicine & Pathobiology, University of Toronto, Toronto, ON, Canada.

^fDepartment of Pharmacology, University of Toronto, Toronto, ON, Canada.

^gDepartment of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by both accelerated clearance of autoantibody-sensitized platelets and suboptimal platelet production. A number of studies have provided evidence of disturbed innate and adaptive immune responses in patients with ITP. This brief review will highlight some of the more recent work in this field and highlight other findings that provide a potential link between ITP, systemic lupus erythematosus (SLE) and autoimmune hemolytic anemia (AHA).

Potential inciting agents

ITP is a heterogeneous group of disorders with potentially differing etiologies, natural histories and response to therapy (1). Some ITP patients appear to have fundamental disturbances in their innate and adaptive immunity, while in others a specific often times self-limiting inciting agent may be involved. Several potential inciting agents have been identified or proposed. In the case of childhood ITP, many patients give a history of a recent infection. In adults, infection with human immune deficiency virus, *Helicobacter pylori* and hepatitis C have been implicated in a high percentage of cases of ITP in endemic areas; the causal relationship is strongest in settings where microbial elimination leads to resolution of the associated ITP (2). Acute ITP can also occur after vaccination. The evidence for vaccine associated ITP is most compelling in those immunized with measles-mumps-rubella vaccine (~1:40,000). There have also been case reports of ITP in children following other vaccinations against hepatitis B, diphtheria-tetanus-pertussis, and hepatitis A, among others, but the relationship is less compelling (3). It has been hypothesized that ITP results from

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Correspondence to: Alan H. Lazarus, PhD St. Michael's Hospital 30 Bond Street Toronto, Ontario, M5B 1W8 Canada
LAZARUSA@smh.ca.

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molecular mimicry engrafted on a normal immune repertoire, such that the immune thrombocytopenia resolves once the inciting antigen has been eliminated.

Although microbial antigens may play a role in the induction of vaccine associated ITP, many vaccines also contain adjuvants (e.g., alum) that might potentiate the immune response. Recent work from Shoenfeld and coworkers suggests that some autoimmune syndromes and inflammatory states might be induced by these immune adjuvants themselves (4). The name they have given to this activity is Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA). The role that ASIA might play in the initiation of ITP requires further study, but the observation that ITP has been seen after the administration of several different vaccines provides an interest in this possibility.

The Innate immune system and ITP

The initiation of B and T cell immunity (i.e., the adaptive immune system) requires the upstream functions of the innate immune system. Among the basic work-horse family of molecules of the innate immune system are Toll-like receptors (TLRs). TLRs are a group of pattern recognition receptors that enable the immune system to rapidly recognize a series of canonical molecular structures found on bacteria, viruses and fungi. Recognition of these “danger” molecules on pathogens leads to TLR signaling that, in turn, initiates the production of proinflammatory cytokines, characteristic of patients with ITP. TLRs are thus sentinels of the innate immune system that endow us with the capacity to stimulate adaptive immunity against invading microorganisms (5).

It has recently been shown that platelets express several functional types of TLRs (5). Platelets, one of the first responders to intravascular pathogens, may thereby play a more pivotal role than previously appreciated by helping to bridge the initial response to pathogens with the downstream adaptive immune system.

Pathogens bound to platelet TLRs may promote antigen recognition by dendritic cells (5) which, along with some subsets of macrophages, are critical to initiate a fully adaptive immune response. In one study, platelets were shown to modulate dendritic cell activity by both contact-dependent and contact-independent activities. Among contact-independent effects, platelets induced dendritic cells to express increased levels of CD80 and CD86, which are involved in antigen presentation (6).

A potential link between innate immunity ITP, SLE, and AHA?

Kang et al. have recently shown that megakaryocyte progenitor cells which do not yet express lineage markers (designated “MM” cells) can act as potent antigen-presenting cells as well (7). MM cells derived from SLE-prone mice were able to break tolerance and induce immune responses to systemic lupus erythematosus (SLE)-associated autoantigens in murine models. In conjunction with this finding, patients with SLE showed a 10-fold expansion of MM cells in their blood compared with controls (7).

There is a higher prevalence of anti-erythrocyte antibodies in patients with ITP than can be explained by chance and platelet-reactive antibodies occur commonly in patients with primary or SLE-associated autoimmune hemolytic anemia (AHA). Approximately 15–20% of patients with SLE develop immune thrombocytopenia. The unique biology of these MM cells may contribute to this apparent overlap. The MM cells studied by Kang and co-workers expressed transcription factors characteristic of bipotential megakaryocyte-erythroid progenitor (MEP) cells, suggesting a possible explanation for the link between AHA and ITP. Although much work remains, it is of interest that the poorly understood relationship between SLE, AHA and ITP may occur in part due to the dual function of MM cells in

mediating innate responses as antigen presenters and concurrently acting as bone marrow-derived cells involved in both platelet and red cell production.

The adaptive immune system

The underlying pathophysiology of ITP is the targeting of highly prevalent platelet and megakaryocyte antigens, most commonly glycoprotein (GP) IIb/IIIa and/or GPIb/IX, by IgG antibodies (8). There is emerging clinical and experimental evidence to indicate that antigen specificity impacts on the response to IVIG (9, 10), possibly reflecting a fundamental difference in the extent to which they impair platelet production vs. accelerate clearance.

In addition to an important role of T helper cells in autoantibody production, cytotoxic T cells can also contribute to the pathogenesis of ITP. Work by Olsson *et al.* first demonstrated that patients with chronic ITP without identifiable anti-platelet antibodies possessed CD8⁺ T cells that lysed autologous platelets *in vitro* (11). These results were confirmed by Zhang and colleagues (12). T cell-mediated thrombocytopenia has also been demonstrated in an animal model of ITP using CD61 knockout mice (10). The direct destructive impact of T cells in ITP is most likely exerted within the bone marrow and possibly other secondary organs where effector:target ratios are far higher than in the circulation.

In addition to platelet and megakaryocyte destruction orchestrated by the adaptive immune system, work from Stasi (13) and recent findings by Yazdanbakhsh's group (14, 15) have shown that there is significant dysregulation in T- and B-regulatory cells and in monocyte function in ITP which contribute to autoantibody development or perpetuation. This work is covered elsewhere in this supplement [1].

CONCLUSIONS

ITP is a complex, chronic, often cell-specific, autoimmune disease that is still not fully understood. The improved understanding of the innate and adaptive immune systems however is allowing us to understand and appreciate some of the complex interactions between platelets, the immune system, and the development and treatment of ITP.

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