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REVIEW

Platelets in Inflammation and Immune Modulations: Functions Beyond Hemostasis

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Abstract Platelets play central roles for maintaining the homeostasis of the blood coagulation. As they are also involved in immune responses and host defenses, increasing evidences have suggested that platelets exert other roles beyond their well-recognized function in preventing bleeding. This review is focused on inflammation, allergy and immune modulations of platelets. Platelets conduct immunoregulation through secretion of functional mediators, interaction with various immune cells, endothelial cells and beneficial for the leukocyte infiltration to inflamed/allergic tissues. In these regulations, the leukocytes are influenced by and receiving the signals from platelets. In contrast, rare attentions were focused on platelet regulations by immune system. An intriguingly example in the intravenous immunoglobulin (IVIg) treatment is discussed, in which dendritic cells exert anti-inflammatory effect through platelets. This further suggests that coagulant and immune systems are tightly associated rather than separate entities. The cross-talks between these two systems implicate that platelet therapy may have application beyond thrombosis, and immune interventions may have potentials to treat thrombosis diseases.

Keywords Platelet · Dendritic cell · Immune regulation · Intravenous immunoglobulin

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Abbreviations

ITP	Immune thrombocytopenia
IVIg	Intravenous immunoglobulin
DCs	Dendritic cells
CD40L	CD40-ligand
FcεR	Immunoglobulin E Fc receptor
FcγR	Immunoglobulin G Fc receptor

Introduction

Not much more than a century ago, people had not yet identified which blood elements prevent bleeding. In 1882, Italian doctor Giulio Bizzozero first described a novel small element in the blood that has a role in hemostasis. The element was named a "platelet" because of its morphology similar to a small plate (Mazzarello et al. 2001; Michelson 2007; Ribatti and Crivellato 2007). The platelet's structure and related functions were continually studied by many research groups thereafter, and it became known that various platelet factors were involved in blood coagulation. In addition to the critical role in blood clotting, increasing literatures have implied that platelets exert other functional roles in immunoregulation (Michelson 2007; Semple et al. 2011).

The average lifespan of a platelet is approximately 5–9 days in humans. Derived from cellular fragments of the bone marrow precursor megakaryocytes, platelets are small anucleate cells with a diameter normally around 1–3 μm and can reach to 6 μm if they are fully activated (Chang and Lo 1998). They patrol in the circulation system and are activated when bound to the collagen substratum or other extra-cellular matrix (ECM) proteins on the injured vessel wall (Joseph 1999). On the site of injury, collagen

exposed from the subendothelial layer of the vessel wall would be allowed binding to the plasma ultra large von Willebrand factor (vWF). Immobilized vWF will then cause conformational changes and recruit circulating platelet via the interaction with platelet glycoprotein (GP) Ib–V–IX receptor complex under the high shear stress (Kumar et al. 2003). This allows platelets to form stable adhesion and transduce signals through two major collagen receptors GPVI and integrin $\alpha 2\beta 1$ on their surfaces (Pugh et al. 2010; Varga-Szabo et al. 2008). During activation and aggregation, surface integrins and mainly the αIIbβ3 are transformed into high affinity structures. This allows platelet binding to some of the most notable ligands, fibrinogen, fibronectin, and vWF (Varga-Szabo et al. 2008) and such integrin–ligand interactions are primarily mediated through the cellular adhesion–receptor integrins and the Arg-Gly-Asp (RGD) tripeptide-motif of matrix proteins (Chang et al. 1993, 1997, 1998, 1999, 2001, 2002, 2005; Lo and Chang 2005). These interactions could transform platelet morphology (Fig. 1) and elicit sophisticated signal transductions in platelets (Michelson 2007; Sun et al. 2005a, b), by which it is critical for subsequent coagulation activation and the formation of blood clots (Davis 1998; Vargaftig et al. 1979). A lack of functional platelets may be fatal in various thrombocytopenic and hemorrhagic conditions (Kau et al. 2005, 2010; Sun et al. 2007).

At the same time, platelets are a natural source of proteins having biological functions other than hemostasis (Funa and Ahgren 1997; Koenen and Weber 2010; Leslie 2010; Nojima 1991). At the site of injury, proteins and cytokines released by platelets could limit the survival and dissemination of invading microbes and recruit leukocytes to the wounds (Huang et al. 2010; Li 2008; Sun et al. 2009; Zander and Klinger 2009). This prevents infection and simultaneously promotes tissue repair (Klinger and Jelkmann 2002; Nurden 2011). A number of investigators have concluded that platelets may act as a bridge to link innate and adaptive immunity (Semple et al. 2011; Vieira-de-Abreu et al. 2011; Weyrich and Zimmerman 2004). Evidence in this line suggests that platelets are versatile cells that play additional roles beyond their primary role in hemostasis. Because platelets can respond to wounding and interact promptly with both endothelial and immune cells, it is reasonable to conclude that a number of vascular and immune diseases (e.g. arthrosclerosis, allergy, and autoimmunity) may be associated with platelet functional disorders. This review is focused on platelet-related immunoregulation, in which the roles of platelets in modulating inflammation, allergy, innate and adaptive immune responses are discussed. In contrast to these platelet-to-leukocyte regulations, the leukocyte-to-platelet regulations are also discussed using an example of dendritic cell-mediated modulation of platelets in intravenous immunoglobulin (IVIg) treatments (Huang et al. 2010; Lazarus 2010).

Platelet and Inflammation

A prominent feature of inflammatory diseases is leukocyte recruitment to the inflamed tissue. This involves multistep processes including an initial interaction among platelets, leukocytes, and endothelial cells through adhesion receptors expressed on their surfaces (Michelson 2007; Passacquale et al. 2011). Among the various molecules involved in these interactions, P-selectin is an adhesion

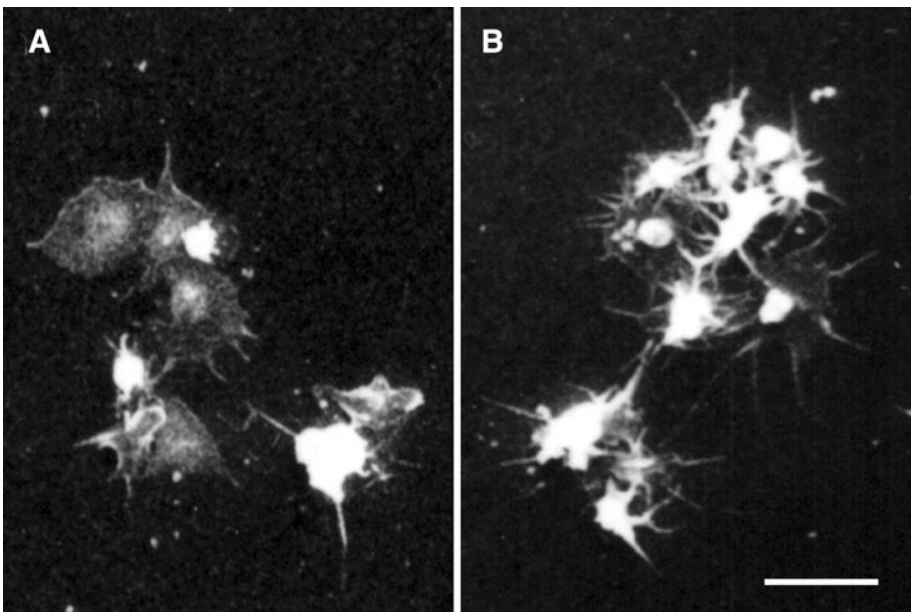

Fig. 1 Scanning electron microscope (SEM) images of platelets adhered on substrates coated with rhodostomin (an Arg-Gly-Asp containing peptide) (**a**) and laminin (**b**). Relatively more lamellipodia were induced after platelets were adhered on a rhodostomin substrate (**a**) as compared to more filopodia structures on a laminin substrate (**b**). Representative images are selected from three independent experiments. *Scale bar* 5 μm

molecule that is essential for mediating leukocyte recruitment and subsequent inflammatory responses (Huo et al. 2003; McGregor et al. 2006; Yokoyama et al. 2005). P-selectin is a transmembrane protein of the selectin family of adhesion receptors, and is synthesized by megakaryocytes and endothelial cells and stored in their α-granules and Weibel–Palade bodies, respectively (Bonfanti et al. 1989; Larsen et al. 1989; Stenberg et al. 1985). Activated platelets and endothelial cells can translocate the P-selectin to their cell surfaces to mediate leukocyte–platelet and leukocyte–endothelial cells interactions, and initiate inflammatory reactions. Platelets are essential for leukocyte recruitment and subsequent firm adhesion to the endothelial cells at the site of inflammation; this consequently triggers autocrine and paracrine activation processes at the vascular wall (Bussolino and Camussi 1995; May et al. 2007). During severe inflammations, abnormal regulation of vascular anticoagulant systems may lead to hypercoagulation and thrombocytopenia (Chang et al. 2012; Sun et al. 2007). Increasing evidence has shown that platelet-induced chronic inflammatory processes at the vascular walls result in the development of atherosclerotic lesions (Gawaz et al. 2005; Huo et al. 2003; Ruggeri 2002). Interactions among platelets, leukocytes, and endothelial cells are now considered important steps leading to inflammation, thrombosis, and atherogenesis. Moreover, platelet–leukocyte interactions contribute to the exchange of signals between platelets and different types of leukocytes that bridge inflammatory immune reactions (Czapiga et al. 2004; Elzey et al. 2003, 2011). These interactions modulate a wide array of responses of both the innate and adaptive immune systems, thus contributing to the pathogenesis of inflammatory diseases and tissue damage (Totani and Evangelista 2010). For example, research has shown that platelet P-selectin is in part responsible for leukocyte–endothelial cell interactions, and responsible for the leukocyte exerting tissue damage in antigen-induced arthritis (Schmitt-Sody et al. 2007a, b). In arthritis, platelets amplify the inflammatory response through interleukin 1 (IL-1) pathway and collagen-dependent microparticle production. In contrast, removing the particles reduces the severity of the disease (Boilard et al. 2010). Platelet-derived P-selectin and RANTES have been detected in intestinal microcirculation, suggesting that activated platelets play a role in mediating leukocyte recruitment to an inflamed colon (Fagerstam et al. 2000). In addition, an increased level of soluble circulating CD40-ligand (CD40L, CD154) released from activated platelets was detected in patients with inflammatory bowel disease (IBD) (Danese et al. 2003). Since CD40–CD40L interactions have been suggested to be essential for angiogenesis in a mouse model of IBD, high levels of soluble CD40L released from activating platelets might play a role in chronic inflammatory processes during IBD formation (Danese and Fiocchi 2005).

Flow chamber and intravital microscopy analyses were used to investigate the molecular events involved in leukocyte recruitment during inflammation in a feline ischemia–reperfusion model (Gill et al. 2005). Evidence revealed that anti-inflammatory IVIg treatment exerted an inhibitory effect on the P-selectin dependent rolling that had led to reduced leukocyte recruitment and vascular dysfunction (Gill et al. 2005). Intriguingly, the in vitro flow-chamber analysis revealed a significant ameliorative effect of IVIg on leukocyte recruitment when whole blood was treated, but not when P-selectin-expressed endothelial cells were treated alone. The findings further suggested that IVIg amelioration of leukocyte rolling might be mediated through a platelet-P-selectin-dependent pathway. However, whether IVIg directly blocks the P-selectin mediating leukocyte interaction or subsequent inflammation requires further clarification.

Platelets and Allergic Inflammation

A different line of evidence also suggests that platelets exert significantly wider roles. Clinical data from patients suffering from allergic inflammatory reactions showed that the platelet counts and platelet activating markers in the plasma were significantly altered after exposure to an allergen (Kasperska-Zajac et al. 2008; Kemona-Chetnik et al. 2007; Kowal et al. 2006). Both intact platelets and platelet-released inflammatory mediators play crucial roles in the sustained inflammatory response of many allergic diseases. This type of allergy involves a change in platelet surface molecule expression, aggregation, adhesion, and arachidonic acid metabolism (Barnes 1987; Edenius et al. 1991; Pitchford et al. 2005). Platelet activation is necessary to transform arachidonic acid into lipid mediators, such as thromboxane A2 (TXA2), cysteinyl leukotrienes, and lipoxins, all of which exacerbates the allergic response (Barnes 1987; Edenius et al. 1991; Kantarci and Van Dyke 2003; Kasperska-Zajac and Rogala 2007). Thus, platelets are likely more directly involved in allergic initiation than simply exerting an accessory role to facilitate leukocyte rolling and adhesion. Research has shown that human platelets constitutively express functional receptors for the Fc fragment of IgE, both the low-affinity immunoglobulin E Fc receptor (FcεRII) (Capron et al. 1986) and the high-affinity receptor (FcεRI) (Hasegawa et al. 1999; Joseph et al. 1997). Upon coupling to the antigen–IgE complex, platelets are capable of releasing a variety of biologically active mediators and may thus participate in hypersensitive reactions, including anaphylaxis (Kasperska-Zajac and Rogala 2006; Pitchford 2007).

One study compared the histology data for mice lungs regarding platelet chemotaxis, between ovalbumin-sensitized wild-type mice versus FcR$\gamma^{-/-}$ mutant mice that lacked the FcεRIγ response. These results revealed that for the wild type, but not the FcR$\gamma^{-/-}$ mice, isolated platelets migrated out of vessels and were localized beneath the airways after the mice had been allergen-challenged (Pitchford et al. 2008). Clarification of platelet chemotaxis further revealed that the binding of allergen–IgE complex to surface FcεRI allows platelets to participate directly in allergic tissue inflammation (Pitchford et al. 2008). This hypothesis has been supported by another line of evidence, which showed that chemotaxis platelets, and subsequently infiltrated leukocytes, might be equally important in generating allergic inflammation in the respiratory tract. For example, allergic asthma has been characterized by airway inflammation, normal platelet counts, but not to those thrombocytopenic animals (Coyle et al. 1990). This suggests that platelets are required for eosinophil infiltration. In a mouse model, allergen exposure appeared to induce platelet migration to the airways, a condition that was necessary for eosinophil recruitment and activation (Pitchford et al. 2005). Thus, platelets played an important role in airway eosinophilia and triggering of inflammatory reactions (Benton et al. 2010; Hogan 2007). Furthermore, platelets were found to be essential for tissue remodeling in a mouse model with chronic allergic airway inflammation (Pitchford et al. 2004, 2008). Platelet membranes were able to induce airway smooth-muscle cell proliferation in a mechanism dependent on 5-lipoxygenase (5-LOX) and reactive oxygen species (ROS) pathways (Svensson Holm et al. 2008, 2011). The consequence was asthma with persistent and chronic inflammation. Another study showed that the platelet activation maker, platelet factor 4 (PF-4), stimulated histamine release from mast cells in a dose-dependent manner (Suzuki et al. 2002). Circulating platelet factor 4 (PF-4) is an important factor in the development of seasonal allergic rhinitis and asthma (Kasperska-Zajac et al. 2008). The expression of the murine homologue of PF-4 was highly increased in the spleen of mice having atopic dermatitis (Watanabe et al. 1999), and the hyper-aggregability of platelets in the physiology of skin inflammation in atopic dermatitis has been demonstrated (Katoh 2009; Tamagawa-Mineoka et al. 2007). As a result, suppression of platelet function or interference of platelet-induced leukocyte recruitment to the site of inflammation might provide an alternative target in the alleviation of allergic diseases.

Platelets in Innate and Adaptive Immunity

Platelet responses in assisting allergy and inflammation have also been found to modulate the immune response. Platelets express toll-like receptors and may serve as sentinels in the circulatory system, with characteristics similar to those of an innate immune cell (Aslam et al. 2006). Innate immune cells can bind rapidly to pathogens, actively mediating innate immune responses and perhaps more importantly activating the mononuclear phagocyte system (MPS) (Johansson et al. 2011; Semple and Freedman 2010; Semple et al. 2011). Thus, platelets are actually potent effector cells of the innate immune system, capable of initiating an inflammatory response at the site of infection (Aslam et al. 2006; Clark et al. 2007; Semple and Freedman 2010). In addition to their roles in innate immunity, many evidences suggest that platelets act as mediators between innate and adaptive immune responses (Aslam et al. 2006; Elzey et al. 2011; Elzey et al. 2003; Semple et al. 2011). Among these, dendritic cells (DCs) are essential to link innate and adaptive immunity (Banchereau and Steinman 1998; Catani et al. 2006; Corrigall et al. 2009; Gallucci and Matzinger 2001; Medzhitov and Janeway 2000). Evidence suggests that platelets serve as early effectors of DC activation in tissue injury by displaying and releasing to DCs the "danger signals" of CD40L and IL-1β (Banchereau and Steinman 1998). Thrombin-stimulated murine platelets induced activation and maturation of primary mouse bone marrow DCs through a platelet-CD40L-dependent pathway (Elzey et al. 2003). At the same time, in a co-cultured system using M-CSF and IL-4, immobilized P-selectin enhanced the generation of $CD14^+CD16^+$ DC-like cells from primary human monocytes. These DC-like cells primed naive allogeneic $CD4^+$ T cells to produce significantly less IFN-γ, and inhibited macrophage maturation from human peripheral blood monocytes (Li et al. 2003). Platelet-mediated leukocyte adhesion may also enhance lymphocyte trafficking during adaptive immunity and host defense (Diacovo et al. 1996, 1998; von Hundelshausen et al. 2007). Recent studies utilizing CD40L knockout mice found that platelet-derived CD40L modulates the adaptive immune response. This led to an enhanced antigen presentation, improved $CD8^+$ T cell responses, and played a critical role in T dependent humoral immunity (Elzey et al. 2005; Sprague et al. 2007). Because CD40L served as part of the interface between platelets and adaptive immunity (Elzey et al. 2011), these findings may provide a basis to expand the current paradigm of B cell activation and germinal center formation (Sprague et al. 2007, 2008).

Dendritic Cell-to-Platelet Regulation: An Example in IVIg Treatments

Featured by increased platelet destruction and insufficient platelet production, the pathophysiology of immune

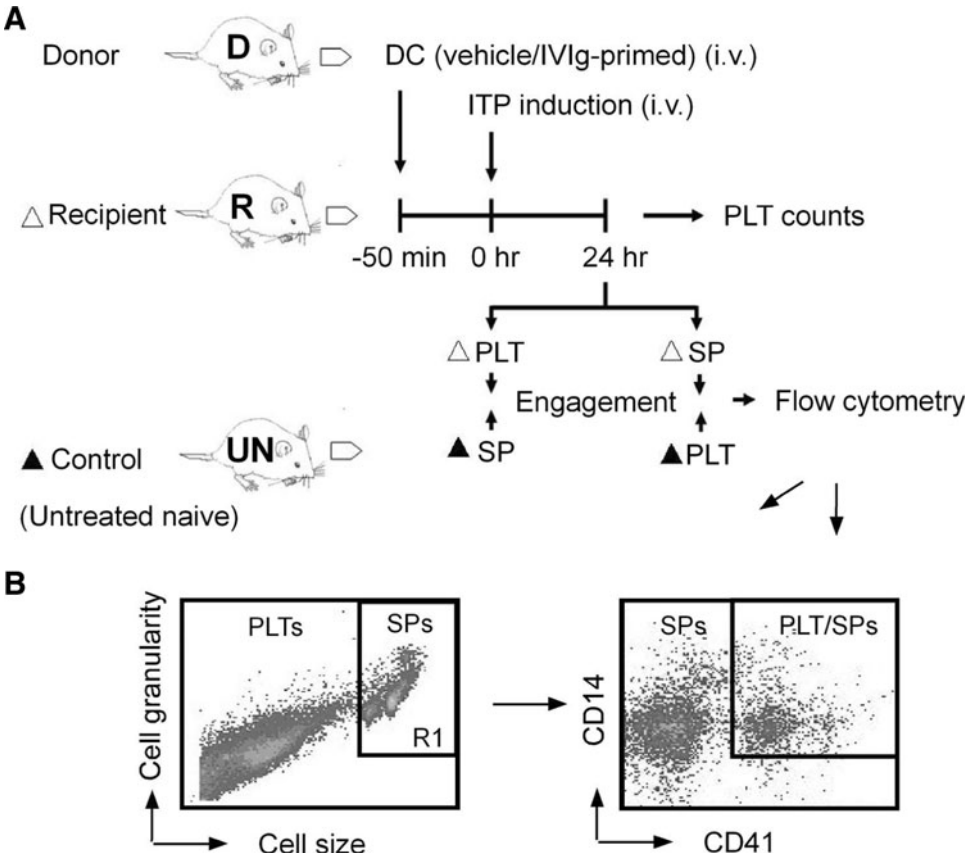

Fig. 2 Adoptive cell transfer mouse model and flow cytometry analyses for platelet-splenic phagocyte (*PLT-SP*) engagement. Schematic illustration of the experiment outline used in the adoptive transfer mice model (**a**). *Open triangle* the recipients, *filled triangle* third party naïve wild type (*WT*) mice. $CD11c^+$ dendritic cells (*DCs*) were isolated from donor mice and then transferred to ITP recipient mice (*filled triangle*) after IVIg priming (**a**). Ameliorative effect of IVIg-primed DCs was analyzed through measuring platelet counts and the engaging properties of platelet (*PLT*) and splenic phagocyte (*SP*) in the recipient mice (flow cytometry analysis) (**b**). Leukocytes were first distinguished from platelets using cell size and granularity characteristics (*left* R_1), and PLT-engaged SPs were then quantified by measuring the percentage of $CD14^+$ (SP marker) $CD41^+$ (PLT marker) double positive cells (*right* PLT/SPs)

thrombocytopenia (ITP) is characterized by the development of autoantibodies against platelet glycoproteins and subsequently the macrophage Fcγ receptor-mediated clearance in patients (Cines and McMilan 2005; Provan et al. 2010; Rodeghiero et al. 2009; Samuelsson et al. 2001). Intravenous immunoglobulin (IVIg) is an effective treatment to ameliorate autoimmune and inflammation diseases, such as ITP (Imbach and Morell 1989; Kazatchkine and Kaveri 2001). The IVIg is prepared from pooled immunoglobulin (Ig)G fractions taken from thousands of healthy blood donors (Ephrem et al. 2005). Despite its high efficiency, the ameliorative mechanism of IVIg remains unclear. Several possible mechanisms have been suggested. It might inhibit complement (Basta and Dalakas 1994), provide immunomodulation through idiotypic antibodies (Levy et al. 1998), modulate cytokine production (Braun-Moscovici and Furst 2003; Gonzalez et al. 2004; Pashov et al. 1997), enhance pathogenic antibody degradation through neonatal Fc receptors (Akilesh et al. 2004), block cell-surface receptors for IgG (FcγRs) (Clynes 2005), or modulate inhibitory Fcγ receptor expression on innate effector cells (Samuelsson et al. 2001).

In addition to these, a more complicated two-step modulation may be involved. This possibility is suggested by the finding that colony-stimulating factor 1 (CSF-1)-dependent sensor macrophages were required for IVIg to induce inhibition of effector macrophages (Bruhns et al. 2003). The two-step model was further supported by data from a study of adoptive cell transfer, in which IVIg-primed splenic DCs were shown to play an ameliorative role in recipient mice with ITP (Siragam et al. 2006). The regulatory role of platelets was rarely discussed in IVIg-mediated amelioration. To investigate the role of platelets in IVIg-mediated amelioration, a novel approach, which combined experimental ITP, adoptive DC transfer, and platelet-splenic phagocyte (PLT-SP) bind/engagement experiments, was established (Huang et al. 2010). As the level of in vitro PLT-SP engagement is associated with the platelet count, and thus reflecting the IVIg ameliorative effect, respective leukocyte and platelet activities could be analyzed through this approach (Huang et al. 2010). Splenic $CD11c^+$ DCs have been shown to initiate the IVIg-induced ameliorative effects (Crow and Lazarus 2008; Siragam et al. 2006). Intriguingly, after adoptively transferred IVIg-primed DCs (IVIg-DCs) into recipient ITP mice, platelets rather than the phagocytes changed their PLT-SP engaging property (experimental outline is shown in Fig. 2) (Huang et al. 2010). As both inhibitory Fcγ receptor IIB (FcγRIIB) and activating FcγRIII receptors (encoded by *Fcgr2b* and *Fcgr3*, respectively) are involved in IVIg-mediated amelioration (Samuelsson et al. 2001; Siragam et al. 2006), these FcγR null mice were tested. The

IVIg-DCs did not ameliorate ITP in *Fcgr2b*$^{-/-}$, *Fcgr3*$^{-/-}$, nor *Selp*$^{-/-}$ (P-selectin null) mice, implicating the potential involvement of these pathways in IVIg action (Huang et al. 2010). These findings suggested that a P-selectin-mediated leukocyte–platelet crosstalk is involved in IVIg-induced amelioration of ITP, and that FcγRs plays a critical role in IVIg-induced amelioration in ITP. As platelets are a component of DC regulatory circuits, these findings may suggest there are potentials to treat coagulant and thrombosis diseases through immune interventions. Agonists and antagonists of P-selectin and FcγRs may provide more maneuverability during the treatments. Further mechanism and application studies are needed for such development.

Conclusion

Aforementioned evidences indicate that platelets play functional roles not only in hemostasis and thrombosis but also in inflammation and immune response. Platelets conduct immunoregulation through secretion of functional mediators, interaction with various immune cells, endothelial cells and even migration to inflamed/allergic tissues. These responses are critically associated with the disease outcomes. DC-to-platelet regulation in IVIg treatments further suggests that coagulant and immune systems are not distinctly regulated. Platelets conduct bidirectional regulations and serve as an important bridge to coordinate the coagulant and immune systems. These results suggest antiplatelet therapy may have application beyond thrombosis, and also shed light upon the potential treatments of coagulant diseases through immune interventions. Although further investigations are required to clarify the underlying mechanism, new findings of immune-coagulant system cross-talks are starting to revolutionize our understanding of platelet biology.

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