Current Trends in Immunology
Vol. 16, 2015

Review

Platelets: essential components of the immune system

Ramadan A. Ali, Leah M. Wuescher and Randall G. Worth*

Department of Medical Microbiology and Immunology, University of Toledo College of Medicine and Life Sciences, Toledo, OH 43614, USA.

ABSTRACT

Platelets are anucleate cell fragments known for their central role in coagulation and vascular integrity. However, it is becoming increasingly clear that platelets contribute to diverse immunological processes extending beyond the traditional view of platelets as fragmentary mediators of hemostasis and thrombosis. There is recent evidence that platelets participate in: 1) intervention against microbial threats; 2) recruitment and promotion of innate effector cell functions; 3) modulating antigen presentation; and 4) enhancement of adaptive immune responses. In this way, platelets should be viewed as the underappreciated orchestrator of the immune system. This review will discuss recent and historical evidence regarding how platelets influence both innate and adaptive immune responses.

KEYWORDS: platelets, innate immunity, adaptive immunity, hemostasis

INTRODUCTION

The classical role attributed to platelets has been in the prevention of bleeding and the initiation of wound healing. However, platelets are now recognized for their activities independent of thrombosis (reviewed in [1]). Platelets are the second most abundant blood cell only outnumbered by erythrocytes in the circulation (approximately 1.5 - 4.0 × 10^{11} platelets per liter of blood in healthy adult humans). In addition to their extremely high numbers, they are capable of storing and releasing bioactive mediators and express a wide range of functional immunoreceptors. Platelets store these bioactive molecules in three types of intracellular storage granules namely dense (δ-) granules, alpha (α-) granules, and lysosomal (λ-) granules that are released into the circulation or translocated to the surface upon platelet activation [1, 2]. The list of proteins housed in each type of granules is summarized in table 1. It is suggested that platelets package these various bioactive molecules discriminately into distinct granule subpopulations and undergo differential patterns of release in order to respond to different types of tissue damage or threats in a specific and selective manner [3-6]. These unique properties are suggested to position platelets to play an important role in effectively communicating with and modulating the function of other cells and to perform sentinel tasks in regulating immunity [6].

Although they contribute to diverse immunological processes, the immune functions of platelets have been underappreciated. The issue of platelet cellularity and the recognition of platelets as 'immune cells' have been controversial. However, platelet immune functions have become increasingly accepted now that their molecular make-up supports viewing these "cells" as unique and essential components of innate immunity [7]. Platelets engage the immune system by interacting with various immune cells [8, 9] and participating in both innate and adaptive immune responses [6]. In this review, we will discuss the recognized role for platelets in both innate and adaptive immunity.

*Corresponding author: randall.worth@utoledo.edu

Table 1. Platelet products, location and immune function.

Storage location	Molecule	Function
δ (dense) granule		
• Bioactive amines	Histamine	Proinflammatory modulator of endothelial cells, leukocytes and lymphocytes.
	Serotonin	Modulate proinflammatory responses and activation of monocytes and T cells.
• Bioactive ions	Ca^{2+}, PO_3^-	Cell adhesion.
• Nucleotides	ADP, ATP, GTP	Activation of purinergic receptors on immune cells.
α granule		
• Adhesion molecules	Fibrinogen VWF P-selectin	Promote adhesion and interactions of leukocytes with platelets and endothelial cells.
	GPIIb-IIIa	Promote platelet aggregation and interaction with endothelial cells and leukocytes.
• Chemokines	CXCL-1 (GROα)	PMN recruitment.
	CXCL-4 (PF4)	PMN recruitment, monocyte differentiation.
	CXCL-5 (ENA-78)	
	CXCL-7 (NAP-2)	
	CXCL-8 (IL-8)	
	CCL-2 (MCP-1)	
	CCL-3 (MIP-1-α)	Recruitment and activation of various leukocytes and lymphocytes.
	CCL-5 (RANTES)	Recruit and modulate the activity of various leukocytes and lymphocytes.
• Cytokines	IL-1β sCD40 ligand	Enhance antigen presentation by DC, B cell-class switching.
• Growth factors	PDGF	Regulate growth, promotes wound healing.
	TGFβ	Immune modulator, immunosuppression.
• Microbicidal proteins	Kinocidins	Antimicrobial peptides.
	Thrombocidins (1 and 2)	Antimicrobial peptides.
	Defensins (1 and 2)	Antimicrobial peptides.
	Thymosin β4	Antimicrobial peptides.
λ (lysosome) granule		
• Proteases • Glycosidases		

Table 1 continued..

Plasma membrane		
• Proinflamatory lipids	Thromboxane A2	Procoagulant, promotes inflammation.
	PAF	Procoagulant, promotes inflammation.
• PRR	TLR1-7	Detection of pathogens.
	TREM1 ligand	Detection of pathogens.
• Co-stimulatory	CD40 ligand*	Enhance antigen presentation by DC, B cell-class switching.

*CD40L can be found in both membrane-bound and soluble forms.

Platelets in innate immunity

The capacity of platelets to participate in innate immunity is largely due to their ability to release a myriad of inflammatory and bioactive molecules stored within granules or synthesized upon activation. These mediators attract and modulate the effector cells of the innate immune system. In addition, platelets themselves demonstrate direct effector function and therefore are regarded as effector cells in innate immunity.

Platelets as effector cells in innate immunity

Platelets are among the first cells to detect endothelial injury and microbial pathogens as they gain access or invade the bloodstream or tissues [10, 11]. Injured endothelium exposes collagen and other membrane proteins which allow platelets to adhere. Stable adhesion to collagen leads to platelet aggregation and promotes the release of such platelet agonists as ADP, thrombin, and vWF, leading to activation and further platelet recruitment to the sites of tissue damage and infection [6]. This serves a two-fold purpose: 1) hemostasis where blood loss is greatest; and 2) frontline host defense against microbial infection. In addition, platelets express CC and CXC chemokine receptors such as CCR1, CCR3, CCR4 and CXCR4 [12] which detect signals for all four classes of chemokines (C, CC, CXC and CX_3C) generated at sites of infection, resulting in rapid accumulation of platelets to the site of infection [2].

Platelets also express pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) [13, 14] which detect pathogen associated molecular patterns (PAMPs) [13, 14]. The detection of PAMPs is an efficient host defense feature of platelets to ensure a rapid response to that particular threat. It was shown that human platelet TLRs can recognize and discern various isoforms of bacterial lipopolysaccharide (LPS) via TLRs and respond differentially to distinct PAMP by releasing different cytokine profiles and effector peptides [15, 16].

Antimicrobial host defense

Platelets interact with bacteria, viruses, fungi and protozoa and demonstrate anti-microbial functions [17, 18]. The mechanism of platelet-bacteria interactions are complex due to the diversity of platelet receptors involved in the recognition of bacteria. Platelets express a wide range of bacterial receptors, including complement receptors, FcγRIIa, TLRs, GPIIb-IIIa, and GPIb, and the interaction of platelets and bacteria is mediated through direct or indirect binding to these receptors [19]. Upon contact with certain bacteria, platelets can become activated, aggregate and degranulate. Activated platelets release over 300 known secretory products including anti-microbial products (collectively known as platelet microbicidal proteins (PMPs)) [20]. Four families of PMPs have been shown to be released from platelets which include kinocidins (CXCL4, CXCL7 and CCL5), defensins (human β defensin 2), thymosin β4, and derivatives of PMPs (thrombocidins and fibrinopeptide A or B) [2]. Recently, a study demonstrated the expression of β defensin 1 (hBD-1) in human platelets and its novel antibacterial activity [21]. It was observed that activated platelets surround *Staphylococcus aureus*

and force the pathogens into clusters which reduce growth rate. Platelet-derived β defensin 1 not only impaired the growth of *S. aureus*, but also triggered neutrophil extracellular trap (NET) formation. Interestingly, platelets released β defensin 1 after being stimulated with *S. aureus* α-toxin, but not by agonists that induce granular secretion.

In addition to the anti-microbial mechanisms as discussed above, platelets can internalize bacteria and viruses. Specifically, platelets have been shown to engulf *S. aureus* and human immunodeficiency virus (HIV) thus promoting pathogen clearance from blood stream and tissues [22]. In fact, platelets are capable of not only internalizing targets but also the killing of various internalized bacterial species including *Escherichia coli* and *S. aureus* [23, 24].Whether this entitles platelets a potential phagocytic role needs further investigation. Furthermore, platelets generate and release hydrogen peroxide and other reactive oxygen species to mediate other anti-microbial effects in response to stimuli [25, 26].

Platelets have the ability to affect immune responses and kill pathogens; however, pathogens have also evolved mechanisms to evade platelet immune activities. For example, the gram-positive *S. aureus* is well known to manipulate multiple aspects of platelet activation. *S. aureus* expresses von Willebrand binding protein (vWbp) which binds von Willebrand factor (vWF) and can also activate prothrombin leading to fibrin production resulting in clot formation [27]. The bacteria can then use the formation of clots and exposure of vWF as an anchoring for colonization of tissue leading to complications such as infective endocarditis [28]. *S. aureus* can also utilize fibrinogen to crosslink platelets and cause their activation via the GPIIb-IIIa integrin making *S. aureus*/platelet/ fibrin complexes leading to platelet activation [29-31].

Streptococcal species have also been widely studied in relation to platelet activation. Similarly to *S. aureus*, *S. pyogenes* M1 protein can bind fibrinogen leading to ligation and crosslinking of the GPIIb-IIIa integrin and subsequent platelet activation and aggregation. However, *S. pyogenes* does not create stable aggregates and it has been shown that the bacteria can then escape from the formed aggregate [32]. *S. pneumoniae* can activate platelets through TLR2 signaling [33], and other *Streptococcal* species can directly bind to the vWF receptor GP1bα [34]. Platelet interactions with bacteria are not limited to gram positive species. In a model of *Klebsiella pneumoniae*, platelet depletion led to accelerated mortality in mice; however, in the follow up article the authors revealed that this was not due to lack of platelet TLR4 signaling (through exclusion of MyD88 signaling) [35, 36].

In parallel to their interactions with and response to bacterial pathogens, platelets encounter protozoa, parasites, and viruses. Specific molecular and immune events are induced upon the encounter and in response to different classes of pathogens [37]. For example, after protozoal *Leishmania* infection in vertebrates, within one minute of blood contact, platelets adhere to *Leishmania* promastigotes which rapidly evolved into large *Leishmania*-platelet aggregates and this is believed as a key mechanism to enhance their phagocytosis and clearance from blood [38]. Off course, this is not a general response mechanism common to all protozoans. Human platelets kill *Toxoplasma gondii* via a mechanism that involves thromboxane A_2 synthesis [39], another example of their defensive role in protozoal infections as well as their unique response to different pathogens.

Earlier observations demonstrated that human platelets inhibit the growth of the known malaria parasite, *Plasmodium falciparum*, *in vitro* [40] whereas a later study reported that human platelets kill *Plasmodium* in infected human red blood cells and mediate survival to infection [41]. In either case, the results from both studies suggested a protective function for platelets only in the early stages of erythrocytic infection. Interestingly, this is distinct from their role in cerebral malaria (CM) as platelets are known to have an adverse role and significantly contribute to the pathogenesis of CM. There are several reports demonstrating different mechanistic roles for platelets in driving the pathology associated with CM [42-48]. These contradictory adverse versus protective effects of platelets in CM and in the early stages of malaria indicates the complexity of the implicated role of platelets in CM. However, a recent study attributed this complex

role to the timing of platelet activation during infection [49]. The results show that platelets are activated very early in experimental CM (ECM) and induce the acute phase response to blood stage infection which in turn limits parasite growth early post infection and protect mice from ECM, whereas continued platelet activation as the disease progress contributes to ECM associated inflammation.

Platelets also contribute to antiviral immunity. They encounter and interact with viruses as demonstrated by experimental and clinical models of viral infections from HIV [50], influenza virus [51], dengue virus [52] and hepatitis C virus [53]. Platelets show a direct interaction with HIV-1 through different mechanisms such as binding, engulfment, and internalization, all of which play a role in host defense during HIV-1 infection, by limiting viral spread and probably by inactivating viral particles [50]. It was shown that supernatants from activated platelets suppressed HIV-1 infection of T cells and that the inhibitory activity was attributed to platelet-derived CXCL4 suggesting that the granule content might exert antiviral activity [54]. In a murine model of lymphocytic choriomeningitis virus (LCMV) infection, platelets prevented lethal hemorrhage by promoting cytotoxic T lymphocyte (CTL)-dependent clearance of the virus [55]. Animals depleted of platelets had reduced viral clearance and impaired virus-specific CTL response. The protective immune response of platelets to LCMV was also demonstrated by preventing splenic necrosis [56]. It is important to note that not all platelet-viral interactions are beneficial. Some interactions alter morphology and hemostatic properties of platelets leading to immune-pathological consequences such as thrombocytopenia as seen in dengue infection [57]. In the instance of dengue virus (DENV) infection *in vitro*, not only do platelets bind to DENV directly, they also release active virions indicating that they can actively spread the infection [58, 59]. This illustrates that the encounter of viruses by platelets are complex and that both host defense and injury can result. This complexity in platelet-pathogen interactions that result in pathogen clearance or host damage depend on the biologic context and platelet interactions with other host immune effector cells [37].

Platelets participate in tissue immunity

Although platelets are mostly located intravascularly, they can greatly affect leukocyte recruitment to areas of inflammation in many tissues, but we limit our discussion to lung, skin and kidney as examples with many overlapping mechanisms. Platelet-leukocyte interactions have been broadly studied in the lung, especially during both sterile and non-sterile inflammation [35, 60-62]. Importantly, studies overwhelmingly show that platelets seem to play an important role in regulation of lung injury due to granulocyte infiltration [63]. For example, in a murine model of ovalbumin (OVA)-stimulated lung inflammation, depletion of platelets using both the busulfan method and anti-platelet serum significantly decreased eosinophil and leukocyte recruitment to the lung tissue [62]. Furthermore, this effect was found to be due to lack of P-selectin on platelets and not on endothelial cells. Thrombocytopenia abrogated eosinophil recruitment and it was only restored when mice were transfused with platelets that were treated with thrombin and then fixed with 1% paraformaldehyde [62]. Not only is the surface receptor P-selectin involved in allergic inflammation, but the purinergic P2Y1 (not P2Y12) receptor has also recently been implicated in recruitment of leukocytes in allergic inflammation [64]. Using specific inhibitors to all purinergic receptors on the platelet surface, inhibition of leukocyte and granulocyte recruitment was only observed with P2Y1 antagonists, showing specificity and possible targets for intervention [64]. Importantly, during allergic inflammation in both rodents and patients, there is an increase in circulating platelet-leukocyte complexes which could lead to increased infiltration to the lung due to platelets binding the inflamed endothelium leading to leukocyte binding and extravasation [65, 66]. Not only do platelets affect granulocytes in allergic inflammation, they induce activation of dendritic cells during allergic inflammation and possibly contribute to antigen presentation by professional antigen presenting cells (APCs) [67].

In patients with atopic dermatitis, a type of allergic inflammation that leads to formation of red patches on the skin mediated by IgE, markers of platelet activation (PF4, soluble P-selectin) are significantly elevated in the blood [68, 69].

Once the skin lesions have cleared, platelet activity returns to normal levels [70]. Similarly, in patients with psoriasis, a chronic immune-mediated inflammatory condition of the skin, platelet aggregation in response to agonist is amplified and elevated plasma P-selectin levels have been reported [71, 72]. Using murine models of acute and chronic skin inflammation, it is clear that platelets play a role in recruitment of leukocytes leading to increased severity of these conditions, due to mechanisms involving P-selectin [60, 73, 74]. In atopic dermatitis platelet depletion showed a decrease in leukocyte recruitment to the dermis which lead to less severity of the disease [73, 74]. In models of contact dermatitis, a condition involving an inflammatory response to a chemical allergen directly on the skin, platelets are also responsible for regulation of hemorrhage and edema by causing leukocyte infiltration. In both of these allergic skin models of inflammation platelet P-selectin appears to be the most important factor. The findings are similar with cutaneous arthus reaction mediated by immune complexes, which also showed that platelet P-selectin plays a major role in leukocyte recruitment [74].

Acute kidney injury (AKI) can occur from multiple mechanisms ranging from ischemic injury to injury from infection. AKI has a high mortality rate, and is characterized by platelet-dependent neutrophil infiltration leading to damage to the organ [75]. Platelet P-selectin is again implicated in the recruitment of neutrophils to the inflamed kidney [75, 76]. Interestingly, it was also shown that neutrophils are required for platelet recruitment to inflamed glomeruli [77]. Activated platelets can release soluble CD40L and are responsible for approximately 95% of the sCD40L in circulation. CD40L is an essential cytokine that leads to activation of a broad spectrum of immune cells [78-82]. Importantly, the receptor for CD40L, CD40, exhibits increased expression in the injured or inflamed kidney [83, 84]. It has been shown that the interaction of sCD40L and CD40 in the kidney is an important factor in mediating both acute and chronic kidney injury [85].

Platelets manipulate leukocytes

Platelets are known to influence the innate immune response through regulation of both the maturation and activation of such innate immune cells as macrophages, neutrophils, and dendritic cells [79, 86, 87]. First shown *in vitro* using co-culture studies, platelets can induce maturation of monocytes into macrophages [88]. Further studies have elaborated on specific platelet components that are responsible for differentiation of monocytes to macrophages. Although platelet cytokines such as RANTES and IL-1β have been shown to activate monocytes, the chemokine CXCL4 plays a major role in this differentiation process from monocyte to macrophage (reviewed in [89]). When platelets are activated or undergo apoptosis they release platelet microparticles (PMPs) which can affect macrophage differentiation and neutrophil activities [90, 91].

Neutrophils are the first line of defense during a bacterial infection. These cells are lethal to bacteria due to their ability to trap them using a neutrophil extracellular trap (NET) [92]. These NETs are composed of the nucleus of the neutrophil and other intracellular contents, which are then used to ensnare and kill bacteria [93]. NETosis (formation of NETs) is an essential mechanism of killing for neutrophils, and inhibition of NETosis leads to increased risk of developing opportunistic infections. Importantly, it has been shown that platelets play an essential role in the development of NETs. Platelet activation via TLR4 was shown not only to induce platelet binding to neutrophils, but subsequent induction of NETs [94]. Platelets release numerous factors when activated, and it has been found that an important factor in the induction of NET formation is hBD-1 [95]. It has also been shown that major cytokines released from platelets contribute to NET formation from neutrophils, which then can lead to their recruitment in a model of sterile inflammation. Further studies revealed that not only are components of platelet releasate important, but even engagement of integrins on the platelet surface can induce NET formation. Platelet αIIbβIII integrin interacts with neutrophil Mac-1 which has been shown to have different effects not just on diapedesis, but on NET formation [79].

Platelets have also been implicated in the maturation and activation of dendritic cells (DCs), indicating platelets can help bridge the innate and adaptive immune systems. Platelets have already been shown to recruit DCs through JAM-C/Mac-1

interaction leading to DC activation [96]. Platelets can also induce activation of naïve DCs through sCD40L after stimulation with thrombin [88]. Interestingly, another report described that platelets need not be in contact with immature DCs to activate them and that sCD40L from platelets was not causative of activation [34]. Dendritic cells are considered professional phagocytes and are critical in bridging the innate and adaptive immune systems. Maturation and activation of dendritic cells lead to presentation of antigen to T cells and induction of the adaptive immune response.

Platelets in adaptive immunity

The role of platelets in innate immune responses has been recognized for at least four decades. However, the role of platelets in adaptive immune response is emerging and has not been clearly elucidated [97]. Growing evidence suggests that platelets and their derived products influence adaptive immunity and play significant roles in shaping the immune response. For example, it was shown that platelets express functional CD154 (CD40L) [98], a molecule critical to the modulation of the adaptive immune response [99, 100].

The role of CD40L in adaptive immunity has been well documented. Ligation of T cell CD40L to CD40 on dendritic cells promotes DC activation and increases expression of co-stimulatory and adhesion molecules which collectively enhance antigen presentation [101]. Effective antigen presentation is central to the development of adaptive immunity to invading pathogens, and consequently the absence of CD40L affects both humoral and cell-mediated immune responses. It was shown that primary and memory T cell responses are impaired in CD40L-deficient mice [102-104]. Additionally, the expression of CD40L on activated CD4 T cells provides the second signal necessary for T-cell-dependent B lymphocyte activation, subsequent isotype switching, and B cell differentiation and proliferation [105-107]. The established importance of CD40L for the adaptive immune response, combined with the abundance of platelets indicates that platelets are a great source of such critical molecules and highlights the role platelets can play in adaptive immunity.

Platelets enhance antigen presentation by APCs

Effective antigen presentation is central to the development of adaptive immunity to invading pathogens. DCs are the most powerful antigen presenting cells. The effect of platelets on dendritic cell activation/maturation state has been widely reported. Having discussed above the significance of CD40L and the potential role of platelet-derived CD40L in adaptive immunity, many reports have demonstrated *in vitro* that activated platelets induce DC maturation in a CD40L-dependent manner [108-111]. The activation and maturation of DCs were revealed by increased expression of co-stimulatory molecules B7.1 and B7.2 along with other cell surface markers, such as ICAM-1 and enhancement of IL-6 and IL-12 production. In contrast, a different study attributed the induction of DC maturation to soluble protein factors expressed by activated platelets other than through CD40L [112]. The discrepancy of these results might be due to different experimental set up such as the ratio of platelets to DC and the agonist used to activate platelets. However, it may also indicate the involvement of other mediators expressed or secreted by platelets. Nonetheless, the role of platelets in DC activation whether by surface contact or by secreted soluble mediators promotes and enhances antigen presentation by DC.

Platelets are also capable of delivering antigens to antigen presenting cells. A recent study showed that platelets shuttle blood-borne bacteria to $CD8\alpha^+$ DC [113]. In this study, *Listeria monocytogenes* associated with platelets in the bloodstream in a manner dependent on GPIb and complement C3, which target the bacterium to splenic $CD8\alpha^+$ DC. This association with platelets was not a unique feature of *L. monocytogenes*, but rather a common feature among gram-positive bacteria. The study concluded that this active shuttling mechanism for systemic bacteria by platelets diverts bacteria from complete clearance by other phagocytes and thus effectively serves as a balance between maintaining sterility of the circulation and induction of the antibacterial adaptive immune responses.

In addition to their role in antigen presentation, enhancement of the immune response by capturing and delivering blood-borne pathogens to splenic DC, by direct interaction via CD40L, and activation of DC, platelets themselves can process

and present antigens. A recent study has shown that platelets present antigen in the context of major histocompatibility complex class I (MHC I) [114]. This is an interesting finding as platelets possess the molecular machinery needed for antigen processing and presentation. For example, platelets express MHC I molecules necessary for antigen presentation and have an active proteasome, endoplasmic reticulum, Golgi, and associated proteins such as calnexin, calreticulin, TAP1 and ERp57, involved in processing, production and assembly of MHC I and the antigenic peptide to be presented [114-119]. Although platelets do not express MHC class II molecules under normal conditions, it is important to note that platelets have been reported to express MHC II in some disease states [120, 121]. Furthermore, platelets, like other antigen presenting cells, express T cell co-stimulatory and adhesion molecules including B7.2, ICOSL, CD40, CD44, ICAM-2, and DC-SIGN [114, 122-125] that are critical for optimal antigen presentation and T cell activation [106, 114-117].

Role of platelets in adaptive T cell response

Platelets not only play a role in antigen presentation, but also influence T cell responses. The ability of platelets to participate in T cell immunity was investigated upon the discovery that activated platelets express functional CD40L as discussed above. An early study showed that platelets via CD40L augmented CD8 T cell responses and enhanced protective secondary immune responses against viral infection [108]. Similarly, platelets promote cytotoxic T lymphocyte (CTL) activity [55] and seem to interact with CD8 T cells to facilitate the targeting of virally infected host cells required for viral reservoir clearance [126]. In the absence of platelets during viral hepatitis, liver inflammation is reduced but viral titers are increased due to lack of CD8 cells. In the presence of platelets, liver inflammation is increased due to CD8 cell infiltration but viral titers are reduced. In this acute viral hepatitis mouse model, transfusion of normal platelets into platelet-depleted mice restored CTL accumulation and targeting of virally infected hepatic cells.

Likewise, platelets enable T cell priming and protection against bacterial pathogens [127, 128]. The mechanism how platelet-derived CD40L coordinates the T cell response is unknown. It is thought that this is due to the maturation signal delivered to DC by platelet CD40L which leads to better antigen presentation and thus better T cell activation. However, it could also be through direct antigen presentation and direct interaction with T cells as was demonstrated recently in an experimental cerebral malaria mouse model [114].

In addition to platelet-derived CD40L-dependent modulation of T cell responses, platelets can also coordinate T cell immunity via cytokine secretion. One report has shown that platelets regulate the differentiation of CD4 T cells indirectly though secretion of chemokines and through direct cell-cell contact. In this study, platelets promote polarization of Th1, Th17, and Treg, but not Th2, and enhance the production of cytokine profiles needed for the polarization of these subtypes of CD4 T cells [129]. The mechanism by which platelets regulate the dynamic of CD4 T cell responses was further investigated. The study concluded that: I) platelets constantly promote Treg cell responses but exert a biphasic regulation of Th1/Th17 activation, namely a transient enhancement followed by a secondary suppression phase, II) platelets are the primary actor in the secondary suppressive phase rather than Treg cells, and III) the distinct regulations are achieved by selective inhibition of FoxP3(-) T-cell proliferation by platelet-derived cytokine TGF β [130]. These results might be inconsistent with the idea that platelet-derived RANTES [131] enhances, while platelet-derived TGF β [132] inhibits, Th1 differentiation and function. It also agrees with previous findings in which platelets seem to modulate the balance between regulatory and non-regulatory T cells by which PF4, a platelet-specific chemokine, attenuates Th1 [133] but enhances Treg cell responses [134]. Collectively, the data presented indicates that platelets regulate CD4 T cell responses in a complex manner. This differential regulation of CD4 T cell subsets suggest that platelets, in response to inflammatory stimuli, promote CD4 T cells for robust pro and anti-inflammatory responses.

Role of platelets in adaptive B cell response

Platelets also modulate B cell adaptive responses to microbial pathogens. As discussed above, it is

well established that CD40L on activated CD4 T cells trigger B cell CD40 providing the second signal necessary for T-cell-dependent B lymphocyte activation, subsequent isotype switching, and B cell differentiation and proliferation [105-107]. This role of platelets in mobilizing B cell humoral immune responses was clearly observed through the use of the murine $CD40L^{-/-}$ mouse model. In this model, transfusion of activated wild-type platelets, but not $CD40L^{-/-}$ platelets, was sufficient to induce B cell isotype switching [108]. This study also demonstrated that depletion of platelets in wild-type mice compromised their ability to mount an efficient IgG response. A subsequent report also demonstrated that adaptively transferred wild-type CD4 T cells alone into $CD40L^{-/-}$ mice failed to generate efficient B cell germinal center and antibody responses to adenovirus, but were able to significantly increase germinal center formation and IgG production upon transfusion along with wild-type platelets [135]. These results were observed under limiting conditions of CD4 T cells or antigen dose which resemble the physiological setting at the time of an initial antigen encounter. However, platelets did not add to the mounted response to high dose adenovirus or upon the transfusion of high number of CD4 T cells. Collectively, these results may suggest that platelets augment T cell-dependent B cell responses through linking T cell and B cell interaction via CD40-CD40L.

SUMMARY

Although platelets were discovered by Bizzozero over 100 years ago, they continue to display activities which should no longer be surprising. For example, platelets have recently been shown to chemotax in response to specific stimuli [136-138] and produce microparticles capable of initiating both thrombosis and inflammation (reviewed in [139]). The vast role of platelets is a world still open to exploration and will provide a continuous source of amazement into the capabilities of these anucleate cells.

ACKNOWLEDGEMENTS

This work was supported by NIH/NHLBI RO1 HL 122401 (to R. G. W.).

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

REFERENCES

1. Smyth, S. S., McEver, R. P., Weyrich, A. S., Morrell, C. N., Hoffman, M. R., Arepally, G. M., French, P. A., Dauerman, H. L. and Becker, R. C. 2009, J. Thromb. Haemost., 7, 1759.
2. Yeaman, M. R. 2014, Nat. Rev. Micro., 12, 426.
3. Sehgal, S. and Storrie, B. 2007, J. Thromb. Haemost., 5, 2009.
4. White, G. C. and Rompietti, R. 2007, J. Thromb. Haemost., 5, 2006.
5. Italiano, J. E., Richardson, J. L., Patel-Hett, S., Battinelli, E., Zaslavsky, A., Short, S., Ryeom, S., Folkman, J. and Klement, G. L. 2008, Blood, 111, 1227.
6. Semple, J. W., Italiano, J. E. and Freedman, J. 2011, Nat. Rev. Immunol., 11, 264.
7. Garraud, O. and Cognasse, F. 2015, Front. Immunol., 6, 70.
8. Ghasemzadeh, M. and Hosseini, E. 2013, Thromb. Res., 131, 191.
9. Li, N. 2008, J. Leuk. Biol., 83, 1069.
10. Al Dieri, R., de Laat, B. and Hemker, H. C. 2012, Blood Reviews, 26, 197.
11. Gardiner, E. E. and Andrews, R. K. 2013, J. Infec. Dis., 208, 871.
12. Clemetson, K. J., Clemetson, J. M., Proudfoot, A. E. I., Power, C. A., Baggiolini, M. and Wells, T. N. C. 2000, Blood, 96, 4046.
13. Cognasse, F., Hamzeh, H., Chavarin, P., Acquart, S., Genin, C. and Garraud, O. 2005, Immunol. Cell Biol., 83, 196.
14. Aslam, R., Speck, E. R., Kim, M., Crow, A. R., Bang, K. W., Nestel, F. P., Ni, H., Lazarus, A. H., Freedman, J. and Semple, J. W. 2006, Blood, 107, 637.
15. Cognasse, F., Hamzeh-Cognasse, H., Lafarge, S., Delezay, O., Pozzetto, B., McNicol, A. and Garraud, O. 2008, Br. J. Haematol., 141, 84.
16. Berthet, J., Damien, P., Hamzeh-Cognasse, H., Arthaud, C.-A., Eyraud, M.-A., Zéni, F., Pozzetto, B., McNicol, A., Garraud, O. and Cognasse, F. 2012, Clin. Immunol., 145, 189.

17. Klinger, M. H. F. 1997, Anat. Embryol., 196, 1.
18. Yeaman, M. R. 1997, Clin. Inf. Dis., 25, 951.
19. Hamzeh-Cognasse, H., Damien, P., Chabert, A., Pozzetto, B., Cognasse, F. and Garraud, O. 2015, Front. Immunol., 6, 82.
20. Coppinger, J. A., Cagney, G., Toomey, S., Kislinger, T., Belton, O., McRedmond, J. P., Cahill, D. J., Emili, A., Fitzgerald, D. J. and Maguire, P. B. 2003, Blood, 103, 2096.
21. Kraemer, B. F., Campbell, R. A., Schwertz, H., Cody, M. J., Franks, Z., Tolley, N. D., Kahr, W. H. A., Lindemann, S., Seizer, P., Yost, C. C., Zimmerman, G. A. and Weyrich, A. S. 2011, PLoS Pathogens, 7, e1002355.
22. Youssefian, T., Drouin, A., Massé, J.-M., Guichard, J. and Cramer, E. M. 2002, Blood, 99, 4021.
23. Antczak, A. J., Vieth, J. A., Singh, N. and Worth, R. G. 2011, Clin. Vac. Immunol., 18, 210.
24. Riaz, A. H., Tasma, B. E., Woodman, M. E., Wooten, R. M. and Worth, R. G. 2012, Fems Immunol. Med. Micro., 65, 78.
25. Chakrabarti, S., Varghese, S., Vitseva, O., Tanriverdi, K. and Freedman, J. E. 2005, Arterio. Thromb. and Vasc. Biol., 25, 2428.
26. Zander, D. M. W. and Klinger, M. 2009, Biotech. J., 4, 914.
27. Claes, J., Vanassche, T., Peetermans, M., Liesenborghs, L., Vandenbriele, C., Vanhoorelbeke, K., Missiakas, D., Schneewind, O., Hoylaerts, M. F., Heying, R. and Verhamme, P. 2014, Blood, 124, 1669.
28. Flick, M. J., Du, X., Prasad, J. M., Raghu, H., Palumbo, J. S., Smeds, E., Hook, M. and Degen, J. L. 2013, Blood, 121, 1783.
29. Arman, M., Krauel, K., Tilley, D. O., Weber, C., Cox, D., Greinacher, A., Kerrigan, S. W. and Watson, S. P. 2014, Blood, 123, 3166.
30. Nguyen, T., Ghebrehiwet, B. and Peerschke, E. I. 2000, Inf. Immun., 68, 2061.
31. Vanassche, T., Kauskot, A., Verhaegen, J., Peetermans, W. E., van Ryn, J., Schneewind, O., Hoylaerts, M. F. and Verhamme, P. 2012, Thromb. Haemost., 107, 1107.
32. Svensson, L., Baumgarten, M., Morgelin, M. and Shannon, O. 2014, Inf. Immun., 82, 4307.
33. Keane, C., Tilley, D., Cunningham, A., Smolenski, A., Kadioglu, A., Cox, D., Jenkinson, H. F. and Kerrigan, S. W. 2010, J. Thromb. Haemost., 8, 2757.
34. Hamzeh-Cognasse, H., Cognasse, F., Palle, S., Chavarin, P., Olivier, T., Delezay, O., Pozzetto, B. and Garraud, O. 2008, BMC Immunol., 9, 54.
35. de Stoppelaar, S. F., van 't Veer, C., Claushuis, T. A., Albersen, B. J., Roelofs, J. J. and van der Poll, T. 2014, Blood, 124, 3781.
36. de Stoppelaar, S. F., Claushuis, T. A., Jansen, M. P., Hou, B., Roelofs, J. J., van 't Veer, C. and van der Poll, T. 2015, J. Thromb. Haemost., 13, 1709.
37. Vieira-de-Abreu, A., Campbell, R. A., Weyrich, A. S. and Zimmerman, G. A. 2012, Sem. Immunopath., 34, 5.
38. Domínguez, M. and Toraño, A. 2001, Parasite Immunol., 23, 259.
39. Yong, E. C., Chi, E. Y., Fritsche, T. R. and Henderson, W. R. 1991, J. Exp. Med., 173, 65.
40. Peyron, F., Polack, B., Lamotte, D., Kolodie, L. and Ambroise-Thomas, P. 1989, Parasitology, 99, 317.
41. McMorran, B. J., Marshall, V. M., de Graaf, C., Drysdale, K. E., Shabbar, M., Smyth, G. K., Corbin, J. E., Alexander, W. S. and Foote, S. J. 2009, Science, 323, 797.
42. Pain, A., Ferguson, D. J. P., Kai, O., Urban, B. C., Lowe, B., Marsh, K. and Roberts, D. J. 2001, PNAS, 98, 1805.
43. Grau, G. E., Mackenzie, C. D., Carr, R. A., Redard, M., Pizzolato, G., Allasia, C., Cataldo, C., Taylor, T. E. and Molyneux, M. E. 2003, J. Infec. Dis., 187, 461.
44. van der Heyde, H. C., Gramaglia, I., Sun, G. and Woods, C. 2005, Blood, 105, 1956.
45. Wassmer, S. C., Combes, V., Candal, F. J., Juhan-Vague, I. and Grau, G. E. 2006, Inf. Immun., 74, 645.
46. van der Heyde, H. C., Nolan, J., Combes, V., Gramaglia, I. and Grau, G. E. 2006, Trends Parasitol., 22, 503.

47. Srivastava, K., Cockburn, I. A., Swaim, A., Thompson, L. E., Tripathi, A., Fletcher, C. A., Shirk, E. M., Sun, H., Kowalska, M. A., Fox-Talbot, K., Sullivan, D., Zavala, F. and Morrell, C. N. 2008, Cell Host & Microbe, 4, 179.
48. Cox, D. and McConkey, S. 2010, Cell and Mol. Life Sci., 67, 557.
49. Aggrey, A. A., Srivastava, K., Field, D. J. and Morrell, C. N. 2013, J. Immunol., 190, 4685.
50. Torre, D. and Pugliese, A. 2008, Current HIV Research, 6, 411.
51. Terada, H., Baldini, M., Ebbe, S. and Madoff, M. A. 1966, Blood, 28, 213.
52. Ghosh, K., Gangodkar, S., Jain, P., Shetty, S., Ramjee, S., Poddar, P. and Basu, A. 2008, J. Elec. Micro., 57, 113.
53. Zahn, A., Jennings, N., Ouwehand, W. H. and Allain, J.-P. 2006, J. Gen. Vir., 87, 2243.
54. Solomon Tsegaye, T., Gnirß, K., Rahe-Meyer, N., Kiene, M., Krämer-Kühl, A., Behrens, G., Münch, J. and Pöhlmann, S. 2013, Retrovirology, 10, 48.
55. Iannacone, M., Sitia, G., Isogawa, M., Whitmire, J. K., Marchese, P., Chisari, F. V., Ruggeri, Z. M. and Guidotti, L. G. 2008, PNAS, 105, 629.
56. Loria, G. D., Romagnoli, P. A., Moseley, N. B., Rucavado, A. and Altman, J. D. 2013, Blood, 121, 940.
57. Hottz, E., Tolley, N. D., Zimmerman, G. A., Weyrich, A. S. and Bozza, F. A. 2011, Drug Discovery Today: Disease Mechanisms, 8, e33.
58. Rondina, M. T. and Weyrich, A. S. 2015, Blood, 126, 286-7.
59. Simon, A. Y., Sutherland, M. R. and Pryzdial, E. L. 2015, Blood, 126, 378.
60. Duerschmied, D., Suidan, G. L., Demers, M., Herr, N., Carbo, C., Brill, A., Cifuni, S. M., Mauler, M., Cicko, S., Bader, M., Idzko, M., Bode, C. and Wagner, D. D. 2013, Blood, 121, 1008.
61. Rossaint, J., Herter, J. M., van Aken, H., Napirei, M., Doring, Y., Weber, C., Soehnlein, O. and Zarbock, A. 2014, Blood, 123, 2573.
62. Pitchford, S. C., Momi, S., Giannini, S., Casali, L., Spina, D., Page, C. P. and Gresele, P. 2005, Blood, 105, 2074.
63. Lellouch-Tubiana, A., Lefort, J., Pirotzky, E., Vargaftig, B. B. and Pfister, A. 1985, Br. J. Exp. Path., 66, 345.
64. Amison, R. T., Momi, S., Morris, A., Manni, G., Keir, S., Gresele, P., Page, C. P. and Pitchford, S. C. 2015, J. Allergy Clin. Immunol., 135, 528.
65. Mine, S., Fujisaki, T., Suematsu, M. and Tanaka, Y. 2001, Internal Medicine, 40, 1085.
66. Page, C. and Pitchford, S. 2014, Clin. Exp. Allergy, 44, 901.
67. Durk, T., Duerschmied, D., Muller, T., Grimm, M., Reuter, S., Vieira, R. P., Ayata, K., Cicko, S., Sorichter, S., Walther, D. J., Virchow, J. C., Taube, C. and Idzko, M. 2013, Am. J. Respir. Crit. Care Med., 187, 476.
68. Kasperska-Zajac, A., Nowakowski, M. and Rogala, B. 2004, Inflammation, 28, 299.
69. Tamagawa-Mineoka, R., Katoh, N., Ueda, E., Masuda, K. and Kishimoto, S. 2009, Clin. Immunol., 131, 495.
70. Kasperska-Zajac, A. 2010, Platelets, 21, 522.
71. Garbaraviciene, J., Diehl, S., Varwig, D., Bylaite, M., Ackermann, H., Ludwig, R. J. and Boehncke, W. H. 2010, Exp. Dermatol., 19, 736.
72. Berrettini, M., Parise, P., Constantini, V., Grasselli, S. and Nenci, G. G. 1985, Thromb. Haemost., 53, 195.
73. Tamagawa-Mineoka, R., Katoh, N., Ueda, E., Takenaka, H., Kita, M. and Kishimoto, S. 2007, Am. J. Pathol., 170, 2019.
74. Hara, T., Shimizu, K., Ogawa, F., Yanaba, K., Iwata, Y., Muroi, E., Takenaka, M., Komura, K., Hasegawa, M., Fujimoto, M. and Sato, S. 2010, Am. J. Pathol., 176, 259.
75. Singbartl, K., Forlow, S. B. and Ley, K. 2001, FASEB J., 15, 2337.
76. Kuligowski, M. P., Kitching, A. R. and Hickey, M. J. 2006, J. Immunol., 176, 6991.
77. Devi, S., Kuligowski, M. P., Kwan, R. Y., Westein, E., Jackson, S. P., Kitching, A. R. and Hickey, M. J. 2010, Am. J. Pathol., 177, 1131.

78. Cognasse, F., Hamzeh-Cognasse, H., Lafarge, S., Chavarin, P., Cogne, M., Richard, Y. and Garraud, O. 2007, Exp. Hematol., 35, 1376.
79. Jin, R., Yu, S., Song, Z., Zhu, X., Wang, C., Yan, J., Wu, F., Nanda, A., Granger, D. N. and Li, G. 2013, PLoS One, 8, e64631.
80. Li, G., Sanders, J. M., Bevard, M. H., Sun, Z., Chumley, J. W., Galkina, E. V., Ley, K. and Sarembock, I. J. 2008, Am. J. Pathol., 172, 1141.
81. Martinson, J., Bae, J., Klingemann, H. G. and Tam, Y. 2004, Cytotherapy, 6, 487.
82. Setianto, B. Y., Hartopo, A. B., Gharini, P. P., Anggrahini, D. W. and Irawan, B. 2010, Heart and Vessels, 25, 282.
83. Laxmanan, S., Datta, D., Geehan, C., Briscoe, D. M. and Pal, S. 2005, J. Am. Soc. Nephrol., 16, 2714.
84. van Kooten, C., van der Linde, X., Woltman, A. M., van Es, L. A. and Daha, M. R. 1999, Kidney International, 56, 41.
85. Haller, S. T., Kalra, P. A., Ritchie, J. P., Chrysochou, T., Brewster, P., He, W., Yu, H., Shapiro, J. I. and Cooper, C. J. 2013, Hypertension, 61, 894.
86. Gudbrandsdottir, S., Hasselbalch, H. C. and Nielsen, C. H. 2013, J. Immunol., 191, 4059.
87. Ruf, A., Schlenk, R. F., Maras, A., Morgenstern, E. and Patscheke, H. 1992, Blood, 80, 1238.
88. Kaneider, N. C., Kaser, A., Tilg, H., Ricevuti, G. and Wiedermann, C. J. 2003, Int. J. Immunopath. and Pharmacol., 16, 225.
89. Gear, A. R. and Camerini, D. 2003, Microcirculation, 10, 335.
90. Lo, S. C., Hung, C. Y., Lin, D. T., Peng, H. C. and Huang, T. F. 2006, J. Biomed. Sci., 13, 787.
91. Vasina, E. M., Cauwenberghs, S., Feijge, M. A., Heemskerk, J. W., Weber, C. and Koenen, R. R. 2011, Cell Death & Disease, 2, e211.
92. McDonald, B., Urrutia, R., Yipp, B. G., Jenne, C. N. and Kubes, P. 2012, Cell Host & Microbe, 12, 324.
93. Brinkmann, V., Reichard, U., Goosmann, C., Fauler, B., Uhlemann, Y., Weiss, D. S., Weinrauch, Y. and Zychlinsky, A. 2004, Science, 303, 1532.
94. Clark, S. R., Ma, A. C., Tavener, S. A., McDonald, B., Goodarzi, Z., Kelly, M. M., Patel, K. D., Chakrabarti, S., McAvoy, E., Sinclair, G. D., Keys, E. M., Allen-Vercoe, E., Devinney, R., Doig, C. J., Green, F. H. and Kubes, P. 2007, Nat. Med., 13, 463.
95. Kraemer, B. F., Campbell, R. A., Schwertz, H., Cody, M. J., Franks, Z., Tolley, N. D., Kahr, W. H., Lindemann, S., Seizer, P., Yost, C. C., Zimmerman, G. A. and Weyrich, A. S. 2011, PLoS Pathog, 7, e1002355.
96. Langer, H. F., Daub, K., Braun, G., Schonberger, T., May, A. E., Schaller, M., Stein, G. M., Stellos, K., Bueltmann, A., Siegel-Axel, D., Wendel, H. P., Aebert, H., Roecken, M., Seizer, P., Santoso, S., Wesselborg, S., Brossart, P. and Gawaz, M. 2007, Arterioscler. Thromb. Vasc. Biol., 27, 1463.
97. Elzey, B. D., Sprague, D. L. and Ratliff, T. L. 2005, Cellular Immunology, 238, 1.
98. Henn, V., Slupsky, J. R., Grafe, M., Anagnostopoulos, I., Forster, R., Muller-Berghaus, G. and Kroczek, R. A. 1998, Nature, 391, 591.
99. Banchereau, J., Briere, F., Caux, C., Davoust, J., Lebecque, S., Liu, Y.-J., Pulendran, B. and Palucka, K. 2000, Ann. Rev. Immuno., 18, 767.
100. van Kooten, C. and Banchereau, J. 2000, J. Leuko. Bio., 67, 2.
101. Caux, C., Massacrier, C., Vanbervliet, B., Dubois, B., van Kooten, C., Durand, I. and Banchereau, J. 1994, J. Exp. Med., 180, 1263.
102. Borrow, P., Tishon, A., Lee, S., Xu, J., Grewal, I. S., Oldstone, M. B. and Flavell, R. A. 1996, J. Exp. Med., 183, 2129.
103. Schoenberger, S. P., Toes, R. E. M., van der Voort, E. I. H., Offringa, R. and Melief, C. J. M. 1998, Nature, 393, 480.
104. Bennett, S. R. M., Carbone, F. R., Karamalis, F., Flavell, R. A., Miller, J. F. A. P. and Heath, W. R. 1998, Nature, 393, 478.
105. Renshaw, B. R., Fanslow, W. C., Armitage, R. J., Campbell, K. A., Liggitt, D., Wright, B.,

Davison, B. L. and Maliszewski, C. R. 1994, J. Exp. Med., 180, 1889.
106. Yang, Y., Su, Q., Grewal, I. S., Schilz, R., Flavell, R. A. and Wilson, J. M. 1996, J. Virol., 70, 6370.
107. Han, S., Hathcock, K., Zheng, B., Kepler, T. B., Hodes, R. and Kelsoe, G. 1995, J. Immuno., 155, 556.
108. Elzey, B. D., Tian, J., Jensen, R. J., Swanson, A. K., Lees, J. R., Lentz, S. R., Stein, C. S., Nieswandt, B., Wang, Y., Davidson, B. L. and Ratliff, T. L. 2003, Immunity, 19, 9.
109. Kaneider, N. C. Kaser, A. Tilg, H., Ricevuti, G. and Wiedermann, C. J. 2003, Int. J. Immunopath. and Pharm., 16, 225.
110. Martinson, J. A., Bae, J. Klingemann, H. G. and Tam, Y. K. 2004, Cytotherapy, 6, 487.
111. Czapiga, M., Kirk, A. D. and Lekstrom-Himes, J. 2004, Exp. Hematol., 32, 135.
112. Hagihara, M., Higuchi, A., Tamura, N., Ueda, Y., Hirabayashi, K., Ikeda, Y., Kato, S., Sakamoto, S., Hotta, T., Handa, S. and Goto, S. 2004, J. Immuno., 172, 5297.
113. Verschoor, A., Neuenhahn, M., Navarini, A. A., Graef, P., Plaumann, A., Seidlmeier, A., Nieswandt, B., Massberg, S., Zinkernagel, R. M., Hengartner, H. and Busch, D. H. 2011, Nat. Immunol., 12, 1194.
114. Chapman, L. M., Aggrey, A. A., Field, D. J., Srivastava, K., Ture, S., Yui, K., Topham, D. J., Baldwin, W. M. and Morrell, C. N. 2012, J. Immuno., 189, 916.
115. Han, S. S. and Baker, B. L. 1964, The Anatomical Record, 149, 251.
116. Elton, C. M., Smethurst, P. A., Eggleton, P. and Farndale, R. W. 2002, Thrombo. Haemo., 88, 648.
117. Schulz, C., Leuschen, N. V., Fröhlich, T., Lorenz, M., Pfeiler, S., Gleissner, C. A., Kremmer, E., Kessler, M., Khandoga, A. G., Engelmann, B., Ley, K., Massberg, S. and Arnold, G. J. 2010, Blood, 115, 4102.
118. Rowley, J. W., Oler, A. J., Tolley, N. D., Hunter, B. N., Low, E. N., Nix, D. A., Yost, C. C., Zimmerman, G. A. and Weyrich, A. S. 2011, Blood, 118, e101.
119. Mitchell, W. B., Li, J., French, D. L. and Coller, B. S. 2006, Blood, 107, 2713.
120. Boshkov, L. K., Kelton, J. G. and Halloran, P. F. 1992, Br. J. Haemat., 81, 552.
121. Semple, J. W., Milev, Y., Cosgrave, D., Mody, M., Hornstein, A., Blanchette, V. and Freedman, J. 1996, Blood, 87, 4245.
122. Inwald, D. P., McDowall, A., Peters, M. J., Callard, R. E. and Klein, N. J. 2003, Circ. Res., 92, 1041.
123. Weber, K. C., Alon, R. and Klickstein, L. 2004, Inflammation, 28, 177.
124. Chaipan, C., Soilleux, E. J., Simpson, P., Hofmann, H., Gramberg, T., Marzi, A., Geier, M., Stewart, E. A., Eisemann, J., Steinkasserer, A., Suzuki-Inoue, K., Fuller, G. L., Pearce, A. C., Watson, S. P., Hoxie, J. A., Baribaud, F. and Pöhlmann, S. 2006, J. Virol., 80, 8951.
125. Koshiishi, I., Shizari, M. and Underhill, C. B. 1994, Blood, 84, 390.
126. Iannacone, M., Sitia, G., Isogawa, M., Marchese, P., Castro, M. G., Lowenstein, P. R., Chisari, F. V., Ruggeri, Z. M. and Guidotti, L. G. 2005, Nat. Med., 11, 1167.
127. Elzey, B. D., Schmidt, N. W., Crist, S. A., Kresowik, T. P., Harty, J. T., Nieswandt, B. and Ratliff, T. L. 2008, Blood, 111, 3684.
128. Sowa, J., Crist, S., Ratliff, T. and Elzey, B. 2009, Arch. Immunol. Ther. Exp., 57, 235.
129. Gerdes, N., Zhu, L., Ersoy, M., Hermansson, A., Hjemdahl, P., Hu, H., Hansson, G. K. and Li, N. 2011, Thromb. Haem., 106, 353.
130. Zhu, L., Huang, Z., Stålesen, R., Hansson, G. K. and Li, N. 2014, J. Thromb. Haemos., 12, 1156.
131. Taub, D. D., Turcovski-Corrales, S. M., Key, M. L., Longo, D. L. and Murphy, W. J. 1996, J. Immunol., 156, 2095.
132. Gojova, A., Brun, V., Esposito, B., Cottrez, F., Gourdy, P., Ardouin, P., Tedgui, A., Mallat, Z. and Groux, H. 2003, Blood, 102, 4052.
133. Fleischer, J., Grage-Griebenow, E., Kasper, B., Heine, H., Ernst, M., Brandt, E., Flad, H.-D. and Petersen, F. 2002, J. Immunol., 169, 770.

134. Liu, C. Y., Battaglia, M., Lee, S. H., Sun, Q.-H., Aster, R. H. and Visentin, G. P. 2005, J. Immunol., 174, 2680.
135. Elzey, B. D., Grant, J. F., Sinn, H. W., Nieswandt, B., Waldschmidt, T. J. and Ratliff, T. L. 2005, J. Leuko. Biol., 78, 80.
136. Valone, F. H., Austen, K. F. and Goetzl, E. J. 1974, J. Clin. Invest., 54, 1100-6.
137. Lowenhaupt, R. W., Silberstein, E. B., Sperling, M. I. and Mayfield, G. 1982, Blood, 60, 1345.
138. Czapiga, M., Gao, J. L., Kirk, A. and Lekstrom-Himes, J. 2005, Exp. Hematol., 33, 73.
139. Varon, D. and Shai, E. 2015, J. Thromb. Haemost., 13(Suppl. 1), S40-6.