

Effects and Side Effects of Platelet Transfusion

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Abstract

Aside from their canonical role in hemostasis, it is increasingly recognized that platelets have inflammatory functions and can regulate both adaptive and innate immune responses. The main topic this review aims to cover is the proinflammatory effects and side effects of platelet transfusion. Platelets prepared for transfusion are subject to stress injury upon collection, preparation, and storage. With these types of stress, they undergo morphologic, metabolic, and functional modulations which are likely to induce platelet activation and the release of biological response modifiers (BRMs). As a consequence, platelet concentrates (PCs) accumulate BRMs during processing and storage, and these BRMs are ultimately transfused alongside platelets. It has been shown that BRMs present in PCs can induce immune responses and posttransfusion reactions in the transfusion recipient. Several recent reports within the transfusion literature have investigated the concept of platelets as immune cells. Nevertheless, current and future investigations will face the challenge of encompassing the immunological role of platelets in the scope of transfusion.

Keywords

- ▶ platelet physiology
- ▶ transfusion medicine
- ▶ inflammatory mediators

The primary role of platelets is to maintain hemostasis.¹ However, platelets can also be actively involved in the inflammatory response by interacting with endothelial cells and circulating leukocytes.^{2,3} Either through direct interactions or the release of soluble mediators, platelets can influence both innate (neutrophils, monocytes, and macrophages) and adaptive immune cells (lymphocytes). Platelets communicate with the immune system to recruit and initiate an inflammatory response^{4–6} and, also by virtue of their number in circulation, can therefore be considered the primary sentinels of the bloodstream.² Aside from initiation, platelets also have a recently appreciated role in resolving inflammation. Platelets

contribute to this resolution in several ways, including interaction and modification of immune (T cells, neutrophils, and macrophages) and nonimmune cells (endothelial cells). Aside from their earlier-described role in *in vivo* inflammation, many biochemical and functional modifications occur during the process of storing platelets for transfusion. These changes, called “storage lesions,” include acidification of the storage medium secondary to anaerobic platelet metabolism, platelet activation, and an increase in biological response modifiers (BRMs) and lipids level in platelet concentrates (PCs). These storage lesions can compromise the viability and change the functionality of the platelets to a more proinflammatory

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phenotype, which ultimately reduces efficacy of the transfusion. In recipients, these changes can also contribute to transfusion reactions.⁷ Below, we discuss how platelet-related inflammation can influence the composition, and ultimately the clinical utility, of PCs.

Inflammatory Roles of Blood Platelets

The role of platelets in inflammation includes the recognition of pathogens, due mainly to the expression of receptors from the Sialic acid-binding immunoglobulin-like lectins (SIGLEC)^{8,9} or toll-like receptor (TLR) families.^{10–13} These are transmembrane receptors which recognize bacterial, viral, or parasite patterns and induce the release of proinflammatory cytokines by immune cells, including platelets. For example, platelets primarily hold TLR-2, TLR-4, and TLR-9 functional receptors, which are capable of stimulating platelet activation, while TLR-3 and TLR-7 are more heavily involved in platelet-viral interactions.^{14–16} The presence of TLRs on and within platelets suggests that they are immune effector cells, that they play a role in surveillance and pathogen detection, and that they are able to transfer information to other immune cells.

Aside from receptor expression, activated platelets secrete or express more than 5,000 proteins or lipids that play a role in hemostasis as well as the platelet's inflammatory function.^{17–19} These mediators are primarily contained in α or dense granules and are mostly preformed and stored. Through these various molecules, blood platelets can be described as tremendously diverse in terms of function and are able to respond to a wide range of inflammatory scenarios by their diversity in secretion mechanisms and diversity of cellular targets.

To speak to the diverse function of platelet secretory products, some of these molecules promote the interaction of platelets with leukocytes, plasma proteins, and endothelial cells (e.g., CD62P [P-selectin]). Others promote the recruitment and activation of immune cells at the site of inflammation such as PF4 (platelet factor 4), RANTES (regulated upon activation, normal T cell expressed and secreted), or platelet-derived microparticles (PMPs). This is not to mention soluble CD40L (sCD40L), which plays a pivotal role between innate and adaptive immunity.^{3,20–22} This list (–Table 1) is nonexhaustive, and we will define a few of these factors later. Given the importance of these secretory mediators for the immune function of platelets, it is incredibly useful to understand how these platelet-derived components can modulate the composition of PCs during storage. In the following section, we also highlight specific examples where these mediators have been investigated in the context of transfusion products.

- One of the essential platelet receptors for direct contact with myeloid cells and stimulated T lymphocytes is CD62P.^{23–26} CD62P is stored in the membrane of platelet α -granules and is then exposed on the membrane surface during platelet activation. Exposure of CD62P on the platelet membrane is used as a marker for degranulation and activation. When exposed on the membrane, CD62P is

able to bind to its receptor, PSGL-1 ligand (P-selectin glycoprotein ligand 1), and primarily expressed on the surface of neutrophils, monocytes, and dendritic cells. This CD62P/PSGL-1 bond enables the recruitment of immune cells to the site of injury, the formation of platelet-leukocyte aggregates, and the activation of myeloid cells and stimulated T lymphocytes via PSGL-1 intracellular signaling. Furthermore, once blood platelets are activated, CD62P can be cleaved and becomes soluble. Soluble CD62P is one of the characteristic markers of platelet activation. Soluble CD62P concentrations differ in apheresis PCs (APCs) and buffy coat-derived PCs.²⁷

- PF4 (CXCL4), contained in α -granules,^{28–30} is one of the most abundant chemokines in the platelet. Belonging to the family of CXC chemokines, CXCL4 is recognized by the CXCR3A and CXCR3B receptors, as well as by glycosaminoglycans present on target cells.^{31,32} CXCL4 is heavily involved in inflammation. In vitro, it is a chemotactic molecule for neutrophils and monocytes²⁸ and also promotes the survival of monocytes and supports macrophage differentiation.³¹ CXCL4 also plays an anti-inflammatory role, as it inhibits T-lymphocyte proliferation and guides their differentiation to a TH2 phenotype.³³ Furthermore, CXCL4 is capable of activating endothelial cells and inducing the expression of E-selectin in human umbilical vein endothelial cells.³⁴ Apseth et al³⁵ demonstrated CXCL4 was detected within PC and showed a significant increase during storage.
- RANTES, also stored in α -granules, is released in soluble form during platelet activation.^{36,37} It has been shown that RANTES acts in synergy with P-selectin expressed on the platelet surface to induce the synthesis of monocyte chemoattractant protein-1 (MCP-1) by monocytes.³⁸ RANTES released by platelets can also immobilize on the surface of the activated endothelium and thus promote the recruitment of monocytes.³⁹ As a factor released by platelets, RANTES accumulates in PCs during storage even after leukoreduction.⁴⁰ We know that, like sCD40L, RANTES is the cause of several transfusion reactions.^{41,42} Nogawa et al showed that sCD40L and RANTES concentrations increased more slowly in SSP+ platelet additive solution (PAS), Composol, and M-Sol compared with Intersol. This suggests that the accumulation behavior of platelet-derived bioactive substances like RANTES or sCD40L depends on the PAS used.⁴³
- Platelet microparticles are the most abundant microparticles in the bloodstream.⁴⁴ They are involved in maintaining vascular homeostasis by preserving endothelial function but may also initiate a harmful process if they are excessively released or if they express inflammatory components. In fact, PMPs expose a procoagulant surface⁴⁵ and act as transporters for bioactive molecules, namely, growth factors, signaling molecules, and genetic material, including messenger RNA (mRNA), microRNA, and mitochondrial DNA (mtDNA).⁴⁵ PMPs can transfer their contents to vascular endothelial cells and regulate the expression and function of recipient cell genes.⁴⁵ During inflammation, PMPs can

Table 1 Characteristics and physiological roles of platelet-released major biological response modifiers (this list is nonexhaustive)

	Source	Ligand	Function	Refs.
CD62P (P-selectin)	<ul style="list-style-type: none"> • Endothelial cells • Platelets 	<ul style="list-style-type: none"> • P-selectin glycoprotein ligand-1 • Heparan sulfate • Fucoidans 	<ul style="list-style-type: none"> • Initial recruitment of leukocytes • Recruitment and aggregation • Helps cancer cells invade into the bloodstream for metastasis • Contribute to the seeding of tumor microemboli in distant organs • Inflammatory reaction 	113–118
PF4 (CXCL4)	<ul style="list-style-type: none"> • Platelets 	<ul style="list-style-type: none"> • CXCR3B 	<ul style="list-style-type: none"> • Promotes inflammatory fibrosis • Promotes blood coagulation by moderating the effects of heparin-like molecules • Play a role in wound repair and inflammation • Strong chemoattractant for neutrophils, monocyte, and fibroblasts 	119–122
RANTES (CCL5)	<ul style="list-style-type: none"> • Platelets • T cells 		<ul style="list-style-type: none"> • Chemotactic for T cells, eosinophils, and basophils, and plays an active role in recruiting leukocytes into inflammatory sites • Induces the proliferation and activation of certain natural-killer (NK) cells to form CHAK (CC-chemokine-activated killer) cells • Natural HIV-suppressive factor 	123–126
Platelet microparticles (PMPs)	<ul style="list-style-type: none"> • Platelets 		<ul style="list-style-type: none"> • Transport and delivery system for bioactive molecules • Participating in: <ul style="list-style-type: none"> i. Hemostasis and thrombosis ii. Inflammation iii. Malignancy infection transfer iv. Angiogenesis v. Immunity 	45,127–131
CD154 (sCD40L)	<ul style="list-style-type: none"> • T cells • Platelets • Mast cells • Macrophages • Basophils • NK cells • B lymphocytes • Smooth muscle cells • Endothelial cells • Epithelial cells 	<ul style="list-style-type: none"> • CD40 • $\alpha 5\beta 1$ integrin • $\alpha 11\beta 3$ 	<ul style="list-style-type: none"> • Promotes B-cell maturation • Costimulation and regulation of the immune response • Activation of endothelial cells by CD40L leads to reactive oxygen species production, as well as chemokine and cytokine production, and expression of adhesion molecules such as E-selectin, ICAM-1, and VCAM-1. • Promotes recruitment of leukocytes to lesions and may potentially promote atherogenesis 	132–137

activate antigen-presenting cells, modulate dendritic cell activation, increase T-cell responses, induce immunoglobulin G (IgG) production by B cells, and improve formation of the germinal center in cooperation with T cells.^{45–47} Marcoux et al suggest that PMPs, such as those which carry mitochondrial damage-associated molecular patterns (mtDAMPs), may be a useful biomarker for predicting the potential risk of transfusion reactions.⁴⁸ In addition, this work implies that further research is needed to determine if mtDAMPs encapsulated in PMPs are associated with a causal pathogenic role compared with mtDAMPs in solution.⁴⁹

On their surface, activated platelets express CD40L, which is also found in soluble form (sCD40L) in the bloodstream.^{50,51} The endothelium is a key target of platelet CD40L, but CD40L also plays both direct and indirect roles in the inflammatory

response, coagulation, tissue remodeling, and defense against infections, with all of these processes overlapping at several levels. At the endothelium, platelet CD40L induces the expression of proinflammatory and chemotactic molecules and the expression of adhesion molecules (e.g., CD62E, CD54, and CD106), leading to the recruitment and activation of leukocytes.^{25,52,53} Once activated, these target cells can recruit and, in turn, activate other cells. Several amplification loops are thus generated, including platelet activation by soluble CD40L itself.^{3,25} The detrimental role of platelet CD40L has been demonstrated in inflammatory pathological conditions like atherosclerosis^{37,54} and systemic lupus erythematosus.^{55,56} sCD40L is described as being partly responsible for certain transfusion reactions following platelet transfusions,^{7,52,57,58} and levels of this molecule are widely thought to be modulated according to processing and storage of PCs.

In conclusion, the mediators released by activated platelets increase the recruitment of blood cells at the vascular wall, thus participating in inflammation, immune processes, vessel repair, and regeneration after injury. Therefore, blood platelets from PCs used in blood transfusions should also be considered to have these inflammatory properties described earlier.

PC Preparation and Storage Lesions Promote Secretion of Biological Response Modifiers

Platelet transfusions are crucial due to thrombocytopenia, but they can be associated with both immediate and delayed transfusion reactions. There is a great deal of literature concerning the characterization and the nature of these transfusion reactions.^{22,59–62} The most frequent complications associated with PC transfusions are allergic reactions and febrile nonhemolytic transfusion reaction (FNHTR), while other (e.g., transfusion-associated circulatory overload, bacterial sepsis, transfusion-related acute lung injury, and posttransfusion purpura) occur less frequently.

PCs, like other blood products, are living cellular products with a limited life span. As such, platelets prepared for transfusion suffer stress-induced lesions during collection, preparation, and storage.^{7,63,64} Platelet storage lesions are defined as alterations that occur at any point in the process from drawing blood to transfusion. Thus, the secretion of BRMs during *ex vivo* processing of platelets^{7,27,63–67} is an example of a platelet storage lesion that modifies the platelet structure and function.

As mentioned in the previous section, many platelet-derived secretory mediators are released during PC storage. An increase in the general inflammatory milieu of PCs is likely to play a direct role in triggering transfusion reactions. For example, our previous study provides new information on the link between sCD40L and transfusion reactions: the level of sCD40L was significantly elevated in PCs that triggered transfusion reactions, and the storage duration of PCs is associated with an increase in secretion of sCD40L.⁵⁷

Some studies have shown that platelets were able to change morphologically based on the methods used to prepare PCs.^{68–72} These different preparation techniques differentially affect platelet physiology because they do not expose the platelets to the same stresses.^{73,74} During the preparation of PCs, platelets are subjected to numerous types of stress, especially in relation to the shear stress inflicted by centrifugation, as well as the way the packs are processed, for example, leukoreduction (by filtration), the use of different preservative/additive solutions, irradiation, and/or the use of pathogen inactivation/reduction treatments. Furthermore, it has been demonstrated that platelet degranulation and vesiculation are influenced by preparation techniques.^{75,76} In fact, Noulis et al have shown that PMP secretion varies based on the different preparation processes used.⁷⁷ In this study, the authors show that the type of apheresis employed activates platelets differently. This was particularly evident with apheresis using the Amicus instrument, where the percentage of both platelet and PMP activation was significantly higher than in other PCs.⁷⁷ Amicus apheresis seems to activate platelets more so than

when compared with the other types of apheresis, namely, Trima.⁷⁸ Another study showed that the PMP content in PCs is predicted by the PMPs present in the donors,⁷⁹ indicating the potential for the donor's inflammatory status to influence that of the recipients posttransfusion. The way PCs are processed also has a direct impact on the production of platelet cytokines and chemokines. For example, one study showed that the reduction of pathogens using UVC light increases cytokine accumulation.⁸⁰

Platelet storage lesions include the appearance of platelet activation markers, morphological changes, mitochondrial dysfunction, loss of glycoprotein Ib α expression, and secretion of α -granules.^{58,81} This may be linked to transfusion reactions incidence, which has been observed to increase as storage time lengthens. To lessen this incidence, we can suggest that PCs should be transfused as soon as possible taking into account the specificities of PCs stock and therapeutic indications. However, this conclusion should be considered relative to both the constraint of production and delivery of PCs and based on the demand for products from healthcare facilities. Our team showed that the concentration of these BRMs—sCD40L in particular—increases significantly starting on the third day of PC storage.⁸² Furthermore, sCD40L induces the production of reactive oxygen species (ROS) during PC storage, causing an increase in production and release of proinflammatory molecules.⁸³ These observations suggest that storage lesions have a major effect on PC-induced inflammation.

How PCs are processed during preparation and storage may affect platelet activation. Leitner et al showed that the extent of initial platelet activation—as reflected in CD62P expression—was significantly greater when platelets were stored in Intersol than when other additive solutions (Composol and SSP +) were used.⁸⁴ Nevertheless, platelet storage in an additive solution has some benefits, including a reduction in the incidence of transfusion reactions,^{69,85} compared with retaining the plasma as the supernatant. To date, pooled PCs (PPCs) and APCs are comparable in quality, but Daurat et al showed transfusion reactions to be associated with PPCs less frequently than with APCs.⁸⁶ These findings suggest that APCs, currently in widespread use, should be limited to specific indications. For any given medical indication, a risk-benefit evaluation considering each kind of PC should allow prescription of the best product. Storage lesions triggered by extrinsic factors (preparation methods) or intrinsic factors (plasma and platelet factors, residual leukocytes) might be largely responsible for a reduction not only in the therapeutic efficacy of PC transfusion but also in the increase in the rate of transfusion reactions.^{87–90}

Numerous studies have shown that sCD40L is involved in reactions following PC transfusion.^{3,21,64,65,91–93} We have also shown that other soluble factors, such as IL-27 and sOX40L, are involved in FNHTRs.⁹⁴ Mathematical models using machine learning have shown transfusion reactions to be very reliably predicted by several other soluble factors, including sCD40L, IL-13, and macrophage inflammatory protein (MIP)-1 α .⁹⁵ Indeed, this study showed that the concentration of sCD40L and IL-13 is correlated with the occurrence of transfusion reactions. In addition, the

concentration of MIP-1 α in supernatants associated with transfusion reactions appears to determine the type of transfusion reactions that occurs: FNHTRs or allergic reaction.

PCs also contain mtDNA, which has been linked to transfusion reactions.^{49,96–98} In fact, Boudreau et al showed that activated platelets release mitochondria, both in encapsulated microparticles and as free organelles. The levels of extracellular mitochondria found in transfused PCs are higher in those having caused transfusion reactions (FNHTR cutaneous and cardiovascular symptoms) in transfusion patients.⁹⁹

In addition to cytokines and chemokines, PMPs, which are important mediators of inflammation and immune response regulation, also seem to be involved in the occurrence of transfusion reactions.^{3,65,100,101} PMPs containing microRNA may also be involved in a pathophysiological response following a PC transfusion. Furthermore, studies have shown that pathogen reduction technologies, which are designed to reduce the potential risk of transfusion-transmitted infections, induce platelet activation and alter mRNA and microRNA levels.^{102,103} These changes in RNA are correlated with an increase in PMP concentration. Consequently, it seems likely that pathogen reduction technologies may also increase the formation of PMPs in PCs.

We recently showed that soluble high mobility group box 1 (HMGB1) levels are also heavily associated with transfusion reactions.¹⁰⁴ It is worth noting that HMGB1 present in PCs is a RAGE (Receptor for Advanced Glycation End-Products), TLR-2, TLR-4, and TLR-9 ligand.^{105–108} As such, HMGB1 is considered a DAMP. Receptors such as TLRs, expressed on and within platelets, can recognize various ligands including HMGB1 and, in turn, induce a receptor-dependent response. A single TLR can recognize several PAMPs and DAMPs, and the structural and molecular mechanisms acting as mediators have so far not been extensively studied. Simultaneous signaling within platelets can modulate the response following the involvement of TLRs. Accordingly, this level of complexity makes studying the platelet inflammatory responses induced by PAMPs and DAMPs difficult, though no less fascinating. As platelets are effectors of hemostasis, inflammation, and the immune *continuum*,¹⁰⁹ it is also interesting to consider the platelet response in situations where infectious (sepsis, HIV, COVID, etc.) and noninfectious (transfusion, vascular inflammation, autoimmune disease, etc.) contexts meet.

Donor factors possibly affect BRM content, particularly microparticles, in PCs, although this point remains generally uninvestigated. To highlight this point, Highton et al¹¹⁰ suggested that acute exercise can increase circulating PMP counts, but regular exercise training can diminish this effect and eventually reduce overall resting MP counts, partially preventing their pathophysiological effects. We can extrapolate these observations to blood donors and evaluate how exercise affects the number and function of microparticles after blood donation. As mentioned earlier, the PMP content in PCs is correlated with the levels of PMPs present in the donors,⁷⁸ which may adversely affect the inflammatory status of the recipient. Melki et al¹¹¹ elegantly suggest

that cell-derived extracellular vesicles are not restricted to pathological onset. In fact, MPs circulate in variable concentrations, also with variable half-times in blood vasculature at a steady state. The physiological functions of PMPs in healthy individuals, and with extrapolation to blood donors, are still not completely understood. Finally, Vafeiadou et al assessed the evidence for the effects of total dietary fat and individual fatty acids on vascular function, cellular microparticles, and endothelial progenitor cells.¹¹² Ultimately, the authors suggest that diet before donation could influence the content of inflammatory mediators in blood products.

Conclusion/Outlook

The various data found in the literature consolidate the hypothesis that activation of the platelets in PCs may directly play a role in an inflammatory response within the recipient posttransfusion. To minimize the risk of transfusion reactions, consideration should be given to reducing the concentration of sCD40L and other BRMs identified as being involved in such reactions, especially those that accumulate in storage.

A transfusion of labile blood products involves elements related to the donor, the product, and the recipient. The systematic—not individual—study of these three elements in transfusion medicine will lead to personalized medicine, that is, the ability to select a PC (and more generally a labile blood product) for transfusion based on its composition (including BRM levels) and the recipient's disease. By taking into account the characteristics of the three “actors” in transfusion (donors, products, and patients) and analyzing databases using machine-learning type biomathematics tools, we will be able to optimize the delivery of the best product to treat each patient in a precise and personalized manner.

Conflict of Interest

The authors declare that they have no conflict of interest.

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