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The Role of Platelets in Host Defence Against Pathogens

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Abstract

Platelets are a type of inflammatory cell. As a result, they exhibit characteristics similar to those of a traditional cell-mediated immune effector cell. Platelets are known to contain and can be stimulated to release a variety of bioactive molecules. These molecules aid in the regulation of vascular tone, increased tissue adhesion, increased vascular permeability, clot dissolution, wound healing, and tissue regeneration. Platelets have traditionally been associated with all of these functions as a cell that maintains haemostasis. Platelets rapidly respond to endothelial trauma as well as chemotactic stimuli associated with microbial colonization, and as a result, they are the earliest and most abundant cells found at sites of microbial colonization of vascular endothelium. They express inducible surface receptors and have cytoplasmic granules similar in structure and function to neutrophils, monocytes, or macrophages.

***Keywords**: Platelets, Host, Defence, Pathogens*

Introduction

Platelets are the second most abundant cells in human blood(1), In normal circumstances, human platelets circulate within the peripheral blood(2) as senescent cells and usually do not bind to vascular endothelium or leukocytes. Platelets display sensitive and multiples of constitutive and inducible receptors on their membrane that are highly responsive to diverse array of agonists associated with tissue damage or inflammation. Following activation, platelets change from normal discoid shape and become amoeboid cells that exhibit inducible membrane receptors mediating the increased adhesion of this cells to tissues. On this regard, platelets have been recognized for long in their ability to maintaining haemostasis and for their contribution to wound healing. However, platelets have historically been overlooked or unrecognised for their important contributions in antimicrobial host defence (1).

Platelets are believed to exhibit important structural and functional characteristics that are associated with their participation in host defence against infectious pathogen. For example, platelets rapidly respond to agonists associated with vascular trauma or infection and accumulate at sites of endothelial damage or microbial colonization, and hence, are recognise as inflammatory cells. Activation of platelets by agonists generated in this occasion of bacterial colonisation enhances platelet ability to interact with complement system proteins and humoral immune components of host defence, as well as leukocytes and endothelial cells. Likewise, molecules

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generated by activated endothelial cells and leukocytes enhance platelet antimicrobial responses toward the pathogen (2).

Platelets have been recognised to have the ability of binding, aggregating, and internalizing microorganisms, which enhances the clearance of pathogens from the circulation(3). Platelets participate in antibody dependent cell cytotoxicity functions especially in killing protozoal pathogens. When platelet got stimulated by microorganisms or agonists generated in the setting of infection(4), they release an array of potent antimicrobial peptides. On the basis of these observations, platelets are believed to significantly contribute to antimicrobial host defence(5).

It has also been shown recently that, response of platelets to infections or infectious agent goes beyond a simple fall in platelets count; evidence has shown that, sepsis-induced thrombocytopenia can be associated with or even anticipated by several changes in platelet, which among others include an altered morphological pattern, receptor expression and aggregation(2).

Platelets are tiny (2–4 μm), discoid cells that are from megakaryocyte line. they have a life span of about 5–10 days in the peripheral blood circulation. These anucleate cells can perform protein translation using stable mRNA templates inherited from their megakaryocyte precursors. Mature platelets possess three different types of cytoplasmic granules. Which are; Dense (δ) granules, that are rich in mediators of vascular tone, such as serotonin, adenosine diphosphate (ADP), calcium, and phosphate. In contrast, alpha (α) granules store proteins that are specialized to platelet's haemostatic functions, including adhesion (e.g., fibrinogen, thrombospondin, vitronectin, laminin, and von Willebrand factor), coagulation (e.g., plasminogen and α2-plasmin inhibitor), and endothelial cell repair (e.g., platelet-derived growth factor (PDGF), permeability factor, and transforming growth factors a and b (TGF-a and TGF-b)). Platelet α -granules also store different types of microbicidal proteins. And lysosomal (λ) granules house enzymes that control thrombus dissolution. Upon activation, platelets respond in specific ways that emphasize their devised roles in antimicrobial host defence, including among others; Activated metabolic status, Metamorphosis from discoid shape to ameboid shape(4), Display of receptors mediating increased adhesivity to injury site or infected tissues, Facilitated movement toward and intensification at sites of tissue injury or infection, Production of reactive oxygen species including superoxide, peroxide, and hydroxyl radicals, Spreading of pseudopodia that interact with microbial pathogens as well as host cells, Cytoskeletal remodelling to enhance granule mobilization and organization and Release of granules and processing of preformed granule molecules, including host defence peptides. The specific platelet granules are subject to synchronous or dyssynchronous release, depending upon the nature (specificity and potency) of agonist. For example, low levels of thrombin or ADP induce δ and α degranulation, whereas λ granules are not secreted until such agonists accumulate to much higher concentrations(5).

Platelets: the Other White Cells

In higher organisms including mammals, platelets, leukocytes, and lymphocytes are often viewed as independently cells mediating haemostasis, inflammation, and immune regulation, respectively(6). Of course, these cells interact with one another in many ways to prevent the host form harm. Nonetheless, while human platelets may be best known for their characteristic

maintenance of haemostasis, these understudied cells have retained features of atypical inflammatory cells corresponding to multiple functions in antimicrobial host defence. The role of Platelet in host defence have been the topic of recent discussion. Thus, the focus of the following discussion in this paper is to provide a solid framework of understanding the antimicrobial structures as well as the functions of platelets in host defence against pathogens(5).

Platelets Ability to Sense Bacterial Infection of Endothelium

Beyond their ability to detect microbes themselves, platelets are exquisite sensors for signals of endothelial infection. Endothelial cells damaged by infection undergo changes in surface protein repertoires and secretory profiles that activate platelet responses. Distinct platelet receptors sense agonists and bind to ligands on the surface of activated endothelial cells, or exposed subendothelium due to infection or tissue invasion. Signals detected by platelet membrane glycoprotein (GP) receptors include; collagen [(GPVI and a2b1 (VLA-2or GPIa-IIa), fibronectin (a5b1 or VLA-5)], laminin (VLA-6), von Willebrand factor (GPIb-IX-V), vitronectin (integrin aVb3), and thrombin](7). Contact with blood or microbes induces tissue factor release from subendothelial stroma, thereby catalysing thrombin production. Thrombin is a potent platelet agonist (8), which induces expression of potent platelet receptors, including the fibrinogen receptor (integrin aIIbb3 [GPIIb-IIIa]). Activated platelets also undergo metamorphosis from a discoid to ameboid form, along with microtubule assembly and granule reorganization(2). Degranulation follows, releasing an array of bioactive molecules, including ADP from δ-granules, and generating thromboxane A2 and platelet-activating factor (PAF) through activation of membrane phospholipase A2. These potent agonists trigger subsequent waves of platelet activation at sites of tissue colonization, promoting an accumulation of antimicrobial proteins from α-granules. In addition, P-selectin (CD62P) is exposed on the activated platelet plasma membrane, potentiating leukocyte rolling and eventual recruitment to this cell to the sites of infection(5).

Platelet Share Structural and Functional Features with Known Host Defense Cells

The believe that thrombocyte will protect host against infection or infectious pathogen is supported by many specific observations that are closely related to the nature of platelet structure and function. Just like professional phagocytic cells, the platelet cytoplasm predominantly consists of granules that contain bioactive molecules against pathogens(5). Platelets like immune effector and phagocytic cells such as neutrophils and monocytes also share common surface antigens receptor as seen in figure 1. These among others include P-selectin (GMP-140), the 40-kD FcgRII receptor, the Fce receptor for IgE, C-reactive protein, and the thrombospondin receptor CD36 (platelet GP-IV). Platelets also express the complement CR3 receptor and respond to presence of cytokines such as TNF-a, IL-1, and IL-6 in a way similar to white cells. These features suggest that platelets possess structural and functional characteristics that facilitate their important role in antimicrobial host defence(6).

Platelets are also found to perform additional functions that mimic their similarities to cell mediated immune effector cells. By their ability to accumulate at sites enriched in stimuli such as *N*-formyl-methionyl-leucyl-phenylalanine (*N-f*- met-leu-phe) or complement proteins such as C3a

and C5a. This support that, platelets exhibit positive chemotactic responses to stimuli present at site of infection and or injury. Platelets are also believed to be capable of interacting directly and or indirectly with a broad array of microbial pathogens both in vitro and in vivo just like other host defence cells. Platelets also have been shown to have the ability to internalise microorganisms into phagosome-like vacuoles, this mechanism help to enhance pathogen clearance from the circulation(5).

Platelets that are stimulated with certain agonists or microorganisms are capable of producing reactive oxygen species (ROS) on various pathways, using membrane oxidases, nitric oxide (NO) synthesis, initiating metabolism of arachidonic acid, phosphoinositol and glutathione cycle. The process of platelet activation is initiated among other, by thrombins, collagen, tromboxan A2, ADP. Most of these factors interact with receptors located on the platelet surface. Platelets and neutrophils are able to create aggregates due to expression of platelet-derived P-selectin and its ligand PSGL-1, and by fibrinogen bridges between platelet glycoprotein GP IIb/IIIa and neutrophilic CD11b/CD18. These types of junctions may facilitate interactions between the cells. The interaction between phagocytic cells and bacteria induces activation of membrane oxidase which in turn triggers a metabolic response as respiratory burst in phagocyte. A number of ROS such as singlet oxygen, hydroxyl radical, superoxide anion is formed during that process. Thus, facilitating destruction of pathogens, similar to neutrophils and macrophages(9).

In the presence of IgE, platelets exhibit cytotoxic capabilities against microfilariae, and in the presence of C-reactive protein, they exhibit cytotoxic activity against *Schistosoma*. many investigations have been reported to shown that platelets inhibit growth of bacterial pathogens or kill these organisms(5). As it will be discussed below, thrombocyte combine directly and indirectly with a diverse array of microbial pathogens, and can engulf microorganisms, this is likely to enhance pathogen removal from the circulation.

Platelet Bridge Both Innate and Adaptive Immunity

Platelet Ability to Recognise Presence of Pathogens

Platelets make an array of constitutive and inducible receptors that confer these cells the ability to sense and respond to hallmark signals of infectious pathogens(5).

Similar to innate host defence cells, platelets also contain pattern recognition receptors (PRRs), which help to identify different components that increase during infection. Different families of PRRs are displayed on platelets, which among others include TLRs (Toll-like receptors), CLRs (C-type lectin receptors), and NLRs (NOD [nucleotide-binding oligomerization domain]-like receptors). interaction of these receptors by pathogens or antigens generally leads to platelet activation, and thus results in differential granules release, and subsequent interaction with leukocytes, this specifically allowing platelets to act as both thrombotic and immune cells(7).

Toll Like Receptor

TLR1, 2, 3, 4, 6, 7, and 9 have been reported to be functional in platelets (Fig 2A)(11) . although, TLR2 and 4 are the best characterized platelet PRRs, and both of them recognize structural components of pathogens, most especially bacterial pathogen. TLR4 is specifically for recognising the Gram-negative bacterial cell wall component lipopolysaccharide, hence activation of platelet

TLR4 is linked to different aspects of the pathogenesis of sepsis (11). Many studies have attempted to examine the role of TLR4 agonists, In, general, studies have shown that, lipopolysaccharide directly induces cytokine release, including sCD40L (soluble CD40 ligand) and platelet activation factor (12). Additionally, lipopolysaccharide has been shown to increase splicing of IL (interleukin)-1β, which may likely contribute to both thrombosis and inflammation mostly experience during sepsis(13,14). Others report have shown lipopolysaccharide potentiates platelet activation upon platelet stimulation with low levels of platelet agonists, this result in increased dense granule release(7), P-selectin expression, and platelet aggregation(15). On the other hand, TLR2 has a broader specificity, binding both peptides from Gram-negative and or Gram-positive bacteria, in conjunction with TLR1 or TLR6, respectively(16). Activation of TLR2 on platelets was first described through the use of a synthetic triacylated lipopeptide, which mimics the N terminus of bacterial lipopeptides, called Pam3CSK4. Activation of TLR2 have also been demonstrated by Gram-negative *Porphyromonas gingivalis*, which increased CD40L (CD40 ligand) expression on platelets surface and induced platelet-neutrophil aggregation(7) It has also been demonstrated that platelets participate in the up regulation of B as well as T-lymphocyte and immunoglobulin-mediated immune responses through CD40/ligand–CD40 interactions(17). Similarly, deduced that soluble CD40 ligand (CD154) supernatants of stored platelets can induce cytokines, chemokines, and lipid mediators through activation of CD40-receptor-bearing cells(18). Although preliminary, this supports the emerging concept that platelets actively participate in bridging the innate and adaptive immune response to infection(7). Taken together, the expression of various TLRs, and an ability to bridge interactions with neutrophils and perhaps T and B cells suggests mechanisms through which platelets may directly or indirectly detect bacterial pathogens by recognition of molecular patterns and early warning signals of infection, and then contribute to optimization of immune response(5).

Additionally, sepsis-inducing Gram-positive streptococci strains through lipoteichoic acid and peptidoglycan interact with TLR2, resulting in subsequent platelet aggregation and αIIbβ3 activation via phosphoinositide 3-kinase signalling(19,20). studies have recently shown that platelet TLR engagement is not exclusive to bacteria only. For example, platelet activation can also be induced by dengue virus (DENV) NS1 (non-structural protein 1) through TLR419 and the viral envelope glycoproteins from cytomegalovirus via TLR2(7). Stimulation of platelet TLR2 and 4 by DAMPs, also resulted in platelet activation(21). Unlike TLR2 and 4, platelet TLR3, 7, and 9 are located intracellularly within the endosomal compartments and help to recognize nucleotide derivatives. TLR3 traditionally recognizes dsRNA (double-stranded RNA) and is the least characterized among the three (3) endosomal platelet TLRs(7).

Platelet Fc Receptor

Besides PRRs, human platelets also express FcγRIIa, which is the only receptor on platelets to recognize the constant fragment of IgG, which enables binding of IgG-immune complexes as seen in figure 2C. IgG bound bacteria, for example, *Escherichia coli* and *Streptococcus oralis,* are recognized by FcγRIIa and trigger platelet activation and aggregation. In addition, FcγRIIa stimulation increases platelets hypersensitive to other thrombotic stimuli as bacteria induced

platelet activation often occurs after repeated stimulation of FcγRIIa and additional platelet surface receptors. Similarly, to the role of FcγRIIa activation in bacterial infections, immunocomplexes due to influenza virus and fungal spores from *Mucor circinelloides* are also known to simultaneously activate platelets via FcγRIIa and αIIbβ3 (4).

Nod-Like Receptors

NLRs are cytoplasmic PRRs that regulate inflammatory and apoptotic responses. The best characterized platelet NLR is NLRP3 (NOD, leucine-rich repeat, and pyrin domain-containing protein 3) a sensor for inflammasome activation (Fig 2A). Platelet NLRP3 function was first described during DENV infection as DENV induces the assembly of the NLRP3 inflammasome, resulting in IL-1β secretion through platelet-derived microparticles. 36 Later, it was determined that NLRP3 activation was dependent on DENV NS1 binding to platelet TLR4. Activation of TLR4 induces splicing and synthesis of pro-IL-1β, while cleavage of pro IL-1β to mature IL-1β occurs in a caspase-1 dependent manner, which is activated by a secondary signal through ATP or other DAMPs. The increased synthesis of IL-1β during dengue infection is thought to enhance inflammation and endothelial cell permeability(7).

C-Type Lectin Receptors

CLRs are a large family of surface receptors specialized in the recognition of glycans through their conserved carbohydrate binding domains. Two platelet CLRs, involved in various infectious diseases, are DC-SIGN (dendritic cell–specific intercellular adhesion molecule-3-grabbing nonintegrin) and CLEC-2 (C-type lectin-like receptor 2) as seen in figure 2B. As a pattern recognition receptor (PRR), DC-SIGN recognizes N-linked high mannose glycans on viral envelope proteins, which enables viruses such as HIV-1(22) and DENV26 to bind platelets. Additionally, extracellular mitochondrial DNA-a DAMP released during inflammation has been shown to induce platelet activation through DC-SIGN based on antibody blocking studies (23). Another platelet CLR with an important role during inflammation and infection is CLEC-2 (22). Similar to DC-SIGN, HIV-1 and DENV bind CLEC-2 on platelets, which contributes to disease severity and the overall inflammatory response, especially during dengue infection (24). CLEC-2 is one of the three platelet receptors which contain immunoreceptor tyrosine-based activation motif sequence along with FcγR (Fc gamma receptor) and FcγRIIa. Besides viral binding to CLEC-2, podoplanin the endogenous CLEC-2 ligand plays an important role in bacterial infections. While the CLEC- 2 podoplanin axis was shown to mediate inflammation triggered thrombosis in the liver after *Salmonella* infection (25), another study reported a thrombosis-independent inhibitory role toward systemic inflammation in sepsis (26). In addition to the role of CLEC-2 in thrombosis, the receptor is critical in regulating vascular integrity during inflammation. Loss of platelet CLEC-2 or podoplanin disrupts high endothelial venules, which are responsible for mediating lymphocyte trafficking to lymph nodes (27). Furthermore, loss of platelet CLEC-2 signalling leads to diminished immune response function of lymph nodes. Recently, hemin a synthetic form of free haeme was also shown to activate platelets in a CLEC-2–dependent manner(28). Considering free

haeme is released during haemolysis, this interaction might be important in haemolytic infectious diseases including malaria and haemolytic uremic syndrome(7).

Role of Platelet in Adaptive Immune Response

In addition to the role of platelet in innate immune response, platelets are also found to be very important cells in optimizing adaptive immune function or response. The periodontopathogens *A. actinomycetemcomitans* and *P. gingivalis* have been shown to induce expression of CD40L on human platelets via TLR2 and TLR4. Platelets can therefore modulate B and T cell responses to microbial pathogens through CD40L, and are able to induce isotype switching of B cells and augment CD8+ T cell function (7). CD40L on platelets enable T cell priming and augment CD8+ T cell responses against bacterial pathogens by enhancing maturation signals to dendritic cells and lowering the threshold for cell activation compare with reports that platelets can have an inhibitory effect on dendritic cells)(5). Platelet mediated modulation of the adaptive immune system has also been shown to enhance protection against viral rechallenge. Platelets expressing integrin β3 and CD40L are essential for lymphocytic choriomeningitis virus (LCMV) clearance by virus specific cytotoxic T cells, and protect the host from virus induced interferon-α/β lethal haemorrhage. Activated platelets can also contribute to immunopathology (e.g, liver damage) by accumulating virus-specific cytotoxic T cells at the site of inflammation in models of acute viral hepatitis. Serotonin released from platelets is vasoactive and can further support viral persistence in the liver by reducing microcirculation, which aggravates virus-induced immunopathology in a model of LCMV-induced hepatitis. Platelets can further shuttle blood-borne gram-positive bacteria to splenic CD8α+ dendritic cells after the bacterium becomes associated to platelets via glycoprotein (GP) Ib and complement C3 to balance bacterial clearance with immune induction. Activated platelets also form aggregates with CD16+ inflammatory monocytes and human leukocyte antigen (HLA)-DR+ CD38+ memory T cells in human immunodeficiency virus (HIV) infection(10).

MHC Class I

Following platelet recognition of pathogen, they are also capable of processing pathogenic antigens through an MHC (major histocompatibility complex) class I dependent manner, just like antigen presenting cells to activate the adaptive immune system, thus serving as antigen processing cells like macrophages. In an experimental cerebral malaria model, it has been shown that platelets were capable of directly presenting antigens to CD8+ (cluster of differentiation 8) T cells as seen in figure 2C. Importantly, robust early antigen presentation by platelets resulted in activation of CD8+ T cells and result in protection against cerebral malaria in experimental model(7).

Platelet Degranulation an Important Role in Host Defense

Platelets act as specialized sentinels for most pathogenic organisms invading the bloodstream. Recognition of this pathogen-associated molecular patterns by different platelet receptors leads to platelet aggregation and activation and thus result in release of platelet granules contents. Granules release by platelet play an important role in host defence against many pathogen(7)

Alpha (α) Granules

One class of α-granule stored proteins within platelets and particularly relevant to infectious pathogens, are ant-microbicidal proteins (AMPs), subdivided into kinocidins, PMPs (platelet microbicidal proteins), and defensins(29).

The most common and abundant kinocidin in platelets is PF4 (platelet factor 4; CXCL4 [chemokine (C-X-C motif) ligand]) and is often used as the prototype to describe this family of AMPs. Its dual function is as a result of direct consequence of its multidomain structure that consists of an anionic N-terminal chemokine domain with CXC motif and a C-terminal AMP-like domain. The latter domain contains the typical amphipathic α-helix, in which cationic and hydrophilic side chains segregate on opposite sides of the protein molecule, allowing for direct disruption of anionic microbial (pathogen) cell membranes(30). The antimicrobial action of PF4 is most particularly well characterised for malaria parasites. Subsequently Intraerythrocytic parasite killing by PF4 has been observed in vitro upon binding to the erythrocytic Duffy antigen receptor for chemokines(31). This binding facilitates endocytosis as well as accumulation of PF4 into the infected erythrocyte resulting in lysis of the *Plasmodium* digestive vacuole as shown in figure 2C(32). This antiparasitic action can be solely attributed to the C-terminal domain of PF4 as it was shown that a cyclic PF4 peptide dimer, containing only the last 14 amino acids, have a similar potency as full-size PF4. Importantly, the clinical relevance was recently demonstrated as PF4-mediated parasite killing occurred in samples of patients infected with all major human *Plasmodium* species(33).

PF4 has antimicrobial activity against bacteria and viruses. For example, platelets are able to destroy bacteria in a PF4- and FcγRIIa-dependent manner. Circulating PF4 binds to bacterial polyanions on *E coli* leading to the formation of anti-PF4/polyanion IgGs. These IgGs opsonized circulating *E coli* leading to platelet FcγRIIa-mediated release of antimicrobial factors to destroy the opsonized bacteria as seen in figure 1C above (34). PF4 has also been shown to inhibit HIV-1 entry into cells by blocking viral attachment. While PF4 has beneficial antimicrobial properties, the kinocidin is not completely protective during infection as PF4 also acts as a chemokine to recruit and activate leukocytes(35). Hypothetically, the immunomodulatory activity of the PF4 chemokine domain contributes to immune activation and T-cell migration to the brain, which aggravates experimental cerebral malaria pathology(36). It's important to states that, this role is consistent with other findings believing that PF4 promotes leukocyte recruitment to the lungs of influenza-infected mice to help which help in significant viral clearance(37). Other kinocidins include platelet basic protein (CXCL7) and RANTES (regulated upon activation, normal T-cell expressed and secreted; CCL5 [chemokine (C-C motif) ligand 5)]. The latter has proven antiviral activity as it blocks HIV-1 entry to T cells via CCR5 (C-C chemokine receptor type 5)(38) and potentiate PF4 in the recruitment of monocytes(39). CXCL7 generated upon proteolytic cleavage of NAP-2 (neutrophil-activating peptide 2), β-thromboglobulin, and CTAP-III (connective tissue-activating peptide III) (38).

Finally, defensins are a group of AMPs, further subdivided into α- and β-defensins. platelet β-defensin 1 have been proven to inhibits the growth of *S aureus*, likewise platelet α-defensin 1 has antibacterial activity against *E coli*. Interestingly, α-defensins are known to regulate human

papillomavirus infection. However, whether the platelet α- defensins antiviral properties is yet to be known. While many of the AMPs and chemokines directly influence viral and bacterial pathogens. Platelets contain yet another molecule, which also help in activating and regulating innate and adaptive immune systems known as P-selectin. P-selectin is surface adhesion molecule that is exposed on the surface of activated platelets binds to injured endothelial cells and leukocytes through PSGL-1 (P-selectin glycoprotein ligand-1) as seen in figure 1C above, and assists in the recruitment of circulating monocytes, neutrophils, and lymphocytes towards the site of inflamed endothelium. While, P-selectin and PSGL-1 initiate platelet-leukocyte aggregate formation, the interaction is further strengthened by leukocyte β2-integrins interacting simultaneous with GP Ib and indirectly through fibrinogen binding to αIIbβ3. Platelet-leukocyte aggregate formation is a common feature in HIV, influenza,78 DENV, severe sepsis(40), and COVID- 1981 and this help to promotes thrombo-inflammation during infection this mechanism by extension help(41) to reduce or limit the spread of the pathogen. Platelets also play an important role in activating adaptive immunity, mainly through the release of CD40L and TGFβ (tumor growth factor beta), which are all found in α-granules. Both the soluble and membrane-bound CD40L possess immunomodulatory property through binding to CD40 on immune cells. Activated platelets also activates dendritic cells through soluble CD40L, resulting in increased phagocytic activity of the cell as well as intracellular killing of bacteria (42-65). Platelet CD40L also help regulates B lymphocytes isotype class switching thus enhancing CD8 T-cell responses in mice infected with adenoviral vectors after prior immunization as shown in figure 2C above). on the other hand, Platelet-derived TGF-β regulates differentiation of CD4+ T cells into regulatory T-lymphocyte, which are immunosuppressive in nature and help maintain tolerance toward self-antigens. Platelets contribute significantly to the level of circulating TGF-β, because this is required for the differentiation of regulatory T cells. Interestingly, the importance of platelet TGF-β is underscored by the observation that regulatory T-cell numbers and function are impaired in thrombocytopenic disorders(7).

Platelets Contribution to Complement Activation

Numerous studies have shown that platelets interact with complement system components to activate or amplify complement fixation. Platelets, for example, are thought to be capable of mediating the formation of the C5-C9 complex (10). Platelet complement surface receptors bind to microorganisms that exhibit this complex. Platelet proteases then cleave C5 to C5a, resulting in a powerful and positive chemotactic stimulus that attracts neutrophils and macrophages to the area of injury or bacteria colonization. Platelet activation, phospholipase activity, and granule release occur as a result of complement-induced thrombocyte stimulation. Prostaglandin synthesis and release by platelets are thought to be triggered by complement proteins C5-C9(43). Furthermore, platelet generation and release of free radicals or reactive oxygen species have been linked to C-reactive protein, C3b, as well as C5-C9, INF-, or TNF-b stimulation. Each of these activities has the potential to increase platelet antimicrobial activity and platelet interactions with leukocytes (10). It has also been demonstrated that in most patients who lack or have inadequate production of complement protein C3, C5, C6, or C7 usually presents with suboptimal platelet function.

Complement alternative pathway factor D (properdin) is found within platelet alpha granules and is thought to be released by thrombin-stimulated platelets. As a result, platelet activation may be inextricably linked to activation of the complement fixation system's alternative pathway (29).

Conclusion

Platelets are a type of inflammatory cell. As a result, they exhibit characteristics similar to those of a traditional cell-mediated immune effector cell. Platelets are known to contain and can be stimulated to release a variety of bioactive molecules. These molecules aid in the regulation of vascular tone, increased tissue adhesion, increased vascular permeability, clot dissolution, wound healing, and tissue regeneration. Platelets have traditionally been associated with all of these functions as a cell that maintains haemostasis. The following observations support the belief that platelets play an important role in host defence against infectious pathogens:

Conflict of Interest: The authors have declared no conflict of interest.

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