Allergology International xxx (2017) 1–8

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Review article

Recent advances in understanding the roles of blood platelets in the pathogenesis of allergic inflammation and bronchial asthma

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ARTICLE INFO

Article history:
Received 31 October 2017
Received in revised form
12 November 2017
Accepted 19 November 2017
Available online xxx

Keywords:
Alarmin
Bronchial asthma
IL-33
Innate immunity
Platelets

Abbreviations:
ADP, adenosine diphosphate; AERD, aspirin-exacerbated respiratory disease; cysLT, cysteinyl leukotriene; DAMPs, danger-associated molecular patterns; EETosis, eosinophil extracellular DNA trap cell death; ILC2, group 2 innate lymphoid cells; LPS, lipopolysaccharide; LT, leukotriene; NETs, neutrophil extracellular traps; PAF, platelet-activating factor; PAMPs, pathogen-associated molecular patterns; PF-4, platelet factor-4; PMP, platelet-derived microparticles; PMPs, platelet microbicidal proteins; PSGL-1, P-selectin glycoprotein ligand-1; tPA, tissue plasminogen activator; TLR, toll-like receptor

ABSTRACT

Platelets play an essential role in hemostasis to minimize blood loss due to traumatic injury. In addition, they contain various immune-associated molecules and contribute to immunological barrier formation at sites of vascular injury, thereby protecting against invading pathogens. Platelets are also crucially involved in development of allergic diseases, including bronchial asthma. Platelets in asthmatics are more activated than those in healthy individuals. By using a murine asthma model, platelets were shown to be actively involved in progression of the disease, including in airway eosinophilia and airway remodeling. In the asthmatic airway, pathological microvascular angiogenesis, a component of airway remodeling, is commonly observed, and the degree of abnormality is significantly associated with disease severity. Therefore, in order to repair the newly formed and structurally fragile blood vessels under inflammatory conditions, platelets may be continuously activated in asthmatics. Importantly, platelets constitutively express IL-33 protein, an alarmin cytokine that is essential for development of bronchial asthma. Meanwhile, the concept of development of allergic diseases has recently changed dramatically, and allergy researchers now share a belief in the centrality of epithelial barrier functions. In particular, IL-33 released from epithelial barrier tissue at sites of eczema can activate the antigen-non-specific innate immune system as an alarmin that is believed to be necessary for subsequent antigen-specific acquired immunological responses. From this perspective, we propose in this review a possible mechanism for how activated platelets act as an alarmin in development of bronchial asthma.

Introduction

Platelets are a kind of blood cell derived from bone marrow megakaryocytes and play essential roles in thrombosis, hemostasis and tissue repair. Vascular endothelial injury due to various causes such as trauma and ischemia leads to activation of platelets at the injured site, resulting in their adhesion, aggregation, release of granules and formation of platelet thrombi (primary hemostasis). Following the primary hemostasis, coagulation factors are sequentially activated, forming fibrin mesh (secondary hemostasis). To date, in addition to playing essential roles in hemostasis and subsequent tissue repair, platelets have been found to be crucially involved in various immune responses, in direct and indirect manners. Notably, clinical and experimental evidence

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Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2017.11.008

Please cite this article in press as: Takeda T, et al., Recent advances in understanding the roles of blood platelets in the pathogenesis of allergic inflammation and bronchial asthma, Allergology International (2017), https://doi.org/10.1016/j.alit.2017.11.008

demonstrates that platelets are actively involved in the pathogenesis of allergic diseases, including bronchial asthma.

In this review article, we focus on the roles of platelets in allergic inflammation and the pathogenesis of bronchial asthma, including the immunological implications of platelet activation in the asthmatic airway. We discuss the relationship between platelet functions *per se*, such as in hemostasis and tissue repair, and the latest concept regarding development of allergic diseases, which emphasizes epithelial barrier functions and the innate immune system. In particular, we propose a hypothesis concerning the mechanistic implications of platelet activation for the pathology of bronchial asthma.

Platelet functions in thrombosis, hemostasis and tissue repair – role of platelets as a physical barrier

When blood vessels are damaged and bleeding due to some cause such as trauma, it is necessary to induce hemostasis in order to promptly stop blood loss, and to repair damaged blood vessels and the surrounding tissues. Platelets are blood cells that play a central role in initiation of the hemostatic and tissue repair responses. Platelets are derived from cytoplasmic fragments of bone marrow megakaryocytes; they are approximately 2 μm in diameter and have no cell nucleus.[1,2] Approximately 10^{12} platelets are circulating in the blood of an adult human, and the lifespan of an individual platelet is about 10 days unless it is consumed in fibrin clot formation (whose process will be explained below). Therefore, an average of 10^{11} new platelets must be produced every day in a healthy adult to maintain a normal platelet count ($150–400 \times 10^9$/L of blood).[3]

Recruitment of platelets to a site of vascular injury is the first step in the process of hemostasis that plays a critical role in minimizing blood loss and forming a physical barrier against invading pathogens.[4] Under physiological conditions, circulating platelets remain in a quiescent state due to the inhibitory effects of both nitric oxide and prostaglandin I_2, which are constitutively produced by vascular endothelial cells.[5] At sites of bleeding, vasoconstriction of the injured blood vessels is the first response in order to limit blood loss. Subsequently, platelets adhere and accumulate on the damaged endothelium via von Willebrand factor. Activated platelets release the contents of their stored granules, which contain adenosine diphosphate (ADP), Ca^{2+}, thromboxane A2 (TXA_2), serotonin and platelet-activating factor (PAF), thereby further promoting platelet aggregation and formation of a platelet plug (primary hemostasis). Because the platelet plug formed during primary hemostasis is unstable and fragile, approximately a dozen coagulation factors that circulate in the bloodstream in an inactive state are quickly and sequentially activated in a so-called “coagulation cascade”, leading to fibrin mesh formation from inactive fibrinogen plasma protein. Hemostasis is completed when the fibrin mesh covers the platelet plug, creating a stable fibrin clot and holding it in place (secondary hemostasis).

Once their role in hemostasis is completed, clots must be broken up and removed, and the damaged tissue surrounding fibrin clots needs to be repaired. Intact vascular endothelial cells around clots produce tissue plasminogen activator (tPA). tPA catalyzes conversion of plasminogen to plasmin, the major enzyme responsible for clot breakdown (fibrinolysis).

It should be noted that, in addition to hemostatic factors, platelets contain various cell growth factors such as transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF), which play important roles in repairing and regenerating damaged tissue.[6] Thus, platelets are key players in all the processes triggered by bleeding, including primary hemostasis, secondary hemostasis, fibrinolysis and repair of damaged tissue, that both minimize blood loss and reinstate physical barriers to external substances.

Platelet functions in immune responses – role of platelets as an immunological barrier

Traumatic injuries cause bleeding and involve serious risk of invasion by foreign pathogens such as viruses and bacteria into the body. Therefore, in addition to physical barrier formation by hemostasis, a functioning immunological barrier to protect against invading pathogens must be formed as rapidly as possible at sites of injury. Indeed, in addition to their essential roles in thrombosis and hemostasis, platelets play important roles in assisting and modulating inflammatory reactions and immune responses in a wide range of ways, as described below.

Immune-associated molecules in platelets

Although platelets are anuclear cells derived from cytoplasmic fragments of bone marrow megakaryocytes, they contain various immune-associated molecules in intracellular granules such as α-granules and dense granules, as well as on their surface membrane.[7] For instance, P-selectin (CD62P), a cell adhesion molecule, is an integral membrane glycoprotein that is stored in α-granules in resting platelets.[8] Upon platelet activation by agonists such as thrombin and ADP, P-selectin is rapidly translocated onto the plasma membrane.[9] There, it plays an important role in initial recruitment of leukocytes, including neutrophils, monocytes and lymphocytes, to sites of injury via its ligand, P-selectin glycoprotein ligand-1 (PSGL-1), which is expressed on those cells.[10,11] Activated platelets also secrete various types of immune-associated molecules such as cytokines, chemokines, growth factors and lipid mediators in order to activate their interacting immune-cells and endothelial cells, and perhaps to modulate inflammatory processes at sites of injury. Regarding the roles of platelets as immune cells, please also see two excellent reviews.[6,7]

Platelets as killers of pathogens

As described above, platelets regulate inflammatory responses through immune cell recruitment and activation, but they can also kill pathogens. As an example, to defend against microbial invasion, platelets store various antimicrobial proteins called platelet microbicidal proteins (PMPs) in their α-granules, and thus platelets have direct antimicrobial functions.[12,13] PMPs include the CXC-chemokine family, such as CXCL4 (also known as platelet factor-4; PF-4)[14] and CXCL7 (also known as neutrophil-activating peptide-2; NAP-2).[15] With regard to platelets' functions in response to protozoan parasite infection, McMorran *et al.* demonstrated that platelets bind to malaria-infected red blood cells and can directly kill the parasites within.[16] This killing was found to be abrogated by aspirin and other platelet inhibitors. Furthermore, both thrombocytopenic and aspirin-treated mice were highly susceptible to death during erythrocytic infection by *Plasmodium chabaudi*, indicating that platelets are important in controlling malarial infection.

Platelets and neutrophils

Following microbial invasion of the body due to traumatic injury with bleeding, neutrophils are one of the first-responders among the various types of immune cells to quickly migrate toward sites of injury and eliminate invading pathogens by phagocytosis. Interestingly, in addition to their conventional phagocytosis function, neutrophils are able to capture and eliminate pathogens using a web-like “throwing implement” similar to a casting net, called

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