Immunology Letters 163 (2015) 32–39

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Review

A comparative examination of thrombocyte/platelet immunity

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ARTICLE INFO

Article history:
Received 17 September 2014
Received in revised form 30 October 2014
Accepted 12 November 2014
Available online 20 November 2014

Keywords:
Thrombocyte
Platelet
Immunity
Innate
Adaptive

ABSTRACT

Among the cells in the blood vascular system, platelets in mammals and thrombocytes in lower vertebrates are the source of crucial mediators in hemostatic functions. Although these cells have been known to be primarily involved in thrombosis and hemostasis, platelets and thrombocytes have been shown recently to have roles in inflammatory functions and the immune response in general. Thrombocytes/platelets are widely recognized contributors to inflammatory responses upon stimulation with various microbial stimulants. In recent years, the role of platelets has been shown in adaptive immune responses. Therefore, thrombocytes/platelets should be considered as specialized immune cells that not only resemble innate effector cells in function but also have a role in affecting adaptive immunity through cellular contact and interaction with antigen presenting cells and lymphocytes.

1. Introduction

Thrombocytes/platelets are small, circulating, and the most abundant cells next to erythrocytes in blood. Although thrombocytes and platelets are homologous in function [1], there are some differences in their origin and morphology. Enucleated platelets are only found in mammals while nucleated thrombocytes are found in lower vertebrates such as reptiles, amphibians, fish and birds [2]. Invertebrate species have circulating nucleated cells in their hemolymph termed hemocytes that are similar in function to thrombocytes/platelets [2–4].

The most recognized physiological role of thrombocytes/platelets is to initiate blood clotting in the process of hemostasis [5–12]. These cells sense damaged vessel endothelium and accumulate at the site of the vessel injury, where blood clotting is initiated to block the circulatory leak. In addition to forming an aggregate, activated platelets favor thrombin and fibrin formation. Platelet membrane associated glycoproteins mediate binding to subendothelial tissue and subsequent aggregation to form the hemostatic plug [7]. Platelets and other immune cells by specific thrombosis-related molecules also play a major role in immunothrombosis to protect host integrity, where an intravascular scaffold is generated to facilitate the recognition, containment and destruction of pathogens [5]. The thrombocyte has been suggested to be the hemostatic homologue of the mammalian platelet due to combined morphologic, immunologic and functional evidence and conservation of major hemostatic pathways involved in platelet function and coagulation [13]. Thrombocyte microparticles are functionally equivalent to platelet microparticles and are first to appear at the site of arterial injury to initiate arterial thrombus formation [14,15]. Defective platelet functions and severe prothrombotic action are often the reason for many bleeding or coagulation disorders.

In the past two decades, thrombocytes/platelets have been found to have roles in innate immunity and inflammation. More recently, thrombocytes/platelets have been shown to have the capability to modulate the adaptive immune response. Although some recent studies report thrombocytes to have potentially similar capabilities, more research needs to be conducted on how these cells are involved. Here, we first discuss the characteristics of thrombocytes in lower vertebrates (fish, reptiles, amphibians, and birds) and platelets in mammals (human, mice). Later, we review thrombocytes/platelets as specialized immune cells with a focus on nucleated thrombocytes.

2. Thrombocytes/platelets characteristics

2.1. Lower vertebrates

Historical studies of thrombocytes in lower vertebrates are focused on characterization of ultra-structural features as well as the involvement of these cells in blood coagulation [1,8,10,13,16–28]. Lower vertebrate thrombocytes are, like

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http://dx.doi.org/10.1016/j.imlet.2014.11.010
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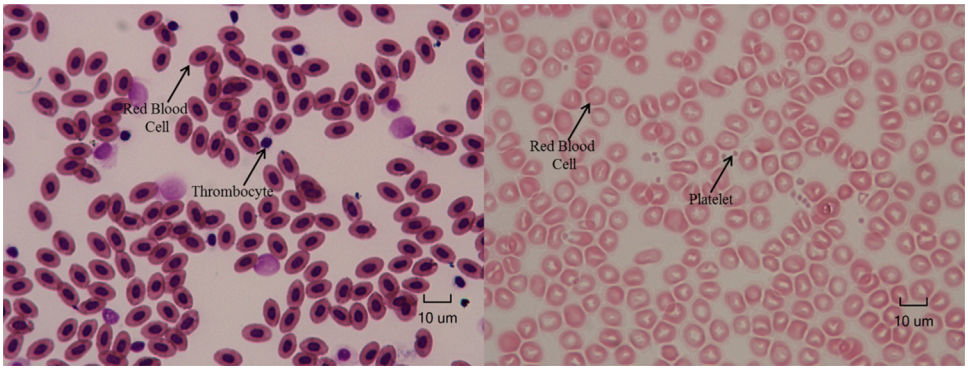

Fig. 1. Photomicrographs of avian thrombocytes and human platelets. The left panel is a Camco Quick Stain® smear of chicken blood (nucleated thrombocytes and red blood cells), and the right panel is Wright stained human blood (platelets and enucleated red blood cells).

platelets of higher vertebrates, the most abundant blood cells after erythrocytes [21,29–31]. According to a hematologic evaluation by Ueda et al. [29] from 10 *Oreochromis niloticus* fishes, there are roughly 2.35×10^6 mm^{-3} erythrocytes, 16.08×10^3 mm^{-3} total leukocytes and 61.69×10^3 mm^{-3} thrombocytes. The average width and length of a mature thrombocyte is approximately 5 and 10 μm, respectively. Thrombocytes bear a superficial resemblance in both shape and general appearance to red blood cells (RBCs) in avian blood (Fig. 1).

Circulating thrombocytes are similar in size to lymphocytes and appear as round, oval, spindle, or spiked cells with long cell processes [1,13,18,19,21–24,32–35]. The cytoplasm of thrombocytes contains numerous vesicles that occasionally open to the cell surface indicating the presence of a surface-connected canalicular system [15]. A marginal band of microtubules maintains the shape of thrombocytes [36]. Some mitochondria, glycogen deposits, and a Golgi apparatus are also found in these cells. Thrombocytes have the capacity to store a number of intracellular secretory granules that can be released into the circulation or translocated to the surface when activated. Thrombocytes are also capable of producing and releasing a vast array of bioactive proteins (e.g. cytokines and chemokines). Presence of large, acid phosphatase-positive granules has been observed histochemically in the cytoplasm of avian thrombocytes, which may be similar to the lysosomal granules in mammalian platelets [37].

The process of thrombopoiesis or thrombocyte generation takes place in different tissues in adult animals, depending on the vertebrate group and species. Thrombopoiesis consists of immature and mature prothrombocytes and thrombocyte cell stages prior to the formation of the circulating thrombocyte [38]. Thrombopoiesis occurs in the lymphomyeloid and lymphoid tissues in fish; the spleen, kidney, liver, and more rarely bone marrow in amphibians; and the bone marrow or spleen in reptiles [36,39–41]. In chicken, thrombocytes originate from cells that resemble multipotent hematopoietic progenitors [42].

2.2. Mouse and human

Among the mammals, mouse and human platelets have been studied more extensively. Platelets are enucleated, small oval disk shaped cells. Despite lacking nuclei, these cells contain a substantial amount of mRNA that is packaged during platelet formation from megakaryocytes. Platelets contain functional spliceosomes, which are a multi-megadalton ribonucleoprotein complex. Spliceosomes process pre-mRNAs in the absence of nuclei during platelet formation from megakaryocytes [43]. In addition, human platelets also contain essential spliceosome factors including small nuclear RNAs, splicing proteins, and endogenous pre-mRNAs; all the translational machinery necessary to generate their own proteins during stimulatory events [43–45]. A human platelet is usually 2–4 μm in diameter and reported platelet counts range from 150 to 400×10^9 platelets per liter of blood [46–49]. Compared to humans, mice platelet counts are generally much higher [48].

The platelet plasma membrane surface is generally smooth except for some periodic invaginations that delineate the entrances to the open canalicular system [7,48]. Similar to avian thrombocytes, this complex network of intertwining membrane tubes permeates the cytoplasm of platelets. Due to this system of folded membranes, platelets have an enormous surface area. When platelets are activated, an influx of calcium initiates the process of rapid change of shape from smooth discs to spiny spheres with development of finger-like filopodia and pseudopods [48,50]. The cytoplasm of a platelet is rich in actin and myosin, which provides the force for this change in shape.

Mammalian platelets have three major types of storage granules: (i) α-granules, (ii) dense granules, and (iii) lysosomes [46,48]. The secretory granules found in avian thrombocytes are not as well characterized as mammalian platelets. The α-granules are the most abundant granules in mammalian platelets; and the granule protein content is derived by a combination of endocytosis and biosynthesis. These granules are involved in secreting several different bioactive proteins including coagulation factors, chemokines, adhesive proteins, mitogenic factors and regulators of angiogenesis. A recent quantitative proteome analysis by Burkhart et al. [51] showed almost 4000 unique proteins in the human platelet and estimated a total of almost 20 million protein molecules per platelet.

The production of platelets is a complex progression of events that results with a single megakaryocyte releasing thousands of platelets into circulation. Platelets originate from the megakaryocytes of the bone marrow. Megakaryocytes produce platelets by rearranging the cytoplasm into long extensions called proplatelets that resemble strings of beads. The process of platelet morphogenesis takes place in platelet-rich plasma where megakaryocyte processes first elongate, then bead and fragment, and then curve and fuse to form disk-shaped platelets [7,52]. Thrombopoietin is the major hormone controlling megakaryocyte development and thus is the regulator of platelet production [7].

3. Thrombocyte/platelet immunity

Several review articles have been written in the past few years in which the role of enucleated platelets in immunity [48–50,53,54] and role or involvement of these cells in infection or various diseases [54–57] have been reviewed. We focused this review on what is known about the nucleated counterpart of platelets (i.e. thrombocytes) in immune function and involvement (or potential) in disease situations.