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Review

Platelet-mediated modulation of adaptive immunity

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ABSTRACT

Besides being the main cellular effectors of hemostasis, platelets possess a plethora of intracellular mediators (e.g. cytokines, chemokines and antimicrobial molecules) as well as surface receptors (e.g. P-selectin, integrins, CD40L, intercellular adhesion molecule [ICAM]-2, junctional adhesion molecule [JAM]-A, CD44, Toll-like receptors, chemokine receptors) known for their involvement in inflammatory and immune responses. These aspects of platelet biology, which suggest an evolutionary link to a more primitive multifunctional innate defensive cell, position platelets at the interface between coagulation and immunity. Whereas platelet functions in direct antimicrobial defense and in the enhancement of innate immunity are being increasingly recognized, platelet-mediated modulation of adaptive immunity is often underappreciated by the immunological community. By using mouse models of viral hepatitis as a paradigmatic example, we will review here how platelets coordinate adaptive immune responses and suggest possible clinical implications.

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Contents

1. Introduction

Mammalian platelets are anucleated cells that circulate in the blood as sentinels of vascular integrity [1]. Platelets are abundant in the circulation, with up to 150–400 $\times 10^3$ or >1000 $\times 10^3$ per μl of human and mouse blood, respectively. The lifespan of platelets is short (4–6 days in mice and 5–9 days in humans [2]); as a consequence, several million platelets have to be produced every hour to maintain their physiological blood counts and to avoid the risk of bleeding. In mammals, platelets originate from bone marrow megakaryocytes, polyploid, sessile cells with a diameter of up to 100 μm. In the bone marrow, megakaryocytes occupy the perivascular niche and form dynamic transendothelial pseudopods [3], which extend into the lumen of bone marrow sinusoids in response to a sphingosine 1-phosphate (S1P) gradient [4]. These intravascular extensions, referred to as proplatelets, continue to elongate and become tapered into multiple platelet-size beads connected to each other and with their maternal megakaryocytes by thin cytoplasmic bridges. Platelets are then sheared from their transendothelial stems by flowing blood, in a process that, again, requires S1P [3,4].

The central role that platelets play in hemostasis, the defense mechanism that prevent blood loss when the continuity of the vascular tree is interrupted by traumatic injury to tissues, is well documented [5]. Recent studies have shown that platelets are also required to maintain normal vascular permeability [6,7]. Indeed, experimental evidence in mice has corroborated the long-known clinical observation that a reduced platelet count of ~2% of normal is sufficient to maintain a normal hematocrit; spontaneous

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hemorrhage, mostly mucocutaneous in nature, and death develop when platelets are further reduced in number or their function is inhibited by a type I interferon-dependent mechanism [6]. These findings suggest that platelets interacting with the inner vessel lining provide an essential control over vascular permeability and that pathogens that induce high levels of type I interferon (e.g. viral hemorrhagic fever viruses) might place the host at risk of a life-threatening hemorrhagic anemia.

Besides posing the risk of blood loss, trauma to tissues can provide microbial pathogens with direct and immediate ways to access or invade the bloodstream or tissue parenchyma. From this perspective, platelets are well placed to support both hemostasis and innate and adaptive host defenses against infection. Indeed, mammalian platelets possess potent inflammatory and immune activities and molecular mechanisms that link the hemostatic with the inflammatory and immune systems, suggesting evolution from more primitive multifunctional innate defensive cells typical of many invertebrates and early vertebrates.

Here, by focusing on T cell-mediated liver immunopathology as a paradigmatic example, we will review how platelets modulate adaptive immunity and discuss potential clinical implications.

2. Recognition of pathogens and priming of adaptive immune responses

Platelets interact with, and respond to, invading pathogens [8]. Early studies demonstrated that platelets localize at sites of bacterial invasion by interacting directly with bacterial components (e.g. bacterial N-formylated peptides recognized by platelet formyl-peptide receptors) or with signals originating from the innate immune response (e.g. complement proteins and chemokines) [9]. At infection sites, platelets can rapidly deploy antimicrobial functions that are mediated by the secretion of antimicrobial effector molecules (e.g. platelet microbicidal proteins [PMPs] and kinocidins, reviewed in [9]). In addition, platelets may direct bacterial pathogen delivery to dendritic cells for efficient induction of T cell responses. For example, circulating platelets have been shown to rapidly associate – via GPIbα – to the bacterial pathogen *Listeria monocytogenes* decorated with complement factor C3 [10]. Such platelet association was required for efficient shuttling of bacteria to splenic immunity-inducing CD8α$^+$ dendritic cells, diverting bacteria away from swift clearance by other, less immunogenic phagocytes [10].

Platelets also play a key role in regulating lymphocyte trafficking to secondary lymphoid organs. Indeed, activated platelets have been reported to mediate lymphocyte delivery to lymph nodes, via platelet-expressed P-selectin recognizing peripheral node addressin on high endothelial venules (HEVs) [11]. The process whereby HEVs permit lymphocyte transmigration while maintaining vascular integrity was also recently shown to involve platelets [12]. This process was found to require C-type lectin-like receptor 2 (CLEC-2) on platelets interacting with podoplanin on fibroblastic reticular cells that surround HEVs.

Besides regulating lymphocyte trafficking to secondary lymphoid organs, platelets have been implicated in the priming of adaptive immune responses. In certain experimental settings (namely with low amount of antigen and in CD40L$^{-/-}$ mice), platelets induce dendritic cell maturation and subsequent priming of B and T cell responses in a CD40L-dependent fashion [13]. In other experimental settings (namely viral infection of wild-type mice) platelet-derived CD40L was shown to be dispensable for CD8$^+$ T cell priming but required for the subsequent expansion phase [6] and, most importantly, for lymphocyte accumulation at infection sites (see below).

3. Lymphocyte recruitment to sites of infection or inflammation

Platelet-mediated regulation of lymphocyte recruitment to sites of infection/inflammation has been perhaps best characterized in the liver. Indeed, several studies in mouse models of hepatitis B virus (HBV) pathogenesis revealed that platelets play a key role in the hepatic recruitment of effector CD8$^+$ T cells [14–16]. Indeed, the first of those studies demonstrated that platelet depletion is associated with a reduction in the hepatic accumulation of effector CD8$^+$ T cells 1–2 days post transfer and with a proportional reduction in the consequent liver disease [14]. Both phenotypes are restored upon reconstitution with platelets, unless platelets are treated with the activation inhibitor prostaglandin (PG) E_1 before transfusion [14]. The notion that platelet activation is required for the hepatic accumulation of effector CD8$^+$ T cells is further demonstrated by the reduction in the liver homing potential of these cells when mice are experimentally treated with a low dose of combined aspirin and clopidogrel, two antiplatelet drugs widely used in humans [15]. Using an ex vivo model-reactive surface simulating the hepatic blood flow conditions, we found that effector CD8$^+$ T cells tightly interact with platelets [14]. The concept of physical platelet-T cell interaction leading to hepatic accumulation of the latter cells has been more recently substantiated in vivo by intravital microscopy experiments; in those studies it was observed that circulating effector CD8$^+$ T cells preferentially arrest within the liver microcirculation by docking onto platelets that have previously adhered to liver sinusoids [16] (Movie 1). Indeed, we were surprised to observe transient platelet adhesion and aggregation occurring in liver sinusoids under basal conditions (Movie 2) and thought initially that this could be due to the surgical preparation required to perform liver intravital microscopy. Quantifying the number of intrasinusoidal platelet aggregates in histological liver sections from HBV replication-competent and wild-type mice that either underwent surgery and were subjected to intravital imaging or were left untreated, revealed, however, virtually identical numbers of platelet aggregates in the liver of all the above-mentioned animals (Fig. 1). The notion that transient platelet adhesion and aggregation can occur within liver sinusoids under basal condition is also supported by recent data from other investigators [17]. This is consistent with the constitutive sinusoidal expression of hyaluronic acid, which we identified as a critical ligand supporting platelet adhesion via CD44 [16] (Fig. 2). Platelets have been recently shown to firmly adhere to bacterially-infected Kupffer cells (the liver-resident intravascular macrophages), preventing the systemic spread of bacteria [17]. In contrast to the abovementioned study, we found no evidence for a preferential formation of platelet aggregates on Kupffer cells in mouse models of HBV pathogenesis, where Kupffer cells are neither infected nor targeted by CD8± T cells. Consistent with these results, Kupffer cell depletion did not affect hepatic effector CD8± T cell accumulation in these mouse models [18].

The reason whereby the initial platelet adhesion leads to a transient aggregation not evolving to thrombus formation is a fascinating issue that will be the subject of future studies. The notion that platelet adhesion to a substrate can occur without detectable signs of global platelet activation is not entirely novel. It has been known for some time that initial interactions with a potent adhesive substrate such as surface-immobilized von Willebrand factor involve non-activated platelets [19] that undergo multiple cycles of attachment/detachment – inducing intracytoplasmic calcium transients – but remain “non-activated” [20]. As documented in the abovementioned studies, many initial events are not productive with respect to transitioning to stable adhesion. Although the adhesive substrate is homogenous (a purified adhesive protein), the proportion of initial contacts that lead to small aggregate formation

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