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Review

Complement links platelets to innate immunity

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ABSTRACT

The complement system is a versatile part of our immune system. Various intersection points of complement with other cells and molecules of the immune response are well described. Platelets are classically conceived as cells of hemostasis. In recent years, however, several functions of platelets "beyond thrombosis" were discovered.

This review depicts the crosstalk of platelets with components of the immune system in the context of thrombo-inflammation. In particular, the various ways, in which platelets interact with the complement system, are illustrated. Platelets cannot only aggravate vascular inflammation and cardiovascular diseases, but they also contribute to organ remodeling and tissue homeostasis. Here, we portray the role of complement factors associated with platelet activation in tissue remodeling. Importantly, the clinical relevance of this platelet-complement crosstalk is addressed. A focus lies on thrombo-inflammatory disorders, other diseases with thromboembolic mechanisms or complications, but also autoimmune diseases. Finally, we draw attention to the growing body of evidence on the role of complement-platelet crosstalk in cardiovascular diseases. For future clinical, translational and basic science approaches, this crosstalk may prove a fruitful area of research in order to procure novel therapeutic and diagnostic targets in cardiovascular medicine and previously less addressed diseases featuring a platelet-complement axis.

At sites of tissue injury or endothelial breaches, thrombocytes – also referred to as blood platelets – prevent prolonged bleeding episodes. Thus, these cells represent the body's system of cellular hemostasis. To initiate the hemostatic process, platelets have to be activated, which can be achieved by a wide range of stimuli [1]. Following activation, they cover the site of endothelial disruption (provisional closure of a tissue wound) or – under pathological conditions – they trigger blood clots within the diseased circulation (thrombosis). The latter commonly follows rupture of vulnerable atherosclerotic lesions with potentially fatal clinical consequences such as myocardial infarction or stroke.

1. Platelet immune cell crosstalk

Apart from thrombosis, inflammation is another key driver of organ damage conferred by platelets. Interestingly, in most thrombotic diseases associated with ischemia-driven organ damage, thrombus formation and inflammatory pathways are closely intertwined (thrombo-inflammation). During tissue injury, sterile inflammation or infections, platelets adherent to the activated endothelium do not only aggravate vascular and tissue inflammation by release of mediators, but also interact with leukocytes and promote the recruitment of further inflammatory cells of the innate and adaptive immune response (Fig. 1) [2–4].

As endothelial cells form the border between the tissue and the blood circulation, they are the first cells to get in contact with adherent platelets during an inflammatory response [5]. Activating mechanisms conferred by platelets, for example during the course of atherogenesis, contribute to endothelial activation and chronic vascular inflammation [6,7]. Once adherent to the activated endothelium or to subendothelial structures, platelet interaction with recruited innate immune cells is crucial for the development of atherosclerotic plaques [8–13]. Increasing evidence also indicates a role of platelets for unexpected pathologies featuring vascular inflammation such as autoimmune diseases [14], cancer [15,16] or neuroinflammatory disorders. In TNF-alpha induced neurovascular inflammation, platelets, endothelial E-selectin and P-selectin contribute to leukocyte recruitment [17]. During experimental autoimmune encephalomyelitis (EAE) and in multiple sclerosis (MS) patients, platelet antigens could be detected within the inflamed tissue, particularly during the inflammatory phase of the disease [18]. Questioning a pathophysiological relevance, platelet depletion – even after clinical onset of EAE – by anti-platelet serum resulted in clearly reduced clinical EAE severity, inflammation and

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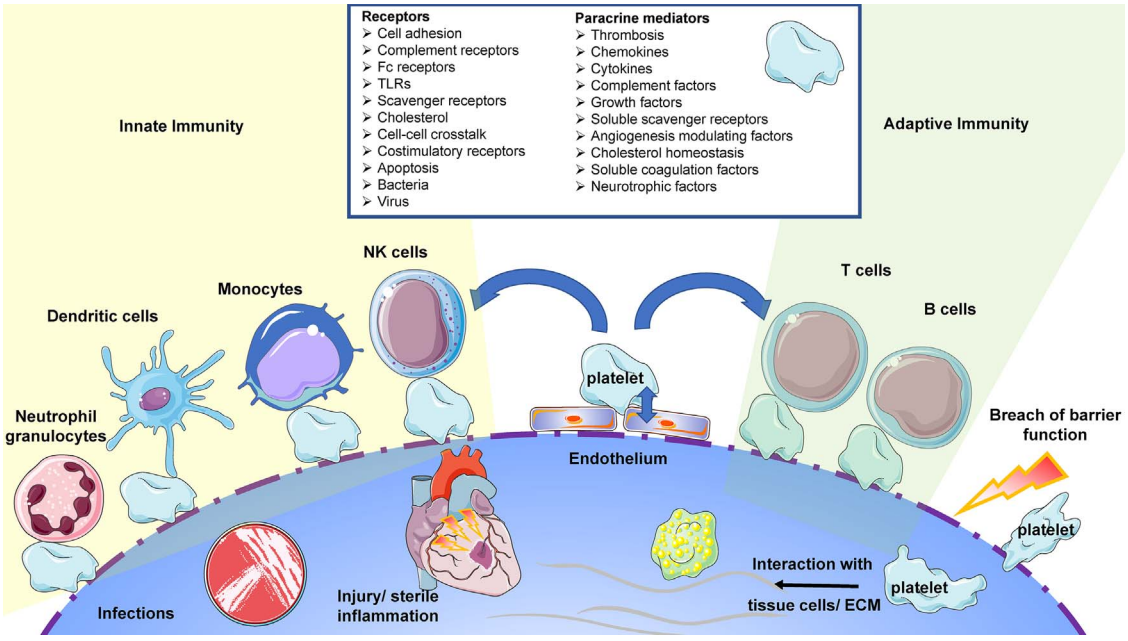

Fig. 1. After tissue injury or infection, the barrier between the circulatory system and the tissue is breached. Platelets get in contact with the extracellular matrix and subendothelial structures/cells. Furthermore, platelets can adhere to the inflamed endothelium and recruit further cells of innate and adaptive immunity to the scene. By release of paracrine mediators and surface-expressed receptors, platelets contribute to inflammation and help to coordinate actions resulting in tissue restoration.

microgliosis [18]. Depleting platelets or blocking the interaction of platelet GPIb with macrophage integrin Mac-1, recruitment of $CD45^{high}CD11b^{+}$ monocytes/macrophages to inflamed spinal cords of animals and EAE disease severity were substantially decreased [18]. Future studies including trials in humans will have to further scrutinize the potential role of platelets in MS and EAE.

In contrast to chronic neurovascular diseases, ischemic stroke is an acute thrombo-occlusive disease, which is initiated by a platelet-forming thrombus in the neuronal macro- and/or microcirculation followed by tissue necrosis and thrombo-inflammation. During ischemic stroke, platelets interact with endothelial cells and T cells at the neurovascular interface, and this interaction further promotes secondary tissue damage and capillary no-reflow [19–21]. While the mechanisms of how platelets mediate intravascular thrombosis during the acute phase of ischemic stroke are well established, their contribution to tissue remodeling and repair at more advanced stages is less well characterized [21–23]. Besides platelets and intravascular thrombus formation, T cells critically contribute to cerebral ischemia, while their detrimental effects do not depend on antigen recognition or T cell receptor (TCR) costimulation [19]. Some authors highlight a platelet-lymphocyte axis contributing to immune mechanisms, and both cell types may reciprocally regulate mutual functions [24]. Thus, the heterotypic interaction between T cells and lymphocytes has emerged as a potential regulatory mechanism contributing to thrombosis, inflammation, immunity, and atherosclerosis. For instance, platelets were reported to induce dendritic cell maturation, B cell isotype switching, and augment $CD8^{+}$ T cell responses both in vitro and in vivo using, for example, CD154 [25,26]. Furthermore, platelets can regulate $CD4^{+}$ T cell differentiation via multiple chemokines in humans, thus connecting them to adaptive immunity [27]. Taken together, the crosstalk of platelets with immune cells should be considered a relevant contributing or regulatory hub in thrombo-inflammatory diseases.

2. Platelets and tissue remodeling

Beyond their role in hemostasis, platelets are increasingly recognized to balance tissue homeostasis in various ways (Fig. 2). The supply of pro-inflammatory, regulatory or regenerative mechanisms

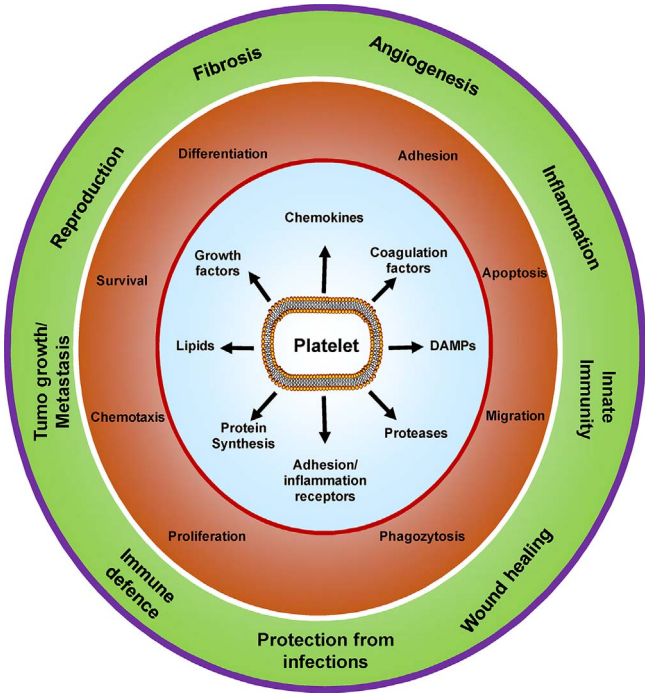

Fig. 2. Platelets participate in various tissue remodeling processes and supply the tissue and other involved cells with molecules and mechanisms determining successful restoration of tissue integrity and function.

and molecules at sites of injury and inflammation makes platelets an important cellular regulator for successful restoration of organ function [28,29]. So far, the function of platelets has been restricted to the circulation and the endothelial/tissue barrier. Platelets, however, may also balance tissue homeostasis in previously unappreciated ways outside the vasculature. For instance, a role of platelets was highlighted recently in the setting of cell apoptosis in ischemic neuronal tissue [30]. Interestingly, in the acute phase of stroke platelets directly interact with apoptotic tissue cells outside the vasculature in ischemic mouse brains.