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Review article

Platelets and immunity: From physiology to pathology

Plaquettes sanguines et immunité : de la physiologie à la pathologie

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Abstract

Blood platelets are cells acting during primary haemostasis. The thrombocytopenia observed in many different types of infectious processes begs the question of the relationship between cells and infectious pathogens and the role of platelets in the detection of biological hazards. This in turn brings us back to the role of platelets – via their molecular, membrane and secretory arsenal – in the detection and repair of vascular hazards. The common denominator between a breakdown of haemostasis and the risk of infection has been shown to be a cutoff point in the inflammatory continuum between physiology and physiopathology. The trophic role of platelets – as topical factor and as platelet transfusions – and their inflammatory complexities appear to correlate this proposed model, as reported in this short review.

Keywords: Blood platelets; Haemostasis; Innate immunity; Inflammation; Infectious pathogens; Blood transfusion

Résumé

Les plaquettes sanguines sont les cellules de l'hémostase primaire. L'observation de thrombopénies observées lors de plusieurs types de processus infectieux a permis de questionner la relation entre ces cellules et les pathogènes infectieux et le rôle des plaquettes dans la détection des dangers biologiques. Cela a à son tour permis de revisiter le rôle des plaquettes – via leur arsenal moléculaire membranaire et sécrétoire – dans la détection et la réparation des dangers vasculaires. Le point commun entre la rupture d'hémostase et le risque infectieux a été démontré comme un point de césure dans le continuum inflammatoire, entre physiologie et physiopathologie. L'observation du rôle trophique des plaquettes – comme topiques tissulaires et des transfusions plaquettaires – et leurs complications inflammatoires semblent corréler cette proposition de modèle, ainsi qu'il l'est rapportée dans cette courte revue.

Mots clés : Plaquettes sanguines ; Hémostase ; Immunité innée ; Inflammation ; Pathogènes infectieux ; Transfusion sanguine

Blood platelets are anucleated elements that are formed by the fragmentation of medullary megakaryocytes. Platelets are small cells (2–5 μm), with a short life-span (about ten days) that are mainly found in the intravascular space in physiological conditions.

Platelets are clearly associated to primary haemostasis: in case of a vascular breach they bind together and form a platelet clot that clogs the breach [1]. A collapse in the number of circulating platelets, whatever the reason, and/or a peripheral hyperconsumption of these same platelets exposes the subject to a risk of bleeding. Some patients may also suffer from bleeding although their circulating platelet count appears normal: this may be the case if they are either taking medication that directly or indirectly acts on the platelets' receptors, such as aspirin and many others or if they carry a genetic deficit that ren-

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ders platelets partially or totally nonfunctional (thrombopathic states). Thrombocytopenia and thrombopathic states thus represent two major risk factors for patients. Platelet transfusions may alleviate these deficits and restore primary haemostasis and/or prevent bleeding for a limited time. However, platelet transfusions to counteract an overdose of platelet inhibitors are generally advised against, with the exception of in life-threatening emergencies.

Thrombocytopenia may be due to one of two major causes: central causes due to a failure in production and peripheral causes due to excessive consummation or accelerated destruction of platelets. Among the main causes for thrombocytopenia with an increased risk of bleeding are infectious causes: viral, bacterial and parasitic causes, which, to some extent, combine central and peripheral factors [2,3]. This begs the question of whether there is a correlation between platelets and infectious agents. Investigations of this relationship – which is generally very complex – have also shown that the relationship between platelets and infectious agents is more often ternary than binary, with a notable interaction of leukocytes [4]. The relationship between platelets, bacteria and leukocytes, such as can be observed in sepsis, also puts primary haemostasis at risk along with soluble and membrane coagulation factors (platelet, leukocyte and erythrocyte counts) [5]. Recent studies of the coagulation sequence, that demonstrate that platelets intervene first before molecular factors engage, have also shown that these factors are not exclusively soluble but also occur on a membrane level, linked to platelets, vascular endothelial cells, leukocytes and erythrocytes. Experimental models have shown the transfer of platelets of the circulatory compartment, which was thought to be geared exclusively towards extravascular tissue, not free but rather linked to either inflammatory leukocytes or in the form of microparticles or microvesicles [6,7].

All of the facts set out above, call into question the unicist model of the blood platelet acting only in primary haemostasis. Other arguments drawn from experimental and clinical findings highlight the trophic role of platelets or platelet extracts in cell or tissue cultures as well as in the healing of epithelial, mucous (cornea, retina, skin, mucous membranes), sinewy or bony tissue [8,9]. Thus, platelets are much more complex than they appear at first glance: it is thus tempting to review their mode of operation not by starting with the pathology to explain the physiology but by beginning with the physiology to explain the pathology.

Blood platelets create platelet plugs to clog injured blood vessels. A reductionist view would be to confine their activity to the pathology and, a fortiori, to an exacerbated lesion such as a wound. Blood vessels and especially the capillaries are exposed to lesions due to the friction caused by blood cells passing "under pressure" through blood vessels with a smaller vascular diameter than that of the cells passing through them on a daily basis. Platelets play a role in repairing blood vessels (a role that has already been studied in prophylactic transfusions and in the topical application of platelets to damaged tissue): to exercise this function, which, as we already know, is linked to the granular content of the platelets that are rich in factors concerning healing (for instance, factors necessary for cell and tissue growth and differentiation), the platelets need to detect the lesions beforehand. To do so, platelets are equipped with an arsenal allowing them to detect signals from endothelial vascular lesions whose exacerbation puts into motion the platelet sequence "activation – aggregation – adhesion" that is already well-known from primary haemostasis. This primary haemostasis also engages leukocytes and erythrocytes in addition to soluble plasma factors: platelets are the principal providers of factor V, a potent agonist in the formation of thrombin in the actual coagulation phase [1,10]. By reviewing their function in primary haemostasis, as an assistant to coagulation, platelets may be described as cells that detect (vascular) danger signals and repair lesions. Platelets – which comprise hundreds of distinct molecules on their membrane surface and more than thousand different molecules for secretion – thus discern which of these to activate during this process [11]. We have described platelets as "cells". Using the term cell instead of cellular debris to describe platelets is not consensual, however, we (within our research group) have described in detail why platelets are not just cells but intelligent cells at that, capable of choosing an activation programme and differentiation options out of several possible options in their metabolome and, in particular, in their transcriptome [12].

This leads us to take a fresh look at the other findings made in connection with platelets in pathological conditions and, in particular, at thrombocytopenia induced by different types of infectious agents. Earlier works revealed that different infectious agents can be seen inside platelets, such as intracellular bacteria or HIV [13]. We now know that, if this is the case, it is that the host cell – here, the platelet – displays a sufficient amount of the necessary receptors to bind the infectious agent and actively penetrate it on its membrane surface. These receptors are not selective to target specific types of infections but are in most cases accidental or shared, as is the case for the expression of members of the "toll-like receptor" (TLR) family on human platelets. In 2005, we were able to demonstrate the expression of TLR on human platelets for the first time followed by their functional and selective role towards bacterial lipopolysaccharides [14,15]. The mechanisms that account for thrombocytopenia following a *Staphylococcus* infection resulting in sepsis, according to the accepted descriptors, are complex and include a central component (thrombopoiesis reduction) and a peripheral destruction which in itself is multicomposite with, in particular, platelet-induced apoptosis [16,17] (Chabert et al., manuscript under review). Here as elsewhere, likely in the case of viral infections with haemorrhagic viruses such as dengue or in the case of *Plasmodium falciparum* malaria, platelets seem to be the victims because they express receptors for different parts of each of these infectious agents [18,19]. In the case of malaria, this is even more complex, as platelets, infectious agents and leukocytes (bacteria) and/or endothelial cells (plasmodia) engage in haemostatic relations and an alternation between hyper and hypercoagulable pathological states can be observed [20].

All of the situations described above have one point in common: inflammation. Inflammation has long been considered only in its pathological expression. We now know that it is a continuum in which the visible component represents