MINI REVIEW

Blood platelets and inflammation: Their relationship with liver and digestive diseases

J. Ripoche∗

Inserm U889, université Victor-Segalen-Bordeaux, 146, rue Léo-Saignat, 33076 Bordeaux, France

Available online 8 April 2011

Summary An expansion of knowledge from basic and clinical research has highlighted the critical role of platelets in inflammation and tissue repair in addition to their established contribution to hemostasis. Activated platelets are a rich source of mediators participating to inflammation and tissue regeneration. Platelet-derived microparticles recapitulate essential platelet functions and their contribution to the pathogenesis of inflammatory diseases has been emphasized. Recent findings suggest that platelets are both friends and foes for the liver. Platelets are essential to liver regeneration, platelet-derived serotonin being critical. However platelets can also exacerbate liver damage, as in immune-mediated injury. The dual role of platelets has recently been exemplified in animal models of liver fibrosis. Platelets release profibrogenic mediators, such as CXC Chemokine Ligand 4, that is instrumental in the progression of liver fibrosis. On the other hand, thrombocytopenia aggravates liver fibrosis, an outcome linked to the downregulation of hepatic stellate cell collagen production by platelet derived hepatocyte growth factor. CD154, a key molecule in inflammation, is expressed by platelets and is a pathogenic mediator in inflammatory bowel disease. Here, we summarize some of the mechanisms linking platelets with inflammation and comment few recent articles indicating why platelets may prove to be important pathogenic mediators in liver and gastrointestinal diseases.

© 2011 Elsevier Masson SAS. All rights reserved.

Platelets transport bioactive mediators

In mammals, platelets are anucleated cytoplasmic fragments originating from the fragmentation of megakaryocyte (MKs). They are rich in secretory organelles, having a distinct content in bioactive peptides. Following platelet activation, the organelle content is released in a process termed secretion [1]. The bulk of proteins secreted by platelets, besides a rich messenger RNA content, is remarkably large and diverse, as shown by transcript profiling or proteomic studies on either platelet releasate or isolated granules [2,3]. In addition to mediators synthesized in MKs, platelets also carry mediators uptaken from plasma and possibly concentrated and/or modified within platelets; some of them being linked to inflammation as for vascular endothelial growth factor (VEGF), histamine or serotonin [4–6]. Platelets also

* Tel.: +33 0557 571 707; fax: +33 0556 514 077.
E-mail address: jean.ripoche@u-bordeaux2.fr

2210-7401/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.clinre.2011.02.012
secrete mediators through an extended time, translational-dependent pathway such as for the inflammatory mediator interleukin (IL-1β) [7]. Finally, the traditional concept of platelet loss of function following activation is debated, as activated platelets circulate or persist in clots while retaining functional properties [8]. It is, therefore, believed that the spectrum of physiological and pathological conditions implicating platelets is higher than classically thought.

Platelets release microparticles

Activated platelets shed microparticles (MPs) [9]. Platelets are the major source of circulating MPs. MP biological role recapitulates essential platelet functions as MPs represent a transport and delivery system of mediators participating to hemostasis, thrombosis, vascular repair and inflammation, acting both locally and systemically [10]. MPs may transfer information to endothelial cells (EC) through adhesion and/or fusion, an event that is believed to contribute to the control of endothelial phenotype in inflammation [11].

Platelets maintain vascular integrity

Platelets are of primary importance in hemostasis and thrombosis and vascular repair. At sites of vascular damage, they adhere to the injured vessel wall, a first step in a sequence of events that lead to the initiation and propagation of hemostasis and thrombosis and to the release of key material contributing to wound repair and tissue regeneration, including extracellular matrix components (ECM) and ECM remodeling proteins matrix metalloproteinases and their inhibitors [12,13].

Platelets are key actors in inflammation

In addition to their haemostatic role, platelets are protagonists of inflammation. Platelets are activated in inflammation; ECM components, chemokines, triggering of platelet receptors by ligands on inflammatory cells can activate platelets. Platelet-derived mediators deliver in turn activating signals to target cells including EC and myelomonocytic cells resulting in amplification of inflammation. The dialog between platelets and EC is a representative paradigm that has been extensively studied because of its relevance in atherosclerosis [14]. Several platelet-derived mediators turn EC phenotype to pro-inflammatory and platelets facilitate leukocyte recruitment through endothelium by providing chemotactic signals and platelet-bound ligands. A special mention in the bulk of platelet-derived signals is CD154 expressed by activated platelets as a soluble and membrane-bound form. CD154 is critical in EC activation through ligation of its receptor CD40 [15]. Platelets are brought to inflammatory sites through vascular leakage, attachment to leukocytes but they also respond to chemotactic signals [16]. Platelets represent an integrating platform for cascades participating to inflammation. For example, they anchor the procoagulant complex leading to generation of thrombin a potent pro-inflammatory mediator and propagate activation of the complement system [17]. Further information may be found in [18–20]. Finally, platelet-derived MPs initiate and sustain inflammation. The synovial fluid from patients with rheumatoid arthritis (RA) contains large amounts of free MPs and MPs attached to leukocytes. Synovial fibroblast-associated collagen induces MP release through GPVI, the main platelet collagen receptor, and platelet-derived MPs stimulate the secretion of cytokines by fibroblast-like synoviocytes, principally through an IL-1-dependent mechanism [21]. These observations stress the contribution of platelet-derived MPs in human inflammatory diseases and interesting questions follow. Circulating platelet-derived MPs are elevated in many inflammatory conditions [9] but how MPs could be generated in specific tissue locations and what is the relative contribution of platelets and platelet MPs? In RA, how do MPs concentrate in the synovial fluid whereas platelets do not? What is the relative role of other MP-born inflammatory mediators?

Platelets as friends or foes for the liver

The close interrelationship between blood and liver cells in sinusoids make platelets prime contributors to liver inflammation and, indeed, recent reports have emphasized their role in liver inflammation. Platelets are critical for liver regeneration, itself intimately dependent on inflammatory signals [22]. Thrombocytopenia or inhibitors of platelet activation impair hepatocyte proliferation following experimental extensive liver resection [23] or after ischemia-mediated hepatic injury [24]. Platelets provide hepatocyte mitogenic signals, serotonin being critical [23,24]. Intriguingly, mice rendered thrombocytopenic show increased survival to otherwise lethal 90% hepatic resection [25]. Further, low immediate platelet count is a risk factor of delayed recovery and increased mortality following liver partial resection or transplantation [26,27]. Several questions remain. Numerous mitogenic signals associated to liver regeneration, including hepatocyte growth factor (HGF), epidermal growth factor or IL-6, are secreted by platelets [28] and likely instrumental. Platelet-derived mediators may act directly or indirectly on liver cells, questioning the relative role of platelets in the global response to partial heptectomy, as nearly all liver cellular components are activated and provide intersecting signals contributing to promote hepatocyte division [29]. Platelets also provide ECM and matrix remodeling enzymes, all essential for liver regeneration [30,31]. Another question relates to platelet activation. If in extensive heptectomy, it is clear that platelets will accumulate [25] and activate, how and to what extent this occurs in partial, surgically well-controlled heptectomy?

Platelets may also prove deleterious to the liver. They exacerbate immune-mediated injury by driving inflammation and favoring the recruitment of immune response effectors. An instructive example is viral hepatitis. Cytotoxic T lymphocyte (CTL) response is a key determinant of liver damage in viral hepatitis. Platelet depletion or inhibitors of platelet activation limit CTL infiltration in the liver in mouse models [32,33]. Platelet-CTL interactions within the liver microcirculation are believed to be critical by favoring their reciprocal recruitment. Interestingly, platelet-derived serotonin was suggested to mediate...
liver damage in a lymphocytic choriomeningitis virus infection model, through microcirculation alterations [34]. Again, important questions follow with reference to roles played by other platelet-derived mediators, other serotonin-secreting cells, and how is serotonin actually acting. Finally, in liver transplantation, platelet transusions are a risk factor for post-transplant morbidity and mortality [35] though this may be not directly related to the liver [36]. In ischemia/reperfusion, platelets contribute to the sinusoidal lining cell damage in the cold preservation/reperfusion injury [37,38].

Liver fibrosis may represent a singular example of the dual role of platelets. Liver fibrosis typically progresses on a chronic rate in which sustained activation of fibrocompetent cells, notably hepatic stellate cells (HSC), and altered ECM remodeling, contribute to excessive ECM accumulation [39]. Platelets accumulate at sites of liver injury [32] and release a range of cytokines involved in fibrogenesis [40], including the potent profibrogenic TGF-β and platelet-derived growth factor that activate HSC, inducing their proliferation, ECM synthesis, and myofibroblastic transdifferentiation. In fact, earlier in vitro results indicate stimulation of HSC proliferation and induction of proteoglycan synthesis by platelet lysates and platelet-derived growth factors [41]. Platelets are also a source of angiogenic and antiangiogenic mediators, of ECM components and remodeling enzymes. Finally, platelets participate to the recruitment of cells of the innate and adaptive immune response implicated in liver fibrosis [42]. These foregoing actions make platelets foreseeable contributors to the initiation and progression of liver fibrosis. Despite this, as remarked [43], they received little attention. Recent results suggest a complex scenario for the role of platelets in liver fibrosis. Increased expression of the CXC chemokine ligand 4 (CXCL4, present in large amounts within platelets), is associated with fibrosis in hepatitis C virus-infected and non alcoholic steatohepatitis patients. CXCL4 deficiency alleviates fibrosis in carbon tetrachloride (CCL4) and thioacetamide (TAA) mouse chronic models. CXCL4 profibrotic effects result from the induction of proliferation, chemotaxis and chemokine expression in HSC, and from neutrophil and CD8− T lymphocyte recruitment [44]. These results suggest that the release of CXCL4 by activated platelets is instrumental and, indeed, liver CXCL4 increased expression in the CCL4 model is inhibited by aspirin [44] and aspirin is protective in a rat TAA chronic model [45]. In contrast, thrombocytopenia, as realized by genetic disruption of Bcl-xL (a regulator gene of apoptosis, controlling platelet life span [46]), aggravates liver fibrosis in both bile duct ligation and chronic CCl4 mouse models [47]. How thrombocytopenia aggravates liver fibrosis is a fascinating issue. In line with these results, thrombocytosis, as realized by the administration of megakaryocyte growth and development factor or by splenectomy reduces liver fibrosis in the chronic CCl4 mouse model [48]. Platelet accumulation is found in the fibrotic liver [48]. HGF, released by activated platelets, reduces collagen production by HSC in vitro and alleviates liver fibrosis in vivo. These findings strengthen the idea that platelets are required for harmonious liver repair and regeneration. Significant issues follow. The CXCL4 and HGF results illustrate how platelet-derived mediators may have a dual effect on fibrosis; what are the relative and global contributions of other platelet-derived mediators? In thrombocytopenic models, could there be an interfering contribution of the accelerated platelet clearance that is likely to implicate liver cells [49,50]? What is the relevance to thrombocytopenia associated to liver diseases in humans? What is the outcome of treatment by the different available antiplatelet drugs on the progression of liver fibrosis? Altogether, these reports underline the friend or foe role of the platelets in liver, a challenging research area that could end in optimizing liver transplantation, regeneration or fibrosis management by manipulating platelet function and/or number [36].

Platelet CD154 contributes to the pathogenesis of inflammatory bowel disease (IBD)

CD40 is expressed by various cells in the intestine mucosa and submucosa. Several lines of evidence implicate platelets in IBD. Initial observations on high platelet and soluble plasma CD154 in IBD patients were followed by the demonstration that CD154 causes inflammation in the gut mucosa through ligation of CD40 [51,52]. Colitis models confirm the CD154/CD40 dyad pathogenic involvement. Indeed, CD154 or CD40 deficiency or antibody-neutralization of CD154 attenuates experimental colitis [53], which may designate platelets as pathogenic mediators in IBD, as they represent a major CD154 reservoir [54].

What future for platelets in hepatogastroenterology?

The implication of platelets in health and disease is rapidly expanding, with unexpected findings, as for the link between platelets and adaptive immune response [55]. As a word of conclusion, it is tempting to speculate that platelets will be of increasing interest to the hepatogastroenterologist; important future questions being the potential role of platelets in non alcoholic fatty liver disease [56] or in hepatocellular carcinoma (HCC). Indeed, existing knowledge supports a reciprocal dialog between platelets and cancer cells. Platelets are activated in the tumor microenvironment and are increasingly perceived as key actors in cancer growth and metastasis [57]. Platelets contribute to tumor angiogenesis [58] as they represent a major transport system of angiogenic mediators, including VEGF [59,60], and may thus also prove to be a significant parameter in HCC deregulated angiogenesis [58].

Disclosure of interest

The author declare that he has no conflicts of interest concerning this article.

Acknowledgements

Sébastien Lepreux, Charles Balabaud and Paulette Bioulac Sage are gratefully acknowledged for critical reading and suggestions.
References


