Platelet pathology and antiplatelet strategies

Resolved and unresolved issues

R. E. Scharf[1, 2, 3]

[1]Dept. of Experimental and Clinical Hemostasis, Hemotherapy and Transfusion Medicine, Heinrich Heine University Medical Center, Düsseldorf; [2]Hemophilia Comprehensive Care Center, Heinrich Heine University Medical Center, Düsseldorf; [3]Biological Medical Research Center, Heinrich Heine University, Düsseldorf, Germany

Blood platelets were the focus of recent issues of this Journal (1, 2). Why do these inconspicuous, small cellular fragments, derived from megakaryocytes in the bone marrow, gain so much attention both in clinical settings and basic science? Platelets contribute essentially to survey the integrity of the vascular system by becoming adherent within milliseconds and by forming platelet aggregates at sites of injured endothelial cells or exposed subendothelial matrix structures (3). Overall, platelets play a pivotal role in hemostasis. However, once stimulated, platelets respond uniformly and do not distinguish between traumatic injury and vascular lesions caused by variety of clinical disorders (4). Thus, under pathological conditions, mechanisms otherwise beneficial for hemostasis and vascular integrity may cause occlusive thrombi and, subsequently, acute ischemic syndromes of the heart, brain and other organ systems (5, 6).

Platelets beyond hemostasis

Recent studies have highlighted a different but equally relevant contribution of platelets to other physiological and pathophysiological processes, including immune-mediated responses to microbial and viral pathogens (7), inflammation (6, 8, 9), angiogenesis, tumor cell growth, and metastasis (10–12). Moreover, like leukocytes, circulating platelets can display multiple functions in innate and adaptive immunity (13). Some of these advances in platelet biology and pathology were reviewed most recently in this Journal (1, 2).

This theme issue of *Hämostaseologie* addresses further relevant aspects of platelet pathology, and covers several other highlights of the GTH Congress 2015 (1, 2, 14, 15). One of these features is the "multitasking" function of platelet serotonin (5-hydroxytryptamine, 5-HT), being stored at high concentrations within the δ-granules. Upon platelet activation and δ-granule secretion, 5-HT, apart from its impact on hemostasis, can exert a variety of additional effects, including host defense of pathogens, activation and proliferation of lymphocytes, modulation of cytokine release, and recruitment of neutrophils at sites of acute inflammation. At the opening session of the GTH Congress 2015, **Duerschmied** presented experimental and clinical findings of platelet serotonin in the Alexander Schmidt Lecture. In their article, **Mauler** et al. now report on these novel aspects of serotonin-induced immune modulation mediated by circulating platelets (16). The authors also review the role of 5-HT in several disorders such as asthma, cancer, myocardial infarction, and autoimmune diseases. Moreover, the effect of selective serotonin reuptake inhibitors on platelet-mediated immune functions is discussed.

Antithrombotic strategies

Antiplatelet drugs are being widely used to prevent and treat thrombotic and thromboembolic complications in patients with arterial disease, while anticoagulants are administered preferentially in venous thromboembolism or used for primary prophylaxis of embolic stroke in patients with atrial fibrillation (17). Numerous randomized trials have evaluated the efficacy and safety of antithrombotic agents in various clinical settings. However, a major side effect of all established antithrombotic regimens is induction of a bleeding diathesis (17, 18). Thus, we are currently facing two unresolved problems: firstly, the more intense antithrombotic therapy is, the more frequently major bleeding occurs; secondly, the agents used should be antithrombotic but not antihemostatic. In other words, we need highly effective drugs capable of preventing thrombus formation but not at the price of a concomitant risk of increased bleeding.

This demand requires innovative and highly selective pharmacological strategies. For example, drugs blocking factor XII or FXIIa have antithrombotic effects without compromising hemostasis, as reported by Labberton et al. (19). Another novel approach to overcome hemorrhagic complications associated with common antithrombotic therapy was recently provided (20). In their review, **Hohmann** and **Peter** illustrate that delayed targeting of CD39 on activated platelets has a strong antithrombotic potency without causing bleeding (21). The ecto-nucleoside triphosphate diphosphohydrolase CD39 converts ATP to ADP, and ADP to AMP, which in turn is degraded to adenosine, thereby reducing platelet-activating ADP. In this setting, *delayed* enrichment of CD39 on stimulated platelets was achieved upon recombinant fusion of CD39 to scFv, a single-chain antibody that binds specifically to activated GPIIb-IIIa (integrin αIIbβ3). The resulting

Correspondence to:
Univ.-Prof. Dr. Rüdiger E. Scharf, F.A.H.A.
rscharf@uni-duesseldorf.de
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construct (targ-CD39) allowed initial sealing of a vascular lesion by activated platelets but abrogated thrombus formation in a mouse model (20).

Until clinical use and approval of such novel strategies, we have to rely on established antithrombotic agents and regimens. However, we can do even better in clinical practice. This is discussed by **Lüscher** and **Steffel** in their article on individualized antithrombotic therapy (22). To optimize the patient benefit, the authors claim a careful and critical approach, taking into account the individual disease condition and co-morbidities, the pharmacological characteristics of the chosen antithrombotic drug(s), and concomitant medication(s). Despite the large arsenal of novel antiplatelet agents and anticoagulants, "classic" drugs will retain their importance. This contention is discussed in detail by **Schrör**, substantiating his statement *"why we should not skip aspirin in cardiovascular prevention"* (23). The author summarizes the pharmacology of aspirin and its potency (at high dosages) to inhibit platelet-driven thrombin generation (and clot formation) in comparison to other antiplatelet agents (24). Moreover, unresolved issues of aspirin related to diabetes, venous thromboembolism, preeclampsia, or colorectal cancer are also addressed in this review (23). Recently established interventional procedures, e.g., transcatheter aortic-valve implantation (TAVI), are challenging with regard to appropriate antithrombotic treatment and include a number of pending issues, as briefly discussed by **Moser** (25). Currently, dual antiplatelet therapy (DAPT, aspirin plus clopidogrel) is recommended early after TAVI (26). However, this regimen is not evidence-based and may not be effective in a rather large proportion of TAVI patients, who display high on-treatment platelet reactivity despite DAPT during the post-procedural period (27).

An original paper on non-arteritic anterior ischemic optic neuropathy (NAION) completes this edition. **Zotz** et al. report on the complex pathology of NAION, suggesting a coincidence of pro-atherogenic, prothrombotic, and pro-inflammatory processes in this setting (28).

> As Editor-in-Chief, I am grateful to the contributors, the members of the Editorial Board, and the many referees for their work and input. Thus, I trust that this issue will be received with the interest, warmth, and candor that the authors deserve.

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