Platelets and coagulation factors

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Platelets and coagulation factors: Established and novel roles in atherosclerosis and atherothrombosis

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The hemostatic system is crucial to prevent blood loss in higher organisms. It consists of a humoral and a cellular aspect: the enzymatic coagulation system and blood platelets, respectively [1]. The enzymatic coagulation is characterized by a cascade of pro-enzymes and co-factors that are triggered either by tissue factor, exposed upon vascular damage, or by negatively charged surfaces that belong to invading microorganisms or non-self materials. After triggering, the coagulation factors are sequentially activated, which strongly amplifies the clotting reaction, ultimately leading to the generation of thrombin, a central enzyme that converts soluble fibrinogen into fibrin and also activates blood platelets. Together with trapped erythrocytes, the platelet aggregate and fibrin are the main constituents of a blood clot.

Platelets are cell fragments without a nucleus that are essential for the cessation of bleeding and for the repair of damaged blood vessels, yet they have many more physiologic functions beyond hemostasis [2]. Particularly during the last 2 decades, platelets have been found to play roles in angiogenesis, host defense, viral replication, transport of information and inflammation. The functions of platelets in inflammation are of special interest. Although these are less obvious as those in hemostasis and thrombosis, they still play a critical role in the pathophysiology of several diseases such as atherosclerosis [2,3]. Large intravascular damage, as caused by the rupture of an atherosclerotic plaque in the larger arteries, leads to massive occlusive platelet aggregation, termed atherothrombosis, cutting off downstream blood supply in the process and unwantedly causing ischemic tissue damage [4]. Clinically, this becomes mainly manifest as myocardial infarctions or ischemic strokes, which take a high toll in terms of healthy life-years. The role of platelets in cardiovascular disease is highlighted by the widespread use of platelet aggregation inhibitors for the prevention of (recurring) arterial thrombosis and the ensuing adverse cardiovascular events [5,6].

Although the inflammatory functions of platelets are not directly involved in the acute thrombotic complications described above, they are believed to play a role in the chronic process of atherosclerosis development, in the attraction of immune cells to active thrombi, and in the remodeling processes that occur after atherothrombosis [7,8]. Similar applies for coagulation factors, which are initially thought to exert their functions mainly in the domain of hemostasis and thrombosis. Several coagulation factors have now been found to play roles in e.g. cancer, vascular remodeling, host defense or inflammation [9]. Interestingly, recent studies have highlighted the importance of the enzymatic coagulation system in the pathophysiology of atherosclerosis and arterial thrombosis. In the COMPASS trial, inhibition of coagulation factor Xa by rivaroxaban alongside the standard antiplatelet drug aspirin was found to be superior over aspirin alone [10]. In addition, a genome-wide association study in over 240,000 veterans revealed that the factor V Leiden mutation (F5 p.R506Q), a risk factor for venous thrombosis, was associated with the development of peripheral artery disease [11].

These observations speak for an intricate involvement of the hemostatic system in the development and clinical precipitation of atherothrombosis. Thus, in this special issue "*Platelets, coagulation factors and atherothrombosis*", the known and novel roles of coagulation and platelets in atherosclerosis and atherothrombosis are highlighted in a series of state-of-the-art reviews.

In the overview by Grover and Mackman [21], the relevance of the tissue factor pathway, with its components tissue factor and tissue factor pathway inhibitors (TFPI) −1 and −2, in the development of atherosclerosis, is discussed. Genetically reduced tissue factor expression in mouse models of atherosclerosis did not affect plaque development [12]. Tissue factor is highly expressed in plaque macrophages and smooth muscle cells (SMC) in humans and mice, and a non-specific knockdown in all cells might obscure cell-specific functions. As several studies did show an involvement of the coagulation pathway in plaque development [13–15], there is a need for conditional deletion models of tissue factor in specific vascular cells and macrophages. The function of TFPI in atherosclerosis is more clear-cut, as reduction of TFPI expression increased atherosclerosis in mice, whereas overexpression led to a reduction of plaque formation. Finally, given the important role of tissue factor in the initiation of blood coagulation, the activities of the

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tissue factor pathway in atherothrombosis are outlined.

As mentioned above, platelets interact with many molecular and cellular partners. This is reviewed by Schrottmaier and colleagues [16] in the context of vascular disease in a broad spectrum of manifestations. Here, the many functions of platelet-leukocyte interactions in physiology and pathophysiology are outlined. The most prominent and timely example is the induction of neutrophil extracellular traps (NETs) by activated platelets. NETs play a role in the initiation of venous thrombosis, but were also found in thrombi of patients with myocardial infarction and stroke [12,17].

In a state-of-the-art overview by Gutmann, Joshi and Mayr [22], the relatively new field of platelet "-omics" is introduced and extensively reviewed. Although being anuclear cells, platelets still contain numerous microRNAs and are able to translate mRNAs to newly synthetize proteins. The RNA content of platelets appears to be dynamic and may change depending on health or disease status [18–20]. Using the possibilities offered by modern bioinformatics, this information might be integrated to the protein and lipid contents of platelets. Given the easy accessibility of platelets as biologic specimen, the high information density in blood platelets may thus be exploited for future diagnostics.

Besides their high potential for diagnostics, platelets are still the only cell type in cardiovascular disease targeted by specific therapeutics. Antiplatelet therapy remains a strong pillar in the management of cardiovascular complications. Most antiplatelet drugs however inhibit platelet aggregation, which is undoubtedly effective against acute thrombotic complications but might not efficiently interfere with the pro-inflammatory functions of platelets. Moreover, since platelet aggregation is crucial for hemostasis, the current antiplatelet therapy is accompanied by a non-negligible risk of bleeding, which precludes the prophylactic administration of antiplatelet drugs to individuals at risk for cardiovascular events. In the review by Nording, Baron and Langer [23], the different pro-inflammatory roles of platelets in the development of atherosclerosis are discussed along with possibilities for their therapeutic targeting. This would ultimately offer the prospect of a safer antiplatelet therapy that might also be indicated for primary prevention of first-time cardiovascular complications in individuals at risk.

In still upcoming contributions, an overview of the role of platelets before, during and after atherothrombosis will be provided, as well as a review on the role of the coagulation system in atherosclerosis. Finally, this theme issue will be concluded with an outline of the importance of microvesicles in atherosclerosis.

As responsible editors, we believe that this review series provides a state-of-the-art on the large diversity of the coagulation system and platelet functions in atherosclerotic and thrombotic vascular disease and we wish you a pleasant, educative and inspiring reading.

Declaration of competing interest

The authors declared they do not have anything to disclose regarding the conflict of interest with respect to this manuscript.

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