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TABLE OF CONTENTS LISTING

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Small GTPases in megakaryocyte and platelet biology
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Small GTPases in megakaryocyte and platelet biology

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Q2

Blood platelets are critical for diverse physiological processes such as hemostasis, angiogenesis, and innate immunity [1]. Every day ~100 billion platelets are produced by megakaryocytes (MKs) in the bone marrow and destroyed by phagocytic cells of the reticulo-endothelial system [2]. Defects in either process can lead to thrombocytopenia (low platelet count) or thrombocytosis (high platelet count). While thrombocytosis is a risk factor for various clinical complications, including venous thrombosis and cancer [3,4], thrombocytopenia is a common cause of bleeding complications [1]. Hemostatic plug formation under shear stress conditions at sites of vascular injury depends on the platelets' ability to sense and to rapidly respond to disruptions in the vascular wall. Small GTPases are critical in the cellular signaling required for proper MK and platelet function. They are binary signaling proteins that rapidly switch between an active, GTP-bound state, and an inactive, GDP-bound state. They are activated by guanine-nucleotide exchange factors (GEFs), inactivated by GTPase-activating proteins (GAPs), or held in an inactive state by guanine dissociation inhibitors, as for RHO-family GTPases [5]. In humans small GTPases belong to a large superfamily that includes 153 members and is divided into 5 branches based on sequence and functional similarities: RAS (cell proliferation, growth, adhesion), RHO (cytoskeletal dynamics), RAB (membrane trafficking), ARF (vesicular transport and actin remodeling), and RAN (nuclear transport and microtubule regulation). Despite the highly conserved structure, variations in sequence, post-translational modifications, subcellular localization and upstream regulatory proteins allow this large family to control a wide range of cellular responses. This review series discusses the current state-of-the-art in our understanding of how small GTPases control MK and platelet biology.

The best studied small GTPases in platelets are members of the RHO family, key regulators of the actin cytoskeleton [6]. RHO GTPases regulate actin-binding proteins directly or indirectly to control actin dynamics and filament geometry [7]. They can have both unique and overlapping functions, and they can regulate one another through feedback and feedforward mechanisms [8]. The review by Pleines et al. summarizes the recent literature documenting a critical role for RHO GTPases in platelet release from MKs, with a focus on mouse lines in which knockout strategies have been applied to study the function of the best characterized members RAC1, CDC42, RHOA, and their downstream effector proteins. The review by Aslan et al. summarizes our current understanding of how platelet RHO GTPase activity is controlled by a very complex signaling network, and how proper regulation or dysfunction of these signaling pathways affects platelet function in health and disease. The review by Thomas et al. will discuss the key role of formins, downstream targets of RHO GTPases, in the organization and interaction of the tubulin and actin cytoskeleton in MKs and platelets.

Small GTPases are also critical in the regulation of intracellular membrane trafficking and integrin-mediated adhesion. Membrane trafficking is a complex process regulated by the coordinated interplay of several members of the Rab, Arf, and Ras subfamilies [9]. In platelets, these processes are critical for the loading and unloading of granules, intracellular storage vesicles that contain a variety of hemostatic and vasoactive factors, proteases, and small molecule compounds. The review by Poole et al. will summarize the most pertinent findings published in this nascent field of study. Members of the RAP subfamily of RAS GTPases are important regulators of integrin signaling [10], the key event during platelet adhesion and hemostatic plug formation [1]. Independent yet synergistic pathways control the activity of the main RAP-GEF and –GAP proteins in platelets, thereby facilitating rapid and sustained RAP activation. The review by Stefanini & Bergmeier will summarize this important topic, including recent studies in transgenic mice that helped identify the key regulators of RAP1 activity in platelets and ongoing work on the downstream targets and spatio-temporal activity control of individual RAP isoforms.

Taken together, the goal of this series of reviews is to provide the readership of *Platelets* a state-of-the-art overview of the role of small GTPases in MK and platelet biology. While the focus is on recent advances in the area of basic science, the clinical relevance of alterations in small GTPase signaling for platelet count and function will also be discussed.

Disclosure statement

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