Neonatal Platelet Function

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KEYWORDS

• Platelets • Megakaryocytes • Primary hemostasis • Platelet hyporeactivity • Neonatal hemostasis • Thrombocytopoiesis

KEY POINTS

- Platelets are crucial hemostatic components and the regulation of their production and function highly affects primary hemostasis.
- In addition to the classic role in hemostasis and thrombosis, platelets have an important role in the immune response.
- The hyporesponsiveness of neonatal platelets correlates with gestational age, concomitant with maturation of the entire hemostatic system.
- Genetic disorders of platelet function are rarely identified in neonates. Temporary acquired disorders, secondary to medications or hypothermia, are typically associated with mild to moderate clinical symptoms.

INTRODUCTION

Platelets arise from the fragmentation of megakaryocytes in the bone marrow, and circulate in the blood as disk-shaped anucleate elements. They have an average diameter of about 1.5 μm, 20% of the diameter of erythrocytes, and a lifespan of 7 to 10 days. Once released from the bone marrow, young platelets enter the circulation where a proportion of them pool in the spleen. A small pool of platelets, on the order of 10% to 15% of the total, stays in the pulmonary vasculature, and these, similarly to those in the spleen, can enter the circulation after exercise or epinephrine administration.[1] Platelets are crucial hemostatic components and the regulation of their production and function is highly relevant to clinical bleeding issues.

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Platelets adhere to sites of vascular injury, generate biologic mediators, secrete their granule contents, form multicellular aggregates, and serve as a nucleus for plasma coagulation reactions. When the vascular endothelium is damaged, platelets adhere to the exposed basement membrane collagen, initiating the process of primary hemostasis, and interacting with subendothelium-bound von Willebrand factor (vWf) via the membrane glycoprotein (GP) Ib complex. Afterward, platelets secrete and release proaggregatory substances, such as ADP, and they synthesize thromboxane A_2 from arachidonic acid. As a consequence, additional platelets are recruited and form aggregates with those platelets that have adhered to the vessel wall, and consolidate the initial hemostatic plug. The platelet GPIIb/IIIa complex mediates platelet-to-platelet interactions. As a result, the primary hemostatic plug is formed, and bleeding is arrested.[2] Platelets also provide an extensive phospholipid surface for the interaction and activation of clotting factors in the coagulation cascade. Enzymes and cofactors of the coagulation system, and a fibrin mesh, further stabilize the initial hemostatic plug. Collectively they help maintain the integrity of the vascular system.[3]

In addition to their classic role in hemostasis and thrombosis, recent studies reveal an important role in inflammation and the immune response.[4] Platelets produce and contain various cytokines and proinflammatory molecules, such as interleukin-1β, P-selectin, CD40L, transforming growth factor-β, and thrombospondin-1, supporting leukocyte-platelet interaction. Furthermore, in association with various functional Toll-like receptors (eg, Toll-like receptors 2, 4, and 9) on their surface, platelets likely act as sentinels, recognizing invading microorganisms, thus linking innate immunity with hemostasis.[5] In addition, activated platelets can directly affect B-cell differentiation and proliferation, which ultimately influence germinal center formation and antibody production.[6] Platelets can actively bind circulating gram-positive bacteria and consign them to splenic CD8α^+ dendritic cells, supporting antibacterial CD8$^+$ T-cell expansion.[7] Thus, the effects of platelets on adaptive immunity may play an important role in host defense. Therefore, defects of platelet function mighty not only result in hemostatic abnormalities but theoretically could adversely affect innate and adaptive immune responses.

PLATELET PRODUCTION IN NEONATES

The complex process of platelet production, from megakaryocyte progenitors to megakaryocytes and then to platelets, initiates early during fetal life. At 8 weeks postconception megakaryocytes are detected in the liver and circulatory system. Platelets increase in number during fetal life, reaching near adult concentrations in the blood around 22 weeks of gestation.[2,8]

Sola-Visner[8] schematically described the process of platelet production as consisting of four steps: (1) production of thrombopoietic factors (mainly thrombopoietin), (2) proliferation of megakaryocyte progenitors, (3) maturation of megakaryocytes, and (4) production and release of platelets into the circulation. These four steps are essentially the same in neonates as in adults, even though substantial developmental differences in megakaryocyte biology exist and may be responsible for the unique responses of fetal/neonatal megakaryocytes to thrombocytopenia.[8]

Plasma thrombopoietin concentrations are higher in healthy neonates than in healthy adults, but neonates with thrombocytopenia usually have lower thrombopoietin concentrations than do adults with thrombocytopenia.[9] Additionally, whereas neonatal megakaryocyte progenitors have a higher proliferative potential than those of adults and are more sensitive to thrombopoietin than adult progenitors, neonatal megakaryocytes are smaller and of lower ploidy than adult megakaryocytes, and