blood volume; however, the increase in blood volume was also accompanied by an ~10-fold increase in platelet mass. How does the mouse achieve such a large increase in total platelets? During the first 14 days of life, the transition of murine hematopoiesis from the fetal liver to the postnatal adult marrow is nearly complete. Using in vivo biotin-labeled platelets in newborn mice, the authors demonstrate that platelet production in neonatal mice during the first 2 weeks of life is similar to that of adult mice, which clearly does not account for the increase in platelet mass. Instead, platelet life span temporarily expands from 4 to 5 days during the murine newborn period. This increase in neonatal platelet life span is accounted for by cell-intrinsic factors, as exogenously injected adult platelets into murine pups have the same life span as those in injected into adult mice. This enhanced life span is only seen for the first 2 weeks of life, after which the murine platelets have a normal life span. These survival findings were confirmed in human cultured cord blood vs adult peripheral blood platelets, suggesting the murine findings also apply to humans.

Recent data have shown that the Bcl-2 family member Bcl-xL, which inhibits the activity of the proapoptotic proteins Bak and Bax, is a critical prosurvival protein that regulates platelet senescence. In the current study, the prosurvival protein Bcl-2 was significantly higher in both cord blood platelets and murine neonatal platelets when compared with their respective adult counterparts. There were no differences in Bcl-xL expression. However, the increased Bcl-2 expression did not account for the increased neonatal platelet life span, as Bcl-2-deficient murine pups had normal platelet counts. In contrast, neonatal platelets are more resistant to apoptosis when cultured with the Bcl-2/Bcl-xL inhibitor ABT-737 when compared with adult platelets, which suggests the increased life span in newborn platelets involves the apoptosis program.

In summary, the authors have nicely demonstrated that the neonatal period is associated with a large increase in platelet mass, which is a result of an increase in platelet life span and not an increase in platelet production. Perhaps that would explain why, in sepsis and other states associated with enhanced platelet destruction in neonates, platelet drop can be precipitous and recovery is often sluggish. The biological mechanism underlying this increased life span is an opportunity for future investigation but likely involves Bcl-2 and Bcl-xL, as well as other components of the apoptosis pathway.

Understanding the regulation of platelet life span may provide new therapeutic opportunities to improve platelet survival, thereby avoiding thrombocytopenic states and their potential for hemorrhagic events in the preterm neonate.

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Comment on Agostinis et al, page 3478

Antibodies in APS with competing interest

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In this issue of Blood, Agostinis et al provide evidence for a dominant role of the complement system in the pathology of the antiphospholipid syndrome by showing that a CH2-deleted antiphospholipid antibody (aPL) prevented and reversed aPL-induced thrombosis and pregnancy failure in rats. With >11 000 PubMed hits and still counting, antiphospholipid syndrome is truly one of the most studied thrombotic diseases both by clinicians and basic scientists. Patients diagnosed with antiphospholipid syndrome suffer from thrombotic episodes...
and/or pregnancy morbidity in combination with detectable aPLs in their blood.² Besides thrombosis and pregnancy morbidity, patients with antiphospholipid syndrome can have additional clinical symptoms belonging to different fields of medicine. Therefore, antiphospholipid patients cannot be defined to 1 medical specialty but are treated by different clinicians such as a hematologist, gynecologist, or rheumatologist. This clinical diversity within the syndrome resulted in studies executed by researchers and clinicians from different fields, resulting in a variety of explanations for the higher occurrence of both thrombosis and pregnancy morbidity.³ The main questions currently asked are as follows: which antibodies are involved and how do these antibodies cause thrombosis and pregnancy morbidity.

Despite their name, “antiphospholipid antibody,” these antibodies are strangely enough not directed against phospholipids but phospholipid-binding proteins. β2-Glycoprotein I (β2GPI), a plasma protein probably involved in the clearance of pathogens, has been accepted as the major antigen for aPLs.⁴ However, not all patients with anti-β2GPI antibodies suffer from either thrombosis or pregnancy morbidity, which has resulted in a long debate about the clinical significance of detecting these antibodies. The last few years, there have been several studies published showing the importance of detecting antibodies directed specifically against the first domain of β2GPI.⁵ A recent multicenter study, including >400 patients positive for anti-β2GPI antibodies, showed that anti-domain I immunoglobulin G (IgG) antibodies have 3 to 4 times better association with thrombosis than anti-β2GPI IgG antibodies, irrespective of specificity.⁶ Whether anti-domain I antibodies are also related to pregnancy failure remains to be studied. Therefore, the study by Agostinis et al is of great interest. They used an anti-domain I antibody in their studies and were able to show that this antibody induced both thrombosis and pregnancy failure in rats, thereby linking both thrombosis and pregnancy failure to 1 type of antibody.

An attractive mechanism involved in the disease process of antiphospholipid syndrome that has recently gained interest from clinicians and basic scientists working in different fields such as hemostasis and immunology is activation of the complement system.⁷ The complement system is part of the immune system responsible for removing pathogens from the human body under physiological conditions. Under pathological situations, such as autoimmune diseases, activation of the complement system can occur without an obvious trigger. In the current study, Agostinis et al show that an aPL with reactivity toward the first domain I of β2-GPI induced both complement-mediated thrombosis and pregnancy failure in rats, linking 2 apparently different clinical symptoms to 1 mechanism.

The complement system consists of 3 pathways: the classical, lectin, and alternate pathways (see figure). The classical pathway has been associated most with antiphospholipid syndrome, indicating an essential role for C1q of the complement system.⁸ C1q is able to further initiate the formation of anaphylatoxin C5α, which is known to cause placental damage and promote tissue factor expression on neutrophils and platelet-neutrophil complexes. To study this supposed role for C1q, Agostinis et al elegantly deleted the CH2 part of the anti-domain I antibody, which is responsible for binding to the C1q complement factor. Deletion of the CH2 part of the antibody resulted in significantly less thrombosis and pregnancy failure in rats compared with the antibody in which the CH2 part was still present.

Treatment of antiphospholipid syndrome is difficult with different strategies for patients suffering from either thrombosis or pregnancy morbidity.⁹ Current treatment strategies involve several different antithrombotic agents such as vitamin K antagonists, platelet inhibitors, and heparin, which are obviously associated with an increased bleeding risk. Increasing efforts are being made to find more specific ways to prevent aPL-induced thrombosis and pregnancy morbidity with limited bleeding risk. An option to specifically target the binding of the antigen-antibody complex to cells is to prevent the binding of this complex. As a final experiment, Agostinis et al show that the addition of the CH2-deleted antibody to mice already injected with a complete aPL prevented and reversed thrombosis and pregnancy failure in rats. This indicates that in their model, the injected CH2-deleted antibody replaced the injected aPL, thereby preventing complement activation. Although this is not a novel strategy, it is tested for the first time in an antiphospholipid syndrome-mediated setting with apparently great potential.

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Comment on McKenzie et al, page 3496, and on Silliman et al, page 3488

Bye-bye TRALI: by understanding and innovation

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In this issue of Blood, McKenzie et al provide further insight into the mechanism of antibody-mediated transfusion-related acute lung injury (TRALI), and
Antibodies in APS with competing interest

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