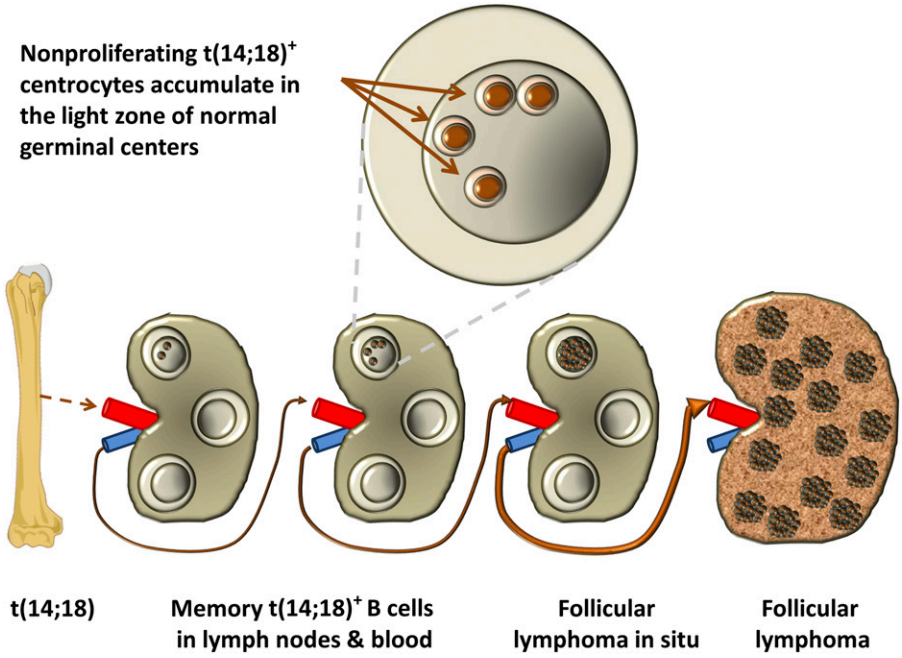

Tellier et al[1] propose that the rare naïve t(14;18)-positive B cells as produced from erroneous VDJ recombinations in bone marrow precursor B cells may preferentially home germinal centers of lymph nodes where they reside as nonproliferating cells. Several rounds of reentry in this compartment in which the cells accumulate DNA damage may lead to functionally important gene mutations and consequently to the development of a so-called follicular lymphoma in situ and ultimately to overt follicular lymphoma.

memory B cells in healthy individuals and their origin from bone marrow precursor B cells by the in situ analysis of t(14;18)$^+$ cells in lymph nodes of healthy individuals. As in peripheral blood, these cells are identifiable in a sizeable proportion of individuals. Using triple staining for CD20, CD10, and B-cell lymphoma 2 (BCL2) and cell sorting for CD20, CD10, and C-X-C chemokine receptor 4 (CXCR4; a marker of centroblasts), translocations are mainly seen in the CXCR4 dim staining centrocytes. Moreover, by labeling for carboxyfluorescein succinimidyl ester (CFSE) before in vitro B-cell stimulation and flow sorting, they are exclusively found in the strongly CFSE-positive nonproliferating cells. The authors suggest that this nonproliferating state is caused by aberrant BCL2 overexpression.

The current paper suggests a preferential homing to germinal centers where these cells undergo somatic mutations and class switching and also further steps in the development of (pre)malignant clones, incidentally giving rise to a follicular lymphoma in situ (see figure). The next, even more challenging step will be to get these rare cells in hand to further investigate them by mutation analysis and in functional assays.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● PLATELETS & THROMBOPOIESIS

Comment on Liu et al, page 3381

A(nother) day in the life of neonatal platelets

Spencer K. Sullivan and Mortimer Poncz THE CHILDREN'S HOSPITAL OF PHILADELPHIA

In this issue of *Blood*, Liu et al demonstrate that neonatal platelets survive longer than their adult counterparts, which provides the rapidly growing fetus and neonate with a mechanism to expand platelet mass and maintain hemostasis during the transition from fetal to adult hematopoiesis.[1]

Thrombocytopenia, which may contribute to intracranial hemorrhage in preterm neonates, is a major clinical problem encountered in the neonatal intensive care unit. Significant intracranial bleeding can lead to hydrocephalus, seizures, neurologic deficits, and death. The current treatment of thrombocytopenia in preterm neonates is platelet transfusions, but the risks of this therapy include viral infections, transfusion-related acute lung injury, and volume overload.[2] New therapies are urgently needed, but first a basic understanding of neonatal thrombopoiesis is needed. In their article, Liu et al reveal a novel biological strategy for maintaining platelet homeostasis in neonates that is independent of the rate of platelet production.[1]

Using a mouse model for neonatal thrombopoiesis, the authors found an approximate doubling of the platelet count during the newborn period despite a 5-fold increase in

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.[1] 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-x_L, which inhibits the activity of the proapoptotic proteins Bak and Bax, is a critical prosurvival protein that regulates platelet senescence.[3] 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-x_L 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-x_L 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.[4] The biological mechanism underlying this increased life span is an opportunity for future investigation but likely involves Bcl-2 and Bcl-x_L, 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.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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● ● ● THROMBOSIS & HEMOSTASIS

Comment on Agostinis et al, page 3478

Antibodies in APS with competing interest

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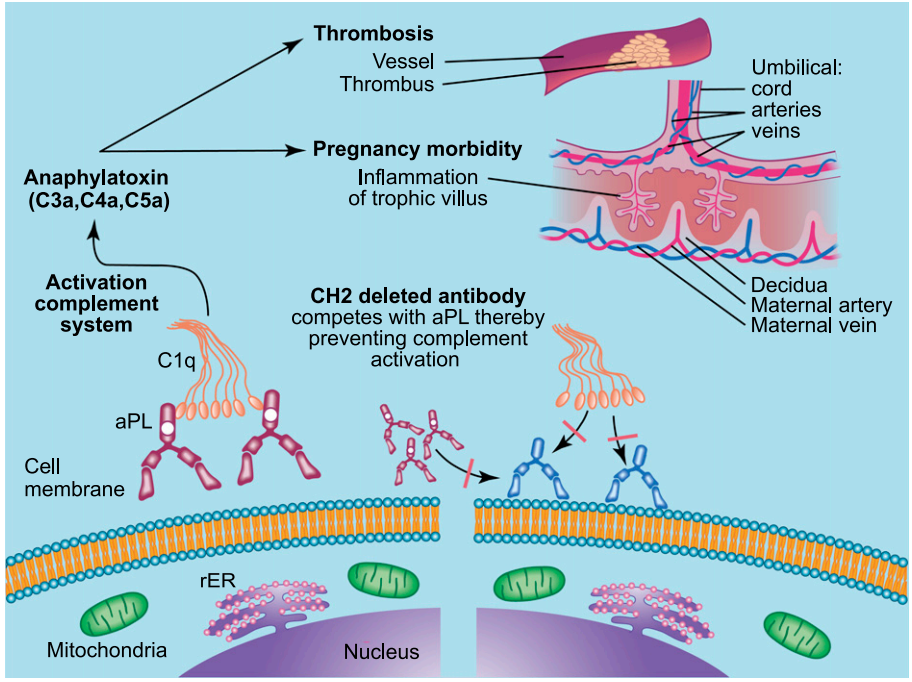
In this issue of *Blood*, Agostinis et al provide evidence for a dominant role of the complement system in the pathology of the antiphospholipid syndrome by showing that a CH2-deleted antiphospholipid antibody (aPL) prevented and reversed aPL-induced thrombosis and pregnancy failure in rats.[1]

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



The mechanism suggested by Agostinis et al. aPL recognizes domain I of β2GPI and stabilizes on the cell surface. This is followed by binding of complement factor C1q resulting in the activation of the complement system. The formed anaphylatoxins will cause cell damage and induce a prothrombotic phenotype, leading to both thrombosis and pregnancy failure. Deleting the CH2 part, responsible for binding C1q, prevents complement activation by competing with aPL for binding domain I of β2GPI. Professional illustration by Paulette Dennis.