The presence of increased numbers of reticulated platelets in ET draws attention to another major mechanism—namely, COX-1 activity in newly released platelets not inhibited by the once-daily low-dose aspirin. This is because of the relatively short half-life of aspirin in plasma. In states with rapid platelet generation, one daily dose of low-dose aspirin may be insufficient because of the immense capacity of bone marrow to accelerate platelet production (even 10-fold of basal rate). Dragani et al go on to show that addition of aspirin (50μM) in vitro abolishes thromboxane production in patients already receiving aspirin, consistent with an effect on COX-1 not acetylated by the single dose of aspirin administered 24 hours earlier. In a study of 60 healthy subjects, Guthikonda et al showed increased thromboxane production in healthy subjects with higher reticulated platelets, while ex vivo addition of COX-1 or COX-2 inhibitor attenuated the thromboxane production; the effect was greater with a COX-1 inhibitor.[4] They also showed decreased inhibitory effects of aspirin and clopidogrel in patients with coronary artery disease with higher numbers of reticulated platelets.[3]

The findings of Dragani et al raise important issues regarding optimum regimen to suppress thromboxane production. What is clear is that low-dose aspirin administered once daily is inadequate to fully suppress thromboxane production in ET and likely in other disorders with increased platelet production. The addition of a COX-2 inhibitor may not be the answer, because of the persistent thromboxane production following a 7-day dual drug therapy with a COX-2 antagonist and aspirin. The short plasma half-life of aspirin argues against added benefits of higher doses at the same dosing interval. The studies of Dragani et al advance strong support for a dosing interval shorter than the traditional once-daily aspirin—and this remains to be tested with clinical endpoints of thrombotic events.

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

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● ● ● RED CELLS & IRON

Comment on Chen et al, page 1070

Getting personal with B19 parvovirus

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In this issue of *Blood,* Chen and colleagues[1] identify the 11-kDa nonstructural protein of the parvovirus B19 as the main culprit for induction of apoptosis in primary human erythroblasts through activation of caspase 10.

Infection with B19 parvovirus, usually spread by the respiratory route, is common in human populations and induces a mild transient and usually benign anemia.[2] In immunosuppressed patients (patients undergoing chemotherapy, undergoing bone marrow or solid organ transplantation, or infected with HIV) and in patients with congenital anemia associated with shorter red cell survival (sickle cell anemia and enzyme deficiencies), the anemia is severe and persistent and may be life-threatening.[3] In some patients, B19 parvovirus infection may even trigger or aggravate autoimmune diseases.[4] In pregnancy, B19 infection may cause severe anemia nonimmune hydrops and fetal loss.[2] The infection may also be transmitted through transfusion,[5] leading transfusion medicine researchers to evaluate pathogen inactivation/purging methods for some blood components and derivatives and to consider whether screening for this virus should be included in routine donor testing, at least in spring when outbreaks appear more likely.[5] Therapy includes intravenous supportive red cell transfusion and immunoglobulin administration (commercial immunoglobulin preparations contain anti-B19 antibodies) and/or reduction in the intensity/frequency of immunosuppressive treatments. However, if autoimmunity develops, immunosuppressive therapy may be indicated. The lack of specific therapies is mostly due to poor knowledge of the pathogenesis of the virus. B19 parvovirus shows a high tropism for the erythroid lineage because the virus enters the cells through the epitope corresponding to the P blood group antigen on the erythroid-specific receptor globoside. The virus kills erythroid cells by inducing apoptosis through a mechanism largely unknown up to now, due to a lack of suitable in vitro models (human erythroid cell lines are resistant to B19 infection).[6] Recently, it was demonstrated that primary $CD36^+$ erythroblasts expanded in vitro from purified human $CD34^+$ cells are permissive to B19 infection,[7] providing the much-needed experimental model to explore in vitro the mechanism of apoptosis induced by this virus.

In this issue of *Blood*, Chen et al,[1] by using this experimental model, finally disclose the mechanism by which B19 parvovirus induces apoptosis of erythroid cells. The authors identify the 11 kDa (1 of 3 nonstructural proteins encoded by the virus) as the protein that triggers the caspase-dependent apoptotic pathway, activating specifically caspase 10. The identification of the 11 kDa–caspase 10 pathway opens the way to structural modeling studies that may identify therapeutic drugs. Competing/inhibiting the 11 kDa–mediated caspase 10 activation will specifically prevent anemia induced by B19 infection. It is predicted that the identification of these drugs will be greatly facilitated by the use of ex vivo expanded human $CD36^+$ erythroblasts as a readout assay. In fact, $CD36^+$ erythroblasts can be expanded in vitro in great numbers from progenitor cells present in both adult blood and cord blood.[8,9] These numbers are similar to those required for transfusion (2×10^{12} erythroid cells). However, cost and logistic considerations suggest that the first clinical application of these cells will not be for transfusion but for drug discovery or delivery.[10] The current article implies that erythroblasts expanded ex vivo from adult or neonatal hematopoietic progenitor cells, as well as from

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human embryonic cell lines (hES) or induced pluripotent stem cells (hiPS), may be used in automated screening assays to identify inhibitors of B19-induced apoptosis. In addition, the fact that these cells can be expanded from almost any donor will allow investigation of individual susceptibility to the consequences of viral infection, opening the way to identification of strategies for patient-specific treatment of B19 infection. These studies will represent one of the first applications to exploit basic science, therapeutic cloning, and regenerative medicine for clinical purposes.

The possibility of obtaining large numbers of "normal" cells for any given tissue from any person provides a glimpse into the rapidly emerging field of personalized medicine. Although many issues, such as the "ontogenetic memory" of hES or hiPS-derived cells, must still be addressed to make this approach a reality, "normal" cell-based experimental systems are needed by the pharmaceutical industry to develop new translational medicine products. Increasing awareness of the ethical barriers to the use of animal experimentation for pharmaceutical purposes is encouraging development of alternative in vitro and computational experimental models. In vitro models based on cell lines, however, are not representative of complex organisms and do not reflect the heterogeneity of the human populations. It is conceivable that in the future the assessment of toxicity and efficacy of new drugs will employ in vitro assays using panels of human primary cells reflecting age, sex, and genetic differences of human populations. This approach could reduce animal experimentation and increase the sensitivity and robustness of preclinical toxicology and efficacy studies.

For these reasons, the article by Chen et al breaks new ground on various fronts, from the basic biology of erythroid cells to mechanisms of B19 parvovirus–induced anemia, and suggests an assay that will predict the efficacy of drugs in the treatment of the associated anemia.[1]

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