regulation of the organism remains intact. Obviously, the side effects of these treatments have yet to be investigated. Current inhibitors of hepcidin, as reviewed by Nemeth and Ganz, include targets of pathways of hepcidin induction (such as the small-molecule inhibitor LDN-193189), antihepcidin antibodies (such as the fully human antihepcidin antibody 12H9m), or synthetically generated hepcidin binders such as anticalins or RNA-based Spiegelmers.

Lexaptepid pegol (lexaptepid) is a synthetically generated PEGylated L-steresioimeric RNA aptamer. It belongs to the Spiegelmers and consists of a synthetic L-oligoribonucleotide with a 3-dimensional structure. Due to the unnatural mirror-image structure, it is of higher biological stability compared with natural D-aptamers. Lexaptepid binds hepcidin conceptually similar to antibodies, forms a complex, and thereby inhibits hepcidin.

In this issue of Blood, van Eijk and colleagues present their study on the use of the Spiegelmer lexaptepid in a first human trial. The efficiency of lexaptepid for inhibition of hepcidin expression was initially tested in cell culture and animal studies. In the current article, experimental endotoxemia was induced in 24 healthy male volunteers by intravenous Escherichia coli lipopolysaccharide (LPS) injection followed by either a single injection of lexaptepid or placebo (see figure). The increase in serum hepcidin levels after LPS injection was comparable in both groups. This indicates that hepcidin measurement cannot differentiate between free hepcidin and the complex of hepcidin-lexaptepid. Both groups presented with similar flu-like symptoms, increase in body temperature and laboratory markers indicative of inflammation such as C-reactive protein, leukocyte counts, and cytokine concentrations. In contrast, the decrease in serum iron levels within 9 hours after injection observed in the placebo group did not occur in patients injected with lexaptepid. These data reveal that lexaptepid does not interfere with the inflammatory reaction but disables hepcidin’s ability to induce hypoferremia.

To summarize, lexaptepid is effective in preventing the first step following hepcidin induction due to endotoxemia: effective prevention of a decrease in serum iron. It is not yet known if lexaptepid prevents the development of anemia of inflammation or treat the anemia of inflammation after it is already established. The future direction is clear: Additional novel data on clinical trials with lexaptepid in patients are expected to be released soon. The authors have already presented data from a phase 2 pilot study in cancer patients (multiple myeloma, low-grade lymphoma, and chronic lymphocytic leukemia) with anemia of chronic disease at the American Association for Cancer Research. In this study, treatment with lexaptepid for 4 weeks resulted in a hemoglobin increase of ≥1 g/dL in 5 of 12 patients. Patients responding to the treatment also presented with an increase in reticulocyte hemoglobin.

Lexaptepid seems to be a promising drug to battle anemia of inflammation.

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MYELOID NEOPLASIA

Comment on Kulasekararaj et al, page 2698

MDS-related mutations in aplastic anemia

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In this issue of Blood, Kulasekararaj et al describe a subgroup of acquired aplastic anemia (AA) that is characterized by myelodysplastic syndrome (MDS)–like somatic mutations and is at high risk for progression to MDS. A is a prototype of acquired bone marrow failure caused by immune-mediated destruction of hematopoietic stem/progenitor cells, whose prognosis has been dramatically improved during the past 3 decades by the development of immunosuppressive therapies (ISTs), especially for those who are not eligible for allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, in some cases (up to 15%), even successful ISTs are complicated by the development of MDS and/or acute myeloid leukemia (AML). In fact, differential diagnosis between AA, especially of nonsevere forms, and hypoplastic MDS has been a long-standing issue in clinical hematology due to close similarities in their clinical presentation, both showing hypoplastic bone marrow that hampers sufficient morphological evaluation for dysplasia, cytogenetic and other evidence of clonal hematopoiesis, and sizable responses to ISTs.

Using next-generation sequencing of targeted exons, Kulasekararaj et al explored somatic mutations in bone marrow samples from 150 cases with AA and investigated their impact on progression to MDS as well as correlation to disease duration.
and telomere attrition. Through an initial screening of 835 known genes in 57 discovery cases, followed by focused sequencing of detected targets in 93 extended cases, a total of 32 somatic mutations typically seen in MDS and other myeloid malignancies were detected in 29 of 150 patients (19%), where the predominant mutational targets included ASXL1, DNMT3A, and BCOR. Transformation to MDS occurred in 17 cases, which included 11 of the 29 mutation (+) cases, or 7 of 12 ASXL1-mutated, 3 of 8 DNMT3A-mutated, and 1 of 6 BCOR-mutated cases. Importantly, somatic mutations were significantly associated with longer disease duration, that is, time from diagnosis to sample collection (37 vs 8 months, P < .04), shorter telomere lengths (median telomere-to-single copy gene lengths (median telomere-to-single copy gene (37 vs 8 months, P < .04), shorter telomere lengths (median telomere-to-single copy gene ratio length, 0.9 vs 1.1, P < .001), and a higher rate of progression to MDS/AML (38% [11 of 29] vs 5.0% [6 of 121], P < .001).

Clonal hematopoiesis in AA has long been discussed based on the presence of cytogenetic abnormalities, skewed X-chromosome inactivation in female patients, appearance of varying degrees of blood cells having paroxysmal nocturnal hemoglobinuria phenotypes, and more recently, recurrent uniparental disomy (UPD) in the 6p arm commonly involving the class I HLA locus. It has been speculated that the clonal hematopoiesis may be derived from some ‘bottleneck’ effect caused by hematopoietic repopulation from a severely reduced number of hematopoietic stem cells, or represent escaped hematopoiesis from autoimmunity, especially in 6pUPD(+) cases and/or premalignant hematopoiesis as has been demonstrated recently in AML. The current study, together with a previous report by Lane et al, demonstrated that clonal hematopoiesis in AA frequently accompanies somatic mutations commonly seen in MDS/AML and also presented the first implication that these “MDS/AML-like” somatic mutations predict a substantial risk for progression to MDS/AML (~40%). The findings not only provide intriguing insight into the relationship between clonal hematopoiesis and malignant transformation in AA, but also have significant clinical relevance in terms of choice of therapies, such as early use of allo-HSCT for mutation (+) cases. On the other hand, a number of important issues are raised with regard to the origin and chronological behavior of these mutated clones that frequently heralded clinically relevant MDS. The higher frequency of mutations in patients with longer disease duration and the trend of larger clone sizes and shorter telomere lengths thereof may indicate clonal dominance of the mutated clones over time. However, to identify the exact origin of mutations and their temporal behavior, analysis of carefully fractionated cells using serially collected samples from the diagnosis to overt MDS would be needed. Also, the entire picture of clonal hematopoiesis in AA and its pathogenic/clinical significance could be better delineated through more exhaustive detection of somatic mutations in an unbiased way, using whole genome/exome sequencing.

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PLATELETS & THROMBOPOIESIS

Comment on Potts et al, page 2725

Diploid, not polyploid: new platelet producers

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In this issue of Blood, Potts et al have identified a unique cell population in the yolk sac (YS) as the source of the first platelet-forming cells in mouse embryos. These cells are diploid and are produced via a pathway independent of hematopoietic progenitor cells (HPCs) generating polyploid megakaryocytes (MKs).

When and how hematopoiesis emerges and proceeds are still intriguing questions. Despite remarkable advances in this field, details of blood cell development are still largely veiled in mystery. Understanding the mechanism by which hematopoietic cells are generated is critical and could lead to novel strategies for the making of functional hematopoietic cells in vitro for regenerative medicine using not only cord blood hematopoietic stem and progenitor cells but also pluripotent stem cells such as embryonic stem (ES) and induced pluripotent stem (iPS) cells.

Mature MKs derived from HPCs, which are characterized by polyploid nuclei, have been thought to generate platelets from the beginning throughout life. However, Potts et al have discovered previously unrecognized diploid cells in the YS as the first platelet-forming cells, which are distinct from polyploid MKs. These unexpected findings provide novel insights into our understanding of the
MDS-related mutations in aplastic anemia

Seishi Ogawa