Introduction to a series of reviews on inherited bleeding disorders

Hematology can proudly claim to have led many of the recent advances in the application of molecular science to enhancing the diagnostic and treatment potential for disease. Although every issue of Blood contains new insights into the integration of molecular knowledge for improved clinical care, the paradigm of molecular medicine can be traced to the late 1970s/early 1980s, with advances in understanding the genetic basis of benign hematologic disease. Among these early molecular discoveries was the cloning of the genes encoding the clotting factors whose deficiency and/or dysfunction results in the common inherited bleeding diseases hemophilia and von Willebrand disease (VWD).

In the inherited bleeding disease community, the mid-1980s was a time of simultaneous despair, with the evolving impact of transfusion-transmitted HIV and hepatitis viruses, and excitement, related to the rapidly evolving new molecular genetic knowledge. Very soon after the cloning of the factor VIII and factor IX genes, molecular genetic diagnosis for the hemophilias was implemented, and not long afterward, recombinant clotting factors became available for protein replacement therapy.

In the 30 years since these initial discoveries, the impact of molecular science on inherited bleeding disorders has continued to grow. Not only has there been a continual enhancement of the therapeutic options for these disorders, the most recent of which has seen early successes for gene transfer in hemophilia B, but knowledge of the basic biology of the clotting factors has also increased, exemplified last year by 2 publications in Blood demonstrating that the endothelium is the predominant site of factor VIII production.

The collection of reviews included in this issue of Blood spans a range of advances involving the basic biology, diagnosis and clinical care of hemophilia, VWD, and the rare bleeding disorders.

For the hemophilias, where molecular diagnosis is now routine in many countries and for which prophylactic treatment protocols have demonstrated marked improvements in long-term musculoskeletal health, the 2 reviews focus on the major treatment complication, factor VIII antibody development, and a detailed analysis of the evolving role of clotting factor prophylaxis to effect optimal outcomes in hemophilia. Although factor VIII inhibitors have been the subject of extensive investigation since the 1980s, our understanding of their pathogenesis and successful strategies to prevent and eliminate these antibodies remain challenging. In contrast, since the original studies from Scandinavia 30 years ago, there has been a progressive incorporation of prophylactic therapy for hemophilia, with the realization that this therapeutic approach results in a markedly reduced bleeding frequency and improved long-term musculoskeletal status. Nevertheless, there are still important questions that remain unanswered in terms of optimizing prophylactic management. Even the most intensive prophylactic protocols are associated with evidence of musculoskeletal pathology in middle age, and thus, although it is clear that this therapeutic approach is invaluable in children and young adults, the role of prophylaxis in adults poses a number of unanswered questions. These issues are all the more timely, given the arrival in the clinic of novel therapies that extend the half-life of clotting factors and provide various other opportunities to maintain effective hemostasis for prolonged periods, without the need for more frequent infusions.

VWD is the most common inherited bleeding disorder, and since the cloning of the VWF gene in 1985, major strides have been made in our knowledge of disease pathogenesis. Nevertheless, the diagnosis of VWD, particularly of the most prevalent form, type 1 VWD, remains problematic. Thus, a review of the optimal approach to diagnose this condition using a range of assays to evaluate the various functional roles of von Willebrand factor (VWF), is timely. As quantitative pathologies of VWF represent important causes of inherited bleeding, advances in our knowledge of the life cycle of this protein are valuable. With this in mind, new information has been derived from a series of cell- and animal-based studies to determine mechanisms regulating VWF biosynthesis, secretion, and clearance. The details of these findings are now summarized in the second review relating to advances in our understanding of VWD.

The final review in this series concerns the diagnosis and treatment of the so-called rare bleeding disorders (neither hemophilia nor VWD). In reality, apart from type 1 VWD, all of the inherited hemorrhagic conditions are rare, and some of the “rare inherited bleeding disorders” are exceedingly uncommon. For this reason, knowledge concerning the clinical presentation, optimal diagnostic approaches, and therapeutic strategies for these traits has been difficult to obtain. Nevertheless, in recent years, principally through the establishment of large rare bleeding disease registries, there has been a significant increase in information that can be used to develop a more evidence-based approach to the management of these disorders. The current review summarizes the knowledge derived from these global resources.

This collection of reviews relating to inherited bleeding disorders presents a timely summary of information ranging from pathogenetic mechanisms to the diagnosis and application of innovative treatments for these conditions. This area of benign hematology has experienced significant advances in clinical management over the last 2 decades, based on innovative basic and translational investigation that promises to further enhance clinical opportunities in the near future. The reviews included in this issue summarize and highlight these advances. I trust you will find the series interesting and informative.

David Lillicrap
Associate Editor, Blood

Authors | Review title
---|---
Peter J. Lenting, Olivier D. Christophe, and Cécile V. Denis | von Willebrand factor biosynthesis, secretion, and clearance: connecting the far ends
Christopher Ng, David G. Motto, and Jorge Di Paola | Diagnostic approach to von Willebrand disease
Johannes Oldenburg | Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens
Jan Astermark | FVIII inhibitors: pathogenesis and avoidance
Roberta Palla, Flora Peyvandi, and Amy D. Shapiro | Rare bleeding disorders: diagnosis and treatment
Introduction to a series of reviews on inherited bleeding disorders

David Lillicrap