and some, but not all, cases of severe congenital neutropenia.2-4

In this issue of Blood, Bellanne-Chantelot and colleagues (page 4119) report on studies of the clinical, hematologic, and genetic characteristics for 81 patients with cyclic or congenital neutropenia followed in the French Neutropenia Registry. The French registry is a national cooperative organization providing data for a geographically defined population with severe chronic neutropenia (ie, patients with blood neutrophil levels regularly or cyclically less than 0.5 × 10^9/L for longer than 3 months). This paper presents several important observations. (1) In a population study, the patients with NE mutations have more severe neutropenia and more severe bacterial infections. These patients are also at greater risk for evolving to myelodysplasia or acute myeloid leukemia (AML). Thus, sequencing of the NE gene may provide important prognostic information for management of individual patients. (2) All NE mutations associated with neutropenia are heterozygous. Relatives of affected individuals are relatively likely to also have NE mutations, although their neutropenia may not be as severe as in the index case. (3) Cyclic neutropenia and severe congenital neutropenia are predominantly autosomal dominant disorders. Thus, finding a patient with severe neutropenia should prompt a review of the history and blood counts in the patient’s relatives and appropriate genetic counseling. (4) The severity of neutropenia and the risk of AML cannot yet be predicted from the location or nature of the NE mutations.

It is now well known that most patients with cyclic and congenital neutropenia respond readily to treatment with granulocyte colony-stimulating factor (G-CSF).5 Based on 15 years of observations, this treatment has not been associated with evolution to acute myeloid leukemia in patients with cyclic neutropenia. On the other hand, patients whose clinical phenotype and mutational analysis are consistent with the diagnosis of severe congenital neutropenia are at risk for evolution to leukemia.6 In this report, 4 of 54 patients with congenital neutropenia developed AML. All of the patients who developed AML had mutations of the NE gene. This report suggests that some, but not all, mutations in the NE gene may lead to AML. A number of laboratories are now deeply engaged in verifying and trying to understand this important observation.

This excellent report clearly shows the steady progress being made in understanding the causes and consequences of disease causing severe chronic neutropenia.

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site-specific phenotypes of the endothelium are regulated by a combination of environmental and mitotically heritable (epigenetic) factors. In other words, some properties become “locked in” (during development and/or in the postnatal period) and are thus uncoupled from ongoing changes in the extracellular compartment, whereas other properties are plastic, marching to the tune of the local microenvironment.

Why are these considerations important? First, plastic (reversible) properties of the endothelium are more likely to be amenable to non–gene-based therapy, compared with their epigenetic counterparts. Thus, a clearer delineation of the “boundaries of flexibility” in various vascular beds may help to refine our therapeutic strategies. As an important corollary, it will be interesting to explore whether loss of plasticity and gain in epigenetic modification are associated with disease and/or aging. Finally, from a practical standpoint, the current study underscores the limitations of studying endothelial cell biology in vitro, particularly as it relates to an elucidation of site-specific properties. Indeed, the cultured endothelial cell is a mere “shadow of its former self” and should be approached with a dose of healthy skepticism.

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HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

Anticoagulant factor V and thrombosis risk

Since its discovery in 1943 by Paul Owren, coagulation factor V (FV) is recognized as an important procoagulant protein, its activated form (FVα) functioning as a cofactor in the generation of thrombin.1 The procoagulant activity of FVα is subjected to regulation by proteolysis mediated by activated protein C (APC), a key component of the protein C anticoagulant system.2 FV deficiency is a rare cause of bleeding problems. Much more common is the involvement of FV gene defects in the pathogenesis of venous thrombosis. A highly prevalent single point mutation in the FV gene (FVLeiden) resulting in the loss of an APC cleavage site in FV affects the regulation of FVα activity by APC. The associated phenotype is referred to as APC resistance and is characterized by a life-long hypercoagulable state and increased risk of thrombosis. During the elucidation of the pathogenesis of APC resistance, it was discovered that FV is a Janus-faced protein. Not only is it a procoagulant but it also has the capacity to function as an anticoagulant APC cofactor in the degradation of coagulation factor VIIIα (FVIIIα).3 The APC resistance associated with the FVLeiden mutation is the result of both impaired regulation of FVα by APC and loss of the anticoagulant APC cofactor activity of FV. Thus, a single point mutation in FV affects the regulation of coagulation on 2 levels: the degradations of FVIIIα and FVα. The relative importance of these 2 distinct mechanisms to the development of the hypercoagulable state that increases the risk for thrombosis has been largely unknown.

In this issue of Blood, Castoldi and colleagues (page 4173) describe methods to quantify the APC cofactor activity of FV and, moreover, they have been able to determine the relative contribution to the APC-resistance phenotype of reduced susceptibility of FVα to APC and impaired APC cofactor activity of FV. They show that FVLeiden exhibits no APC cofactor activity in FVIIIα inactivation and that APC resistance due to FVLeiden is caused by equal contributions of poor susceptibility of FVα to APC and impaired APC cofactor activity. These results are of conceptual importance and point to the involvement of the anticoagulant properties of FV in the regulation of blood coagulation. The dual effects of the FVLeiden mutation on the anticoagulant protein C system cause the increased thrombosis risk associated with this mutation. In this context it is interesting to note that mutations affecting another important APC cleavage site in FV (ie, FVCambridge [R306T] and FVHong Kong [R306G], neither of which are strong thrombosis risk factors) mainly impair the susceptibility of FVα to APC but leave the APC cofactor activity of FV virtually intact.4 In contrast, another FV gene mutation associated with thrombosis, FVLiverpool (I359T), results in the loss of the APC cofactor activity of FV. Additional supporting evidence for the in vivo importance of the anticoagulant APC cofactor activity of FV comes from studies of genetically modified mice.5 With these exciting results on record one might expect a renewed interest in the Janus-faced FV molecule and an intensified search for other genetic and acquired deficiencies of anticoagulant FV activity.

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Endothelial cell heterogeneity: a case for nature and nurture

William C. Aird

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