blood cells of patients with SDS, and likely impact their clinical evolution.

In the future, SGR will probably be detected in other conditions. Thus, one can imagine that cheaper and improved sensitive sequencing methods will enable the systematic search for or longitudinal follow-up of SGR events. This would represent considerable progress of patient-centered medicine by helping adopt the best therapeutic decisions for patients with Mendelian hematopoietic diseases, including SDS.

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THROMBOSIS AND HEMOSTASIS

Comment on Skjeflo et al, page 2129

Complementing venous thromboembolism, a risky move

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In this issue of *Blood*, Skjeflo et al demonstrate an association between plasma complement factor 5 (C5) levels and risk of future venous thromboembolism (VTE) in a nested case-control study of patients enrolled in the Tromsø population-based cohort study.[1]

Resembling the coagulation cascade in organization, the complement system is a key component of innate immunity. Experimental studies have demonstrated complex interplay between the complement system and the coagulation cascade promoting VTE. As with the coagulation cascade, there are 3 pathways, which can activate independently or converge to cleave C5. Cleavage of C5 results in release of a potent anaphylatoxin, C5a, as well as C5b to initiate formation of C5b-C9, the membrane attack complex (MAC). Cleavage of C5 potentiates hemostasis via the actions of both C5a and the MAC. Neutrophil recruitment and priming, through increased expression of tissue factor on the neutrophils, occurs in response to C5a.[2,3] This recruitment and priming can lead to release of neutrophil extracellular traps, which further promote thrombosis through platelet aggregation and activation as well as thrombin formation.[4,5] The MAC contributes to the activation of the coagulation cascade through platelet activation leading to the release of platelet factor V and assembly of the prothrombinase complex.[6]

In a prior study, complement factor 3 (C3) levels were associated with an increased risk of future VTE.[7] As with the study by Skjeflo et al, the association of C3 with VTE remained with only slight modification of the risk estimates after adjustment for general inflammation, as measured by C-reactive protein, and after adjustment for body mass index. Cleavage of C3 to C3b generates C5 convertase, resulting in cleavage of C5 to C5a and C5b. Thus, higher levels of C3 result in higher levels of C5a and the MAC. In the current study, the association between C5 and risk of VTE remained, with only slight modification of the risk estimate, after similarly adjusting for C-reactive protein and body mass index. Accordingly, the agreement in findings between these 2 studies support the noted associations between complement and the development of VTE.

An additional finding of importance of this study relates to determination of drivers of plasma C5 levels. Although the acute phase reactant C-reactive protein can activate complement, the magnitude of increase in complement proteins (ie, C3) during inflammatory stimuli (eg, infection) is less pronounced. In fact, plasma C5 levels did not differ from baseline in 1 preclinical study, but were elevated at the site of inflammation.[8] In this study, the authors found only a weak linear relationship between C-reactive protein and C5 levels, indicating that chronic inflammation explains only a minor part of the association between C5 and VTE. In addition, using a protein quantitative trait loci analysis, the authors found no significant SNP in either whole genome or *cis*-restricted analyses of 1 033 970 variants in the whole-exome data set. Although experimental studies suggest a role for C5 in hemostasis, Skjeflo et al demonstrate C5 as a risk factor for VTE within the general population. This transition from bench to bedside not

only strengthens the evidence for the role of complement in hemostasis, but also provides rationale for future studies confirming this association as well as those considering novel therapeutic interventions. Inhibition of C5 in patients with paroxysmal nocturnal hemoglobinuria improves outcomes and decreases the risk of clinical thromboembolism (relative reduction 85%).[9,10] The findings in the study by Skjeflo et al raise the question of whether there is a subgroup of VTE patients that could similarly benefit from complement inhibition.

In summary, Skjeflo et al demonstrate important evidence toward the role of complement in hemostasis, particularly the risk of VTE. These findings contributing to this growing body of literature and provide rationale for continued scientific investigation with the goal of improving outcomes in patients with and at risk of VTE.

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MYELOID NEOPLASIA

Comment on Marcault et al, page 2142

Sentinel mutations: the roses in the vineyard

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A central challenge in the care of patients with myeloproliferative neoplasms (MPNs) is identifying those individuals at high risk for transformation into acute leukemia, an exacerbation that carries a very poor prognosis.[1] In this issue of *Blood*, Marcault and colleagues[2] describe a novel type of mutation, for which I propose the term "sentinel mutation" (see figure). The acquisition of a "sentinel mutation" drastically increases the likelihood of leukemic transformation, even though in some patients the mutation does not occur in the cells that form the leukemic clone. "Sentinel mutations" function like roses planted in vineyards. Ailing flowers forecast the vines' impending infection with black rot or downy mildew as the roses are affected first, even if the species that blight the flowers differ slightly from those that spoil the grapes. Similarly, Marcault and colleagues have shown that patients with MPN that acquire mutations in the transcription factor "nuclear factor erythroid 2" (NFE2) carry an increased risk of leukemic transformation, even though in some patients the mutations are not found in the leukemic cells.

The results are remarkable and carry implications beyond the field of MPNs. NFE2 "sentinel mutations" act by a mechanism distinct from that of the 2 previously recognized categories of MPN oncogenic mutations, "driver mutations" and "high-risk mutations." "Driver mutations" initiate and promote disease development, whereas "high-risk mutations," which may be incurred in addition, increase the risk of disease exacerbation.[3] In most patients, the proportion of cells carrying "driver" and "high-risk" mutations increases during leukemic transformation. In contrast, in some patients, the proportion of cells carrying NFE2 mutations decreased following leukemic transformation, suggesting, as the authors point out, a paracrine mechanism in which the presence of an NFE2 mutation facilitates the acquisition of secondary mutations in other cells of the neoplastic clone. Intriguingly, it is known that in some patients who carry the $JAK2^{V617F}$ driver mutation during the chronic disease phase, the transformed leukemic blasts do not show the $JAK2^{V617F}$ mutation, although they display other genetic abnormalities present during the chronic phase.[4,5] These observations demonstrate that leukemic transformation occurred in residual neoplastic cells that had not acquired the $JAK2^{V617F}$ mutation. The novel observations by Marcault et al suggest that paracrine effects on