in Bruton tyrosine kinase or its downstream intermediary drives ibrutinib resistance, whereas presence of a complex karyotype and Del17p are predictive of progression while on ibrutinib. Additional work in larger cohorts of samples may be required to address whether USP7 inhibition would be sufficient to target disease in this subgroup of patients.

In conclusion, despite unresolved queries, this study identifies that USP7 is an attractive therapeutic target in CLL and warrants its investigation both mechanistically and in clinical trials.

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PHAGOCYTES, GRANULOCYTES, AND MYELOPOIESIS

Comment on Panicker et al, page 181

Soluble P-selectin is the smoke, not the fire

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In this issue of Blood, Panicker and colleagues have clarified the role of soluble P-selectin (sP-selectin) in inflammation and cardiovascular disease by showing that monomeric sP-selectin, the form that circulates in plasma, does not promote inflammation or promote coagulation, but the dimeric form of P-selectin does.1

P-selectin, which is expressed on the membrane of activated platelets and the endothelium, interacts with its primary cell-adhesion partner, P-selectin glycoprotein ligand-1 (PSGL-1), on leukocytes; this occurs best when both are dimers.2 This interaction mediates leukocyte rolling and promotes inflammatory pathways. These in turn induce proteolytic shedding of the P-selectin ectodomain into the circulation, releasing sP-selectin, a monomer.3 In the circulation, P-selectin is also found on the surface of platelet-derived microparticles, where it may be a dimer, and as an alternatively spliced form. sP-selectin has been evaluated as a biomarker and is reported to be elevated in a number of conditions, including atherosclerosis, hyperlipidemia, myocardial infarction, postangioplasty stenosis,3 pulmonary arterial hypertension,4 and venous thrombosis.5,6 The prevailing view had been that sP-selectin is not only a biomarker, but directly contributes to vascular disease.7

Panicker et al show that dimerized P-selectin binds with 20-fold greater avidity than monomeric P-selectin to a glycosulfopentide that mimics PSGL-1. Artificially, dimerization of the monomer is achieved by producing sP-selectin with an Fc tail, or by producing sP-selectin with an HPC4 tag and using an antibody directed against that tag. The authors show that sP-selectin needs to be a dimer to trigger activation of mouse leukocytes in vitro, manifest as leukocyte adhesion to ICAM-1 and to fibrinogen, and the release of citrullinated histones and neutrophil extracellular traps. After establishing the pharmacokinetics of the monomer and dimer, they demonstrate that administered sP-selectin needs to dimerize, by using the artificial means described above, to induce leukocyte rolling and firm adhesion and to increase the amount of tissue factor-bearing microparticles in blood. In a mouse inferior vena cava ligation model, administering dimeric sP-selectin increases the frequency of venous thrombosis, but administering monomeric sP-selectin does not. Similarly, administering dimeric sP-selectin shortens clotting times, but administering monomeric sP-selectin does not.

Consistent with these findings, transgenic mice that overexpress monomeric sP-selectin, compared with wild-type mice, do not have altered leukocyte rolling or adherence, altered inflammatory cytokines or chemokines, or frequency of venous thrombosis. Thus, the fire is dimerized P-selectin, prevalent on membranes; (monomeric) sP-selectin is the smoke.

So how do we interpret the hundreds of publications where sP-selectin is described? Depending on assay conditions, these publications may have included microparticles in the samples where “sP-selectin” was measured. If microparticles were not specifically excluded by high-speed centrifugation, then assays for “sP-selectin” would have included microparticle P-selectin, which may be a dimer. Alternatively, perhaps microparticle P-selectin could be measured by subtracting the amount of sP-selectin in a high-speed centrifuged sample from the amount in a plasma sample.

In conclusion, although (monomeric) sP-selectin might have use as a biomarker, it is unlikely to directly contribute to disease (see figure); in contrast, agents that target dimeric P-selectin might put a brake on this coagulation-inflammation pathway.
PLATELETS AND THROMBOPOIESIS

Comment on Sim et al, page 192

Factor V marks platelet-primed megakaryocytes

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In this issue of Blood, Sim et al identify novel distinct human megakaryocyte populations primed for platelet release and establish a new approach to isolate such populations to generate either in vitro or in vivo functional human platelets.1

Platelets are circulating anucleate cells that play a central role in hemostasis, thrombosis, and inflammation. Platelets are the final products of a complex maturation process that involves the differentiation of multipotent hematopoietic stem cells in mature megakaryocytes. This maturation process is characterized by increase in cell size, ploidy, granular components, megakaryocyte-specific surface receptors, and the formation of an invaginated membrane system.2

Platelet transfusions are commonly used clinically to treat or prevent hemorrhage in people with either thrombocytopenia or platelet function defects. Platelet transfusions are employed extensively and increasingly, although they have some associated risks, such as allergic reactions and bacterial and viral infections.3 At present, the only source of platelets for transfusion is donation from volunteers. One of the main difficulties associated with platelet transfusions is the availability of adequate hospital platelet inventories. To overcome this limitation, efforts have been made to find alternative, efficient, non–donor-dependent systems to generate platelets, exploiting in vitro culture systems to differentiate megakaryocytes from hematological stem cells or induced pluripotent stem cells.

There are 2 principal strategies used to generate platelets ex vivo. One method relies on the collection of platelets from megakaryocytes or in a bioreactor system. This method

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