response was improved in a quarter of patients by the addition of lenalidomide. To determine the effect of therapy on immune function, T-cell immune synapse formation was assessed at various times after treatment, when CLL cells obtained before treatment were incubated with autologous T cells obtained during and after therapy. Increased immune synapse formation was seen in 82% of patients after PCR, which appeared to be directly related to the reduction in tumor cell burden. Immune synapse activity increased further with lenalidomide and was paralleled by an increase in T-cell number and IgG levels.

This study is important in that it extends previous observations showing that T-cell immune synapse function can be improved in CLL with lenalidomide, suggesting that part of the activity of this drug is related to improved immune surveillance. Moreover, the study confirmed previous work showing that lenalidomide can improve overall immune function in CLL, producing an increase in immunoglobulin levels. Unfortunately, the study also confirmed that lenalidomide is toxic in CLL, with neutropenia and infections being the most common adverse effects.1,7,8 Thus, a search for new analogs with improved tolerability and enhanced immunomodulation over lenalidomide is required. At this time, the only treatment to produce long-term remissions, and possibly cures, in CLL is allogeneic stem cell transplantation.9

The present study indicates that T-cell immune synapse formation is enhanced after PCR therapy and suggests that minimizing tumor burden before transplantation would optimize the graft vs leukemia effect. Finally, it is tantalizing to speculate that increasing immune surveillance in CLL with lenalidomide or chemoimmunotherapy may reduce the high incidence of second malignancies seen in this disease.2

Conflict-of-interest disclosure: The author declares no competing financial interests.

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PHAGOCYTES, GRANULOCYTES, & MYELOPOIESIS

Comment on Jakob et al, page 4184

Gimme a brake: HPK1 regulates LFA-1 and neutrophil traction

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In this issue of Blood, Jakob et al report that hematopoietic progenitor kinase 1 (HPK1) participates during signaling of neutrophil recruitment by acting as a regulator of the adhesiveness of the β2-integrin lymphocyte function-associated antigen 1 (LFA-1) during acute inflammation.1 Neutrophils are first responders when the innate immune system calls the inflammatory alarm. Produced in the bone marrow at a rapid rate of ~1010 per second, neutrophils are expendable since they are cleared in the spleen and bone marrow within hours if not called into action from the blood stream. Neutrophils surveil the circulation for signs of infection and tissue insult and, at precisely the appropriate location, engage a highly efficient braking system to overcome the significant drag forces of blood flow. In response to acute inflammation, a multistep process has been identified that is initiated by tethering neutrophils via E- and P-selectin adhesion receptors upregulated on inflamed endothelium. Following capture, neutrophils roll a distance of only a few cell diameters (~10 μm) during which they engage chemokines (eg, interleukin–8) that signal via G-protein coupled receptors that in turn activate integrins to bind intercellular adhesion molecules upregulated on inflamed endothelium.2 It is at this stage of the multistep process that the neutrophils, in cooperation with endothelium, make the decision to adhere tightly and proceed to immigrate to the site of tissue insult or be carried away in the circulation.

Perhaps The Clash summed up the situation best in their song lyrics: “…Should I stay or should I go now?/If I go there will be trouble/An’ if I stay it will be double…” The trouble is clinically manifest in patients with leukocyte adhesion deficiency (LAD) syndrome that presents early in life and manifests by infections without pus formation, despite a state of leukocytosis.3 In contrast to LAD-I and LAD-II syndromes, which lack expression of β2-integrins and selectin ligands due to homozygous mutations in the genes that produce these adhesion molecules, a variant denoted LAD-III exhibits normal integrin
and selectin ligand expression but has hematopoietic defects in receptor activation and adhesive functions that are attributed to the lack of expression of kindlin-3. Kindlin-3 forms a ternary complex with the cytoplasmic tail of β-integrin along with talin. The LAD-III defect has provided solid evidence that focal clusters of bound integrins effectively mechanotransduce outside-in signals that are critical to both stable adhesion and migration necessary to navigate the final steps of immigration.

In this issue of Blood, Jakob et al report that HPK1 participates during inside-out and outside-in signaling of neutrophil recruitment during acute inflammation.1 Whereas HPK1 has previously been reported to participate in signaling lymphocyte functions, Jakob et al have provided the first data to reveal its function during chemokine induction of neutrophil arrest, adhesion strengthening, pseudopod formation, and cell migration via high-affinity lymphocyte function-associated antigen 1. Using HPK1-deficient mice, Jakob et al observed a significant defect in the neutrophils’ capacity to efficiently arrest and migrate along and across inflamed endothelium, analogous to the kindlin-3 defect in LAD-III. One caveat in this comparison is that HPK1 appears to specifically modulate LFA-1 and not Mac-1 function. A particularly exciting component of this study was the finding that HPK1 formed a complex with the adaptor mammalian actin-binding protein 1, previously shown by this same group to reinforce neutrophil adhesion-dependent functions.4 These observations begin to shed light on how tension transmitted through focal clusters of LFA-1 serves to reinforce its linkage to the cortical cytoskeleton via outside-in signaling. Still unknown is the relationship between HPK1, mammalian actin-binding protein 1, kindlin-3, and talin, all of which are enriched on the cytoplasmic domain of CD18 and function to stabilize high-affinity LFA-1. An intriguing possibility is that enrichment of these adaptors facilitates assembly of a cytoskeletal linkage critical to efficient neutrophil mechanotaxis, or directional sensing using shear stress. Such a process would involve signal transduction modulated by focal clusters of high-affinity LFA-1 bound at sites enriched in dimeric intercellular adhesion molecule 1 near endothelial junctions.5 Future studies should shed light on the precise nature of force-facilitated integrin activation and signaling. One proposed scenario is that LFA-1 functions as a traction sensor by converting tensile bond forces to conformational changes that in turn initiate dynamic recruitment of these linking molecules to the cytodomain of the integrin.6 HPK1 is now established as one such link that reinforces the integrin connection to the cortical actin cytoskeleton, perhaps functioning as a clutch that engages active mechanotactic crawling that guides a neutrophil efficiently to the site of inflammation.

Conflict-of-interest disclosure: The author declares no competing financial interests.

Comment on Mazharian et al, page 4205

SHPing in different directions in platelet production

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In this issue of Blood, Mazharian and colleagues characterize Shp1 and Shp2 conditional knockout (KO) murine models, underscoring the role of these phosphatases not only on platelet function but also on megakaryocyte development and platelet counts and size.1 Protein tyrosine phosphatases (PTPs) are a superfamily of enzymes that, along with protein tyrosine kinases, act in a coordinate manner to allow phosphorylation and dephosphorylation of proteins, therefore regulating intracellular signaling. Two members of this family, the ubiquitously expressed Src homology 2 domain tyrosine phosphatases SHP-1 and SHP-2, are involved in a vast array of cellular functions through their role in tyrosine phosphorylation of intracellular proteins. From cell development to growth and differentiation, several reports have characterized the involvement of these non-transmembrane PTPs in cell signaling pathways for hormones, growth factors, and cytokines and their potential implication in disease states such as autoimmunity, diabetes, and cancer.2 Both SHP-1 and SHP-2 have been implicated in platelet activation responses such as adhesion and aggregation, particularly by interacting with ITAM-containing receptors and integrins. Nevertheless, despite sharing similar signature sequences, their role appears to differ substantially, with SHP-1 being mostly a negative regulator of intracellular signaling and SHP-2 facilitating signaling via the Ras-mitogen-activated protein kinase pathway.3,4

Human SHP-1 and SHP-2 are encoded by PTPN6 and PTPN11, respectively, with highly conserved orthologs in mice. Complete murine nulls for both PTPs have been developed and they either result in death within a few weeks after birth (Shp-1) or exhibit embryonic lethality (Shp-2). Although these models have provided

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