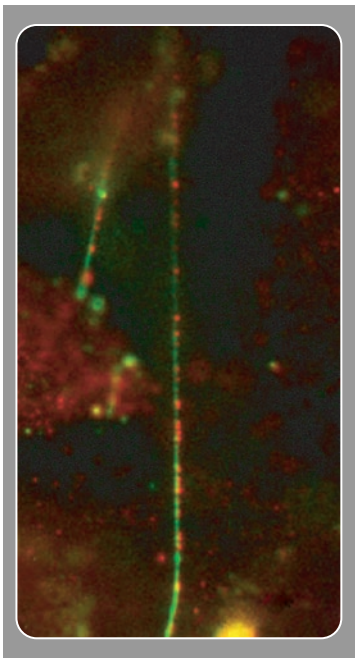
platelet rolling and participate in hemostasis). The word on a consummated relationship recently became apparent when it was shown that mice lacking VWF displayed reduced P-selectin–mediated leukocyte rolling in calcium ionophore–stimulated mesenteric venules.[1] In addition, transfection of VWF into a cell line that expressed P-selectin, but not VWF, induced formation of WP-like structures and sorting of P-selectin into these granules.[2] Although the interpretation of the data is confounded by the fact that VWF is necessary for the formation of WP bodies, the results suggested that VWF multimers might somehow be important in the storage of P-selectin in these organelles.

VWF is secreted through either a constitutive or a regulated pathway. Constitutively secreted VWF, consisting of dimers or low-molecular-weight multimers, is rapidly transported toward the plasma membrane.



High-molecular-weight (ultralarge) VWF (ULVWF) is stored in WP bodies. These ULVWF multimers are highly active and may lead to platelet aggregation and thrombus formation when secreted without-further alteration. Proteolytic processing of VWF by ADAMTS13, a metalloproteinase deficient in thrombotic thrombocytopenic purpura (TTP), likely prevents spontaneous thrombosis. Previous studies by Dong et al revealed that ULVWF multimers can form long strings on endothelial cells that are efficiently cleavable by ADAMTS13 under shear stress.[3] In this issue of *Blood*, Padilla and colleagues (page 2150) show that these VWF strings are anchored to the endothelial surface by clustered P-selectin, which appears to tie the strings by forming a series of small P-selectin and VWF-enriched "knots." A direct interaction between P-selectin and VWF is strongly suggested by adhesion assays, colocalization using immunofluorescence staining, and coimmunoprecipitation experiments. Strikingly, string formation was completely prevented by incubation of endothelial cells with anti–P-selectin antibody or soluble P-selectin. Whether these strings play a role in the pathogenesis of TTP remains to be demonstrated, however. These results nevertheless raise the interesting possibility of therapeutic interventions in TTP directed at inhibiting P-selectin. In addition, ULVWF presented by endothelial P-selectin may conceivably contribute to some P-selectin–mediated platelet-endothelial interactions, although platelet translocation on VWF in vivo was shown to be independent of P-selectin.[4]

The study is also notable because P-selectin had only one major physiologic counterreceptor, P-selectin glycoprotein ligand-1 (PSGL-1), which interacts through the coordinated presentation of sialyl Lewis X on O-glycans in the context of sulfated tyrosines. The restricted binding to ULVWF suggests a cryptic binding site for P-selectin within ULVWF. Carbohydrates comprise a significant fraction (about 20%) of the molecular weight of VWF; the VWF amino acid sequence indeed contains 22 probable glycosylation sites, of which 10 are O-glycans.[5] Although the authors' results suggest that the interaction between P-selectin and VWF occursonly after endothelial activation, the possibility that this interaction plays a role in the physiologic targeting of P-selectin to WP bodies still remains and will undoubtedly be the subject of future studies.

—Paul S. Frenette
Mount Sinai School of Medicine

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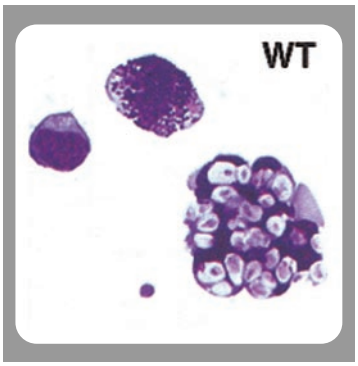
Integrins, mast cells, and innate immunity

Over the past several years, there has been increasing awareness of the importance of mast cells in initial host defense against invading bacteria.[1] In several different models of infection of normally sterile body cavities, mast cells have a significant role in initiating the process of innate immunity, especially in the chemoattraction of professional phagocytes, particularly polymorphonuclear neutrophils (PMNs), to the site of infection. Early influx of PMNs can be critical for control of infection. This essential early role for mast cells results from their unique property of synthesizing tumor necrosis factor α (TNFα) constitutively, so that it can be released rapidly in response to an appropriate secretion signal. Mast cell–derived TNFα is a major chemoattractant during early PMN recruitment, as is mast cell–derived LTB4, which is made in response to interaction with bacteria. While

mechanisms of mast cell secretion in response to crosslinking immunoglobulin E (IgE) receptors and secretagogues have been studied extensively, not much is known about how bacteria and bacterial products activate secretion of the mast cell mediators of host defense. Now, in this issue of *Blood*, Edelson and colleagues (page 2214) have shown that mast cell expression of the integrin α2β1, a receptor for extracellular matrix collagens and for at least one cell-surface molecule, E-cadherin, is required for PMN influx and interleukin-6 (IL-6) accumulation induced by intraperitoneal infection with the gram-positive bacterium *Listeria monocytogenes*. Although an important role for α2β1 on monocytes and inflammatory T cells in the process of migration to sites of inflammation had been established,[2] the high level of expression of α2β1 on



mast cells and its requirement in innate immune responses were not previously appreciated. The mast cell defect in α2β1 deficiency appears to be one of cell activation rather than of development, because peritoneal mast cell number, size, and granularity are comparable in wild-type and $\alpha2\beta1^{-/-}$ mice, and the nonspecific secretagogue compound 48/80 causes degranulation identically in mast cells from the 2 strains. As with all good experiments, the findings published in this paper suggest several new, important problems for understanding how mast cells contribute to host defense. The mast cell receptors for *Listeria* and zymosan, a derivative of the fungal cell wall that also induces PMN influx into the peritoneum in an α2β1-dependent fashion, are not known. The relevant ligand for the α2β1 integrin likewise is not clear. There is precedent for the possibility of synergy between integrin ligation and other signaling receptors in both the anchorage dependence of growth of many cell types[3] and the adhesion-dependent activation of PMNs in response to inflammatory stimuli,[4] but no understanding of whether and how crosstalk between bacterial and matrix protein signals might work in mast cells. Finally, Edelson et al show that early dissemination of *Listeria* infection is enhanced by the absence of α2β1 integrin but not of mast cells. This clearly demonstrates that α2β1 function on a cell type in addition to the mast cell is important in early control of infection. There are more surprises yet to come as the role for this integrin in innate immunity and host defense is discovered.

—Eric J. Brown
University of California–San Francisco

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T cells in mouse follicular lymphoma

Common B-cell non-Hodgkin lymphomas (B-NHLs) arise by malignant transformation of defective germinal center (GC)–stage B cells.[1] These lymphomas include follicular lymphoma (FL) and more aggressive Burkitt (or Burkitt-variant) and diffuse large B-cell lymphomas. A characteristic t(14;18) is detectedin over 80% of FL, which causes overexpression of the *BCL2* cell survival gene by rearrangements with immunoglobulin (Ig) heavy chain locus control elements. Initially indolent, FL may transform to a more aggressive tumor with increasingly complex cytogenetics over time.

FL is also the most common B-cell lymphoma naturally arising in old mice and in *Eμ-Pim-1* transgenic mice. White pulp expansions of $sIgM^+/B220^+/CD19^+$ GC B cells usually begin in the spleen and may contain large (centroblasts, immunoblasts), small (centrocytes), or a mixture of large and small tumor cells that lose the usual GC spatial relationships. Unlike human FL, naturally occurring mouse FLs are not associated with *Bcl2* gene overexpression and do not display a typical follicular pattern. Despite several attempts, a *BCL2*-based model of FL has not been generated in mice, until now.

In this issue of *Blood*, Egle and colleagues (page 2276) describe a new model of FL by *Bcl2* overexpression using *VavP* control sequences. About 15% to 25% of mice developed a syndrome resembling autoimmune glomerulonephritis that was strain dependent. However, 37% to 50% of mice developed FL by 18 months of age following a florid GC hyperplasia.[2] Other hematologic tumors occurred at lower frequencies, including plasma cell tumors, lymphoblastic or large B-cell lymphoma, thymic lymphoma, and histiocytic sarcoma. Interestingly, levels of the *Bcl2* transgene expression were independent of lymphomagenesis; rather, $CD4^+$ T-cell help appeared essential for FL.

There are several exciting features in this valuable genetic model of human FL. The key seems to be panlymphoid *Bcl2* expression and time, which yield increased numbers of $CD4^+$ T cells that support robust GC B-cell expansions. Antigenic stimulation through surface Ig (sIg), with associated somatic hypermutation (SHM), has been described previously in human FL but not in mouse FL, which usually lacks