to be free of widespread intravascular fibrin deposition and had no signs of a consumption coagulopathy, whereas nonchallenged mice had normal bleeding times. In these elegant proof-of-principle experiments it is demonstrated that targeted delivery of anticoagulant agents at the surface of activated cells (ie, at the site of coagulation activation) may be a worthwhile approach to pursue. Additional bone marrow reconstitution experiments in this article show that endothelial cells in particular may be the pivotal target for this local treatment.

A detailed analysis of the function of coagulation in vivo has in recent years led to the development of new, potent, and highly specific antithrombotic agents. The experiments of Chen et al indicate that targeting the cell surface may well be the next step in further improving anticoagulant treatment. ■

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IMMUNOBIOLOGY

Comment on Majstoravich et al, page 1396

The core of the lymphocyte microvilli–WASp issue

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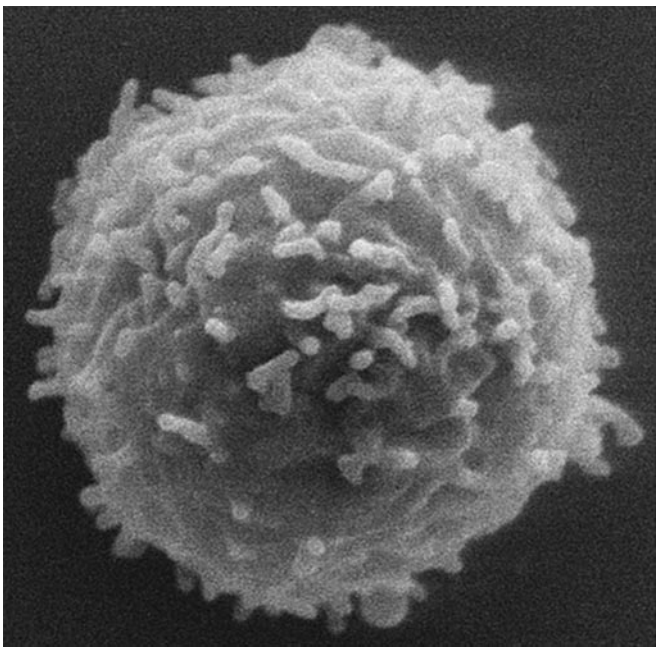
Majstoravich and colleagues have determined that the short microvilli of lymphocytes, although uniform in length and density, are highly dynamic actin filament bundle–containing structures that do not depend upon WASp for their morphology.

Lymphocytes are known to have short, actin filament–rich, microvillus-like projections, and these structures have been implicated in processes of key importance, such as the initial phase of rolling during extravasation and virus recognition. But, primarily because these structures are so short (~ 0.3 μm), relatively little is known about their internal organization and dynamics. An issue of central importance is the role of Wiskott-Aldrich syndrome protein (WASp), the archetype of a family of actin nucleation–promoting factors that stimulate actin-related protein 2/3 (Arp2/3) complex–mediated actin polymerization. WASp is expressed preferentially in hematopoietic cells and is mutated in patients with Wiskott-Aldrich syndrome (WAS), which is characterized by immunodeficiency, thrombocytopenia, and eczema.



Lymphocytes from WASp knock-out mice have normal microvilli. See the complete figure in the article beginning on page 1396.

Of the classes of cell surface specialization assembled using an actin filament–based scaffold, 2 major ones, lamellipodia and filopodia, are believed to involve WASp family members directly or indirectly. The branched actin filament network of lamellipodia uses WASp family members to activate the Arp2/3 complex to form new branches.[1] This lamellipodial actin network can, in turn, be rearranged, cross-linked, and elongated to form the parallel actin bundle scaffold of filopodia.[2] In contrast, remarkably little is known about how the parallel actin bundle scaffolds of microvilli are established and maintained.[3] Compared with lamellipodia and filopodia, microvilli may seem more stable, but recent studies indicate that the actin filaments in the parallel actin bundle at the core of epithelial cell microvilli turn over rapidly through actin treadmilling.[3]

Majstoravich and colleagues used scanning electron microscopy to examine lymphocytes isolated from mice and humans and the larger cells of a transformed pre-B-lymphoma line, and they found a remarkable conservation in microvillar length and density. In addition, using transmission electron microscopy, they observed what appeared to be a parallel actin bundle at the core. Importantly, when the authors exposed the lymphocytes to the actin monomer–sequestering drug Latrunculin A, they observed a rapid and reversible shrinkage of these projections. This behavior was consistent with the existence of actin treadmilling in the filaments of the core actin bundle at a rate of about 1 to 2 actin monomers per second, which is remarkably similar to the treadmilling rate measured in the brush-border microvilli of a kidney epithelial cell line.[3] Finally, these authors found that lymphocytes isolated from WASp knockout mice or human WAS patients of 3 different genotypes showed minimal defects in microvillar length or density, suggesting that wild-type WASp was not required for expression of this baseline microvillar morphology. Although at first glance this result appears to contrast with earlier reports of microvillar abnormalities on lymphocytes from WAS patients[4] and WASp-deficient mice,[5] these earlier studies examined cells under conditions likely to favor lymphocyte activation. This raises the intriguing possibility that there are multiple mechanisms for microvillus formation in lymphocytes and suggests that a WASp-dependent pathway becomes dominant under conditions of activation. ■

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CLINICAL OBSERVATIONS

Comment on Solal-Céligny et al, page 1258

The "FLIPI" is no "FLOPI"

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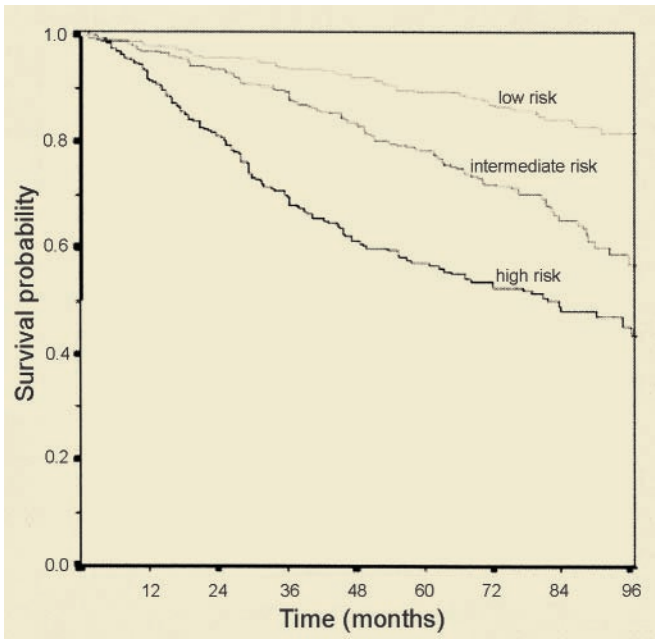
The FLIPI provides an important tool to predict outcomes for patients with follicular lymphoma and may ultimately help to tailor therapy.

The management of indolent lymphoma presents a challenge to clinicians as well as to patients and their families because they are confronted with a new diagnosis of an illness that goes against many of the "rules" of cancer, particularly with respect to the role of early diagnosis and aggressive treatment. Follicular lymphoma is by far the most common indolent subtype, and it comprises approximately a quarter of non-Hodgkin lymphoma cases overall. Median survival rates have been reported in the range of 10 years,[1] although outcomes vary widely.

In many settings, particularly in those involving asymptomatic patients with low tumor burden, observation without therapy, or a "watch and wait" approach, may be reasonable. When treatment is necessary due to symptoms or substantial tumor progression, deciding on a strategy is equally difficult. Patients and clinicians have an array of options, including alkylating agents, purine analogues, antibody therapy (rituximab), combination chemotherapy alone or with rituximab, radiolabeled antibodies, and autologous and allogeneic transplantation.[2] The choices are complicated by the inconsistency of the disease course, and while some data may suggest short-term advantages (such as improved progression-free survival), there is a relative paucity of randomized trials demonstrating a long-term benefit (survival) of one approach over another.[3] The fact that an individual patient may reasonably receive recommendations that run the gamut from observation to allogeneic stem cell transplantation highlights the lack of clear guidelines.

A critical first step to optimizing therapy for a heterogeneous disease is the definition of patient subsets associated with favorable or unfavorable prognosis. In aggressive lymphoma, the International Prognostic Index (IPI) has been extremely helpful in this regard and has consistently identified low-, intermediate-, and high-risk individuals to evaluate novel "risk-adapted" therapeutic approaches for different populations.[4] For indolent lymphoma, however, relatively few patients fall into the high-risk IPI group, and, therefore, its discriminatory power is limited.[5] In an important international effort reported in this issue of *Blood*, Solal-Céligny and colleagues have studied a group of more than 4000 follicular lymphoma patients in order to develop the Follicular Lymphoma International Prognostic Index (FLIPI). The authors identified 5 characteristics (referred to by the acronym "NoLASH") associated with unfavorable survival: (1) more than 4 nodal areas; (2) elevated LDH; (3) age greater than 60 years; (4) stage III or IV; and (5) hemoglobin level less than 120 g/L (12 g/dL). Patients falling into the low-risk group (0-1 risk factor; 36% of patients) had a median 10-year overall survival rate of 70.7%, whereas high-risk patients (3 or more risk factors; 27% of patients) were associated with a median 10-year overall survival rate of 35.5%.

The FLIPI provides a simple, inexpensive tool for routine use in follicular lymphoma. Where do we go from here in order to best use this important information? First, the FLIPI should be applied retrospectively where possible to populations in previous clinical trials in follicular lymphoma. This may put phase 2 studies into context and identify patient subsets from randomized trials who might particularly benefit from one treatment or another. In these smaller data sets, correlation of the FLIPI not only with overall survival but also with progression-free survival is of interest, as is its usefulness in relapsed patient populations. Second, the FLIPI should be prospectively incorporated in new trials for indolent lymphoma, including stratification criteria for randomization. Finally, when superiority of a particular regimen is determined for a specific FLIPI patient subset, one can anticipate that treatment strategies will ultimately be defined by the accurate assessment of risk.



Overall survival of follicular lymphoma patients by FLIPI risk group. See the complete figure in the article beginning on page 1258.