methodologies and results (summarized by Raccor et al and Zanger and Klein). However, the present study is the first based on a prospective, controlled clinical trial and is the first to indicate an impact of host pharmacogenetics in CLL. Given the extensive use of CPA for malignancies in general, the observation is relevant for the whole field of cancer chemotherapy and may contribute to progress toward tailored therapy.

But what will this observation mean for the use of CPA-containing regimens in the future? Although 4OH-CPA can be measured by routine methods (high-performance liquid chromatography), it is cumbersome and hardly feasible in larger clinical trials. Instead, a pharmacogenetic approach like the present study may make it possible to intervene in future trials, for example by CPA dose adjustment in individuals or groups with variant CYP enzymes including CYP2B6.

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the head domain points away from the membrane bilayer surface, contrasting to what has been posited from the crystal structure of the ectodomain (see figure). The upward orientation of the αIIbβ3 head domain was further confirmed by the antibody-based epitope mapping and is also consistent with the previous cryo-EM model of intact integrin αIIbβ3. The lower legs connecting to the transmembrane domain were coiled, which were also significantly different from the straight conformation in the crystal structure. This coiled conformation is likely the underlying basis to allow the upward orientation of the head domain. Based on these data, Choi et al proposed a modified switchblade model for integrin activation: rather than going through a bent-to-extended change in a single fulcrum, integrin ectodomain undergoes multiple interdomain movements as initiated by the transmembrane-cytoplasmic domain, which ultimately leads to an extended/active conformation of the receptor (see figure).

The resolution of the new αIIbβ3 model was not sufficient to resolve the transmembrane-cytoplasmic domain and hence continued effort is needed to overcome the technical limit. However, the results derived from this study are already of significant value to the integrin field as well as to membrane protein structural biology in general. First, the new αIIbβ3 model challenges the existing paradigm for the inactive integrin ectodomain conformation and orientation relative to membrane, leading to a revised model for the integrin activation. Second, the study emphasizes the importance of the transmembrane domain in influencing the global structure and orientation of any transmembrane protein. Because many ectodomain structures of transmembrane receptors have been deposited in the Protein Data Bank and more are being determined, the Choi et al study calls upon cautious interpretation of these structures. In the case of αIIbβ3, it is clear that the transmembrane domain was crucial for influencing the lower leg conformation and ultimately the upward orientation of the head domain. On the other hand, it should be pointed out that the Choi et al study was performed in the absence of extracellular ligands and intracellular regulators. It remains to be further investigated, hopefully at higher resolution, if integrin does undergo the proposed conformational transition upon binding to physiological ligands such as fibrinogen or intracellular activators such as talin and kindlin. It also remains to be seen whether integrin maintains the proposed inactive conformation in the presence of intracellular inhibitors such as calcium integrin-binding protein, Sharpin, and filamin. With the rapid improvement of biotechnology, such as protein sample preparation and high-resolution structural biology equipment, one may expect additional breakthroughs in the near future, which will further advance our understanding of the integrin function in diverse biological processes and hopefully also promote the development of better therapy for treating integrin-dependent human diseases.

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Comment on Roach et al, page 4264

Superficial venous thrombosis: recognizing the risk

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In this issue of Blood, Roach and colleagues show that individuals with prior superficial venous thrombosis are at increased risk of developing venous thromboembolism when exposed to acquired clinical risk factors.1

Although superficial venous thrombosis was originally perceived as a benign disease with a self-limited clinical course, it is now recognized that this condition is often associated either with concomitant venous thromboembolism or with early development of deep vein thrombosis and pulmonary embolism.2-4 Further, Heit et al reported in 2000 that individuals with previous superficial venous thrombosis were more than 4 times more likely to develop future deep vein thrombosis or pulmonary embolism,5 and this finding has subsequently been confirmed by several investigators.7,8 However, because most individuals with superficial venous thrombosis do not develop venous thromboembolism, it has been difficult to know how best to use this information to risk stratify patients.

Prior research has shown that genetic thrombophilias only minimally increase the risk of venous thromboembolism in patients with a history of superficial venous thrombosis.8 In the report published in this issue of Blood, Roach et al use data from the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) population-based case control study9 that enrolled 4956 consecutive patients between 18 and 70 years of age with a first symptomatic objectively confirmed deep vein thrombosis or pulmonary embolism, together with 6297 age- and sex-matched controls, to examine the risk of venous thromboembolism in individuals with a self-reported history of superficial venous thrombosis and various clinical risk factors. Acquired risk factors included in this analysis were surgery, pregnancy, plaster casting and hospitalization within 3 months of venous thromboembolism diagnosis or study enrollment, oral contraception or hormone replacement therapy within the preceding 1 month, and malignancy in the 5 years prior to the index event.

Clinical risk factors were categorized as mild (smoking or overweight), strong (surgery, hospitalization, plaster casting, or malignancy), or reproductive (oral contraceptive use, postmenopausal hormone replacement therapy, or pregnancy and the postpartum period). Consistent with previous reports, individuals with prior superficial venous thrombosis had a 6-fold increase in the risk of venous thromboembolism compared with those without a similar history. The odds ratio for venous thromboembolism was increased to 9 with the addition of a mild clinical thrombotic risk factor and to approximately 30 in those with a major risk factor and in women with reproductive risks. The highest risks in the latter 2 categories were seen in patients with previous superficial venous thrombosis undergoing surgery or requiring hospitalization and those using oral contraceptives. Although one cannot directly infer absolute risks from a case-control study, the authors use previously established background incidences to determine the impact of their findings on the thrombotic risks associated with various clinical risk factors. In individuals with prior superficial venous thrombosis, the calculated risks were 1 in 32 in those undergoing surgery, 1 in 27 for those requiring hospitalization, and 1 in 51 in oral contraceptive users.

Although this study has several strengths, including its large size, objective diagnosis of the index venous thromboembolic event, and similar method of data collection for patients and controls, there are important limitations. Most importantly, the 95% confidence intervals for many of the risk estimates are wide; the diagnosis of superficial venous thrombosis and occurrence of clinical risk factors are based solely on patient self-report, and no information was obtained on the location of the superficial venous thrombosis or on the temporal relationship between it and the various clinical risk factors or the diagnosis of venous thromboembolism.

The results of this study are not sufficient to allow physicians to confidently modify standard recommendations for thrombosis prophylaxis in patients with a history of superficial venous thrombosis undergoing surgery or requiring hospitalization or to recommend against oral contraceptive therapy in affected women. How best to incorporate a history of superficial venous thrombosis into prophylaxis risk stratification schemes and decision making about the use of hormonal therapy in these patients has yet to be determined. However, in the interim, individuals with prior superficial venous thrombosis and their treating clinicians should have a heightened awareness of the potential for developing venous thromboembolism in these clinical settings.

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A new view of integrin αIIbβ3 bound to membrane

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