Turning their attention to outside-in signaling across integrins, the authors evaluated platelet adhesion and spreading on fibrinogen and platelet-mediated clot retraction. These responses are all dependent on outside-in signaling across integrin αIIbβ3, and all were similar with platelets from RIAM-null and wild-type mice.

Of course, a particularly crucial issue is whether the absence of RIAM affects platelet integrin αIIbβ3 activation-dependent responses in vivo. The authors address this question by assessing tail bleeding time, an assessment of hemostasis, and time to occlusion following $FeCl_3$-induced injury to the mesenteric arterioles, an assessment of thrombus formation. Both of these assays are known to have limitations but are among the most widely used models to evaluate hemostasis and thrombus formation in the mouse. In both models, the RIAM-null and wild-type mice did not differ significantly. Thus, two of the most relevant physiological/pathological responses mediated by platelets and their integrins appear to be fully functional in the absence of RIAM.

The compilation of these findings leads to a clear conclusion: RIAM is not essential for integrin activation in platelets or for platelet responses dependent on integrin activation. How is this conclusion reconciled with previous data showing that manipulation of RIAM levels in model cells influences activation of integrins, including integrin αIIbβ3? Several possible explanations can be considered. As currently envisioned, integrin activation depends on the binding of talin via its head domain to the cytoplasmic tail of the integrin β subunit.[3] Talin exists in the cytosol in an autoinhibited state, in which its rod domain occludes the integrin-binding site in its head domain.[7,8] RIAM was envisioned as being involved in activating talin for binding to integrin and in recruiting talin to the membrane, a step needed for appropriate orientation of talin's head for integrin activation.[5] However, talin activation and recruitment can be achieved by multiple mechanisms (see figure), and RIAM provides only 1 route to the end of integrin activation. Thus, 1 plausible explanation for the observations is that these other pathways are sufficient in platelets, making RIAM dispensable for integrin activation-dependent responses. A second possibility is that other MLR family members or other Rap1 effectors may fulfill the integrin activating functions of RIAM in platelets. With the absence of a platelet phenotype in RIAM-null mice but substantial defects in integrin-mediated responses in Rap1-deficient mice,[9] it is clear that RIAM-independent mechanisms exist for Rap1 to exert its effects on integrins. A third possibility is that the functions of RIAM may display species specificity in terms of the integrins, talins, or additional cofactors needed to display its integrin-activating function. The RIAM pathway may also become important in the contribution of platelets to disease development, a scenario that has yet to be explored.

The study by Stritt et al provides the first step and identifies a key tool, the RIAM-null mouse, in defining the functions of RIAM. Immediate questions needing to be addressed are whether integrin functions in other hematopoietic cells are compromised in the RIAM-null mice and what phenotypes manifest when these mice are subjected to various challenges.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

REFERENCES

1. Stritt S, Wolf K, Lorenz V, et al. Rap1-GTP-interacting adaptor molecule (RIAM) is dispensable for platelet integrin activation and function in mice. *Blood.* 2015;125(2):219-222.
2. Coló GP, Lafuente EM, Teixidó J. The MRL proteins: adapting cell adhesion, migration and growth. *Eur J Cell Biol.* 2012;91(11-12):861-868.
3. Das M, Subbayya Ithychanda S, Qin J, Plow EF. Mechanisms of talin-dependent integrin signaling and crosstalk. *Biochim Biophys Acta.* 2014;1838(2):579-588.
4. Han J, Lim CJ, Watanabe N, et al. Reconstructing and deconstructing agonist-induced activation of integrin αIIbβ3. *Curr Biol.* 2006;16(18):1796-1806.
5. Lee HS, Lim CJ, Puzon-McLaughlin W, Shattil SJ, Ginsberg MH. RIAM activates integrins by linking talin to ras GTPase membrane-targeting sequences. *J Biol Chem.* 2009;284(8):5119-5127.
6. Lafuente EM, van Puijenbroek AA, Krause M, et al. RIAM, an Ena/VASP and Profilin ligand, interacts with Rap1-GTP and mediates Rap1-induced adhesion. *Dev Cell.* 2004;7(4):585-595.
7. Goksoy E, Ma YQ, Wang X, et al. Structural basis for the autoinhibition of talin in regulating integrin activation. *Mol Cell.* 2008;31(1):124-133.
8. Song X, Yang J, Hirbawi J, et al. A novel membrane-dependent on/off switch mechanism of talin FERM domain at sites of cell adhesion. *Cell Res.* 2012;22(11):1533-1545.
9. Chrzanowska-Wodnicka M, Smyth SS, Schoenwaelder SM, Fischer TH, White GC II. Rap1b is required for normal platelet function and hemostasis in mice. *J Clin Invest.* 2005;115(3):680-687.

● ● ● CLINICAL TRIALS & OBSERVATIONS

Comment on Cannegieter et al, page 229

Superficial venous thrombosis: deeper than meets the eye?

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In this issue of *Blood*, Cannegieter et al use the Danish National Patient Registry to report on the high incidence of venous thromboembolism (VTE), mortality, and arterial thrombosis following a diagnosis of superficial vein thrombosis (SVT). Remarkably, individuals with SVT had nearly a 14% risk of VTE over 10 years, with a 3.3% risk of VTE in the 3 months following the SVT.[1] Although during the 10 years of follow-up this translated into an 8-fold increased risk of VTE, the risk was much higher within the 3 months following an SVT (71-fold increased risk of VTE). The hazard ratios of arterial events and death over the entire follow-up were more modest (around 1.2-1.3), however, with noticeably increased risk within 3 months of the SVT event with a 1.5- to 3.5-fold increased risk.

Thrombosis is a family of diseases, with common manifestations such as VTE and SVT and rarer ones such as cerebral sinus thrombosis and splanchnic vein thrombosis. Although there are common themes and risk factors for each site of thrombosis, risks and benefits of treatment as well as individual risk factors

may differ. In the case of SVT, the traditional paradigm of it being a benign, self-limiting disease treated with anti-inflammatories and warmth is quickly giving way to the recognition of significant morbidity and even mortality.[2] Recent trials of anticoagulants to treat SVT demonstrate reduced progression to VTE and improved patient comfort, both on anticoagulants and after anticoagulants were stopped.[3] In fact, this has led to a recommendation for anticoagulant treatment of SVT by the American College of Chest Physicians,[4] with some experts recommending that SVT be treated similarly to VTE.[2]

Cannegieter et al elegantly demonstrate the power of administrative databases to study either rare diseases or common diseases with no centralized care. Because care for SVT, and thrombosis in general, is spread across different provider types and treatment locations, the epidemiology and consequences of SVT are infrequently reported in the literature.[5] The Danish National Patient Registry was established in 1977 and over the years has evolved to record more components of health and illness in the population of Denmark.[6] Despite multiple insights into the health of the Danish population, this registry was never designed for research, but as a monitoring instrument for hospital activities and a basis for payment for public and private hospitals. The major weakness of this registry is that it is not linked to clinical databases such as electronic health records (EHRs) and so further conformation about the diagnoses and treatments cannot be obtained.[1,6]

Imagine the potential of harnessing all the information of an EHR in addition to an administrative database, linking billing codes, inpatient and outpatient diagnoses, vital signs, anthropomorphic measures, family and social history, laboratory studies, physician notes, and results from imaging studies.[7] At best, EHRs are a means of streamlining health care to improve communication and efficiency. The reality has been a mishmash of incompatible systems designed to improve billing and comply with government mandates in which a "simple" question such as the date of an initial or recurrent VTE event requires human abstraction of the medical record. The potential to assess the health of a population with the EHR, to study rare diseases, and to study common diseases with no centralized care is not realized.[7] Hospitals, acute care facilities, laboratories, imaging facilities, and outpatient physician offices all use different records that do not communicate with each other—making it impossible to capture the health of an individual over time.

In the case of SVT, many questions remain unanswered. Despite the recommendation that most SVT be treated with anticoagulants, how commonly is this done in clinical practice? Does anticoagulation change the frequency of VTE or mortality following an episode of SVT? What is the role of the newer oral anticoagulants in treating SVT? How often does bleeding complicate treatment of SVT? Harnessing the power of the EHR could help us efficiently gain insight into the answers to these questions. But first, we need to ensure the EHR accurately captures important outcomes in a manner that improves clinical care and can be used for research.

Overall, this study conclusively demonstrates that SVT is not a benign disease and has consequences for patients. This study also demonstrates the power of population registries in improving health care. With the advent of EHRs in the United States and other nations, we must focus on how we can accurately record the health and illness of populations with the goal of providing cost-conscious, evidence-based care for everyone.

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

REFERENCES

1. Cannegieter SC, Horváth-Puhó E, Schmidt M, et al. Risk of venous and arterial thrombotic events in patients diagnosed with superficial vein thrombosis: a nationwide cohort study. *Blood*. 2015;125(2):229-235.
2. Kitchens CS. How I treat superficial venous thrombosis. *Blood*. 2011;117(1):39-44.
3. Decousus H, Prandoni P, Mismetti P, et al; CALISTO Study Group. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med*. 2010;363(13):1222-1232.
4. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl): e419S-494S.
5. Decousus H, Quéré I, Presles E, et al; POST (Prospective Observational Superficial Thrombophlebitis) Study Group. Superficial venous thrombosis and venous thromboembolism: a large, prospective epidemiologic study. *Ann Intern Med*. 2010; 152(4):218-224.
6. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011; 39(7 suppl):30-33.
7. Lin J, Jiao T, Biskupiak JE, McAdam-Marx C. Application of electronic medical record data for health outcomes research: a review of recent literature. *Expert Rev Pharmacoecon Outcomes Res*. 2013;13(2):191-200.

● ● ● LYMPHOID NEOPLASIA

Comment on Jing et al, page 273

Yin and yang of glucocorticoid receptors in apoptosis

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In this issue of *Blood*, Jing et al have identified 2 novel pathways involved in the dexamethasone response in pediatric B-precursor acute lymphoblastic leukemia (ALL).[1]

Using patient-derived xenografts, the authors show that the glucocorticoid receptor (GR) coordinately regulates both the antiapoptotic protein Bcl2 and the proapoptotic protein BIM (see figure). Using gene expression profiling, chromatin immunoprecipitation (ChIP), and ChIP sequencing (ChIP-seq) analysis, the authors identified a novel intronic GR binding site within the BIM coding region. The group also showed that both the GR promoter in KLF13 and the intronic BIM GR promoter were absent in leukemia cells resistant to dexamethasone.